A NHK Approach Towards the Total Synthesis of the Cornexistins

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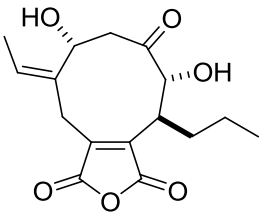
Abstract

Cornexistin and hydroxycornexistin were both isolated from the fungus *Paecilomyces variotii*. They were found to possess significant herbicidal activity, which triggered the interest of agrochemicals companies. Their structures consist of a nine-membered carbocyclic ring fused to a cyclic anhydride with various oxygen functionalities decorating the nine-membered core.

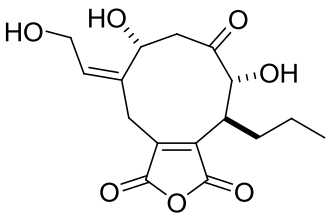
Previously, the synthesis of (±)-5-*epi*-hydroxycornexistin was successfully achieved in the group, using a Stille-coupling reaction between a chloride and stannane fragments, followed by a key ring-closing metathesis reaction to form the core of the nine-membered ring. However, the desired stereochemistry on the C-5 centre could not be installed despite the use of a variety of methods.

A new strategy, involving an intramolecular Nozaki-Hiyama-Kishi reaction was investigated, leading to the formation of an advanced intermediate for the synthesis of hydroxycornexistin. The reaction proved efficient and X-ray crystallography was used to confirm the desired formation of the natural C-5 configuration of cornexistins. The stereoselectivity of the reaction was considered and alternative methods to improve the diastereoisomeric ratio were attempted.

The asymmetric synthesis of hydroxycornexistin was studied, using an advanced model substrate and an efficient strategy for the asymmetric syntheses of both Stille-coupling partners was performed. The synthesis of the chloride fragment involved a cross-metathesis reaction and a [3,3]-sigmatropic rearrangement reaction as main steps of the reaction sequence. Using a chiral auxiliary, the stannane fragment was obtained with excellent enantiomeric excess. Finally, the sequence leading to the synthesis of the NHK precursor was accomplished.



cornexistin



hydroxycornexistin

Declaration

I declare that the substance of this thesis has not been submitted, nor is concurrently being submitted in candidature for any other degree. I also declare that the work embodied in this thesis is the results of my own investigations. Where work of other investigators has been used, this has been fully acknowledged in the text.

Anthony Aimon

Prof. J. Stephen Clark

Acknowledgements

Firstly, I would like to thank my supervisor, Prof. J. Stephen Clark, for all his support over the past three years, and for giving me the opportunity to work on such a fascinating project. I appreciated having the freedom to conduct the project in the way I wanted, but also the precious help he provided me when needed. I would also like to thank EPSRC and WestCHEM for funding.

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The current group members equally deserve a special mention, Laetitia, super buddy Dory who somehow managed to always cheer me up and has been tremendously helpful and supportive over the past months, perfect Michi, always ready for indoor/outdoor sports (true story), smarty Filo, and generous & funny Chao. Good luck to the newbies Verena, Ian, Ludo and Tintin. Last of the Clarky Cats, I would like to thank the final year undergraduate students especially Louise, Kate and this year's remarkably enthusiastic students Gayle, Joanna and Sam.

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Last but not least, I am most thankful to my family, especially my brother and my parents, for their invaluable support and patience.

Abbreviations

Ac — acetyl
9-BBN — 9-bora-bicyclo[3,3,1]norane
aq. — aqueous
Ar — aryl
BINAP — 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn — benzyl
bp. — boiling point
brsm — based on recovered starting material
Bu — butyl
Bz — benzoyl
cat. — catalytic
CBS — Corey-Bakshi-Shibata
CI — chemical ionisation
conc. — concentrated
cod — cyclooctadiene
COSY — correlation spectroscopy
Cp — cyclopentadienyl
Cp* — pentamethylcyclopentadienyl
m-CPBA — *meta*-chloroperoxybenzoic acid
CSA — 10-camphorsulfonic acid
Cy — cyclohexyl
dba — di(benzylidene)acetone
DBN — 1,5-diazabicyclo[4.3.0]non-5-ene
DBU — 1,8-diazabicyclo[5,4,0]undec-7-ene
DCC — dicyclohexylcarbodiimide
1,2-DCE — 1,2-dichloroethane
DEAD — diethyl azodicarboxylate
DIAD — diisopropyl azodicarboxylate
DEPT — distorsionless enhancement by polarisation transfer
DDQ — 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP — dihydropyran
DIBAL-H — diisobutylaluminium hydride
DIPEA — diisopropylethylamine
DIPT — diisopropyl tartrate
DME — dimethoxyethane
DMAP — 4-dimethylaminopyridine
DMDO — dimethyldioxirane
DMF — *N*,*N*-dimethylformamide
DMP — Dess-Martin periodinane
DMS — dimethyl sulfide
DMSO — dimethylsulfoxide
dppp — 1,3-bis(diphenylphosphino)propane
dr — diastereomeric ratio
EDCI — 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee — enantiomeric excess
EI — electron ionisation
Enz — enzyme
ESI — electrospray ionisation
Et — ethyl
Eq. — equation
equiv — equivalent
FAB — fast atom bombardment
h — hour
hυ — irradiation with light
HMDS — hexamethyldisilazane
HPLC — high performance liquid chromatography
HRMS — high resolution mass spectrometry
Hz — hertz
i — iso

IR — infrared spectroscopy
IUPAC — international union of pure and applied chemistry
L — ligand
LRMS — low resolution mass spectrometry
LD — lethal dose
LDA — lithium diisopropyl amide
m — meta
Me — methyl
Mes — mesityl
MOM — methoxy methyl
mp. — melting point
Ms — mesyl (methanesulfonyl)
MS — molecular sieves
MTPA — α-methoxy-α-trifluoromethylphenylacetic acid
n — normal
NBS — *N*-bromosuccinimide
NHK — Nozaki-Hiyama-Kishi
NIS — *N*-iodosuccinimide
NMO — *N*-methylmorpholine-*N*-oxide
NMR — nuclear magnetic resonance
o — ortho
p — para
P, PG — protecting group
PCC — pyridinium chlorochromate
PE — petroleum ether
Ph — phenyl
PMB — *para*-methoxybenzyl
PMPTCA — *para*-methoxybenzyl trichloroacetamidate
PMP — *para*-methoxyphenyl
ppm — parts per million
PPTS — pyridinium *para*-toluenesulfonate
Pr — propyl
Pv — pivaloyl
quant. — quantitative
RCM — ring-closing metathesis
Red-Al — sodium bis(2-methoxyethoxy)aluminium hydride
R_f — retention factor in chromatography
rr — regioisomeric ratio
rt — room temperature
s — sec
t — tert
TAS-F — tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF — tetra-*n*-butylammonium fluoride
TBAI — tetra-*n*-butylammonium iodide
TBAT — tetra-*n*-butylammonium triphenyldifluorosilicate
TBME — methyl *tert*-butylether
TBS — *tert*-butylsilyl
TBDPS — *tert*-butyldiphenylsilyl
TCA — trichloroacetamidate
Tf — triflyl (trifluoromethanesulfonyl)
TFA — trifluoroacetic acid
THF — tetrahydrofuran
THP — tetrahydropyran
TIPS — triisopropylsilyl
TMEDA —*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS — trimethylsilyl
TPAP — tetra-*n*-propylammonium perruthenate
p-TSA — *para*-toluenesulfonic acid
Ts — tosyl
X — halogen

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Part I: Introduction

1.1 The cornexistins — activity and isolation

Cornexistin (**1**) was originally isolated in 1987 from a culture of the fungus *Paecilomyces variotii* Bainier (strain SANK 21086) by researchers Sankyo Co. during a screen of new microbial products possessing herbicidal activity (Figure 1.1).[1] The fungus had previously been isolated in 1982 from a sample of deer faeces collected in Canada. A few years later in 1995, the company DowElanco (now Dow Agrosciences) reported the isolation of hydroxycornexistin (**2**), from the same strain of *P. variotii*.[2]

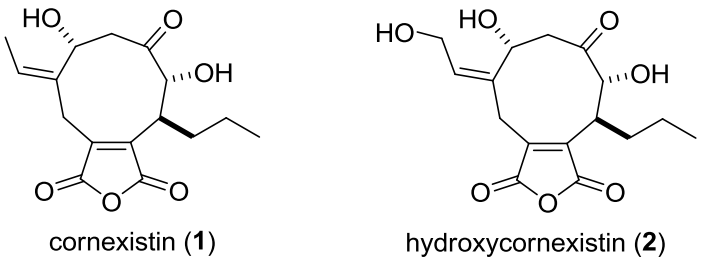


Figure 1.1

The structures of the cornexistins were elucidated using NMR spectroscopy and by X-ray crystallography, but absolute configuration was not established. Cornexistin (**1**) possesses a nine-membered carbocycle fused to a cyclic anhydride. The nine-membered ring also features an exocyclic alkene, a ketone, a propyl chain and two hydroxyl groups on the α- and β'-positions in relation to the ketone. The core of hydroxycornexistin (**2**) presents similar features, the only difference being the presence of a hydroxyl methyl group on the exocyclic alkene rather than a methyl group.

At the time of their isolation, both compounds were tested for post-emergence herbicidal activity, and found to exhibit significant herbicidal activity against grasses and broadleaf weeds that are problematic in maize production (Table 1.1).[1,2] Even at low concentration, hydroxycornexistin was particularly active against broadleaf weeds, while both compounds left maize (*Zea mays*) largely unaffected. The toxicity of cornexistin was found to be low, with a LD_{50} value greater than 1 $mg \cdot g^{-1}$ when administered orally to mice.[1b] Cornexistin also exhibited no antimicrobial activity against a variety of micro-organisms.[1b] Consequently, these two phytotoxins triggered considerable interests from agrochemical companies.

	cornexistin (ppm)			hydroxycornexistin (ppm)		
Test species	31.25	15.63	7.81	31.25	15.63	7.81
Crops						
Zea mays	30	20	0	20	0	0
Triticum aestevium	85	0	0	40	20	35
Broadleaf weeds						
Xanthium strumarium	20	10	0	100	80	80
Chenopodium album	30	30	30	90	80	20
Ipomoea hederaceae	0	0	0	85	0	0
Amaranthus sp.	0	0	0	80	60	0
Abutilon theophrasti	30	60	0	70	40	40
Polygonum convolvulus	90	40	20	100	100	40
Grass weeds						
Echinochloa crus-galli	95	80	0	40	40	0
Setaria faberi	20	20	20	70	0	0
Sorghum bicolor	30	0	0	0	0	0
Avena sativa	100	0	0	45	25	30
Digitaria sanguinalis	20	20	0	80	20	20

Table 1.1[2b] **-** Herbicidal activity of cornexistin and hydroxycornexistin. The activity was assessed visually 2 weeks after treatment on a scale of 0-100 where 100 represents complete death and 0 represents no effect.

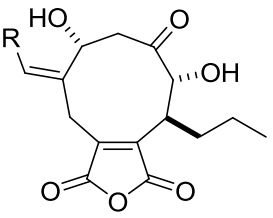
The molecular mode of action of the two phytotoxins was unknown. It was suggested that they might be pro-herbicides, inhibiting an aspartate amino transferase isoenzyme in their active form.[3] In 2012, Dayan and Zaccaro reported that cornexistin (**1**) has an effect on the photosynthesis of leaves, which maybe a secondary response to its ability to disrupt the plasma membrane.[4] Despite these advances, more than 20 years after the isolation of cornexistins, the exact mode of action remains unclear.

The cornexistins, each containing a nine-membered carbocycle, are just two of the numerous natural products belonging to the nonadride family. Several of these, possessing intricate structures and varied biological activities are described below.

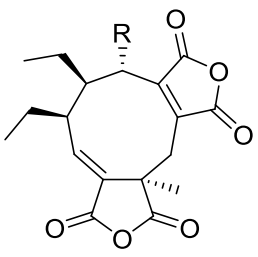
1.2 The nonadride family

1.2.1 Structure and activity of the nonadrides

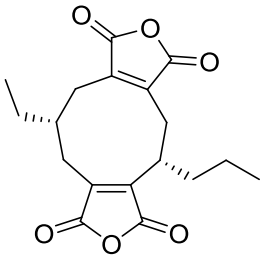
The term 'nonadride' was introduced by Barton and Sutherland in the mid 1960s in reference to the bisanhydrides glauconic acid (**3**), glaucanic acid (**4**) and byssochlamic acid (**5**), since their biosyntheses appeared to be derived from two C_9-units (Figure 1.2).[5] This was generally accepted and has since been extended to cover any related natural products containing a nine-membered carbocycle fused to at least one maleic anhydride unit. Cornexistins are rather unusual members of the nonadride family of compounds because they possess just a single anhydride unit, while to date, all the other ones bear two. The first of the nonadrides to be discovered were glauconic acid (**3**) and glaucanic acid (**4**) which were both isolated by Wijkman in 1931 from the fungus *Penicillium glaucum* (reclassified later as *Penicillium purpurogenum*).[6,7] This was followed by the isolation of byssochlamic acid (**5**) in 1933 from the fungus *byssochlamys fulva*.[8] The structures and absolute configurations of these three natural products were elucidated chemically and confirmed by X-ray crystallography.[5,6,9] For each of them, the nine-membered carbocycle is substituted with simple alkyl side chains, with an additional hydroxyl group in the case of glauconic acid (**3**).



R = Me cornexistin (**1**)
R = CH_2OH hydroxycornexistin (**2**)



R = OH glauconic acid (**3**)
R = H glaucanic acid (**4**)



byssochlamic acid (**5**)

Figure 1.2

Subsequently, two toxic metabolites — rubratoxin A (**6**) and B (**7**) — were isolated from the fungus *Penicillium rubrum* (Figure 1.3).[10] The relative configurations of both structures were determined by Moss *et al.* in 1969, and adjusted one year later by Büchi and co-workers.[11,12] Both species possess more elaborate side chains on either side of the nine membered ring. Rubratoxin B (**7**) does exhibit some phytotoxic activity, but this activity is much weaker than in the case of the cornexistins.[1]

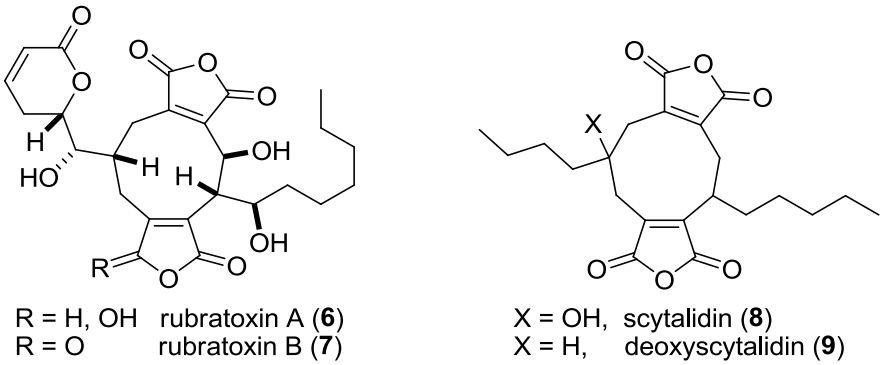
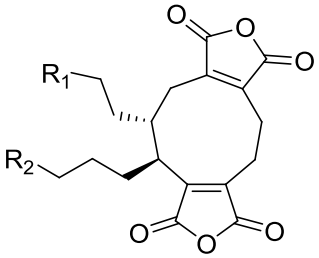
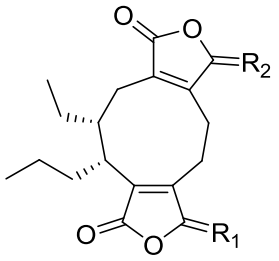


Figure 1.3

Scytalidin (**8**, Figure 1.3), isolated in 1972 from the fungus *Scytalidium sp.*, was found to be a relatively active anti-fungal agent, with low phytotoxic activity.[13,14] Deoxyscytalidin (**9**) was isolated later during a chemosystematic study.[15] Heveadride (**10**, Figure 1.4) was discovered at the same time as scytalidin and was isolated from the fungus *Helminthosporium heveae*.[16] Homoheveadride (**11**) is to date the only naturally occurring nonadride extracted from a lichen (*Cladonia polycarpoides*).[17] More recently, the group of Hosoe isolated two new derivatives, dihydro- and deoxo- epiheveadride (**13** and **14** respectively).[18] Oxidation of dihydroepiheveadride (**13**) to give epiheveadride (**12**) and subsequent X-ray crystallographic studies allowed the absolute configuration of the heveadride family to be deduced.[18a] In 2010, the six epiheveadrides were isolated from the same aquatic fungus *Wicklowia aquatica*.[19] This family exhibits anti-fungal activities, with the most effective one, dihydroepiheveadride (**13**), showing activity against some human pathogens.



R_1, R_2 = H heveadride (**10**)
R_1, R_2 = Et homoheveadride (**11**)

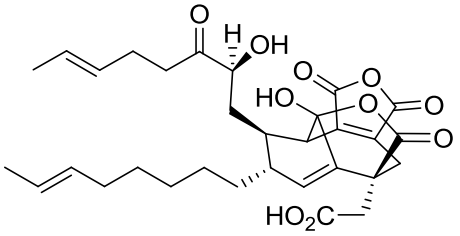


R_1 = O, R_2 = O epiheveadride (**12**)
R_1 = O, R_2 = H, OH dihydroepiheveadride (**13**)
R_1 = O, R_2 = H, H deoxoepiheveadride (**14**)
R_1 = H, OH, R_2 = H, OH tetrahydroepiheveadride (**15**)
R_1 = H, H, R_2 = H, H dideoxoepiheveadride (**16**)
R_1 = H, OH, R_2 = H, H deoxodihydroepiheveadride (**17**)

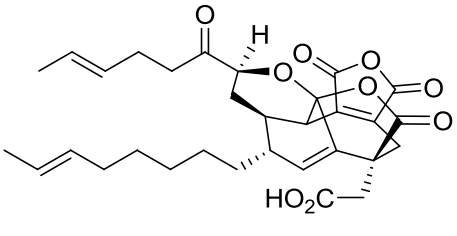
Figure 1.4

The last and most structurally complex members of the nonadride family of natural products isolated to date are the fungal metabolites CP-225,917 and CP-225,114, also known as phomoidrides A (**18**) and B (**19**) (Figure 1.5). Both were isolated from an unidentified fungus by workers at Pfizer in 1997.[20] They aroused considerable interests in the pharmaceutical industries due to their inhibitory activity on the enzymes squalene synthase and Ras farnesyl transferase. Inhibitors of these enzymes have been found to possess cholesterol-lowering and anti-cancer properties.[20a,21]

Structurally, the nine-membered carbocycle of the phomoidrides is embedded within a bicyclo[4.3.1]deca-1,6-diene framework. The only structural difference between the two CP-molecules is that in phomoidride B (**19**), a γ-lactone forms part of a γ-lactone acetal whereas in phomoidride A, the acetal unit is hydrolysed, to form a γ-lactone hemi-acetal.



CP-225,917 (**(+)-18**)
phomoidride A

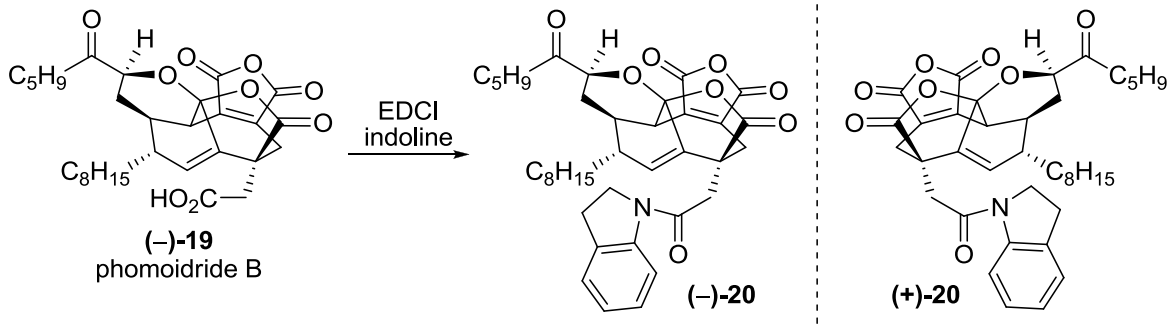


CP-263,114 (**(–)-19**)
phomoidride B

Figure 1.5

Due to their unique and challenging structures, phomoidrides A (**18**) and B (**19**) have been, and still are, an inspiration for many research groups interested in the total synthesis and structure elucidation of natural products, resulting in the development of new methodologies and synthetic strategies.[22]

When isolating phomoidrides A (**18**) and B (**19**), Kaneko and co-workers deduced the overall structure and relative configuration based purely on NMR spectroscopic data.[20b] The group of Nicolaou was the first to accomplish the total syntheses of **(±)-18** and **(±)-19** in 1999, only two years after their isolation. The key step in the synthesis involved a Lewis acid mediated intramolecular Diels-Alder reaction.[23] Focusing next on the asymmetric syntheses of phomoidride A (**18**) and B (**19**), Nicolaou and co-workers obtained the advanced intermediate **(+)-20** one year later (Scheme 1.1). Coupling of natural phomoidride B (**19**) with indoline in the presence of EDCI furnished **(−)-20**, which was found to be exactly identical to **(+)-20**, except for opposite optical rotation.[24] Accordingly, the absolute configuration of phomoidride B **(−)-19**, and hence that of phomoidride A **(+)-18** could be assigned.



Scheme 1.1

During their syntheses of phomoidrides, the group of Danishefsky encountered epimerisation issues at the C-7 centre of their synthetic material, by comparison with samples obtained from the natural source.[25] Further investigations led to the identification of variable amounts of ***7-epi*-19** in samples obtained from various fermentation broths of the unidentified fungus (Figure 1.6). This was confirmed by Sulikowski's group in 2001, which showed the natural co-production of ***7-epi*-18** (phomoidride C) as well as ***7-epi*-19** (phomoidride D) by fermentation. Results from pH and fermentation time studies suggested that phomoidride B (**18**) was the first-formed metabolite and the source of the remaining three phomoidrides (A, C and D).[26]

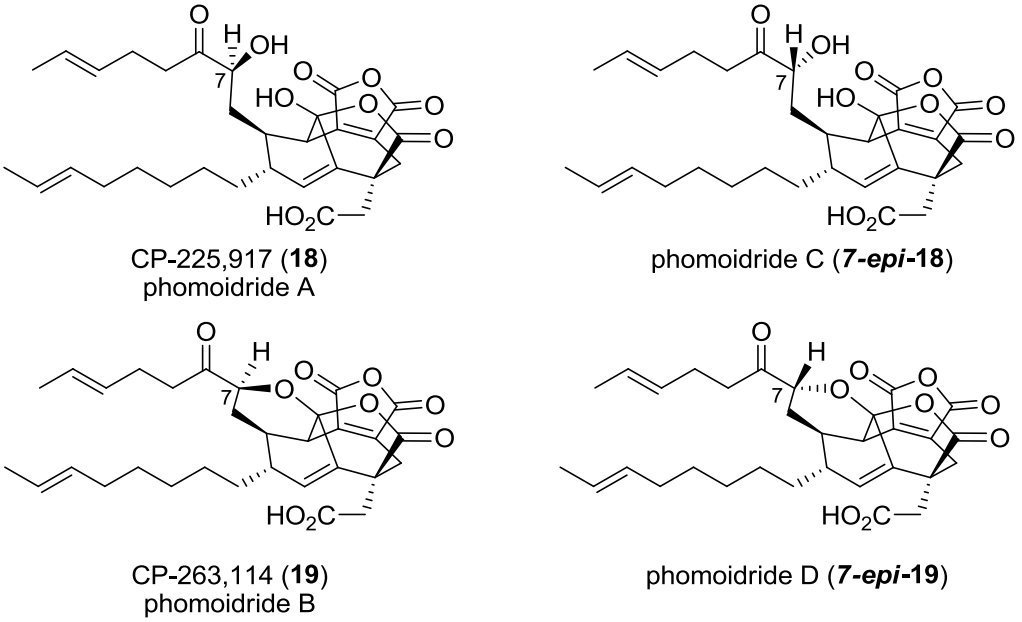
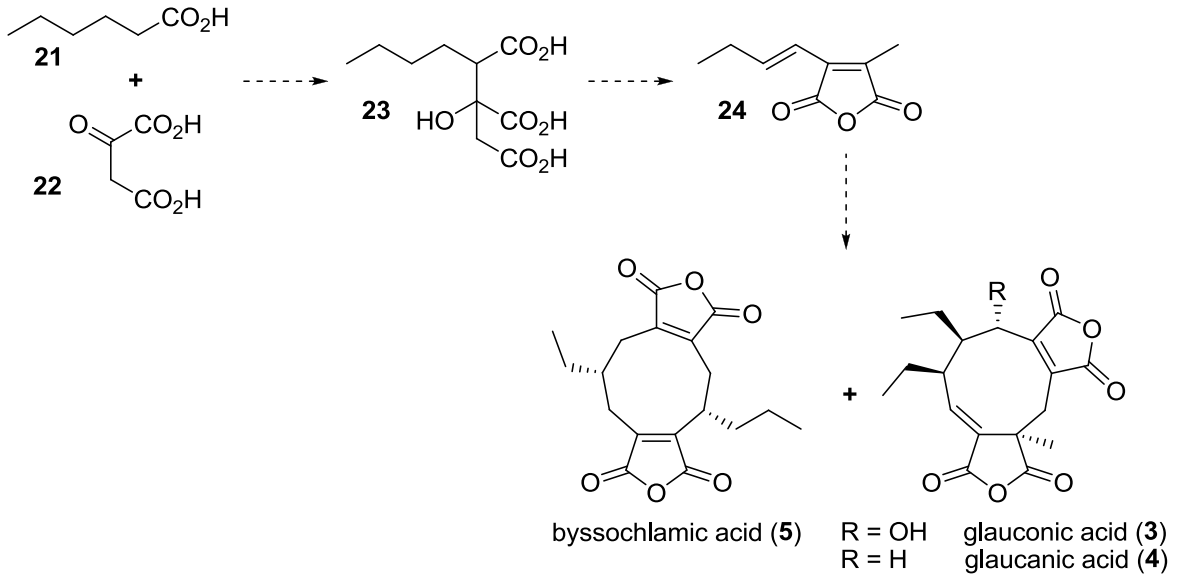


Figure 1.6

1.2.2 Biosynthesis of the nonadrides

Biosynthesis of glauconic, glaucanic and byssochlamic acids

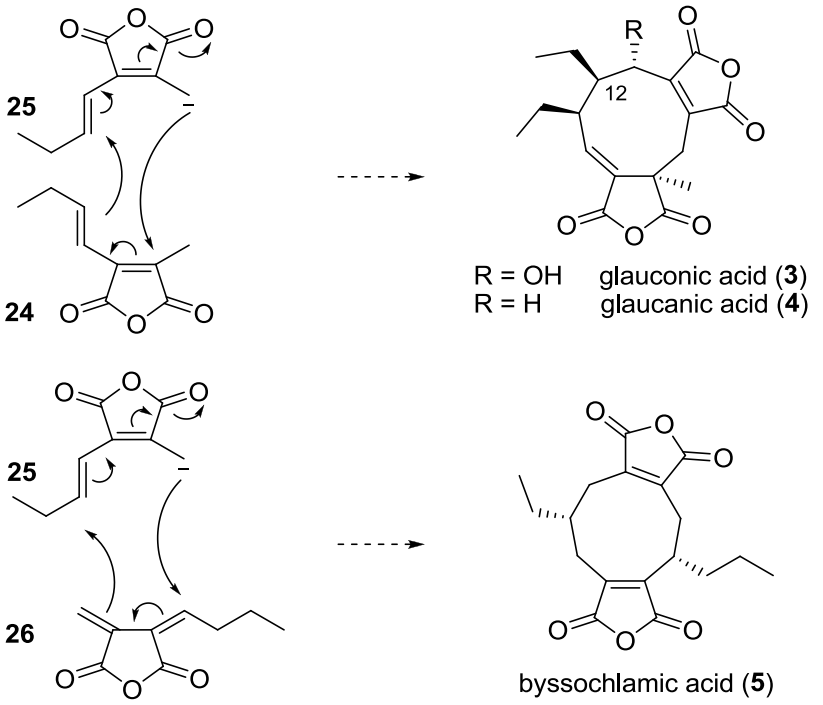
When the nonadride family was discovered, a lot of effort was focused on the elucidation of the biosynthesis of these natural products, with special attention given to glauconic acid (**3**), glaucanic acid (**4**) and byssochlamic acid (**5**). Along with the confirmation of the structures, Sutherland and co-workers proposed that the three acids were formed by dimerisation of the nine-carbon anhydride **24** (Scheme 1.2).[5a] Head to head dimerisation of **24** would first lead to glaucanic acid (**4**), which would then undergo oxidation to afford glauconic acid (**3**). On the other hand, head to tail dimerisation of **24** would lead to the formation of byssochlamic acid (**5**). It was predicted that the anhydride unit **24** could be derived from the citric acid derivative **23**, formed by condensation of *n*-hexanoic acid **21** and oxaloacetic acid **22**.[27]



Scheme 1.2

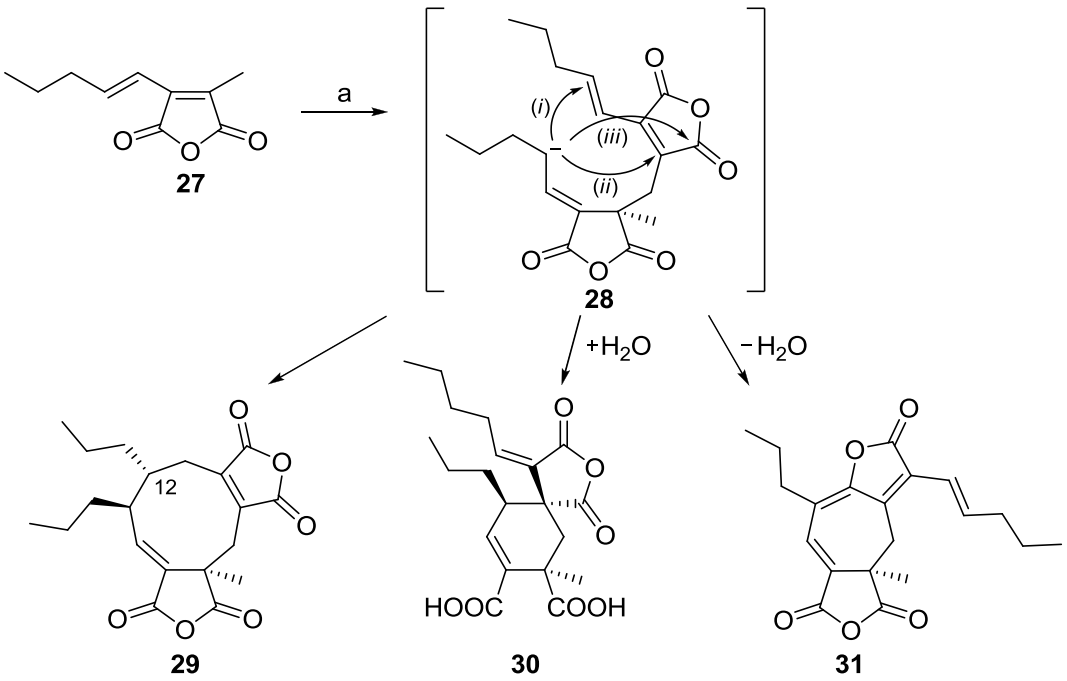
Impressive results were obtained by means of carbon-14 labelling methods. Feeding ^{14}C-labeled acetic acid or pyruvic acid to the fungus *Penicillium purpurogenum* gave glauconic acid (**3**).[27,28] Oxaloacetic acid **22** can be synthesised in living organisms from acetic or pyruvic acid,[29] and so the hypothesis that oxaloacetic acid **22** was a precursor to the formation of glauconic acid (**3**) was confirmed. The same method was employed for anhydride **24** previously synthesised, with the similar *in vivo* formation of glaucanic and glauconic acids (**4**) and (**3**), leaving little doubt that anhydride **24** was the nine-carbon dimerisation precursor in the synthesis of both acids.[30,31]

The group of Sutherland also presented a possible mechanism for this dimerisation reaction, consisting of an electrocyclic addition of diene **24** with the anion derived from it (Scheme 1.3). Accordingly, diene **24** was treated with sodium hydride in DMF or triethylamine. Unfortunately, only small amounts of dimerised product were isolated, corresponding to 12-*epi*-glaucanic acid instead of (**4**). The formation of byssochlamic acid (**5**) was also attempted by reaction of the diene **26** and the anion **25** under various conditions, but without success.[30,31]



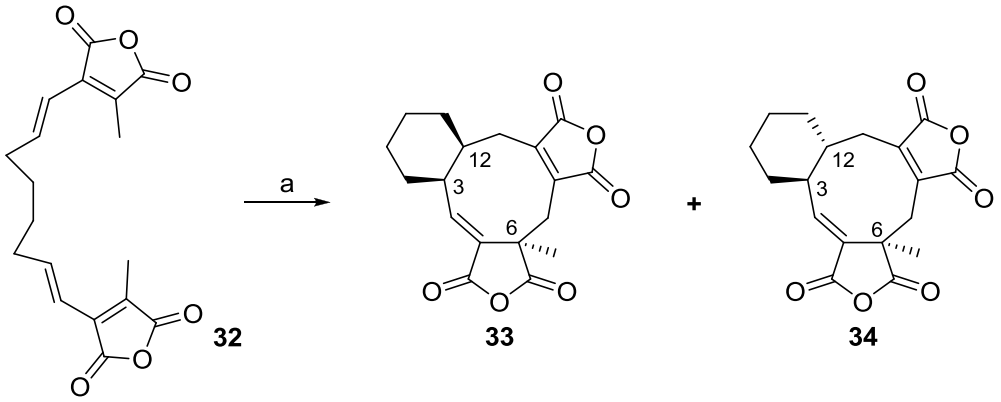
Scheme 1.3

Intrigued by these results, Baldwin and co-workers further investigated the dimerisation reaction leading to the formation of glaucanic acid (**4**). Using diene **27**, bearing an additional methyl group in the alkyl chain compared to that of **24**, three different products were obtained; **29** (with the same relative configuration than 12-*epi*-glaucanic acid), a spiro compound **30** and a seven-membered carbocycle **31** (Scheme 1.4).[32] This result suggested that the formation of the two by-products were formed as a consequence of a stepwise mechanism. Michael addition reaction would form the anionic intermediate **28**; the nonadride **29** would be obtained through pathway (*i*) and the other products **30** and **31** through the nucleophilic attack of the anion on two different electrophilic sites (pathway (*ii*) or (*iii*)).



Scheme 1.4 – Reagents & conditions: a) $MgCl_2$, Et_3N, DMSO, rt [9% **29**, 6% **30**, <2% **31**].

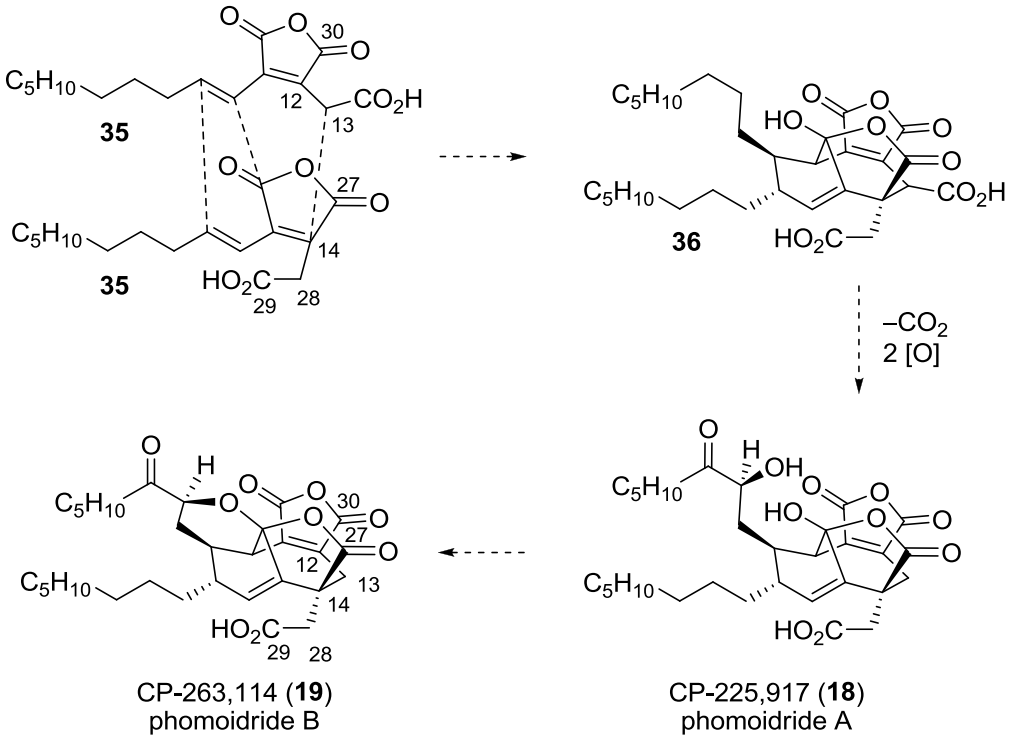
Interestingly, Baldwin *et al.* also synthesised the model substrate **32** in an attempt to mimic the way an enzyme might combine the two anhydrides (Scheme 1.5).[33] Treated with DBU in a mixture of THF and DMSO, *bis*-anhydride **32** formed two cyclised products, **33** and **34**, in a 3:2 ratio. The major product **33** bears a *cis*-C_3—C_{12} ring junction and an *anti*-relationship with the methyl group on C-6, analogously to glaucanic acid, whereas **34** has an *anti*-C_3—C_{12} ring junction corresponding to 12-*epi*-glaucanic acid. It was proposed that the first Michael addition was forming the six-membered ring, followed by the nine-membered ring formation.



Scheme 1.5 – Reagents & conditions: a) DBU, THF—DMSO, rt [14%; **33**:**34**, 3:2].

Biosynthesis of the CP-molecules

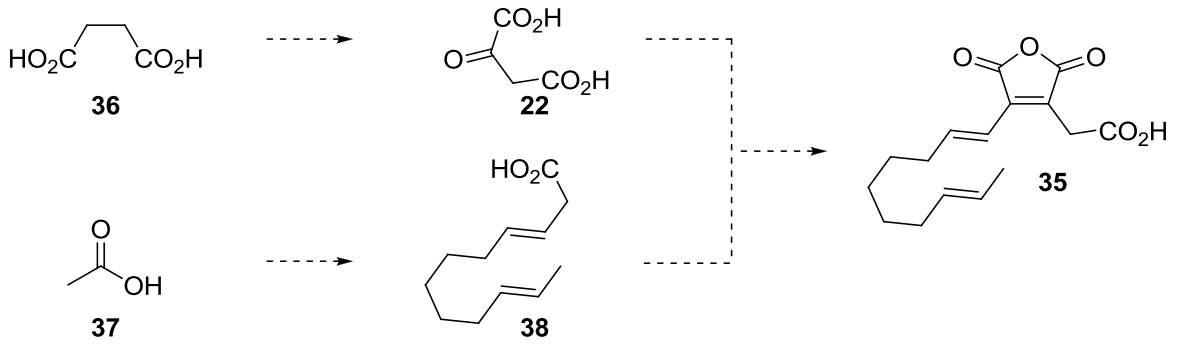
Following the approach pioneered by Sutherland and co-workers for the biosyntheses of acids (**3**), (**4**) and (**5**), the group of Sulikowski extended the dimerisation hypothesis to the biosynthesis of the more complex phomoidrides (**18**) and (**19**).[34] They proposed a biosynthetic pathway based on the dimerisation of the 16-carbon unit **35** to form the nine-membered carbocycle **36**. Subsequent decarboxylation followed by oxidation would lead to phomoidride A (**18**), which could be converted to phomoidride B (**19**) by dehydration thereafter (Scheme 1.6).



Scheme 1.6

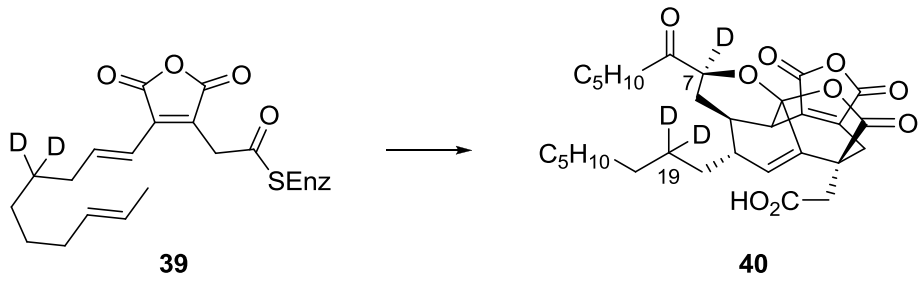
Analogously, they proposed that the 16-carbon anhydride **35** would be formed by condensation of oxaloacetic acid **22** and the unsaturated fatty acid **38** (Scheme 1.7). Using carbon-13 labelling, the group of Sulikowski fed [2,3-$^{13}C_2$]-succinic acid **36** to the fungus responsible for the formation of the phomoidrides.[35] In agreement with previous work done by Sutherland and co-workers for the biosynthesis of glauconic acid (**3**), ^{13}C incorporation to the phomoidrides was observed, at C-12, C-13, C-14 and C-28. Feeding the fungus with [1,4-$^{13}C_2$]-succinic acid **31** provided ^{13}C incorporation at C-27, C-29 and C-30, confirming that succinic acid was indeed a precursor involved in the biosynthesis. The same method was employed for the unsaturated fatty acid **38**. Studies in which ^{13}C-labelled acetic acid was used were inconclusive, therefore they used the acetic acid derivative [2-^{13}C]-*N*,*S*-diacetyl cysteamine. Incorporation of labelled material into the

side chains of phomoidride B (**19**) was successful, supporting the proposed synthesis of the fatty acid chains **38** from acetic acid.



Scheme 1.7

These results looked promising and only the proposed 16C—16C dimerisation theory remained to be validated. Sulikowski and co-workers synthesised deuterated anhydride **39**, and fed it to the fungus (Scheme 1.8). When product **40** was isolated, deuterium incorporation was observed at both C-7 and C-19 positions, strongly supporting the dimerisation step theory.[36]

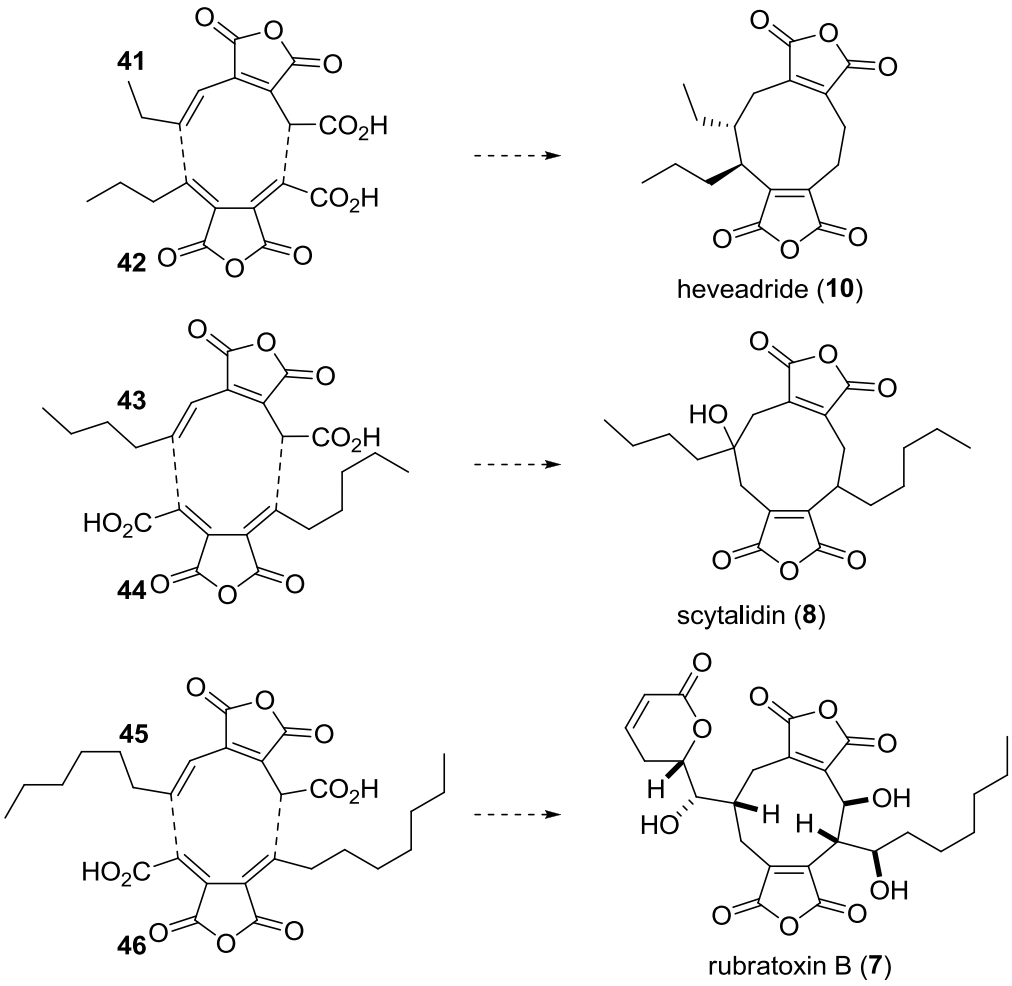


Scheme 1.8

Biosynthesis of the other nonadrides

As much as the studies of the biosyntheses of glauconic acid (**3**) or CP-molecules (**18** and **19**) were successful, far less literature has been published regarding the other nonadrides. Feeding ^{13}C- and ^{14}C-labeled proposed biosynthetical precursors to the fungus often showed mixed results, as reported by Cox and Holcker[37] and the group of Tamm,[38] working on the biosyntheses of glauconic acid (**3**) and rubratoxins (**6** and **7**), respectively. Sulikowski and co-workers suggested that the two main steps of the biosynthesis in the CP-molecules — polyketide-oxaloacetic acid condensation and subsequent decarboxylative dimerisation of the resulting anhydride — could occur in

most nonadride biosyntheses (Scheme 1.9).[39] The diversity of the nonadrides would be the result of variations in the polyketide structure, oxidations and regio- and stereo-chemistry of the dimerisation reaction.

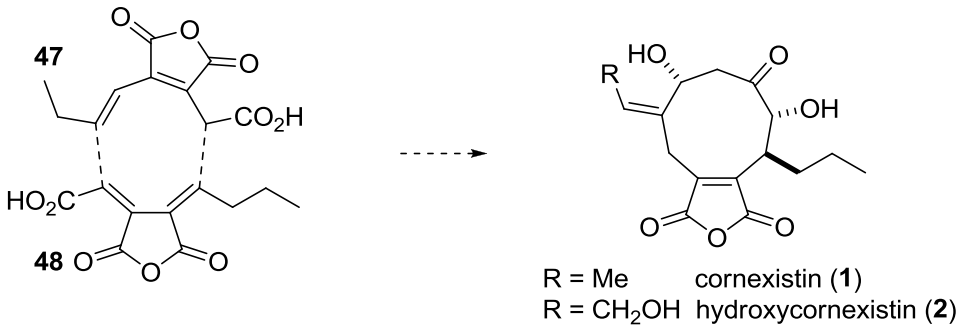


Scheme 1.9

Glauconic acid and CP-molecules are natural products perfectly suited for direct dimerisation of the precursors. However, most of the other nonadrides are less symmetrical, increasing the difficulty of potential precursors syntheses. Furthermore, although head-to-head dimerisation has been observed, the head-to-tail coupling proposed for the synthesis of byssochlamic acid (**5**), scytalidin (**8**) and rubratoxin B (**7**) has never been achieved.

Following Sulikowski's approach, the biosynthesis of cornexistins could be seen as a process in which condensation of oxaloacetic acid with a triketide is followed by subsequent head-to-tail dimerisation of the intermediate anhydride (Scheme 1.10). Decarboxylation and oxidation steps would then give cornexistin (**1**) and an additional oxidation step would lead to the formation of hydroxycornexistin (**2**). However, because the core of the cornexistins are the least symmetrical of all nonadrides, with only one

anhydride unit, formation of the nine-membered ring by direct coupling of two anhydride units seems unlikely.



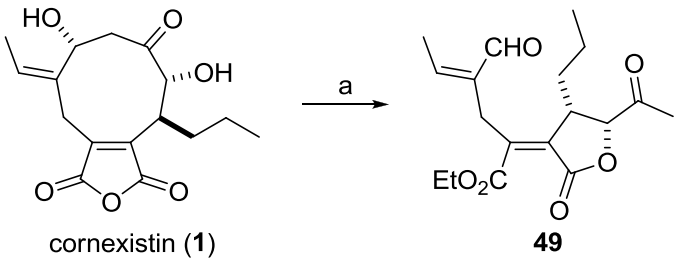
Scheme 1.10

1.3 Previous endeavours towards the cornexistins

The selective herbicidal activity of the cornexistins triggered considerable interest from the agrochemical industry, especially Sankyo Co.,[1] Dow Agrosciences,[2,40] and Syngenta.[41] However, the high degree of acid and base sensitivity of both natural products prevents their development into commercial herbicides.[40] The development of more stable analogues, which retain the same level of phytoxicity than cornexistins, was the ambition of these companies. In spite of their significant potential as lead compounds for new post-emergence weed control agents, the cornexistins have been the subject of relatively few synthetic studies. Aside from our work, only Taylor and co-workers have attempted the total synthesis of cornexistins. This section describes the research activities regarding the cornexistins.

1.3.1 Preliminary studies of the reactivity of cornexistins

The sensitivity of cornexistins is almost certainly due to the highly reactive cyclic anhydride unit. Consequently, researchers at Dow Agrosciences investigated reversible protection of the cyclic anhydride as a *bis*-ester (Scheme 1.11).[40]

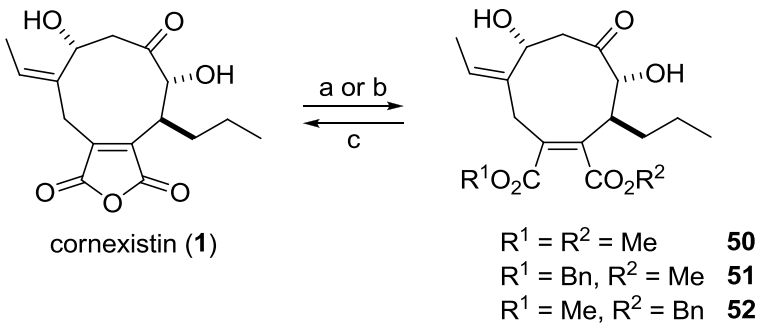


cornexistin (**1**) **49**

Scheme 1.11 – Reagents & conditions: a) H_2SO_4 (cat.), EtOH, reflux.

Treatment of cornexistin under acidic conditions resulted in a retro-aldol cleavage, forming lactone **49** as the major product. The same product was observed using basic conditions. Investigations of neutral conditions revealed that the use of trimethylsilyl-diazomethane in a mixture of THF—MeOH afforded complete conversion of (**1**) to *bis*-methylester **50** (Scheme 1.12). The classic conditions required for the deprotection of the methyl esters were unfortunately too harsh, resulting in retro-aldol cleavage once again. However, substituting methanol for benzyl alcohol as the co-solvent during the protection reaction furnished a mixture of mono-methyl esters **51** and **52** in a 1.5:1 ratio, which could be cleanly debenzylated by phase-transfer hydrogenolysis, without hydrogenation of the exocyclic alkene. Hence, this protection—deprotection sequence

of the reactive cyclic anhydride moiety could be useful in the synthesis of cornexistin analogues.



Scheme 1.12 – Reagents & conditions: a) $TMSCHN_2$, THF—MeOH (1:1), rt [70-75% **50**]; b) $TMSCHN_2$, THF—BnOH (1:1), rt [61%, **51**—**52** (1.5:1)]; c) **51** and **52**, Pd/C (10 mol%), cyclohexene, EtOH, reflux [68%].

1.3.2 Semi-synthesis of cornexistin analogues

Researchers at Sankyo synthesised numerous analogues of cornexistin, simply by modification of the main functional groups (Figure 1.7).[42,41] *Mono*- and *bis*-protection of the two hydroxyl groups of cornexistin gave analogues **53**. Compounds **54** were the result of *bis*-methyl ester protection of the cyclic anhydride. Reactions of **53** and **54** with various amines formed amides **55**, which could be converted into the corresponding maleimide derivatives **56** by reaction with a carbodiimide.

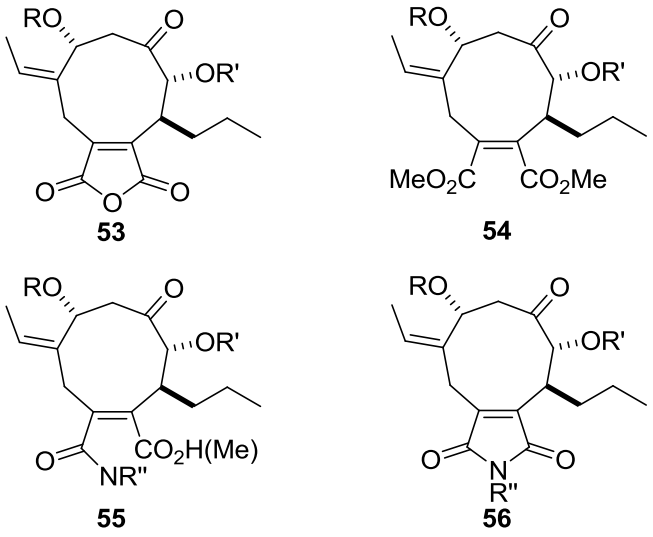


Figure 1.7

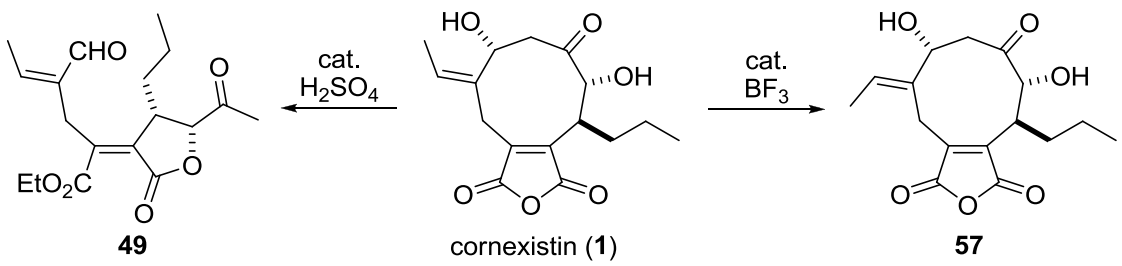
When tested *in-vivo*, most compounds showed excellent post-emergence herbicidal activity, killing between 70 and 100% of the grasses and broadleaf plants examined.

However the level of application, 1000 ppm, represented an impressively large amount of each compounds, and no further results concerning these cornexistin analogues were reported.

1.3.3 Previous work towards the total synthesis by Taylor and Dow Agrosciences

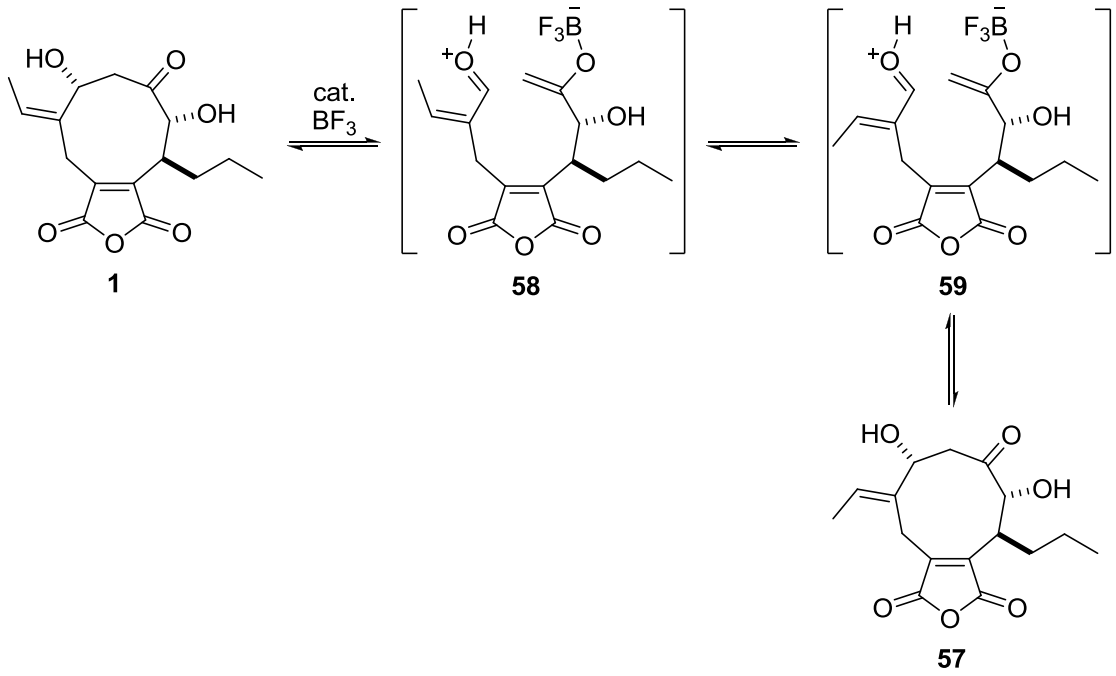
Observation of the retro-aldol cleavage

As mentioned previously, researchers at Dow Agrosciences discovered that treatment of cornexistin with a catalytic amount of sulphuric acid in ethanol promotes a retro-aldol reaction and leads to formation of lactone **49**. Interestingly, when boron trifluoride was used as the catalyst, the cornexistin isomer **57** was isolated, with isomerisation of the exocyclic ethylidene (Scheme 1.13).[43]



Scheme 1.13

To explain this isomerisation reaction, a mechanism was proposed where a Lewis acid-assisted retro-aldol cleavage would allow the formation of intermediate **58** (Scheme 1.14). Isomerisation of the ethylidene moiety would be possible *via* tautomerisation of the conjugated aldehyde. Subsequent aldol reaction would close the nine-membered ring, affording **57**. This unexpected result inspired the researchers at Dow Agrosciences, in collaboration with the research group of Richard E. Taylor, to develop a strategy based on a final intramolecular aldol reaction for the total synthesis of cornexistin.

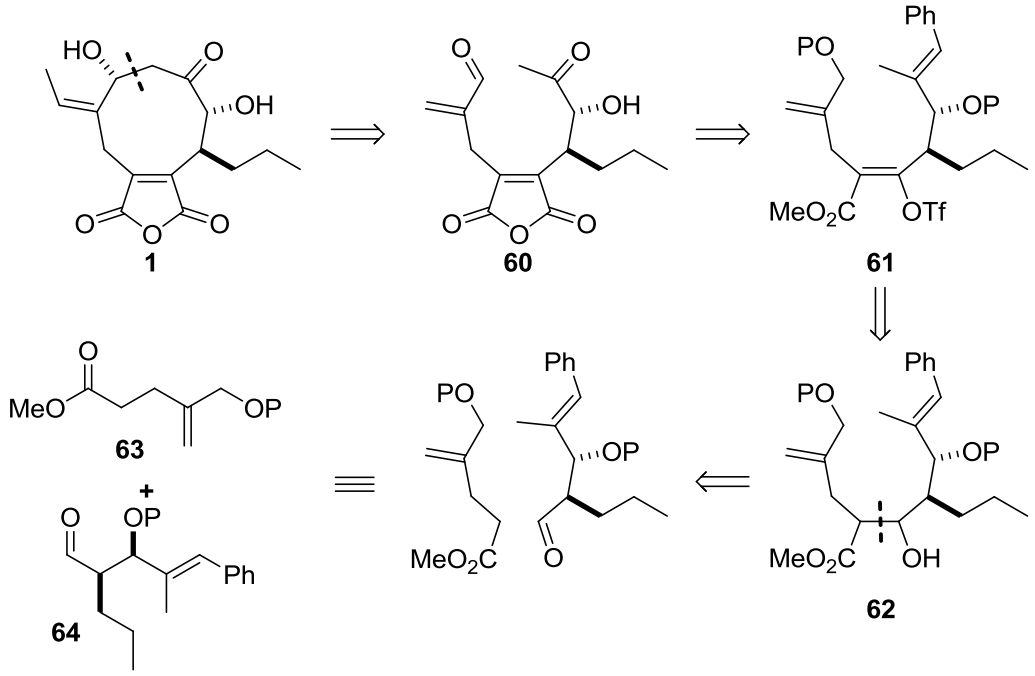


1 **58** **59** **57**

Scheme 1.14

Intramolecular aldol reaction strategy

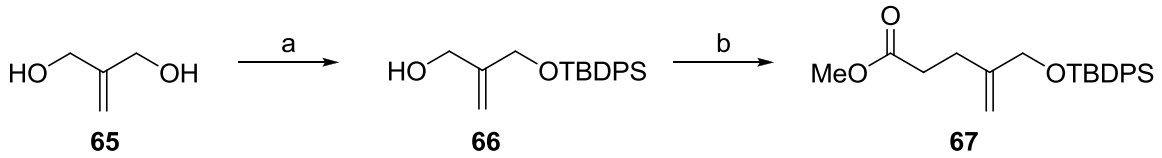
The strategy was based on construction of the unsaturated aldehyde **60** as the precursor required for the intramolecular aldol reaction (Scheme 1.15). The methyl ketone in **60** would be masked as a styrene unit, and the unsaturated aldehyde as a protected allylic alcohol. The cyclic anhydride moiety would be derived from an enol triflate, *via* palladium-catalysed carbonylation, leading to intermediate **61**.[44] The enol triflate precursor **62** would be obtained through an intermolecular aldol reaction between ester **63** and aldehyde **64**.



Scheme 1.15

Synthesis of the two fragments

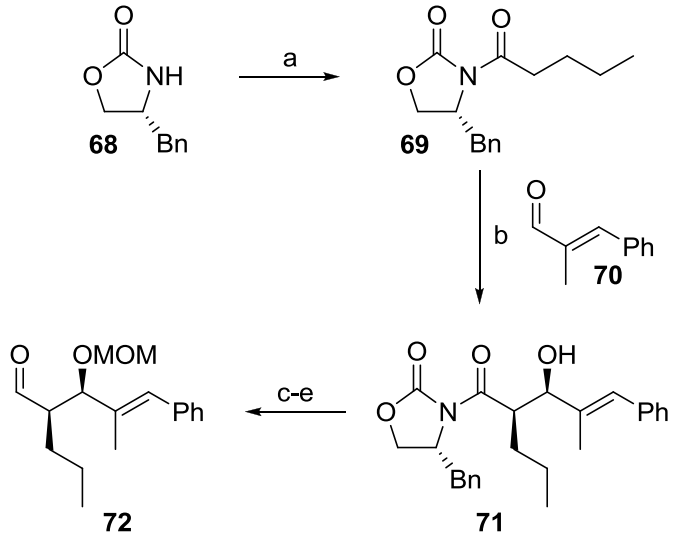
Starting from 2-methylene-1,3-propanediol **65**, mono-silyl protection of the diol using TBDPS chloride afforded **66** (Scheme 1.16). Using a Johnson-Claisen rearrangement,[45] the desired ester **67** was obtained in 86% yield, by reaction of alcohol **66** with trimethyl orthoacetate.



65 **66** **67**

Scheme 1.16 – Reagents & conditions: a) TBDPSCl, *n*-BuLi, THF, −78 ºC to reflux [94%]; trimethyl orthoacetate, propanoic acid (cat.), toluene, reflux [86%].

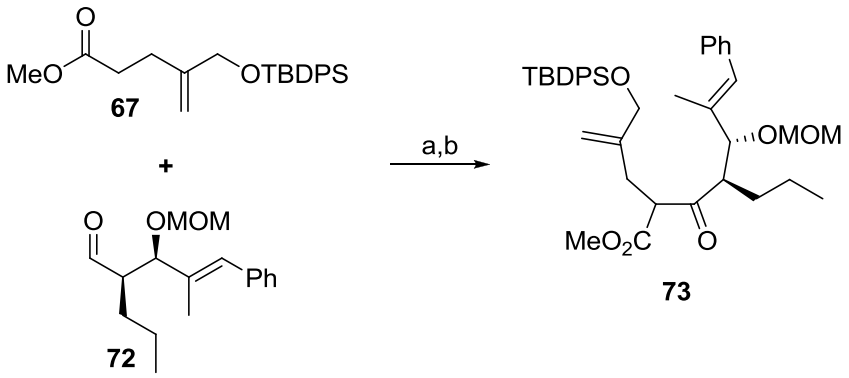
For the second fragment, the Evans' auxiliary **68**[46] was acylated using valeryl chloride to furnish **69** (Scheme 1.17). The aldol reaction between **69**, *via* the *Z*-enolate, and α-methyl-*trans*-cinnamaldehyde **70** afforded the desired *syn*-aldol product **71**. Initially, alcohol **71** was protected as a silyl-ether, but because of problems encountered at a later stage in the synthesis, the alcohol was protected as a MOM-ether. Removal of the oxazolidinone with lithium borohydride followed by Swern oxidation of the resulting alcohol afforded aldehyde **72** in good yield.



Scheme 1.17 – Reagents & conditions: a) *n*-BuLi, valeryl chloride, THF, −78 °C [85%]; b) **70**, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C to 0 °C [60%]; c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt [79%]; d) $LiBH_4$, THF, 0 °C to rt [75%] e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N, −78 °C to rt [71%].

Intermolecular aldol reaction

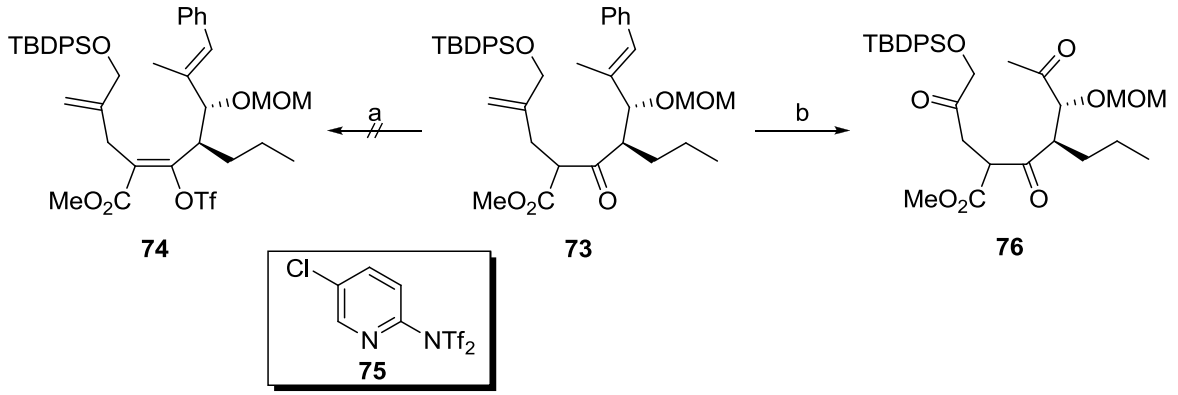
After much effort, deprotonation of ester **67** using LDA and subsequent nucleophilic attack of the resulting enolate on aldehyde **72** was successful, using three equivalent of ester **67** (Scheme 1.18). The mixture of diastereoisomers obtained was oxidised using Swern conditions, allowing the formation of the desired β-ketoester **73** in 85% yield over two steps.



Scheme 1.18 – Reagents & conditions: a) LDA, THF, −78 °C; b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N, −78 °C to rt [85% (2 steps)].

Unfortunately, attempts to form the vinyl triflate **74** using KHMDS and the Comins reagent **75**[47] failed, with only recovery of the starting material (Scheme 1.19). The formation of the methyl ketone leading to precursor required for the intramolecular aldol reaction was also investigated. Under ozonolysis conditions, the two alkene units

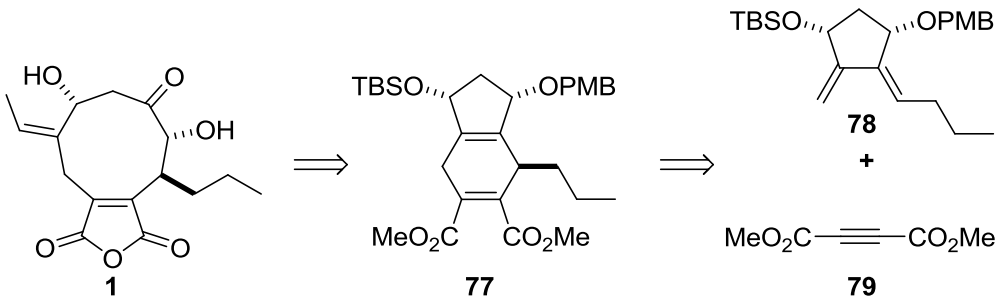
reacted, providing the undesired triketone **76**. Sharpless dihydroxylation and epoxidation reactions also proved unsuccessful. The desired precursor **60** (*cf.* Scheme 1.15), required for the intramolecular aldol reaction could not be prepared, and so this first strategy was discontinued.



Scheme 1.19 – Reagents & conditions: a) KHMDS, **75**, THF, −78 °C [starting material]; b) O_3, PPh_3, CH_2Cl_2.

Second strategy: a Diels-Alder approach

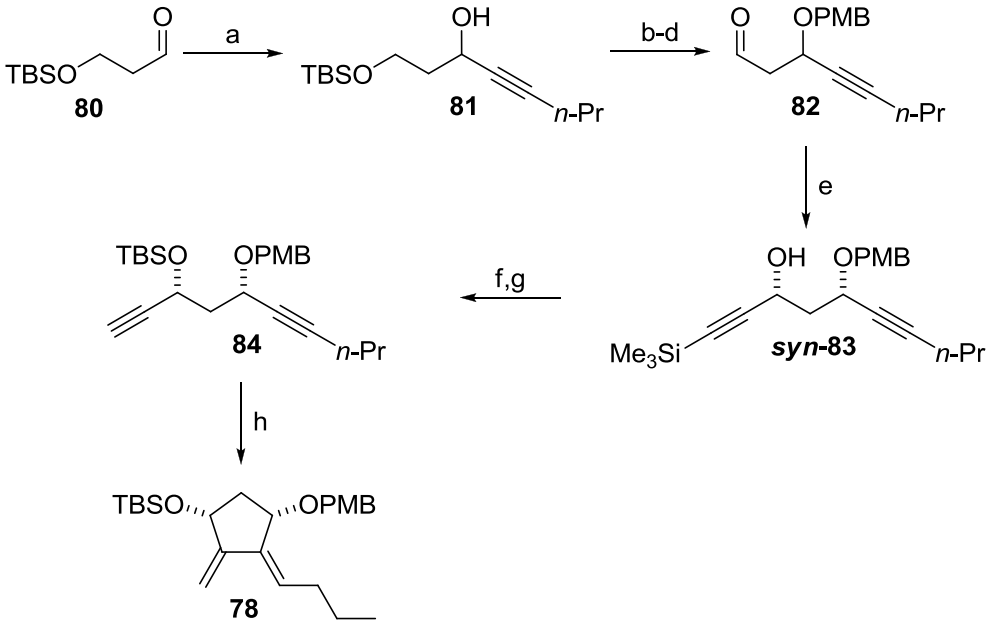
In 2007, Taylor and co-workers published an approach towards the synthesis of the cornexistin core through a Diels-Alder cycloaddition/oxidative cleavage strategy.[48] Their retrosynthetic analysis was based on the inherent symmetry of functionality within the nine-membered ring system (Scheme 1.20). By bisecting the molecule horizontally, each substituent was mirrored across the ring, except for the propyl chain and the ethylidene unit. That led them to the structure **77**, where chemoselective oxidative cleavage would expose a nine-membered cyclic diketone. The cyclohexa-1,4-diene **77** could be derived from a Diels-Alder reaction of dienophile **79** and diene **78**.



Scheme 1.20

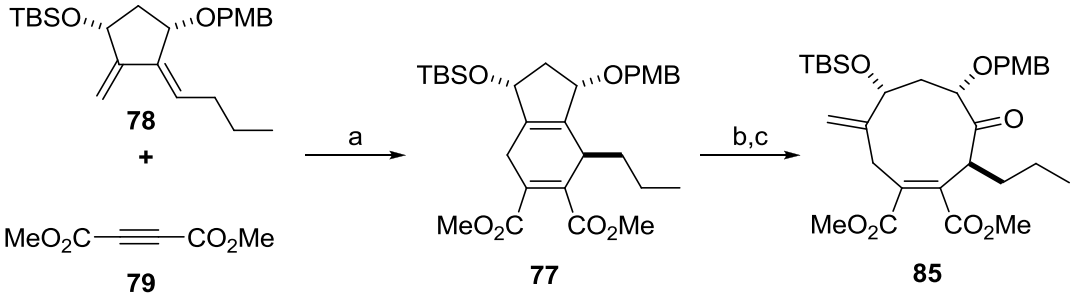
The synthesis of the cyclopentadiene began with aldehyde **80**, previously obtained from TBS monoprotection of 1,3-propandiol and TEMPO oxidation (Scheme 1.21). Nucleophilic

attack of the lithiated pentyne on aldehyde **80** gave alcohol **81** in 91% yield. The resulting alcohol was protected as a PMB-ether, the TBS group removed using TBAF. The exposed alcohol was then oxidised using Swern conditions to provide aldehyde **82**. The aldehyde was immediately reacted with lithiated TMS-acetylene to give a separable mixture of the *syn*- and *anti*-diastereoisomers. The *anti*-diasteroisomer could be converted to the desired alcohol ***syn*-83** *via* Mitsunobu reaction. Desilylation of the terminal alkyne was carried out using TBAF and the propargylic alcohol was protected as a TBS-ether to give **84**. Finally, the diyne was subjected to Trost reductive cyclisation conditions to provide cyclopentadiene **78** in excellent yield (98%).[49]



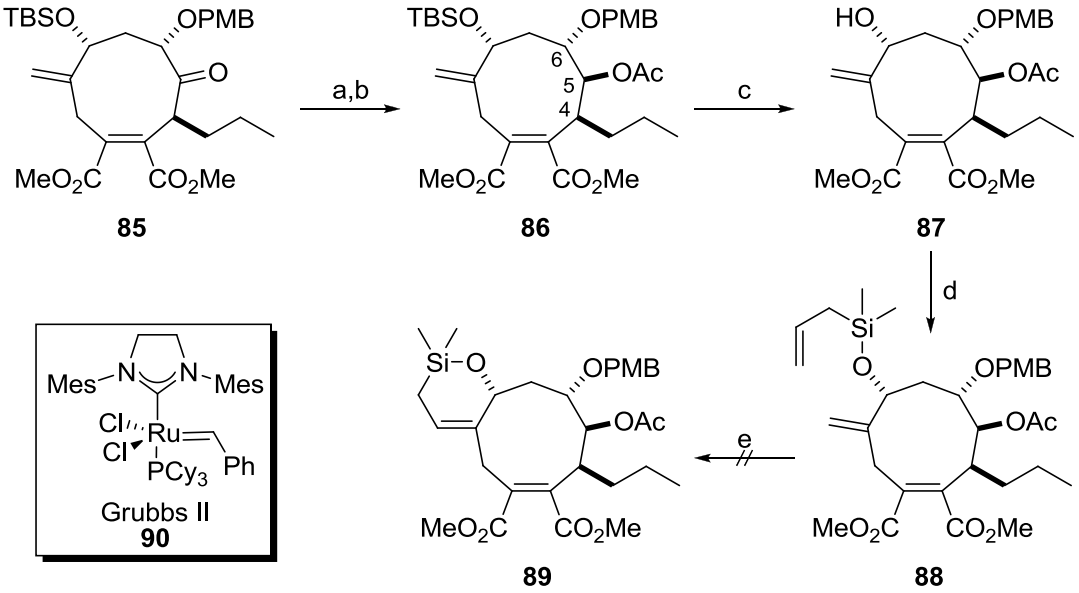
Scheme 1.21 – Reagents & conditions: a) pent-1-yne, *n*-BuLi, −78 °C to 0 °C [91%]; b) PMBBr, NaH, *n*-Bu_4NI (cat.), THF, −10 °C to 0 °C; c) *n*-Bu_4NF, THF, rt; d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N, −78 °C to rt [70% (3 steps)]; e) (trimethylsilyl)acetylene, *n*-BuLi, THF, −78 °C to 0 °C [46% ***syn*-78**, 26% ***anti*-78**]; f) *n*-Bu_4NF, THF, rt [quant.]; g) TBSCl, imidazole, DMF, rt [75% (2 steps)]; g) $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), P(*o*-PhMe)$_3$ (10 mol%), AcOH, Et_3SiH, benzene, rt [98%].

Diene **78** was then reacted with dimethyl acetylenedicarboxylate to provide the Diels-Alder cyclohexadiene **77** in 50% yield (Scheme 1.22). The *anti* relationship between the propyl chain and 4-methoxybenzyl ether was determined by X-ray analysis, confirming that the facial selectivity of the cycloaddition reaction was controlled by steric influences. Oxidative cleavage of the internal alkene using ozone revealed the diketone and further chemoselective methylenation using Tebbe's reagent and an excess of pyridine gave the desired alkene **85** in 45% yield over the two steps.



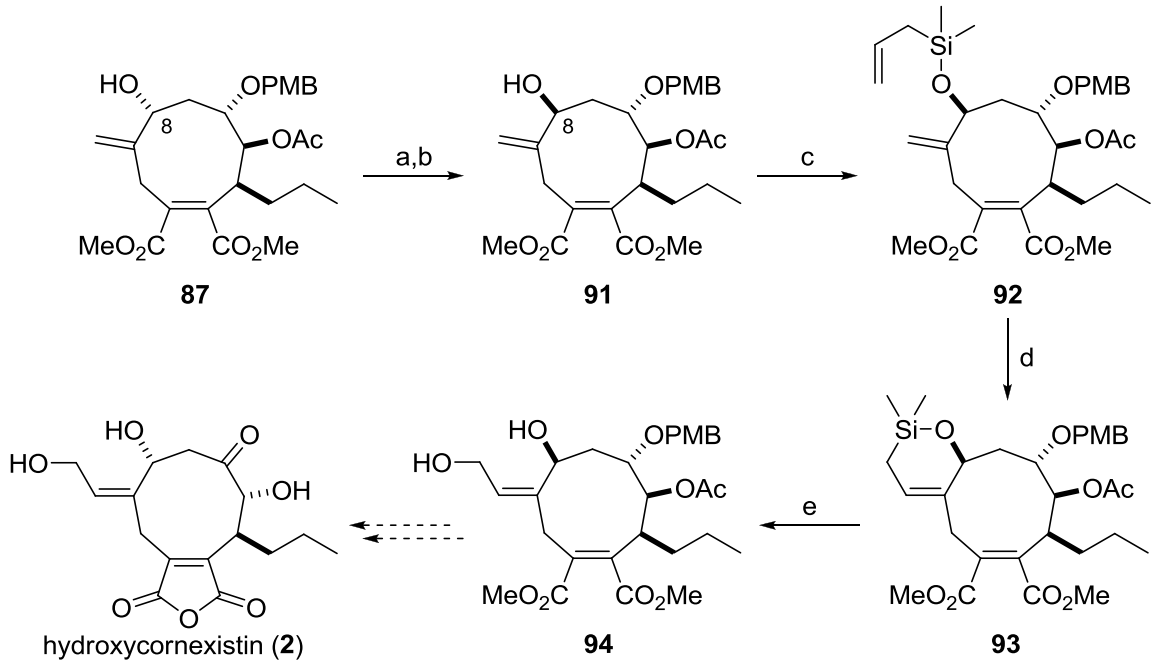
Scheme 1.22 – Reagents & conditions: a) hydroquinone (cat.), toluene, reflux [50%]; b) O_3, Sudan III dye, CH_2Cl_2—MeOH (2:1), −78 °C; c) $TiCp_2CH_2ClAlMe_3$, pyridine, THF, −15 °C to −22 °C [45% (2 steps)].

The ketone was reduced using sodium borohydride to give the corresponding alcohol in an excellent yield and as a single diastereoisomer (Scheme 1.23). Subsequent acetylation of the resulting alcohol furnished acetate **86**. Although all attempts to grow suitable crystals for X-ray crystallography failed, NMR analysis of the acetate **86** revealed a strong NOE between the hydrogens in C-4 and C-5, and the multiplicity of the C-5 proton suggested a 4,5-*cis*-5,6-*trans* relationship. For the functionalisation of the 1,1-disubstituted alkene, the use of a silicon-tethered diene ring-closing metathesis (RCM) reaction was considered. Silyl group exchange provided allyl silane **88**, unfortunately, the ring-closing metathesis reaction using Grubbs II **90** as catalyst provided only dimeric by-products.



Scheme 1.23 – Reagents & conditions: a) $NaBH_4$, MeOH, 0 °C [98%]; b) Ac_2O, pyridine, DMAP (cat.), rt [70%]; c) *n*-Bu_4NF, THF, rt [87%]; d) allyldimethylsilyl chloride, Et_3N, CH_2Cl_2, rt [50%]; e) Grubbs II **90** (cat.), CH_2Cl_2, reflux.

Supposing that the conformation of the molecule was inappropriate for the RCM reaction, inversion of the alcohol stereocentre on C-8 was attempted (Scheme 1.24). While Mistunobu inversion resulted in elimination, Dess-Martin oxidation of **87** followed by simple reduction using sodium borohydride provided alcohol **91**, the C-8 epimer of **87**, in a good yield and as a 4:1 ratio of isomers. Silyl protection gave the desired silicon-tethered diene **92** which was subjected to RCM reaction conditions using Grubbs II **90** as catalyst. This time the trisubstituted alkene **93** was obtained in quantitative yield.



Scheme 1.24 – Reagents & conditions: a) DMP, CH_2Cl_2, rt; b) $NaBH_4$, MeOH, 0 ºC [60% (2 steps), *dr* 4:1]; c) allyldimethylsilyl chloride, Et_3N, CH_2Cl_2, rt [50%]; d) Grubbs II **90** (cat.), CH_2Cl_2, reflux [quant.]; e) KF, H_2O_2, $KHCO_3$, THF—MeOH (1:1), rt [quant.].

Manipulation of the siloxacycle **93** could provide both cornexistins. Protodesilylation of **83** to form the *exo*-cyclic ethylidene was unsuccessful, but Fleming-Tamao oxidation reaction gave diol **94** in quantitative yield.[50] To date, further elaboration of diol **94** to give hydroxycornexistin has not been reported.

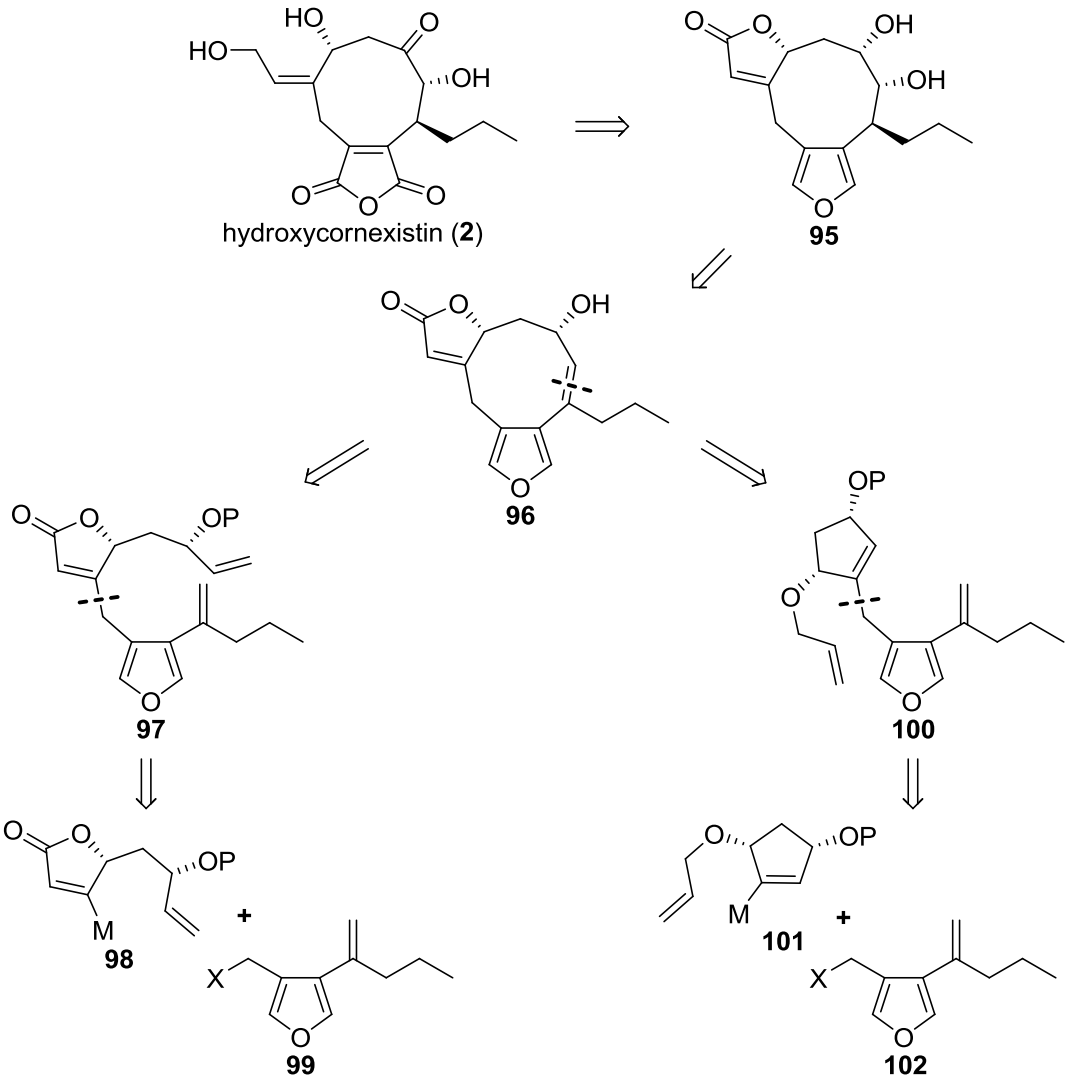
Aside from the two approaches attempted by the group of Taylor and Dow Agrosciences, the only other published research targeting the total synthesis of the cornexistins is by the Clark group.[51] A review of the past endeavours within the group to synthesise the cornexistins will now follow.

1.4 Previous work toward the synthesis of cornexistins by the Clark group

1.4.1 Original synthetic analysis of hydroxycornexistin

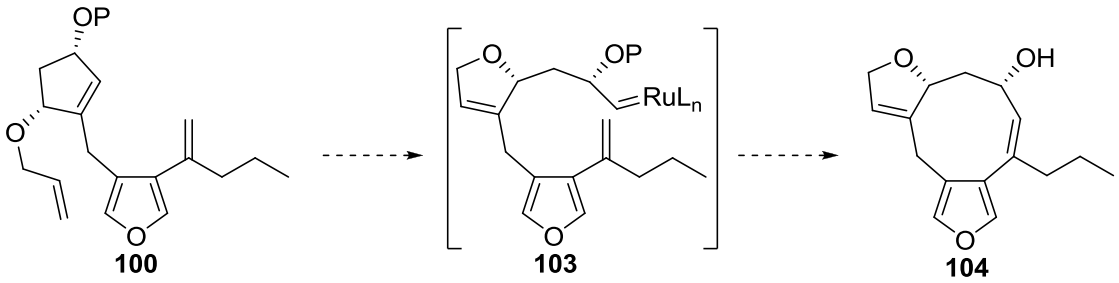
The initial approach envisioned by the Clark group was based on the formation of the nine-membered carbocycle by RCM reaction. It is believed that at the time a functionalised nine-membered carbocycle had never been formed in this way. This was a challenge as a medium carbocyclic system, containing from eight to eleven carbons, combines poor flexibility in comparison to a straight-chain alkane, and important transannular interactions — Prelog strain[52] — between the substituents of the ring. As a result they are extremely difficult to synthesise. Thus, synthesis of the core of the cornexistins using RCM would highlight the growing use of the reaction for the formation of medium rings, in addition to its widespread use for the assembly of small and large rings.

Concentrating on hydroxycornexistin (**2**), a first retrosynthetic analysis was conceived. Due to the chemically sensitive nature of the cyclic anhydride, it was decided that it should be formed as late in the synthesis as possible and a furan was chosen to act as a latent form (Scheme 1.25). This strategy had previously been used with success in the total synthesis of the CP-molecules by the group of Danishefsky.[25,53] Synthesis of the exocyclic alkene with the desired (*Z*)-alkene geometry was anticipated as a potential problem, which could be avoided by connecting the two hydroxyl group in the form of a α,β-unsaturated lactone. Further conversion of the ketone carbonyl group into a hydroxyl group would reveal lactone **95** as key late stage intermediate. Alkene **96** could be obtained by retrosynthetic dehydration of **95**, and after disconnecting the ring through the alkene, two options could be possible. A simple retrosynthetic RCM would afford diene **97**, which could be formed by palladium-catalysed coupling of the unsaturated lactone **98** and the furan **99**. On the other hand, a more ambitious metathesis disconnection would reveal triene **100**, obtained by palladium-catalysed coupling of cyclopentene **101** and furan **102**.



Scheme 1.25

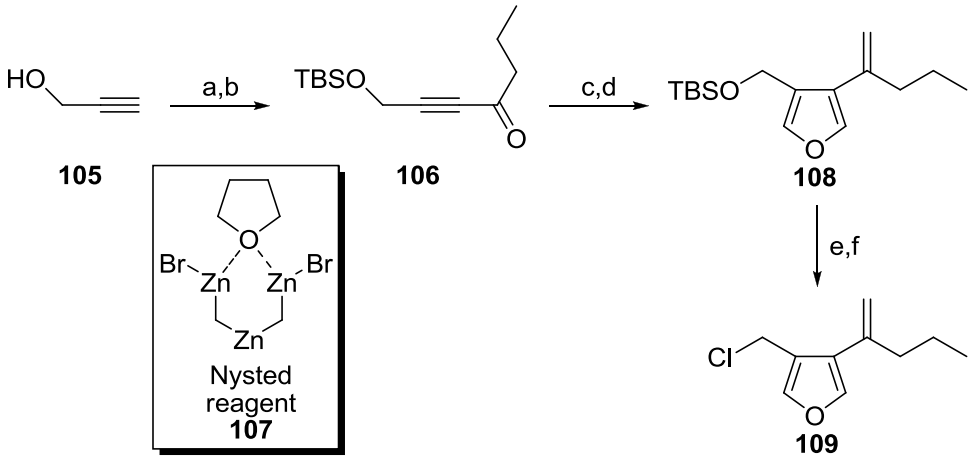
In the latter synthetic approach, the conversion of the triene **100** into the nine-membered carbocycle **104** represents a tandem ring-opening, ring-closing, ring-closing metathesis sequence (Scheme 1.26). Initial ring-opening, ring-closing sequence would generate the alkylidene **103**. A subsequent ring-closing metathesis reaction would provide the desired nine-membered carbocycle **104**.



Scheme 1.26

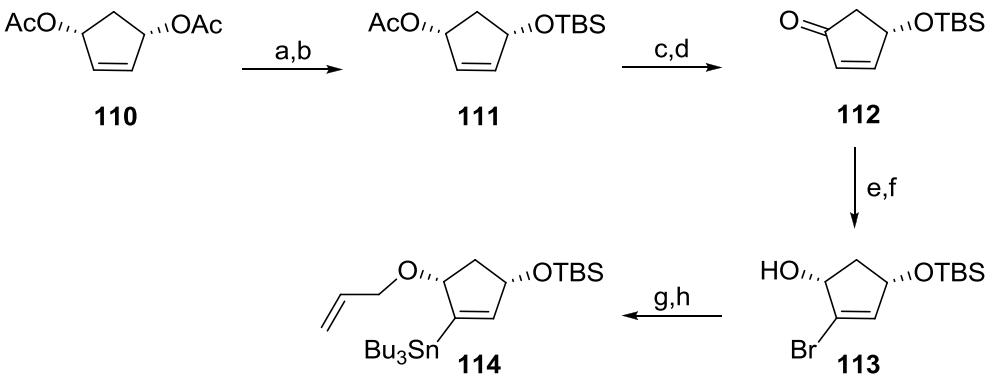
Tandem ring-opening, ring-closing, ring-closing metathesis approach

The more ambitious tandem approach was explored first, and the two fragments were prepared. The chloride fragment **109** was prepared in six steps, starting from propargyl alcohol (Scheme 1.27). Protection of the hydroxyl group as a TBS-ether followed by alkyne acylation using butyric anhydride afforded ketone **106**. Heating ketone **106** and 4-phenyl-1,3-oxazole at 200 ºC resulted in a Diels-Alder cycloaddition reaction, and immediate retrocycloaddition to give the furan. Ketone methylenation using Nysted reagent **107** furnished the 1,1-disubstituted alkene **108**. Finally, removal of the TBS group and conversion of the resulting alcohol to the chloride afforded the furan fragment **109**.



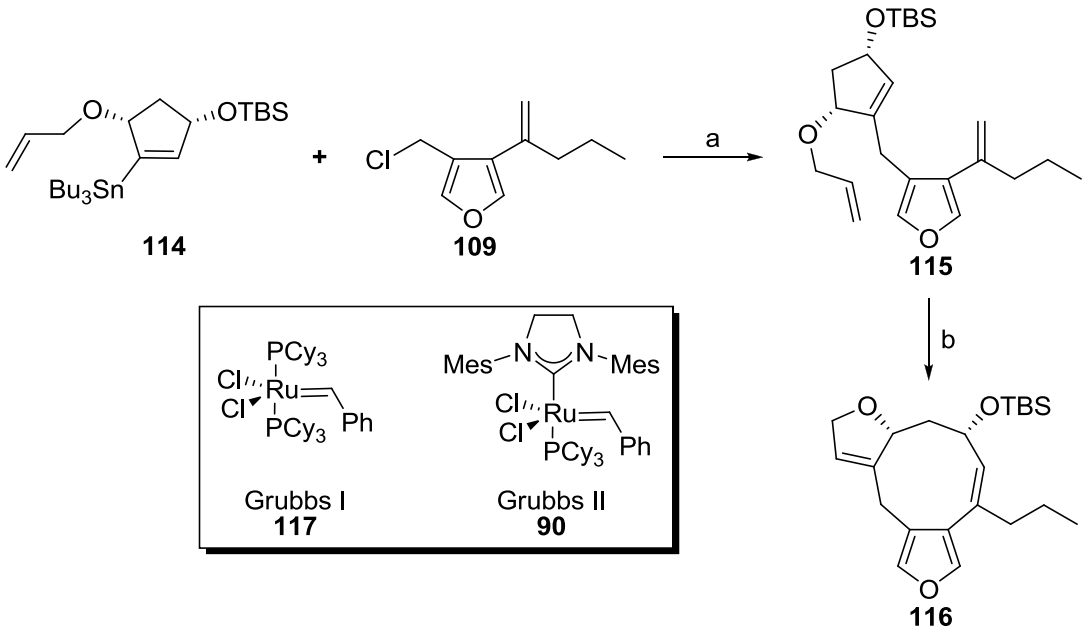
Scheme 1.27 – Reagents & conditions: a) TBSCl, imidazole, DMAP, CH_2Cl_2, reflux; b) *n*-BuLi, $(n\text{-PrCO})_2O$, THF, −78 ºC [55%, 2 steps]; c) 4-phenyl-1,3-oxazole, 200 ºC [76%]; d) Nysted reagent **107**, $TiCl_4$, THF, rt [81%]; e) $n\text{-Bu}_4NF$, THF, rt [93%], f) MsCl, 2,4,6-collidine, LiCl, CH_2Cl_2, 0 ºC to rt [81%].

The synthesis of the second fragment began with the asymmetric desymmetrisation of diacetate **110** (Scheme 1.28). Using electric eel acetylcholine esterase, the selective hydrolysis of one of the two acetate groups provided the alcohol (93% *ee* by HPLC), which was re-protected to give the TBS-ether **111**. Hydrolysis of the remaining acetate group followed by oxidation of the resulting alcohol in the presence of PCC afforded enone **112**. The vinyl bromide was obtained in good yield using bromine, and subsequent stereoselective Luche reduction of the enone gave alcohol **113**. Allylation of the alcohol followed by lithium-halogen exchange on the bromide, and subsequent trapping with tributyltin hydride produced the stannane **114**.



Scheme 1.28 – Reagents & conditions: a) electric eel acetylcholine esterase, NaN_3, pH 7 buffer, rt [69%, 93% *ee*]; b) TBSCl, imidazole, DMAP, CH_2Cl_2, rt [93%]; c) K_2CO_3, MeOH, rt [94%]; d) PCC, CH_2Cl_2, rt [73%];, e) (*i*) Br_2, CH_2Cl_2, 0 °C; (*ii*) Et_3N, CH_2Cl_2, 0 °C [92%]; f) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C; g) allyl bromide, NaH, THF, rt [63% (2 steps)]; h) *s*-BuLi, Bu_3SnCl,[54] THF, −78 °C to rt [68%].

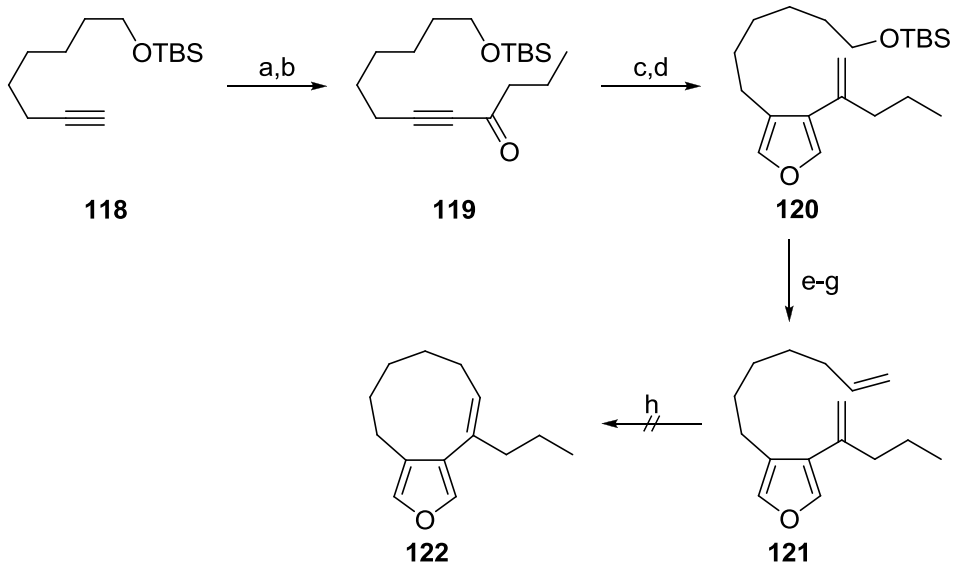
The coupling of chloride **109** and stannane **114** was accomplished by a palladium-catalysed Stille cross-coupling reaction, providing the metathesis precursor in modest yield without optimisation (Scheme 1.29).[55] Unfortunately, using Grubbs I or Grubbs II catalysts under various conditions, the desired trisubstituted alkene **116** could not be obtained from the precursor **115**. Instead, only dimerisation of the allylic ether was observed.



Scheme 1.29 – Reagents & conditions: a) $Pd(PPh_3)_4$ (5 mol%), toluene, reflux [33%]; b) **90** or **117** as catalysts, various conditions.

Ring-closing metathesis approach

Given the failure of the challenging tandem metathesis sequence, the alternative RCM-based approach was considered (Scheme 1.25). A simple model was conceived in order to quickly estimate the feasibility of the key RCM reaction, starting from TBS-protected 7-octyn-1-ol **118** (Scheme 1.30). Reaction of butanal with the lithium acetylide derived from alkyne **118** and immediate oxidation of the resulting alcohol using TPAP afforded ketone **119**. The oxazole cycloaddition—retrocycloaddition sequence followed by ketone methylenation delivered furan **120**. The protecting group was then removed and the resulting alcohol oxidised using Swern conditions. Wittig methylenation of the aldehyde delivered RCM precursor **121**.



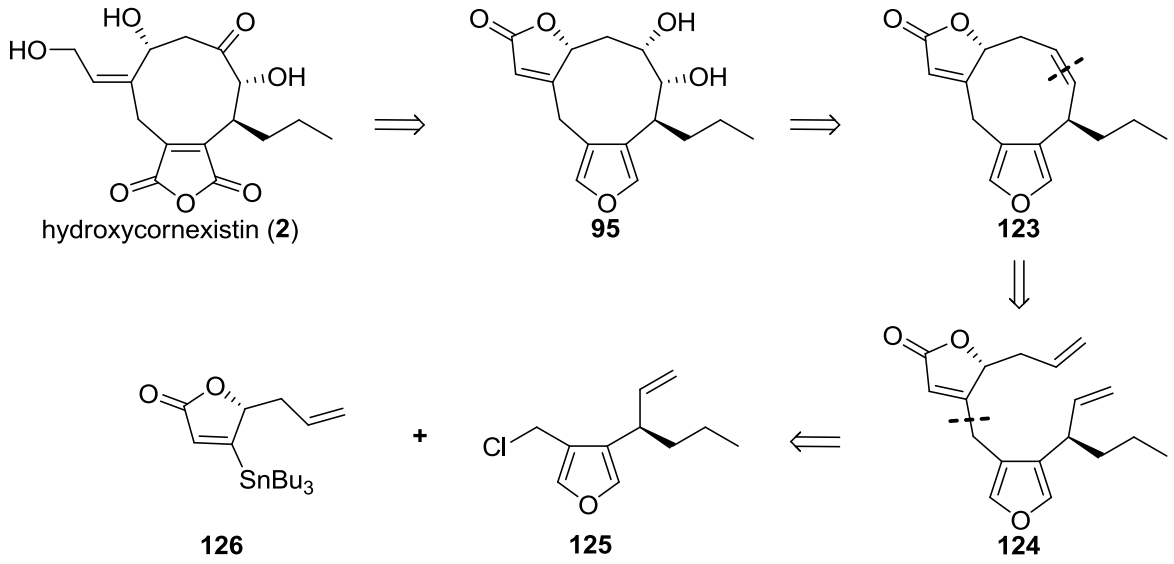
Scheme 1.30 – Reagents & conditions: a) *n*-BuLi, *n*-PrCHO, THF, −78 °C; b) TPAP, NMO, CH_2Cl_2, rt [66% (2 steps)]; c) 4-phenyl-1,3-oxazole, 200 °C [70%]; d) Nysted reagent, $TiCl_4$, THF, 0 °C to rt [89%]; e) *n*-Bu_4NF, THF, rt [99%]; f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N, −78 °C to rt [91%]; g) $PPh_3{=}CH_2$, THF, rt [85%]; h) **90** or **117**, CH_2Cl_2, rt or reflux.

Unfortunately, all attempts to effect ring closure by RCM failed to deliver the nine-membered ring **122**. This unsuccessful attempt was attributed to the flexibility of the alkyl chain, and to difficulties in forming a conjugated trisubstituted alkene during the metathesis reaction. This led to a revision of the synthetic strategy.

1.4.2 Second strategy and synthesis of 5-epi-hydroxycornexistin

Revised retrosynthetic analysis of hydroxycornexistin

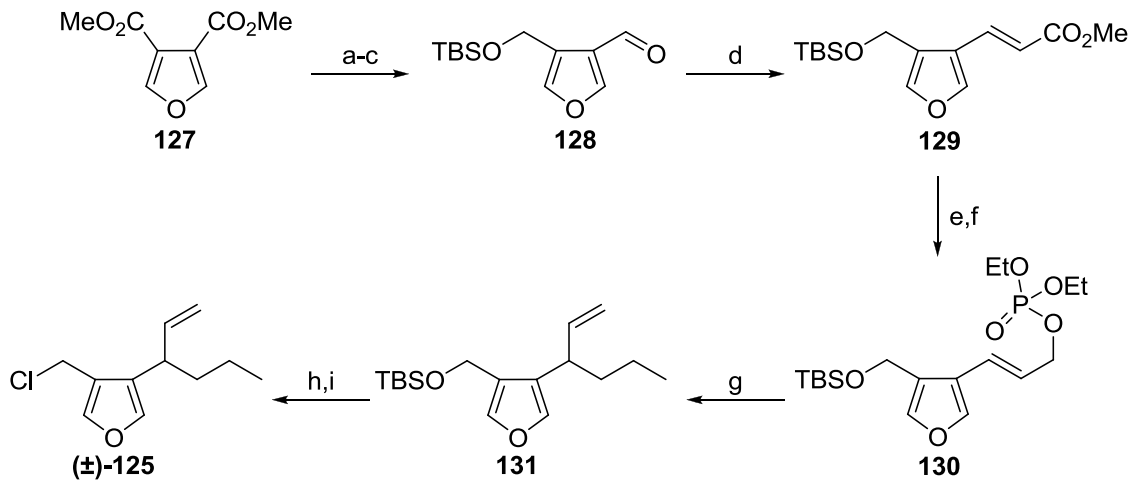
The problem with the previous strategy was the disconnection of a trisubstituted alkene, which proved difficult to obtain by RCM in the forward synthesis. Making the key disconnection of the nine-membered ring at a different position could potentially solve the problem. In the revised retrosynthetic analysis, the 1,2-*syn*-diol **95** could be recognised as the product resulting from the dihydroxylation of an alkene, which would lead to cyclononene **123** (Scheme 1.31). This time, disconnection of the carbocycle at this double bond would reveal diene **124**, containing two terminal olefins. Next, disconnection at one of the two C—C bonds linking the two rings would give the chloride **125** and the stannane **126**, precursors of the Stille coupling product.



Scheme 1.31

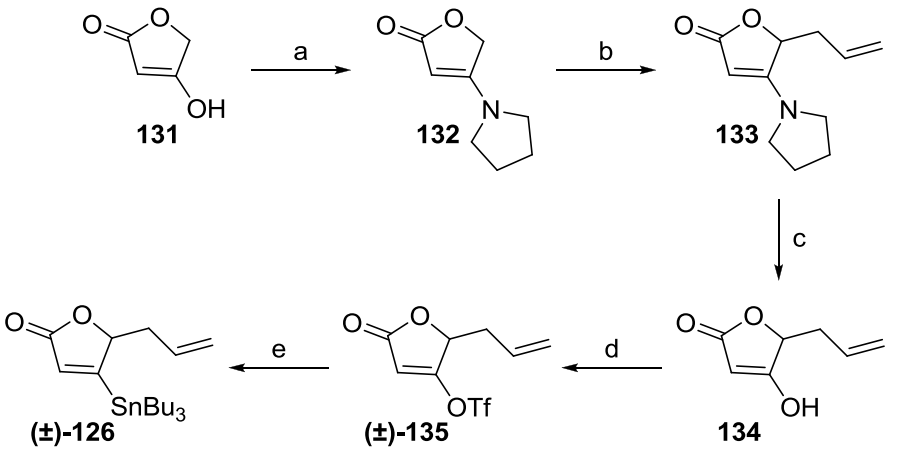
Preparation of the Stille coupling precursors

The synthesis of the chloride fragment **(±)-125** was achieved in nine steps (Scheme 1.32). Lithium aluminium hydride reduction of the diester **127** to the corresponding diol followed by selective mono-oxidation with manganese dioxide gave the aldehyde. The remaining alcohol was protected as a TBS-ether, delivering aldehyde **128** in 73% yield over three steps. Wittig reaction of the aldehyde with methyl-(triphenylphosphoranylidene)acetate furnished the α,β-unsaturated ester **129**. Reduction of the ester using lithium aluminium hydride and treatment of the resulting alcohol with diethyl chlorophosphate afforded allylic phosphate **130**. The propyl chain was installed by copper-catalysed S_N2' displacement of the allylic phosphate with *n*-propylmagnesium bromide, allowing the formation of alkene **131**. The TBS-ether was cleaved and finally, the alcohol was converted to the corresponding chloride *via* the mesylate gave chloride **(±)-125**.



Scheme 1.32 - Reagents & conditions: a) $LiAlH_4$, THF, −78 °C to rt; b) MnO_2, CH_2Cl_2, rt; c) TBSCl, imidazole, DMAP, CH_2Cl_2, rt [74% (3 steps)]; d) $Ph_3P{=}CHCO_2Me$, THF, rt [99%]; e) $LiAlH_4$, THF, −78 °C to −30 °C [98%]; f) $(EtO)_2P(O)Cl$, pyridine, DMAP, CH_2Cl_2, 0 °C to rt; g) *n*-PrMgCl, CuCN (10 mol%), LiCl (30 mol%), THF, Et_2O, −78 °C to rt [64% (2 steps)]; h) *n*-Bu_4NF, THF, 0 °C; i) MsCl, 2,4,6-collidine, LiCl, DMF, 0 °C to rt [79% (2 steps)].

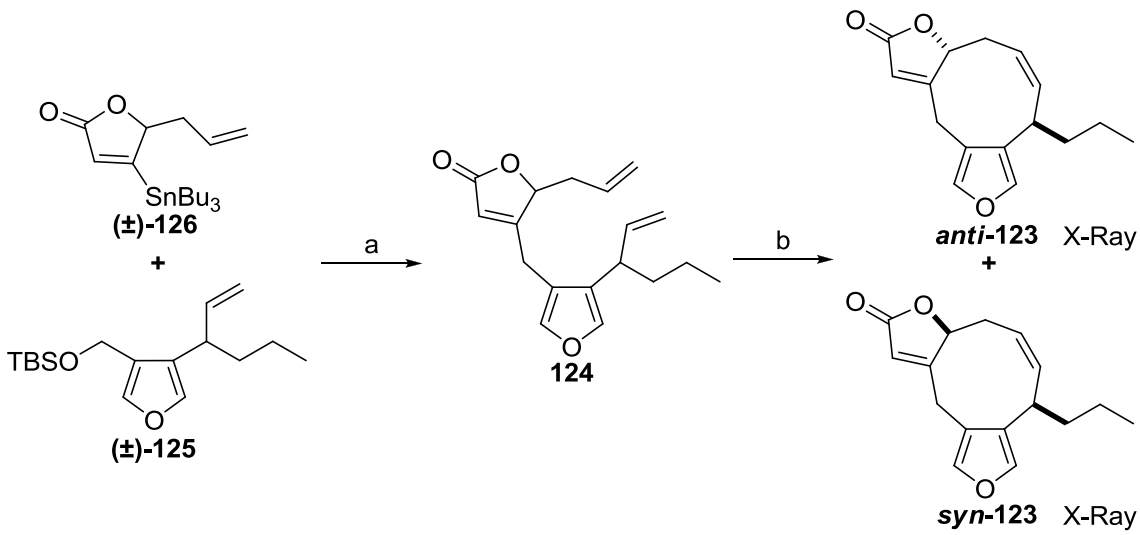
The coupling partner **(±)-126** was prepared as shown in Scheme 1.33. Condensation of tetronic acid **131** with pyrrolidine gave compound **132**. The vinylogous carbamate was then deprotonated using *tert*-butyllithium and treatment of the resulting anion with allyl bromide afforded the alkylated lactone **133**. Acid-catalysed hydrolysis afforded **134** which was converted into the corresponding triflate **(±)-135**. Finally, a palladium-catalysed reaction with hexa-*n*-butylditin furnished the desired stannane **(±)-126** in reasonable yield.[56]



Scheme 1.33 - Reagents & conditions: a) pyrrolidine, heat, reduced pressure; b) *t*-BuLi, allyl bromide, THF, −78 ºC to rt [76% (2 steps)]; c) aq. HCl (0.2 M), 60 ºC [85%]; d) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 ºC [89%]; e) Sn_2Bu_6, $Pd(PPh_3)_4$ (3 mol%), LiCl, THF, 60 ºC [54%].

Stille coupling and ring-closing metathesis reactions

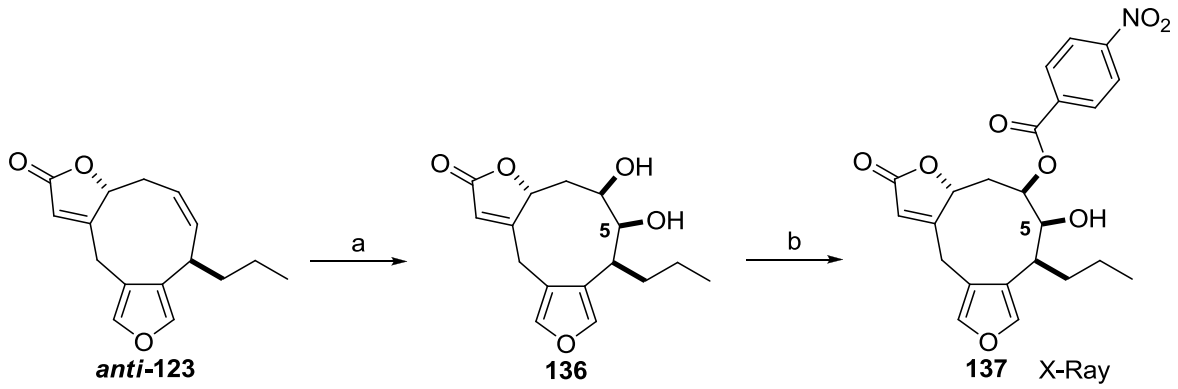
Following the preparation of both coupling partners, the precursor of the key RCM reaction was obtained by Stille coupling (Scheme 1.34). Treatment of a mixture of the chloride **(±)-125** and the stannane **(±)-126** with $Pd_2(dba)_3$ and triphenylarsine in THF provided coupled products **124** as an inseparable 1:1 mixture of diastereoisomers. The mixture of dienes **124** were subjected to the RCM reaction conditions using the Grubbs I metathesis catalyst **117**, to afford the desired tricyclic products **123** in 77% yield and as a 3:2 mixture of diastereoisomers. The diastereoisomers were separable and X-ray crystallographic analysis of both isomers ***syn*-123** and ***anti*-123** revealed that the major diastereoisomer was ***syn*-123**. At the time, the formation of a nine-membered carbocycle using a RCM reaction was unprecedented.



Scheme 1.34 - Reagents & conditions: a) $Pd_2(dba)_3$ (2 mol%), $AsPh_3$ (8 mol%), THF, 60 ºC [87%, *dr* 1:1]; b) Grubbs I **117** (20 mol%), CH_2Cl_2, reflux [81%, *dr* 3:2 (***syn*-123**—***anti*-123**)].

Selectivity of the Upjohn dihydroxylation reaction

The diastereoisomer ***anti*-123** was found to possess the relative configuration found in the cornexistins, therefore the elaboration of this compound was attempted (Scheme 1.35). Dihydroxylation of the alkene ***anti*-123** using Upjohn conditions was sluggish, but the single diastereoisomer **136** was obtained in consistent yields.[57] To determine the stereochemical outcome of the dihydroxylation reaction, the mono-*p*-nitrobenzoate **137** was prepared. X-ray analysis confirmed the conclusions made on the basis of preliminary NMR studies in that the dihydroxylation had delivered diol **136** with the opposite configuration on C-5 to that found in hydroxycornexistin (**2**). This was a surprise because the X-ray structure of ester ***anti*-123** clearly showed that the most accessible face in the structure was not the one where the dihydroxylation had occurred. However, enough material had been prepared to complete the synthesis of 5-*epi*-hydroxycornexistin, and it was thought that the configuration at C-5 could be inverted at a later stage.

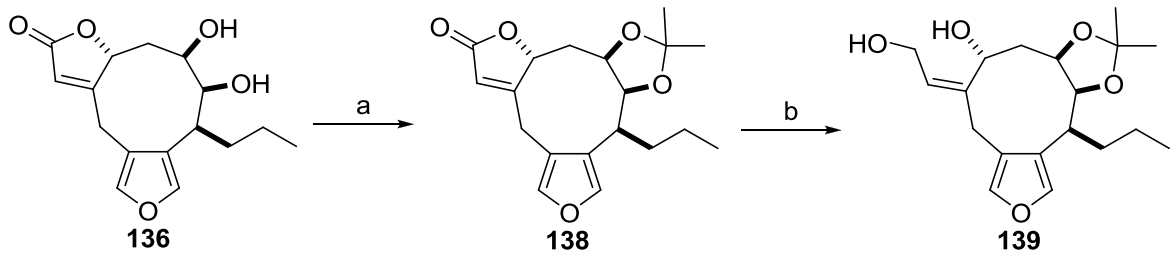


Scheme 1.35 – Reagents & conditions: a) OsO_4 (10 mol%), NMO, acetone, H_2O, rt [50-55% (55-70% based on recovered starting material)]; b) *p*-$O_2NC_6H_4C(O)Cl$, DMAP, pyridine, CH_2Cl_2 , 0 ºC to rt [67%].

Reduction of the α,β-unsaturated lactone

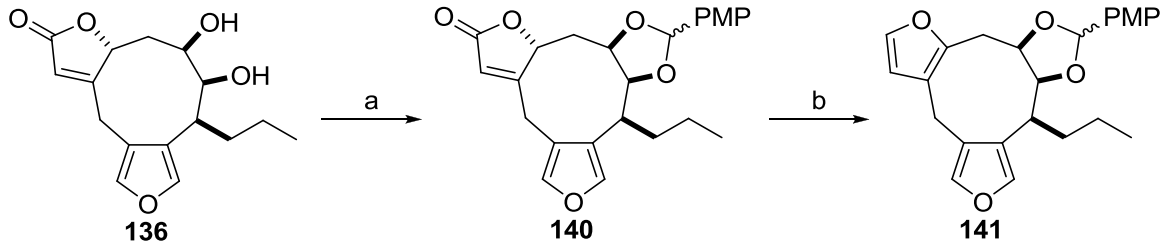
During preliminary studies, diol **136** was converted into the acetonide **138** (Scheme 1.36). From a literature precedent, it was known that the reduction of the α,β-unsaturated ester using lithium aluminium hydride can result in the formation of a furan.[58] Various reducing agents including sodium borohydride, lithium borohydride, lithium aluminium hydride were employed for the reduction of **138** without success. Eventually, the reduction was achieved using a two-step, one-pot procedure. Lactone **138** was reduced to the corresponding lactol using DIBAL-H, and *in situ* addition of

lithium aluminium hydride to the reaction mixture afforded diol **139** in a good 74% yield.



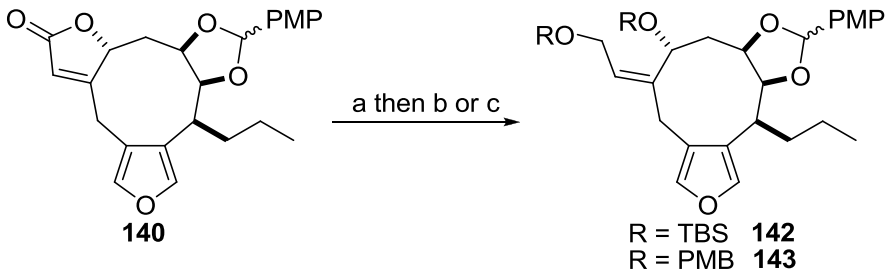
Scheme 1.36 - Reagents & conditions: a) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, rt [quant.]; b) DIBAL-H, THF, −78 ºC, then $LiAlH_4$, THF, −78 ºC to 0 ºC [74%].

For a strategic point of view, diol **136** was converted into the PMP-acetals **140** instead of the acetonide **139** (Scheme 1.37). Unfortunately, treatment of the lactones **140** with DIBAL-H afforded an isomeric mixture of the *bis*-furans **141**.



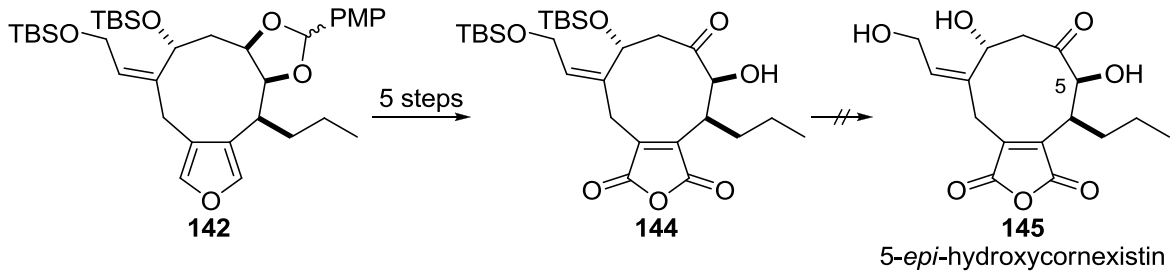
Scheme 1.37 - Reagents & conditions: a) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, MS (4 Å), CH_2Cl_2, 0 ºC to rt [93%, *dr* ~1:1]; b) DIBAL-H, THF, −78 ºC [53%].

The alternative found involved the reduction of the lactones **140** using $LiAlH_4$ in the presence of TMEDA (Scheme 1.38). Double TBS or PMB protection of the resulting diols afforded acetals **142** and **143** respectively, in good yield.



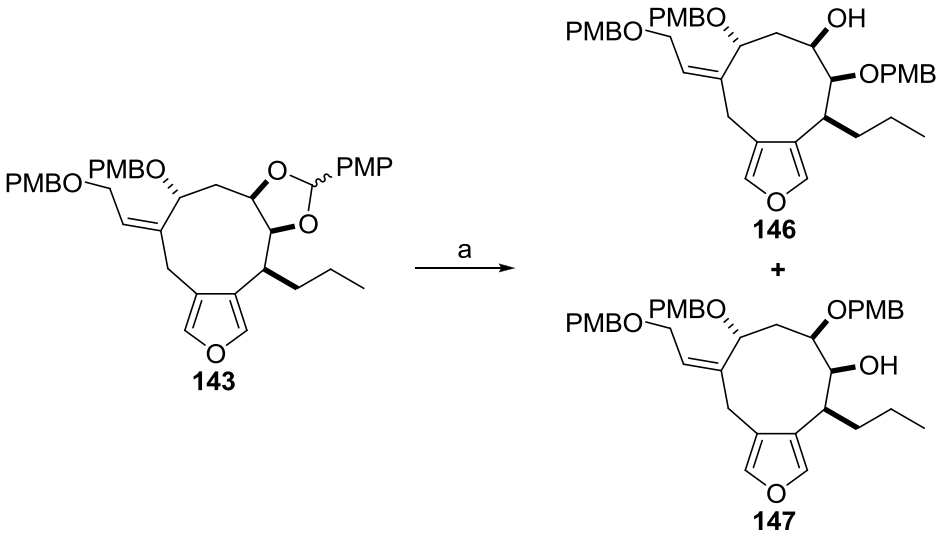
Scheme 1.38 - Reagents & conditions: a) $LiAlH_4$, TMEDA, Et_2O, 0 ºC; b) TBSOTf, pyridine, CH_2Cl_2, −78 ºC to rt [**142**, 74% (2 steps)]; c) PMBCl, NaH, *n*-Bu_4NI, DMF, 0 ºC to rt [**143**, 49% (2 steps)].

Focusing first on the TBS-ethers **142**, a five-step sequence led to the synthesis of the advanced intermediate **144** (Scheme 1.39). The very last step of the synthesis, a double TBS-ether cleavage reaction, failed to deliver the final product **145**. Presumably, the sensitivity of the cyclic anhydride unit to the deprotection conditions employed accounted for this unfortunate failure.



Scheme 1.39

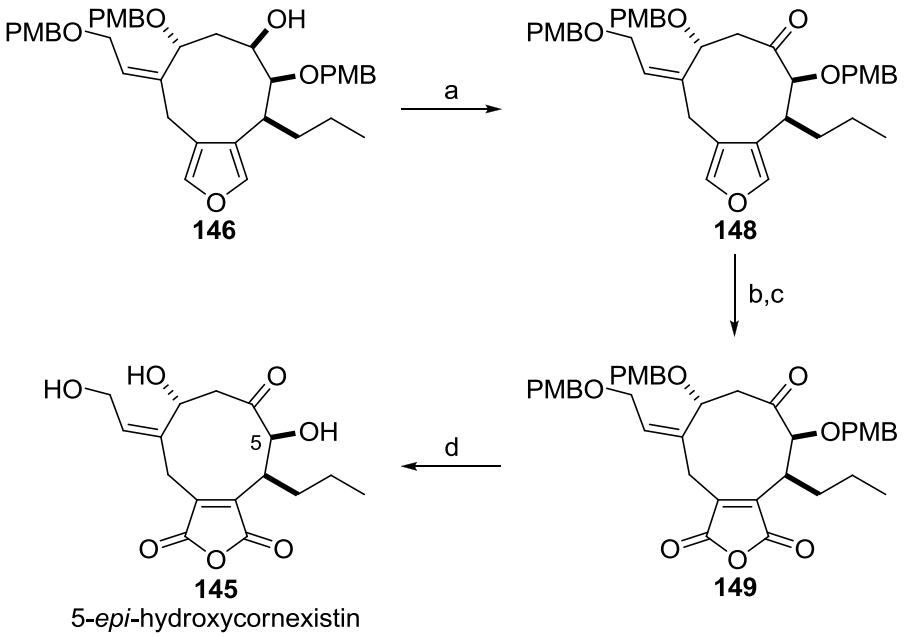
A similar sequence was used for the PMB-ethers **143** (Scheme 1.40). Reductive opening of the mixture of cyclic acetals with DIBAL-H produced regioisomers **146** and **147** in 62% yield (1.3:1 mixture). Despite the lack of regioselectivity, the two alcohols could be separated, and the desired regioisomer **146** used to complete the synthesis.



Scheme 1.40 - Reagents & conditions: a) DIBAL-H, CH_2Cl_2, toluene, −78 ºC to rt [33% **146**, 29% **147** (81% based on recovered starting material)].

Alcohol **146** was oxidised to the corresponding ketone **148** using TPAP (Scheme 1.41).[59] The reaction with singlet oxygen afforded a complex mixture of products that was directly treated with TPAP to deliver the unstable cyclic anhydride **149**. The final removal of the two PMB groups was thus performed as quickly as possible with DDQ to

reveal (±)-5-*epi*-hydroxycornexistin **145**, after extensive work-up and reverse HPLC purification. The modest overall yield of 10% obtained for the final three steps was unavoidable, given the instability of the cyclic anhydride on silica gel and the difficulties of purifying a triol, especially after a PMB-ether cleavage reaction using DDQ. Despite this challenging final sequence, the synthesis of (±)-5-*epi*-hydroxycornexistin **145** was successfully achieved, in a total of 25 synthetic steps, with a longest linear sequence of 20 steps.[51b]



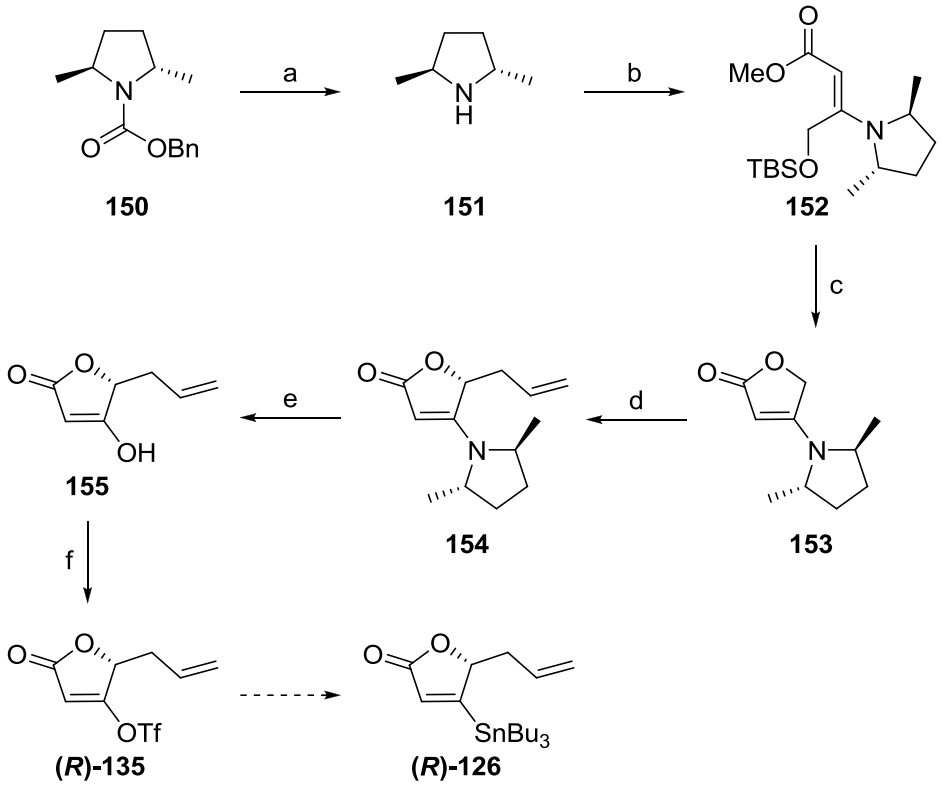
Scheme 1.41 – Reagents & conditions: a) TPAP, NMO, MS (4 Å), CH_2Cl_2, rt [80%]; b) O_2, hυ, rose Bengal, *i*-Pr_2NEt, CH_2Cl_2, −78 ºC to rt; c) TPAP, NMO, MS (4 Å), CH_2Cl_2, rt; d) DDQ, CH_2Cl_2, H_2O, rt [10% (3 steps)].

1.4.3 Asymmetric approaches to the Stille coupling fragments

In addition to the synthesis (±)-5-*epi*-hydroxycornexistin, the enantiopure synthesis of the two Stille coupling precursors was studied.[41,60] The chloride fragment proved difficult to synthesise enantioselectively whereas more success was obtained for the formation of the stannane fragment.

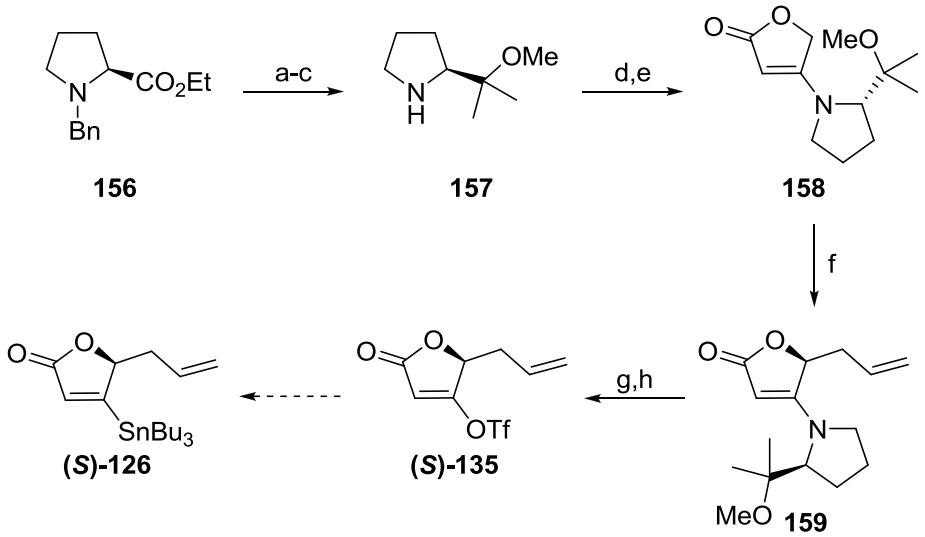
Asymmetric synthesis of the stannane fragment

During the synthesis of stannane **(±)-126**, the allyl group had been introduced by deprotonation of the pyrrolidine enamine **132**, prepared from tetronic acid (Scheme 1.33). The same procedure could be applied with a pyrrolidine derivative possessing a chiral centre, only this time the chiral auxiliary would potentially control the stereochemical outcome of the *γ*-alkylation reaction. The first chiral auxiliary chosen was the C-2 symmetrical *trans*-2,5-dimethylpyrrolidine (Scheme 1.42). Following the synthetic pathway developed by Schlessinger and co-workers, benzyl carbamate **150** was obtained in six steps starting from L-alanine.[61] Carbamate **150** was converted into dimethylpyrrolidine **151** *via* treatment with trimethylsilyl iodide.[62] Conjugate addition of the amine **151** to TBS-protected methyl 4-hydroxy-2-butynoate, followed by removal of the TBS group using TBAF afforded the lactone **153**. Upon deprotonation with *tert*-butyllithium and subsequent treatment of the enolate of **153** with allyl bromide, the alkylated product **154** was obtained in 81% yield. Only one diastereoisomer could be detected by ^{1}H NMR. Surprisingly, the hydrolysis of the auxiliary under acidic conditions was largely unsuccessful, and only a small amount of the tetronic acid derivative **155** could be converted to enol triflate **(*R*)-135** by treatment with triflic anhydride. Other acidic conditions were explored but without success, and careful analysis of the literature revealed that the hydrolysis of *trans*-2,5-dimethylpyrrolidine was actually unprecedented. Although this chiral auxiliary, due to its C-2 symmetry, would have been the most suited for the stereoselective introduction of the allyl group, a different auxiliary, which could be removed under hydrolysis conditions, was investigated.



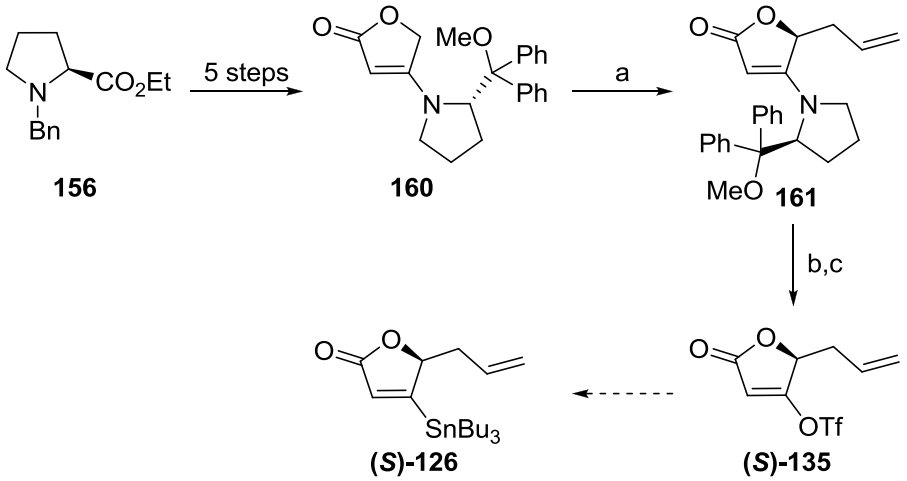
Scheme 1.42 – Reagents & conditions: a) TMSCl, NaI, MeCN, 0 ºC to rt; b) $TBSOCH_2CCCO_2Me$, Et_2O, *t*-BuOH, 60 ºC; c) *n*-Bu_4NF, THF, rt [44% (3 steps)]; d) *t*-BuLi, allyl bromide, THF, −78 ºC to rt [81%]; e) aq. HCl (0.2 M), 60 ºC; f) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 ºC [<5% (2 steps)].

Following the procedure developed by Enders, the chiral proline derivative **157** was prepared in three steps starting from ester **156** (Scheme 1.43).[63] Double Grignard addition to the ester **156**, followed by methylation of the resulting alcohol and hydrogenolysis of the benzyl group afforded auxiliary **157** in good yield. Carbamate **158** was prepared by conjugate addition of the amine **157** to the TBS-protected methyl 4-hydroxy-2-butynoate, followed by removal of the TBS group with TBAF. This time the alkylation reaction provided the allylated product **159** as the major product, with a good level of diastereoselectivity (5:1). Further hydrolysis and conversion of the tetronic acid derivative into the corresponding triflate delivered **(*S*)-135** in a modest yield of 48% and with 65% *ee*. Although the enantiopurity of the triflate obtained was not as good as when it was prepared using dimethylpyrrolidine, the hydrolysis of the carbamate was more efficient with this substrate.



Scheme 1.43 – Reagents & conditions: a) MeMgBr, Et_2O, rt [91%]; b) MeI, NaH, THF, reflux [84%]; c) H_2, $Pd(OH)_2$, EtOH, EtOAc [90%]; d) $TBSOCH_2CCCO_2Me$, Et_2O, *t*-BuOH, 60 ºC; e) *n*-Bu_4NF, THF, rt [54% (3 steps)]; f) *t*-BuLi, allyl bromide, THF, −78 ºC to rt [86%, *dr* 5:1]; g) aq. HCl (0.5 M), 60 ºC; h) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 ºC [48% (2 steps), 65% *ee*].

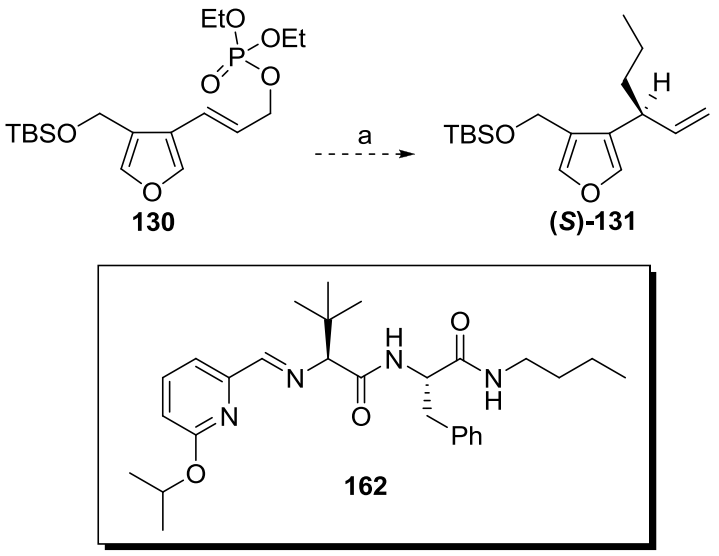
In ordered to evaluate the effect of the bulk of the auxiliary on the diastereoselectivity of the alkylation step, a modification of the auxiliary was attempted (Scheme 1.44). Carbamate **160** was prepared analogously to the previously described synthesis, the only modification being the introduction of two phenyl groups instead of the methyl ones during the Grignard reaction. As expected, a greater level of diastereocontrol was achieved during the alkylation step. The diastereoisomeric ratio was 8:1 in favour of the allylated product **161**, and the diastereoisomers could be separated by flash column chromatography. Consequently, after hydrolysis of the auxiliary and triflate formation, the enantiopurity of the compound **(*S*)-135** was excellent (95% *ee* as determined by chiral HPLC). The hydrolysis step of the auxiliary accounted for the overall low yield obtained for the two steps, but the enantiopurity of the triflate obtained was very promising. This pathway seemed to offer a very good method for the asymmetric synthesis of stannane fragment **(*S*)-126**.



Scheme 1.44 – Reagents & conditions: a) *t*-BuLi, allyl bromide, THF, −78 °C to rt [79%, *dr* 8:1]; b) aq. HCl (0.5 M), 60 °C; c) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 °C [28% (2 steps), 95% *ee*].

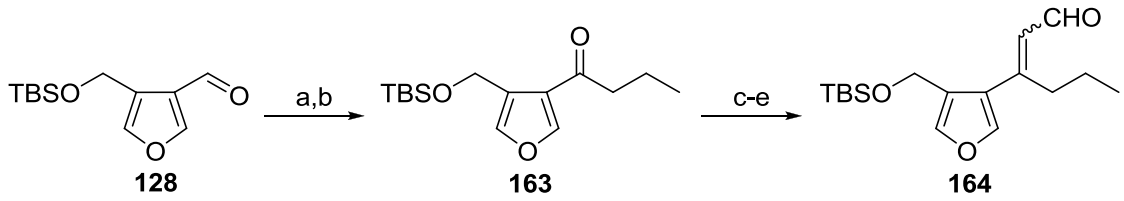
Asymmetric synthesis of the chloride fragment

Less success was met when trying to synthesise the chloride fragment in an enantiopure fashion.[60,41] The sequence allowing the formation of the chloride fragment involved a copper-catalysed S_N2' displacement reaction of the allylic phosphate **130** with *n*-propylmagnesium bromide (Scheme 1.32). An asymmetric version of this reaction had been reported by Hoveyda in 2001, using dialkylzinc compounds and pyridinyl peptide ligands such as **162** (Scheme 1.45).[64] The possibility of adapting this methodology to allylic phosphate **130** was investigated by the Clark group, but unfortunately was completely unsuccessful.



Scheme 1.45 – Reagents & conditions: a) **162** (10 mol%), CuCN (10 mol%), Pr_2Zn, THF, −78 °C.

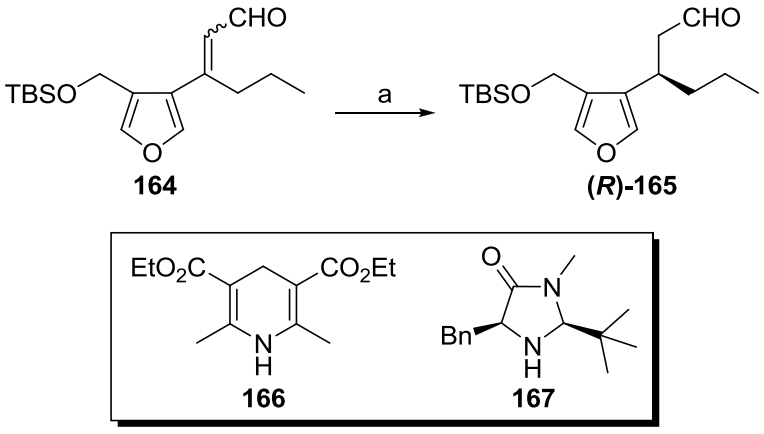
The second approach investigated was inspired by the work of List and MacMillan, who almost simultaneously developed the enantioselective reduction of α,β-unsaturated aldehydes *via* organocatalysis.[65,66] The required substrate **164** was prepared in five steps, starting from readily available aldehyde **128** (Scheme 1.46). Grignard addition followed by the oxidation of the resulting alcohol using manganese dioxide afforded ketone **163**. A Wadsworth-Horner-Emmons reaction afforded an *E*, *Z* mixture of α,β-unsaturated esters that was reduced using DIBAL-H to give a mixture of alcohols. Manganese dioxide oxidation furnished the α,β-unsaturated aldehydes **164**.



128 **163** **164**

Scheme 1.46 – Reagents & conditions: a) *n*-PrMgCl, THF, −78 °C to rt; b) MnO_2, CH_2Cl_2, rt [80% (2 steps)]; c) $(EtO)_2P(O)CH_2CO_2Me$, NaH, THF, reflux [88%; *E*:*Z*, 1:0.9]; d) DIBAL-H, THF, −78 °C to rt [85%]; e) MnO_2, CH_2Cl_2, rt [77%].

The organocatalytic hydride reduction was attempted using Hantzsch ester **166** as hydride source and the trichloroacetamide ammonium salt of **167** (Scheme 1.47). Unfortunately, most of the starting material was recovered after the reaction, with the desired aldehyde **(*R*)-165** obtained in approximatively 20% yield, suggesting that there had been no catalytic turnover. Alternative salts of the organocatalyst **167** and solvents were screened but without success.



164 **(*R*)-165** **166** **167**

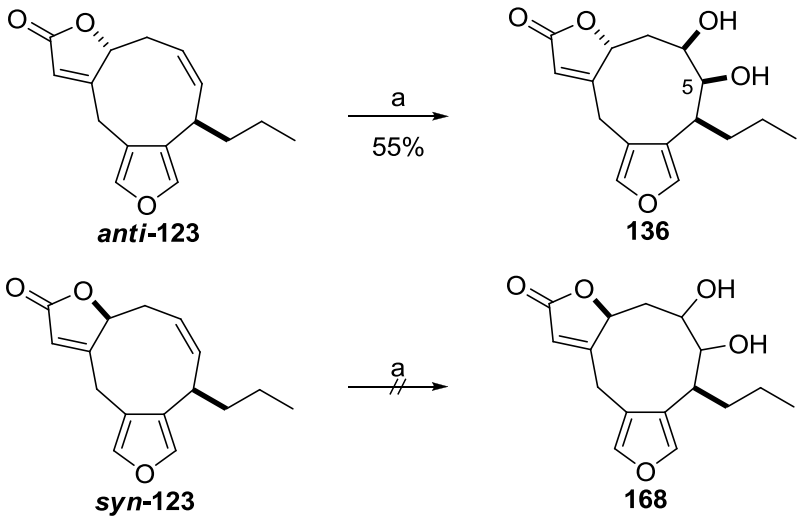
Scheme 1.47 – Reagents & conditions: a) **167**·TCA (20 mol%), **166**, dioxane, 0 °C to rt [*ca* 20%].

1.4.4 Attempts to install the natural C-5 configuration

A tremendous effort was undertaken to introduce the desired natural configuration at the C-5 stereocentre of hydroxycornexistin (2). Unfortunately, all the alternative methods investigated were unsuccessful, as shown in the following section.[41]

Dihydroxylation reaction

As previously mentioned (*cf*. Section 1.4.2), Upjohn dihydroxylation of alkene ***anti*-123** gave a single diastereoisomer **136**, bearing the wrong configuration at the C-5 stereocentre (Scheme 1.48). Alternative dihydroxylation methods using TMEDA or quinuclidine as additives gave similar results, and epoxidation reactions using DMDO or *m*-CPBA led to the decomposition of the starting material. Surprisingly, when the diastereoisomeric alkene ***syn*-123** was subjected to the same reaction conditions, the starting material was recovered along with decomposition products, showing that in this case, the double bond was inaccessible to osmium tetroxide (Scheme 1.48).



Scheme 1.48 - Reagents & conditions: a) OsO_4 (10 mol%), NMO, acetone, H_2O, rt.

It was thought that the α,β-unsaturated lactone moiety was affecting the conformation of the nine-membered ring system and possibly impeding the dihydroxylation reaction. Accordingly, three model substrates were prepared from ***syn*-** and ***anti*-123** and subjected to two different dihydroxylation conditions (Table 1.2). Along with Upjohn dihydroxylation conditions, the substrates **169**, **170** and **171** were treated with a stoichiometric amount of osmium tetroxide in the presence of quinuclidine, an approach that was inspired by the work of Donohoe and co-workers for the directed

dihydroxylation of allylic alcohols.[67] In all cases, most of the starting material (**169**, **170** or **171**) was recovered following attempted dihydroxylation under Upjohn conditions, while the second method resulted in a complex mixture of products with no evidence of diol formation.

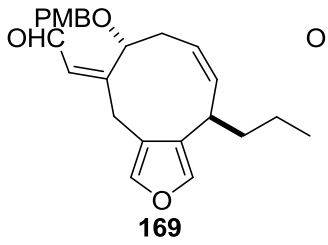
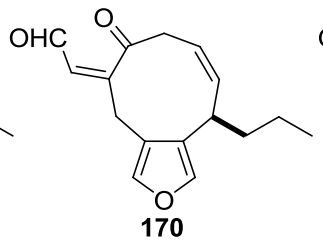
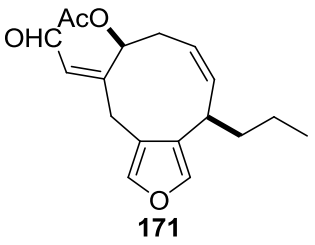
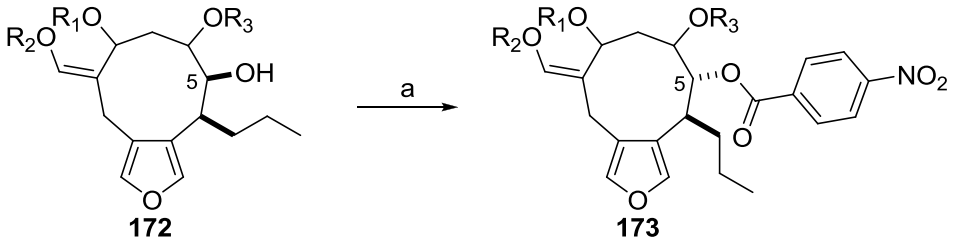
dihydroxylation precursors	 **169**	 **170**  **171**
dihydroxylation conditions	OsO_4 (10 mol%), NMO, acetone, H_2O, rt	
	OsO_4, quinuclidine, CH_2Cl_2, 0 °C	

Table 1.2

Mitsunobu inversion reaction and other alternatives

The second approach involved inversion of configuration at C-5 *via* Mitsunobu reaction of the secondary alcohol, to afford **173** from **172** (Scheme 1.49).[68]



Scheme 1.49 - Reagents & conditions: a) *p*-$NO_2C_6H_4CO_2H$, DEAD, PPh_3, THF, 0 °C to rt.

Diol **136** was subjected to Mitsunobu reaction conditions (Figure 1.8). Unfortunately, no reaction occurred with either of the two hydroxyl groups, which suggested that both the C-5 and C-6 hydroxyl groups were particularly sterically hindered. With mono-acetate **174**, the same result was obtained. Even without the α,β-unsaturated lactone, only starting material was recovered when diol **175** was subjected to the inversion reaction conditions.

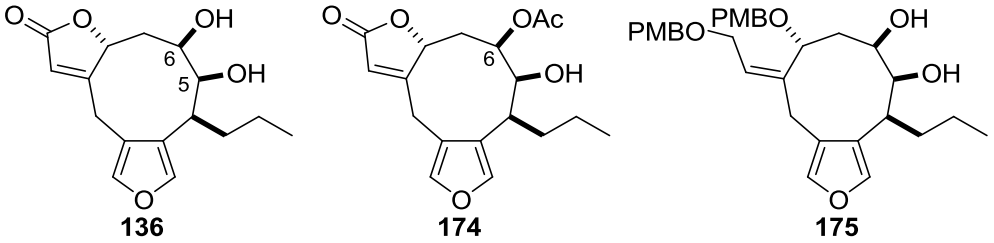
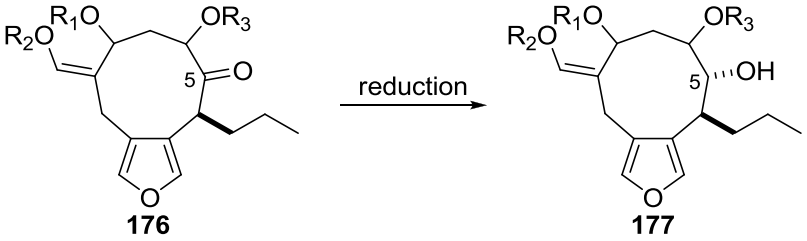


Figure 1.8

The third approach that was investigated involved selective reduction of the C-5 centre. It was hoped that at least one set of conditions for the reduction of ketone **176** would provide the alcohol **177** with the desired configuration at C-5 (Scheme 1.50).



Scheme 1.50

Five model substrates were prepared and subjected to various reducing reagents (**178** to **182**, Figure 1.9).[41] Using $NaBH_4$, $Me_4NBH(OAc)_3$, DIBAL-H, $Al(O\textit{i}\text{-}Pr)_3$ or $Zn(BH_4)_2$ under a range of solvents and temperatures, the alcohol bearing the undesired configuration at C-5 was invariably obtained after the reduction reaction. In the case of ketone **182**, it was hoped that the presence of the allylic alcohol might direct the reducing agent on the α-face of the nine-membered ring. The reduction reaction was attempted using sodium triacetoxyborohydride, but only starting material was recovered.

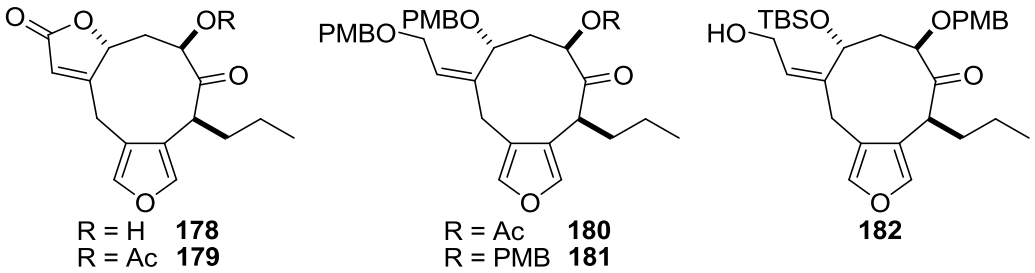
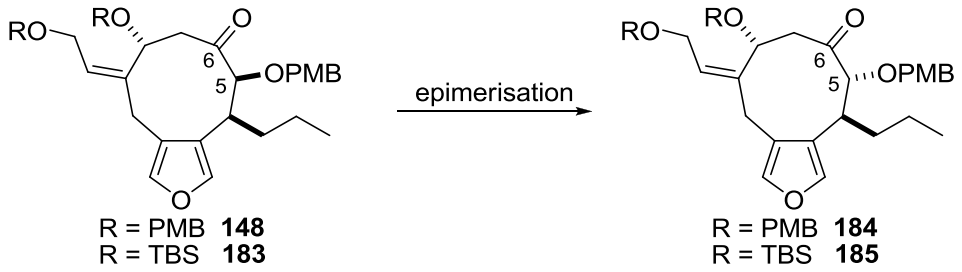


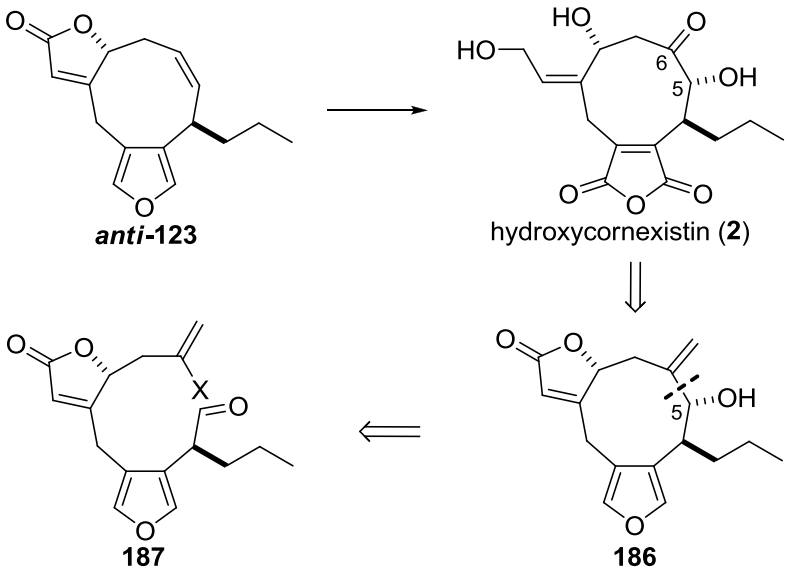
Figure 1.9

Lastly, epimerisation of the C-5 stereocentre of **148** and **183** was attempted (Scheme 1.51). A variety of bases were used to epimerise the C-5 position of ketones **148** and **183** but unfortunately, these reactions failed to deliver any of the desired isomeric compounds **184** and **185**.



Scheme 1.51 - epimerisation reagents employed: DBU, DBN, imidazole, K_2CO_3, KO*t*-Bu, *n*-Bu_4NF, *p*-TSA, HCl.

These results led to a simple observation: after the RCM reaction and formation of ***anti*-123**, the desired C-5 configuration of hydroxycornexistin (**2**) is extremely difficult to introduce because of the conformation of the nine-membered ring (Scheme 1.52). As much as the RCM reaction had been useful for the formation of the core of cornexistins, an alternative method for ring closure had to be found to introduce the correct configuration at the C-5 centre. In a retrosynthetic approach, the ketone on C-6, formerly derived from a hydroxyl group, could also be accessed from a 1,1-disubstituted alkene. Using the same C—C bond disconnection, the allylic alcohol **186** could be the result of the intramolecular nucleophilic addition of an alkenylmetallic species to an aldehyde. Knowing that chromium(II) readily inserts into alkenyl halides, the precursor to allylic alcohol **186** could therefore be vinyl halide **187**. This led to a new strategy with an intramolecular Nozaki-Hiyama-Kishi reaction as key ring-closing step of the synthesis. It was hoped that closure of the nine-membered ring using this reaction would offer a better chance to form the natural C-5 configuration of cornexistins.



Scheme 1.52

The Nozaki-Hiyama-Kishi reaction is a powerful tool for advanced organic synthesis and has been applied successfully in many total syntheses. The main features of this reaction will be described in the following chapter.

1.5 The Nozaki-Hiyama-Kishi reaction

1.5.1 Organochromium chemistry — pioneering studies

The first studies of organochromium chemistry started in 1914 with the report from Bennett and Turner of a reaction between phenylmagnesium bromide and chromic chloride ($CrCl_3(H_2O)_x$) affording phenylbenzene in excellent yield according to the following equation:[69]

Eq. 1.1 – $2CrCl_3 + 2C_6H_5MgBr \rightarrow C_6H_5C_6H_5 + 2CrCl_2 + MgCl_2 + MgBr_2$

Four years later, a first communication from Hein was published, dealing with the isolation of the first organochromium compound: 'pentaphenylchromium bromide' by transmetalation of phenyl Grignard reagents with $CrCl_3$.[70] Hein and co-workers subsequently reported an impressive series of results related to the formation of 'polyphenylchromium' compounds.[69a] At that time, those compounds were surprising and the mechanism for the formation of these species was unknown because of the limited analytical methods and the lack of theoretical understanding of chemical bonds. What was found in the 1950's was that Hein had in fact been the first to form bis(benzene)chromium species (or η^6 sandwich complexes of biphenyl and benzene with Cr). Zeiss and Tsutsui, Hafner and Fisher were the main actors of this fascinating tale leading to the elucidation of Hein's compounds, and brilliantly summarised by Seyferth in 2002.[71]

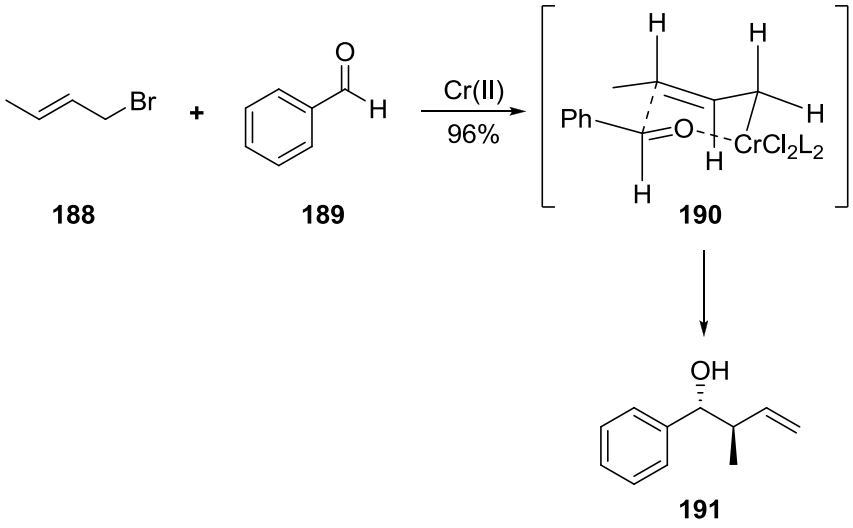
In 1957, Anet and Leblanc were the first to prepare aqueous solutions of benzyl chromium species, by reaction of Cr(II) with benzyl chloride.[72] Kinetic and spectroscopic studies allowed Kochi and Davies to formulate the mechanism of the oxidative addition of Cr(II) into the C—X bond of benzyl chloride as a two—step sequence including the generation of benzyl radicals as intermediates in the reaction (Eq. 1.2 and 1.3).[73] The first rate-determining step forms the benzyl radical using one equivalent of Cr(II) and another equivalent of Cr(II) is needed for the second step; the rapid coupling of the free radical and generation of the benzylchromium ion.

Eq. 1.2 - $C_6H_5CH_2{-}X + Cr(II)_{aq} \rightarrow C_6H_5CH_2\cdot + Cr(III)X^{2+}{}_{aq}$

Eq. 1.3 - $C_6H_5CH_2\cdot + Cr(II)_{aq} \rightarrow C_6H_5CH_2Cr(III)X^{2+}{}_{aq}$

The reactivity of benzylchromium and related reagents was studied by Kochi *et al.*, and over the years the chromium(II) salts were mostly recognised as reducing reagents for organic halides.[74] Realising that the preparation of chromium(II) salts in water was to some extent limiting the potential use of Cr(II) in organometallic chemistry, Hiyama and Nozaki reported in 1977 the preparation of $CrCl_2$ by reduction of $CrCl_3$ with lithium aluminium hydride in THF.[75] This was a major breakthrough because it allowed the use of chromium(II) in aprotic media, making it available for C—C bond forming reactions. In the following publications they demonstrated that Cr(II) readily inserts into allyl-, alkenyl-, alkynyl-, propargyl- and aryl halides to form organochromium(III) nucleophiles that could react with a wide range of carbonyl electrophiles.[76]

Another interesting characteristic of the preliminary screening made by Hiyama *et al.* was the isolation of a single diastereoisomer **191** obtained from the chromium mediated reaction of crotyl bromide **188** with benzaldehyde **189** (Scheme 1.53).[75b] The *anti*-configuration of the resulting product **184** was subsequently determined by Heathcock and co-workers and it was assumed that a chair-like transition state **190** accounted for the stereoselectivity of the reaction.[77] Starting from either *E*- or *Z*- crotyl bromide resulted in the same product formation, suggesting that the rapid equilibrium between *E*- and *Z*- allylchromium(III) species was in favour of the *E*-configuration.[78]



Scheme 1.53

Finally, independently and almost simultaneously, in 1986 the group of Takai and Nozaki, and the group of Kishi discovered that the addition of a catalytic amount of nickel(II) chloride promoted more consistently the Grignard-type reaction between alkenyl halides or triflates and aldehydes.[79] Nickel catalysis was then extended to a

variety of chromium-mediated coupling reactions and the now called Nozaki-Hiyama-Kishi (NHK) reaction became a powerful method of C—C bond formation where classical Wittig or aldol approaches were unsuccessful. It combines many unique and important features:

i) pronounced chemoselectivity of the organochromium(III) reagents for aldehydes, even in the presence of ketones;
ii) a wide range of substrates including allyl, propargyl, alkenyl, alkynyl, aryl halides, alkenyl triflates, sulfonates and phosphates are suitable precursors for the formation of the organochromium(III) intermediates;
iii) compatibility with an array of functional groups in both reactions partners;
iv) low basicity of organochromium(III) reagents;
v) alkenyl halides react with complete retention of their double bond geometry.

These advantages render the NHK reaction particularly well suited for application in total synthesis. Chromium-induced inter- or intramolecular carbon—carbon bond formations have been used as key steps in the synthesis of many complex targets. One of the most famous examples features in the total syntheses of the complex polycyclic ethers halicondrin B and norhalicondrin B, achieved by Kishi and co-workers in 1992. The NHK reaction is used three times in the first generation synthesis of these targets (Figure 1.10).[80]

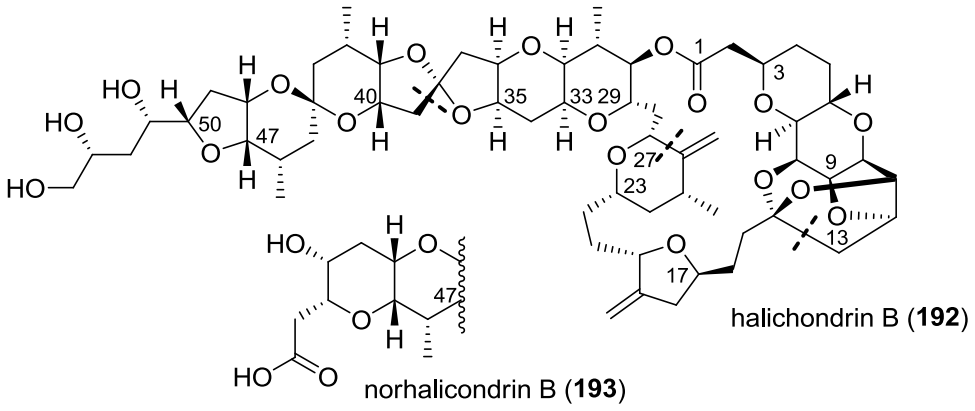


Figure 1.10

1.5.2 NHK — mechanistic studies

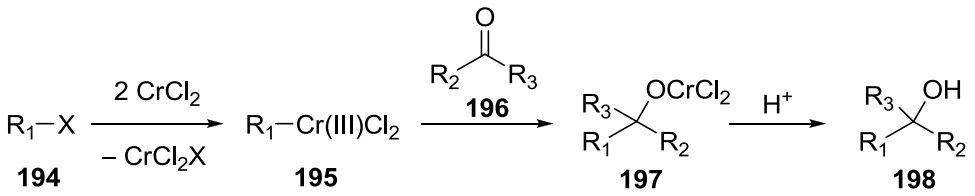
Stoichiometric reactions

With the absence of a catalyst, the oxidative addition of Cr(II) into a C—X bond proceeds as two consecutive single electron transfer (SET) events (Eq. 1.4 and 1.5).[72a] The first SET allows the formation of the radical species (Eq. 1.4) and the second provides the organochromium(III) complex (Eq. 1.5).

Eq. 1.4 - $R{-}X + Cr(II)Cl_2 \rightarrow [R{-}X]^{\bullet -} + Cr(III)Cl_2^{+} \rightarrow R\cdot + Cr(III)Cl_2X$

Eq. 1.5 - $R\cdot + Cr(II)Cl_2 \rightarrow R^{-} + Cr(III)Cl_2^{+} \rightarrow RCr(III)Cl_2$

Overall, the nucleophilic addition of the organochromium(III) nucleophile **195** to carbonyl **196** can be formally depicted as shown in Scheme 1.54. The product formed is the chromium alkoxide **197**. In stoichiometric reactions, the high stability of the resulting O—Cr(III) bond is an advantage because it acts as a thermodynamic sink driving the reaction to completion. This bond is hydrolysed during acidic work-up to form the alcohol **198**.

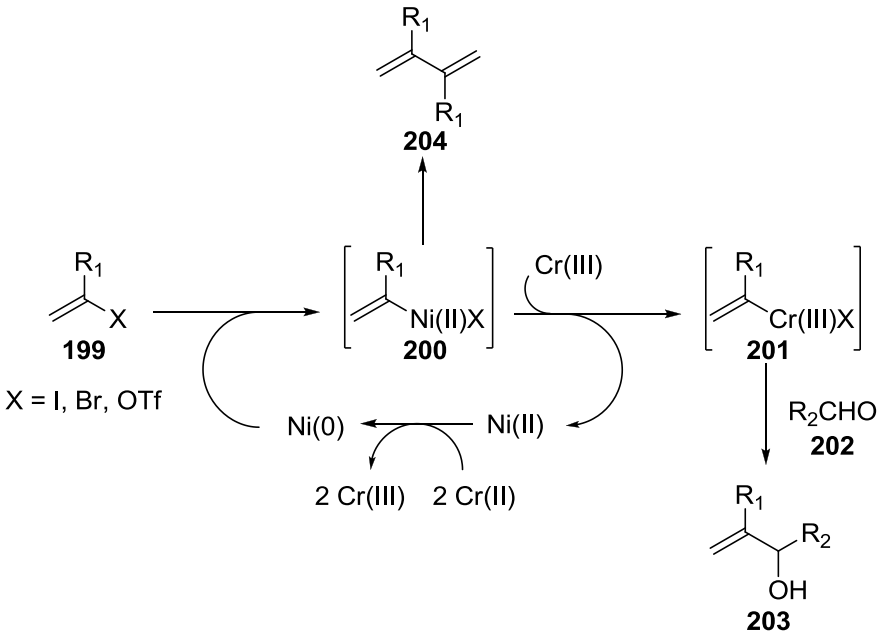


Scheme 1.54

Catalytic effect of nickel on chromium-mediated coupling reactions of alkenyl halide or triflate with aldehydes

As previously mentioned, the catalytic effect of nickel in chromium-mediated coupling reactions was discovered by Takai and Kishi, both disconcerted by the dramatic effect that the batch of $CrCl_2$ had on the success of the reaction, especially starting from less reactive alkenyl halides or triflates. Careful analysis of the commercial sources of chromium dichloride revealed that nickel was the major contaminant, and that the addition of sub-stoichiometric nickel dichloride to the reaction improved the consistency of the outcome.[79] The catalytic cycle of the reaction was proposed by Takai (Scheme 1.55).[79a] $NiCl_2$ is first reduced to nickel(0) with two equivalents of $CrCl_2$. Next,

oxidative addition of the alkenyl species **199** with Ni(0) affords complex **200**.[81] Transmetalation between a chromium(III) salt and the nickel complex **200** allows for the formation of the alkenylchromium(III) reagents **201**, which upon reaction with an aldehyde **202** and subsequent hydrolysis produces alcohol **203**. The nickel source and the amount of nickel used in the reaction were found to be crucial for the success of the reaction. Indeed Takai pointed out that using nickel with donor ligands like $NiCl_2(PPh_3)_2$ was accelerating the formation of the undesired dimer **204**, whereas Kishi had encountered the same issue using a $NiCl_2$ content in $CrCl_2$ of greater than 0.1 to 1% in weight.[79,82] Pd(II) acetate was also found to have the same catalytic effect on the reaction, but this additive was markedly less studied.[72a,79b]

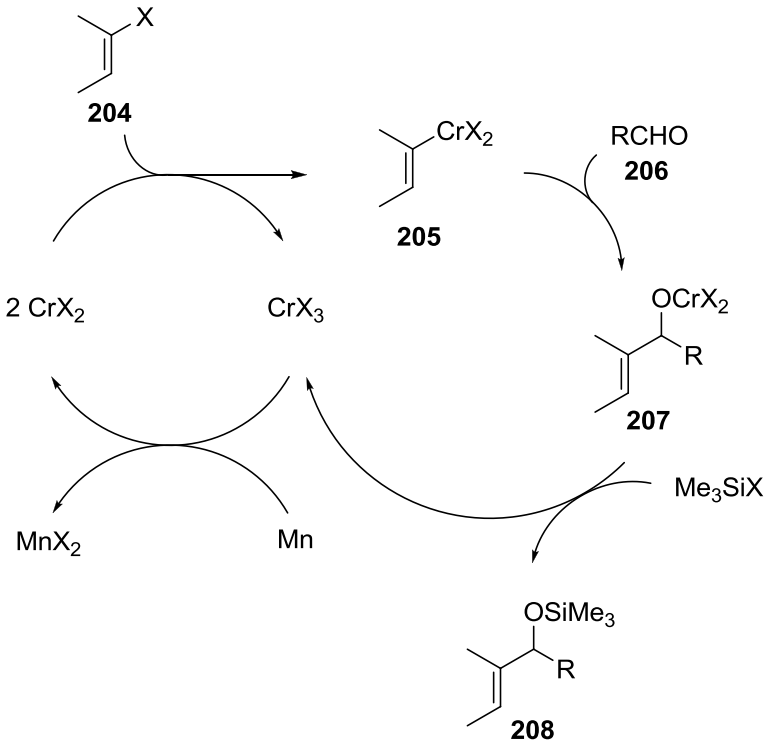


Scheme 1.55

Chromium-catalysed NHK

The major drawback of the NHK reaction using two equivalents or more of chromium in the reaction is the amount of toxic chromium and nickel salts generated. To circumvent this problem, the group of Fürstner developed the first chromium-catalysed process (Scheme 1.56).[83] The key feature of this catalytic cycle is that the chromium alkoxide **207** is silylated using trimethylsilyl chloride, which releases the chromium salt from the organic product. Thus, the liberated chromium(III) salt, upon reduction to Cr(II) with manganese powder, can take part in the reaction again. Apart from rendering the process catalytic in chromium, this methodology offers two advantages. First, manganese powder is cheap, non-toxic and does not react on its own with the organic compounds in the reaction.[72a] Secondly, it makes it possible to start the reaction with a

sub-stoichiometric amount of $CrCl_3$ which unlike $CrCl_2$, is cheap and insensitive to oxygen and moisture. It appeared to be applicable for most halides with the exception of alkenyl- and aryl halides where a co-catalytic amount of $NiCl_2$ was required. Samarium, iron and other sources were later used for the regeneration of the active Cr(II) species.[72a,84]



Scheme 1.56

1.5.3 NHK — enantioselective reactions

Given the importance of the NHK reaction, an efficient enantioselective version to control the absolute stereochemical outcome for a range of processes would definitely broaden the scope of this reaction, and would be useful for total synthesis. However, due to difficulties such as ligand coordination and specificity, combined with the tendency of chromium(II) to form dimers or clusters with polydentate ligands, relatively few reports of an enantioselective variant have been reported. The first successful enantioselective versions relied on over stoichiometric amounts of chiral ligands. For example, Kishi reported the application of the chiral bipyridine ligand **209** (Figure 1.11) in the allylation and alkenylation of benzaldehyde and obtained enantioselectivities of 28-74% *ee*.[85] Kibayashi's *N*-benzoylpropinol ligand **210** gave enantioselectivities of up to 98% *ee* for the reaction of allyl bromide with a range of aldehydes.[86] In 1999, the group of Cozzi was the first to report a successful enantioselective NHK reaction using a catalytic amount of a chiral chromium complex (10 mol%).[87] Using chiral Salen ligand **211**, 89% *ee* was obtained for the chromium-mediated allylation of various aldehydes. Berkessel *et al*. later modified the Salen ligand **211** to **212**, which was then employed successfully with vinyl halides or triflates for the enantioselective synthesis of allylic alcohols.[88]

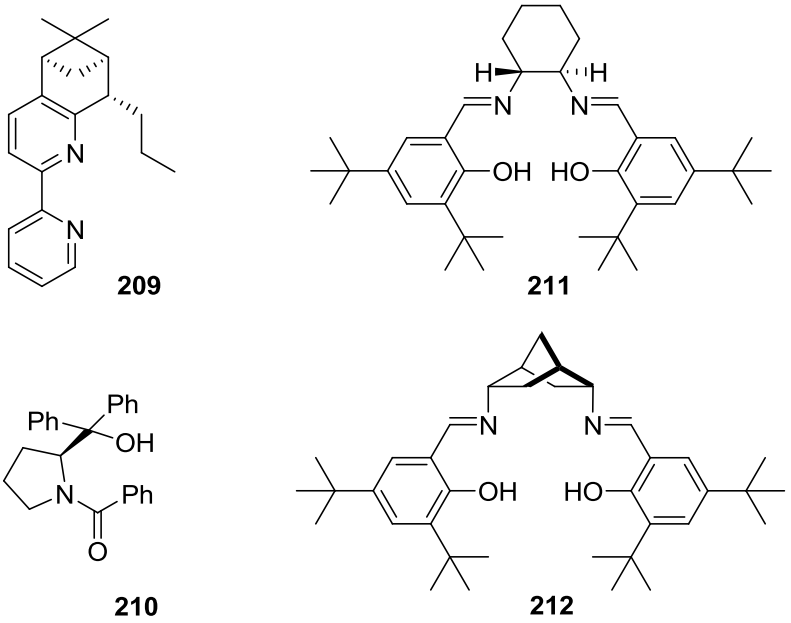
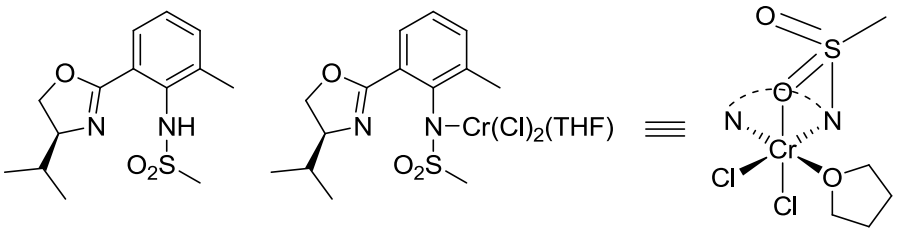


Figure 1.11

Oxazoline-based enantioselective NHK

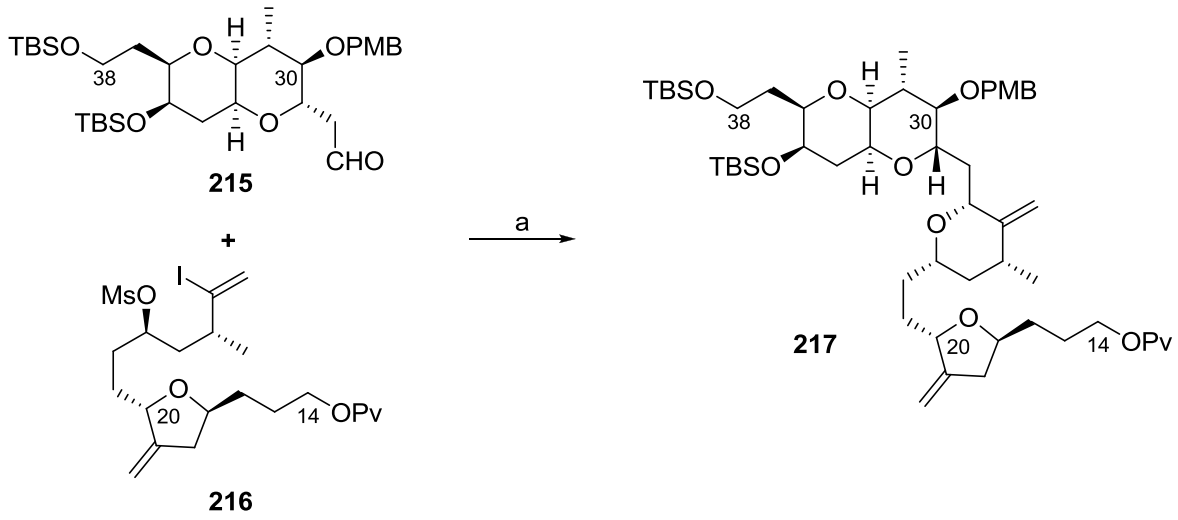
The use of oxazoline-based ligands for asymmetric induction in metal-mediated reactions has already been investigated by several research groups,[86,89] but Kishi and co-workers managed to obtain the best results when using them in asymmetric NHK reactions. In connection with their efforts to improve the synthesis of halicondrin B (Figure 1.10), they investigated the asymmetric chromium-mediated addition of alkenyl iodides with aldehydes, and found that oxazoline **213** was efficient in delivering asymmetric induction during the reaction.[90] Remarkably, X-ray analysis of a single crystal of the Cr(III)/sulphonamide ligand complex **214** revealed that the ligand **213** was tridentate, allowing an almost perfect octahedral structure to be attained in the chromium complex (Figure 1.12).



213 **214**

Figure 1.12

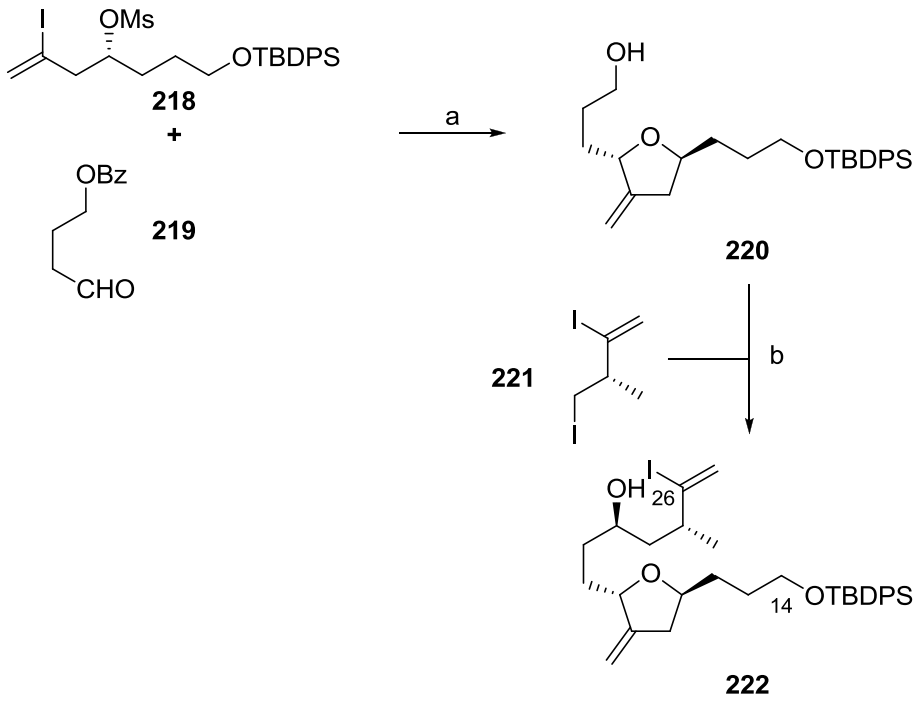
The diastereoselectivity of the NHK reaction when forming the C14—C38 fragment of halicondrin B was 3.5:1. With the addition of the sulphonamide **213** to the reaction, a massive improvement in the selectivity was observed (20:1), demonstrating the usefulness of this ligand for total synthesis (Scheme 1.57).



Scheme 1.57 – Reagents & conditions: a) NaH, **213** (3 equiv), $CrCl_3$ (3 equiv), (Bn)(*n*-Bu)$_3$NCl, (1 equiv), **215** (1 equiv), **216** (2 equiv), $NiCl_2$ (1 equiv), THF, rt then *t*-BuOK, *t*-BuOH, −15 °C [55%, *dr* 20:1(3.5:1 without **213**)].

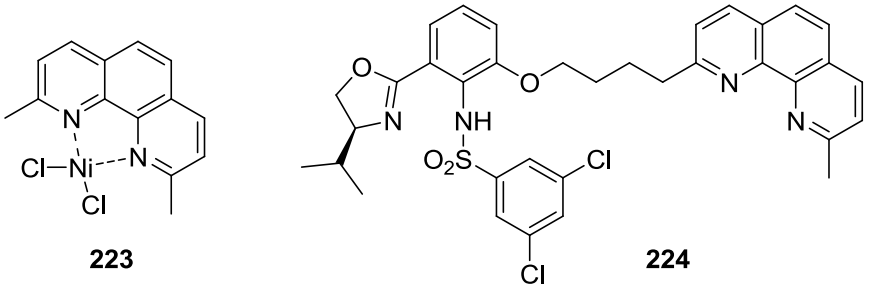
In the following paper the group of Kishi pursued their investigations and, using the pre-formed chromium(III)/ligand complex **214**, performed the asymmetric chromium-mediated addition of alkenyl iodides to aldehydes in a catalytic process.[91] This methodology was applied twice during the construction of the C14—C26 fragment of halicondrin B (Scheme 1.58). Using the antipode of **214** (10 mol%), and either $NiCl_2$ (40 mol%) or $Ni(cod)_2$ (5 mol%), the coupling of vinyl iodide **218** to the aldehyde **219** furnished the desired product **220**. Following Fürstner's work, manganese was used as the reducing agent for the chromium(III) species and TMSCl was employed as the dissociating agent for the chromium alkoxide. It was also found that addition of (Bn)(*n*-Bu)$_3$NCl or $Et_3N{\cdot}HCl$, and LiCl enhanced the coupling efficiency. Subsequent TMS-silyl ether removal and S_N2 reaction using PPTS and pyridine gave the cyclised product in a good diastereoisomeric ratio (6:1 when the reaction was conducted in THF). The benzoyl group was then cleaved using potassium carbonate and methanol to afford the tetrahydrofuran **220**. After DMP oxidation, the coupling of the resulting aldehyde with **221** was more complex. In 1989, Takai and co-workers achieved the coupling of alkyl halides with aldehydes, in the presence of $CrCl_2$ and a catalytic amount of vitamin B12 or cobalt phthalocyanine. With this work in mind, the asymmetric Co/Cr-mediated reaction was attempted.[92] After a screening to identify the optimum reaction conditions, the selective activation of the alkyl iodide over the vinyl iodide in **221** and

subsequent Cr/Co-catalysed coupling with the aldehyde provided the desired product **222** in 73% yield and with a high level of diastereoselectivity (5.3:1).



Scheme 1.58 – Reagents & conditions: a) (1) **218** (1 equiv), **219** (2 equiv), the antipode of **214** (10 mol%), $NiCl_2$ (40 mol%) or $Ni(cod)_2$ (3 × 1 mol%), Mn (2 equiv), TMSCl (2 equiv), $(Bn)(n\text{-}Bu)_3NCl$ (20 mol%), LiCl (2 equiv), THF, rt; (2) PPTS, pyridine, *i*-PrOH, rt [*dr* 6.0:1]; (3) K_2CO_3, MeOH, rt [70—80% (3 steps)]; b) (1) DMP, CH_2Cl_2, rt [90%]; (2) the aldehyde (1 equiv), **221** (2 equiv), **214** (50 mol%), Co-phthalocyanine (10 mol%), Mn (2 equiv), TMSCl (2 equiv), $Et_3N{\cdot}HCl$ (20 mol%), LiCl (2 equiv), DME, rt; (3) oxalic acid (aq.), THF, rt [73% (2 steps), *dr* 5.3:1].

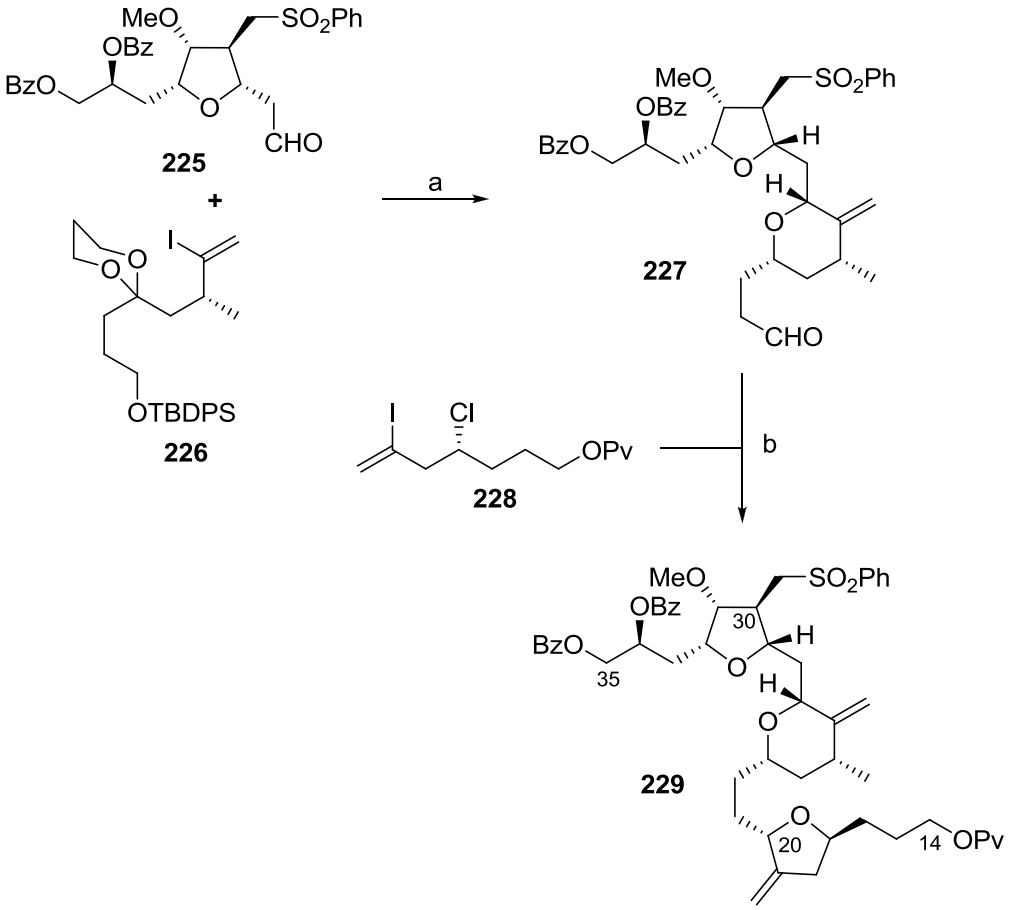
This was still not good enough for Kishi's group, who realised that the nickel ligands were playing a central role in the reaction. Subsequent screening of the ligands revealed that using 2,9-dimethylphenanthroline·$NiCl_2$ **223** complex allowed a decrease in the loading of the nickel catalyst to 2 mol% (Figure 1.13).[93] This was important because it had already been shown that the more nickel(II)-catalyst was introduced in the reaction, the higher the chances of forming homo-coupling side products (Scheme 1.55). It was next envisaged that a bimetallic ligand for both nickel and chromium would improve the asymmetric NHK reaction, by placing the two metals in close proximity.[94] The transmetalation step would be faster, preventing the intermediate alkenyl nickel halide to form any homo-coupling side products. Consequently, instead of the usual excess of alkenyl iodide required (1.5 to 2 equivalents), the equimolar amounts of coupling partners could be used. This led to the synthesis of ligand **224**, where the left-hand site would complex the chromium and phenanthroline unit would complex the nickel (Figure 1.13).



223 **224**

Figure 1.13

Promising results were obtained using the ligand **224** in model studies. Ultimately, the formation of two C—C bonds during the synthesis of the C14—C35 fragments of halicondrin/E7389 was successfully achieved (Scheme 1.59). Only 3 mol% of the Cr/Ni-catalyst was used for the coupling of **225** and **226** with only 1.2 equivalent of the vinyl iodide **226**. Manganese was again used as the reducing agent but Cp_2ZrCl_2 was preferred instead of TMSCl as the dissociating agent. The coupled product was obtained in excellent yield and with high selectivity (91% yield and *dr* 19:1). Cyclisation with TBDPS-ether cleavage using triethylsilane and TMS triflate gave the corresponding alcohol and this was then oxidised to form aldehyde **227**. Similar coupling conditions afforded the desired product from aldehyde **227** and vinyl iodide **228** in 91% yield and with 19:1 selectivity. Subsequent S_N2 displacement of the chlorine substituent with the alkoxide generated using potassium hydride and 18-crown-6 afforded the C14—C35 fragment of halicondrin/E7389 **229**.

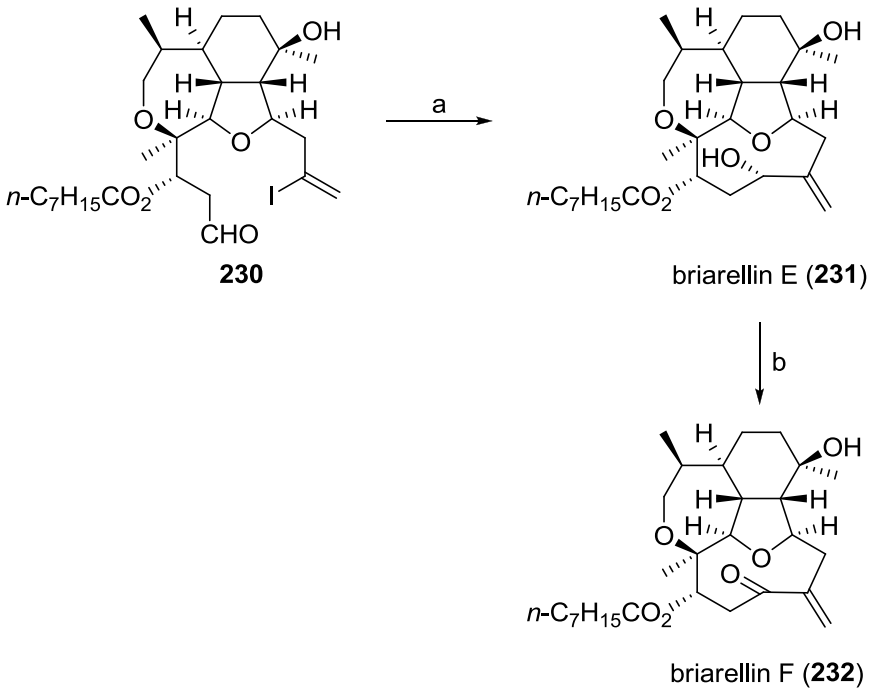


Scheme 1.59 – Reagents & conditions: a) (1) proton sponge (3 mol%), **224**·$NiCl_2$ (3 mol%), $CrCl_2$ (3 mol%), **225** (1 equiv), **226** (1.2 equiv), LiCl (5 equiv), Mn (2 equiv), Cp_2ZrCl_2 (1.2 equiv), MeCN, rt [86%, *dr* 19:1]; (2) Et_3SiH, TMSOTf, CH_2Cl_2, −78 °C to 0 °C [95%]; (3) oxidation step; b) (1) proton sponge (2 mol%), the antipode of **224**·$NiCl_2$ (2 mol%), $CrCl_2$ (2 mol%), **227** (1 equiv), **228** (1.1 equiv), LiCl (0.5 equiv), Mn (2 equiv), Cp_2ZrCl_2 (1.2 equiv), MeCN, rt [91%, *dr* 19:1]; (2) KH, 18-crown-6, toluene, −20 °C [88%].

Starting from stoichiometric Cr-mediated coupling, Kishi has enhanced the NHK reaction in both asymmetric and catalytic aspects, always keeping in mind the goal of developing methodology suitable for more complex targets that can be encountered in total synthesis. In their most recent paper concerning Ni/Cr-mediated coupling reactions, Kishi and co-workers have developed an air-stable hetero-bimetallic catalyst, which opens the way to asymmetric, catalytic NHK reactions without the use of a glove box.[95]

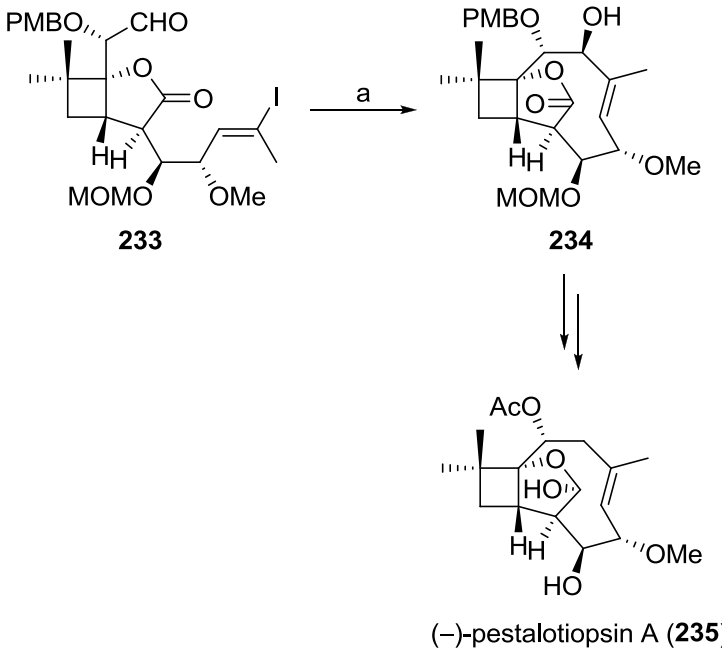
1.5.4 Application of the NHK reaction in total synthesis

The NHK reaction has been applied many times in total synthesis. As shown previously, intermolecular NHK reactions have been extensively used by Kishi and co-workers. They also reported a catalytic Ni/Cr-mediated macrocyclisation reaction for the synthesis of the halicondrins,[96] but generally the classic $CrCl_2/NiCl_2$ couple with addition of a greater than stoichiometric amount of chromium is employed for intramolecular NHK reactions. In 2009, the group of Overman published the enantioselective total syntheses of briarellin E and F involving a key intramolecular NHK reaction to form the nine-membered ring of the tricyclic structure (Scheme 1.60).[97] The late-stage intermediate **230** containing the desired aldehyde and proximal vinyl iodide functionalities was reacted under the NHK conditions to deliver briarellin E (**231**) in 79% yield, as a single isomer. Briarellin F (**232**) was subsequently obtained by simple DMP oxidation of briarellin E (**231**). It should be noted that 100 equivalents of $CrCl_2$ were used for the reaction, although at this stage of the synthesis, the scale of the reaction minimised the amount of toxic waste generated.



Scheme 1.60 – Reagents & conditions: a) $CrCl_2$—$NiCl_2$ (100:1 equiv), DMSO—DMS (100:1), rt [79%]; b) DMP, CH_2Cl_2, rt [79%].

The same year Takao *et al*. achieved the asymmetric synthesis of pestalotiopsin A, also containing a nine-membered ring (Scheme 1.61).[98] An excellent yield of 92% was obtained for the intramolecular NHK reaction of **233**, with formation of the single diastereoisomer **234**. This success allowed them to complete the first synthesis of (−)-pestalotiopsin A (**235**), followed by the synthesis of the natural (+)-pestalotiopsin A using the same strategy.



233 **234**

(−)-pestalotiopsin A (**235**)

Scheme 1.61 – Reagents & conditions: a) $NiCl_2$ (0.06 equiv), $CrCl_2$ (7.6 equiv), DMSO, rt [92%].

These examples emphasize that the intramolecular NHK reaction with intermediate sized ring systems can be achieved efficiently, which is promising for the new strategy that we want to develop for the synthesis of cornexistins.

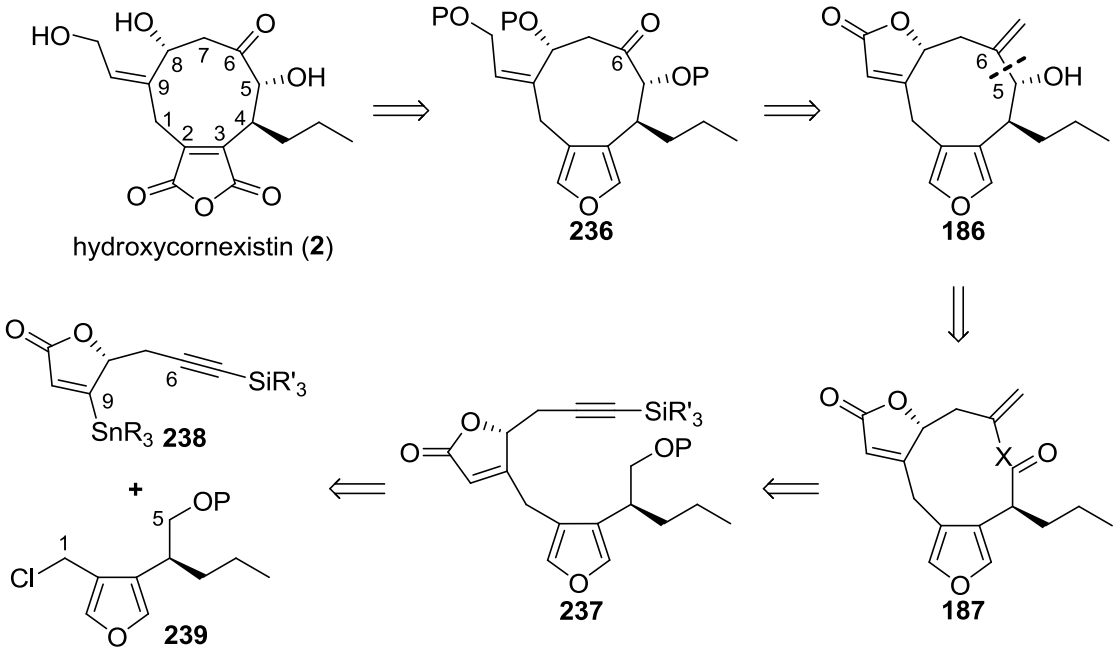
1.6 New strategy for the synthesis of hydroxycornexistin

The synthesis of 5-*epi*-hydroxycornexistin (**145**) was achieved using a RCM metathesis reaction as ring-closing step. Because the correct C-5 stereochemistry could not be installed, an alternative strategy was needed. The Nozaki-Hiyama-Kishi reaction has proven to be a powerful method for the formation of ring systems of various sizes in many total syntheses. The primary objective was the synthesis of the potential NHK reaction precursor in the most efficient manner. Modifications of the previous synthesis of 5-*epi*-hydroxycornexistin (**145**) were needed although the main disconnections remained. The feasibility of the new ring-closing step was to be evaluated as well as the stereoselectivity of the reaction. Providing the formation of the required C-5 configuration for the synthesis of cornexistins, the NHK reaction was expected to be the method leading to the first synthesis of hydroxycornexistin (**2**). Finally, the enantioenriched approach during the two Stille-coupling fragments was to be further investigated, for the potential highly enantioselective synthesis of hydroxycornexistin (**2**).

Part II: Results and discussion

2.1 New retrosynthetic analysis

The aim of the project was the synthesis of cornexistins using an intramolecular NHK reaction as key step of the strategy. Concentrating on hydroxycornexistin (**2**) the new strategy was built upon previous work. The cyclic anhydride unit was to be masked as a furan (Scheme 2.1). The C-6 ketone could be made from a terminal alkene, and the exocyclic allylic alcohol from the unsaturated lactone **186**. Ring opening at the exocyclic α-hydroxy alkene functional group, between the C-5 and C-6 centres reveals **187**, the key NHK precursor in the revised strategy. It was anticipated that the closure of the nine-membered ring would favour the natural (*R*) configuration of the C-5 centre. Functional group interchanges leads to **237**, which could be obtained through Stille coupling between the stannane **238** and the allyl chloride **239**.

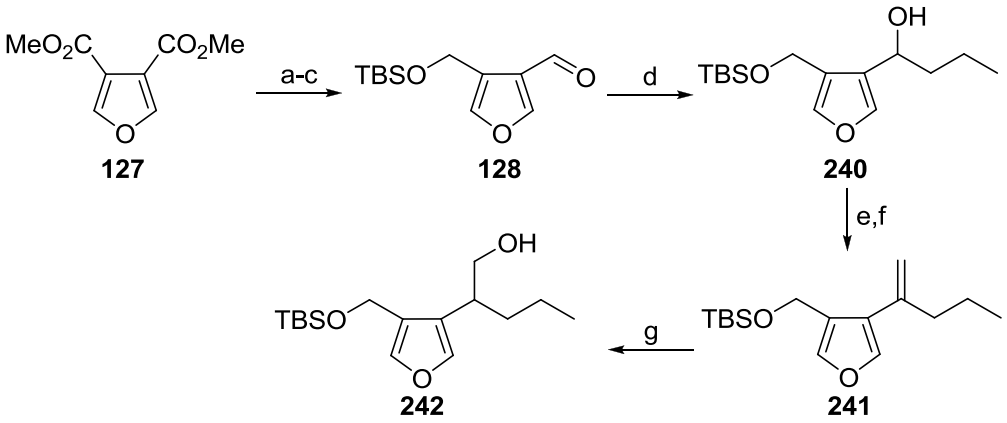


Scheme 2.1

2.2 An approach using racemic material to the Nozaki-Hiyama-Kishi cyclisation

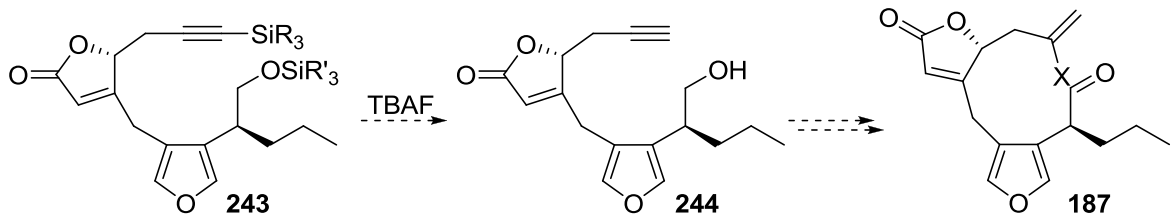
2.2.1 C-1 — C-5 Chloride fragment synthesis

Following previous work carried out within the group,[41,60] the synthesis of the C-1—C-5 fragment **239** started from commercially available 3,4-dimethylfurandiester **127** (Scheme 2.2). Global reduction of the ester functionalities with lithium aluminium hydride was followed by selective mono-oxidation using manganese dioxide. Protection of the remaining free hydroxyl group as a TBS-ether gave aldehyde **128**. Direct alkylation of the crude aldehyde, with *n*-propylmagnesium chloride, gave alcohol **240** in 69% yield over four steps. A second MnO_2 oxidation of secondary alcohol **240** was followed by methylenation under Wittig conditions to give alkene **241**. Hydroboration of the 1,1-disubstituted alkene was accomplished with 9-BBN and upon oxidation primary alcohol **242** was formed, in 88% yield.



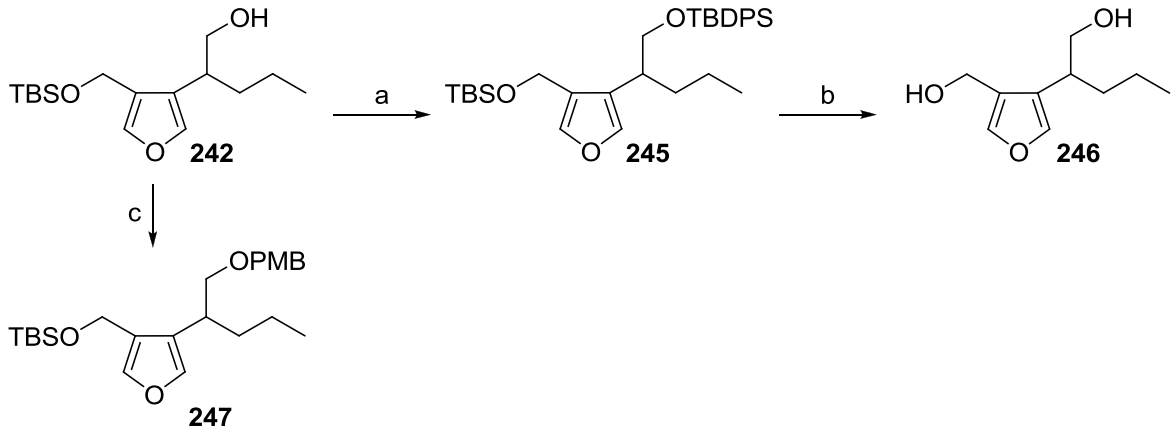
Scheme 2.2 – Reagents & conditions: a) $LiAlH_4$, THF, −78 °C to rt; b) MnO_2, CH_2Cl_2, rt; c) TBSCl, imidazole, DMAP, CH_2Cl_2, rt; d) *n*-PrMgCl, THF, −78 °C to rt [69% (4 steps)]; e) MnO_2, CH_2Cl_2, reflux [86%]; f) Ph_3PCH_3Br, NaHMDS, THF, 0 °C to rt [95%]; g) (*i*) 9-BBN, THF, 55 °C; (*ii*) EtOH, 3 M NaOH, 0 °C; (*iii*) 30% H_2O_2, 50 °C [88%].

For strategic purposes, protection of the free hydroxyl group of **242** as a silyl-ether would be advantageous, as a subsequent double cleavage of silyl groups within coupled fragment **243** would save a step in the synthesis (Scheme 2.3).



Scheme 2.3

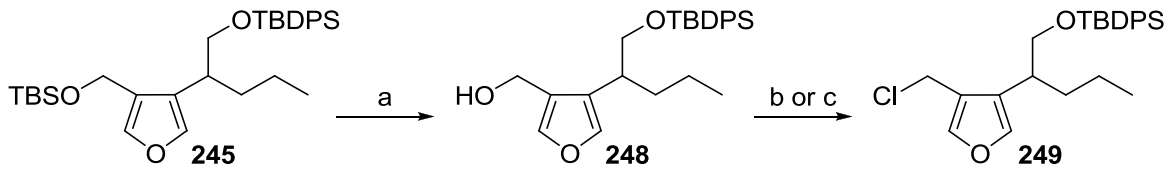
Due to the requirement for an orthogonal protecting group, the primary alcohol **242** was protected as a TBDPS-ether to afford *bis*-protected diol **245** in good yield (Scheme 2.4). Attempted removal of the TBS group of **245**, using CSA in methanol, led to the loss of both silyl groups to give diol **246**. As this first attempt was unsuccessful, protection of **242** as a PMB-ether was investigated next.



Scheme 2.4 – Reagents & conditions: a) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt [91%]; b) CSA (30 mol%), MeOH, rt [30%]; c) PMBTCA, CSA (10 mol%), CH_2Cl_2, rt [35%].

Basic conditions using PMBCl and sodium hydride failed to deliver the desired product. It was assumed that the TBS-ether was too labile because traces of *bis*-PMB-ether were detected among other decomposition products. The use of PMBTCA with a catalytic amount of CSA allowed the formation of **247**, albeit slowly and in a disappointing yield. As the PMB protection was not adequate, other selective desilylation methods were investigated. Fortunately, treatment of **245** with PPTS in ethanol allowed for the selective cleavage of the TBS group in excellent yield (Scheme 2.5). The next step was the formation of chloride **249**, which was accomplished in 85% yield through mesylation of alcohol **248** and chloride substitution using conditions previously optimised by the group.[41,60] Although this reaction gave acceptable results, alternative conditions

designed for allylic alcohols were also successful, allowing for the improved formation of the chloride fragment in 92% yield.[99] This method has the advantage of substituting dimethylformamide for dichloromethane as the solvent, thus facilitating the work-up of the reaction. Additionally mesyl chloride acts as the chloride source for the reaction, removing the requirement for a secondary chloride salt source. The synthesis of the desired chloride fragment **249** was completed in 10 steps from **127**, in an overall yield of 40%.

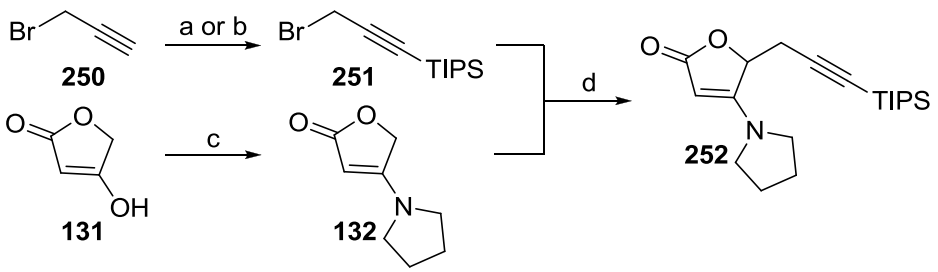


Scheme 2.5 – Reagents & conditions: a) PPTS (50 mol%), EtOH, 40 °C, [95%]; b) $MeSO_2Cl$, LiCl, 2,4,6-collidine, DMF, 0 °C [85%] or c) $MeSO_2Cl$, Et_3N, CH_2Cl_2, rt [92%].

2.2.2 Synthesis of the stannane fragment

Formation of the triflate

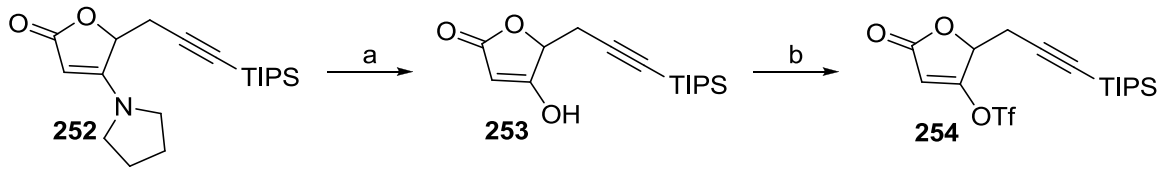
The synthesis began with the silyl protection of the terminal alkyne CH group of propargyl bromide **250** (Scheme 2.26). The bulky TIPS group was selected to protect the terminal alkyne. Treatment of the lithium acetylide of **250** with TIPSCl afforded silyl alkyne **251** in 72% yield.[100] Alternatively, substituting LiHMDS for *n*-butyllithium allowed isolation of alkyne **251** in quantitative yield.



Scheme 2.6 – Reagents & conditions: a) *n*-BuLi, TIPSCl, THF, −78 °C to rt [72%]; b) LiHMDS, TIPSCl, THF, −78 °C to rt [quant.]; c) pyrrolidine, toluene, 50 °C, reduced pressure [81%]; d) *t*-BuLi, THF, −78 °C to rt [70 to 90%].

The conversion of tetronic acid **131** into the vinylogous carbamate **132** through condensation with pyrrolidine had been described by our group previously,[41,60] and using

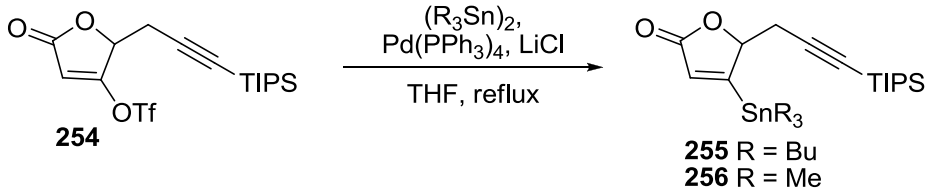
this methodology, carbamate **132** was obtained in 81% yield. Deprotonation of compound **132** with *t*-butyllithium and treatment of the resulting anion with **251** afforded the alkylated product **252** in 70 to 90% yield. The isolated yield was dependent on the amount of propargyl bromide used, and the use of five equivalents was found to give the best yield. Hydrolysis of the pyrrolidine moiety using aqueous hydrochloric acid as previously described (*cf*. Section 1.4.2, Scheme 1.31) was unsuccessful due to poor substrate solubility. However, it was found that the hydrolysis using hydrochloric acid in refluxing ethanol was a good alternative (Scheme 2.7). Instead of purifying the keto-enol product **253**, which dramatically reduced the isolated yield of the reaction, the crude material was used directly in the formation of the triflate **254**, which was obtained in good yield over both steps (80%). It is worth noting that the triflate could be purified under normal chromatography conditions without the use of triethylamine deactivated silica. The material is a stable solid which can be stored indefinitely at room temperature.



Scheme 2.7 – Reagents & conditions: a) HCl (1.26 M in EtOH), H_2O, 80 °C; b) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 °C [80% (2 steps)].

Conversion of the triflate to the stannane

Investigations into the conversion of the triflate **254** to the corresponding vinyl stannane were then attempted. The first conditions examined involved the use of bis(tributyltin), $Pd(PPh_3)_4$ and lithium chloride in refluxing THF (Table 2.1, entry 1).[41,60,56] The results were disappointingly poor and proved to be irreproducible with yields varying from 5 to 33% (entry 2). On the other hand, the formation of trimethylstannane **256** was accomplished in a reproducible manner and with a better yield of 54% (entries 3 and 4). As the reaction became sluggish after one or two hours at reflux, almost certainly because of the deactivation of catalyst, further addition of $Pd(PPh_3)_4$ during the reaction helped to improve the rate of the reaction.

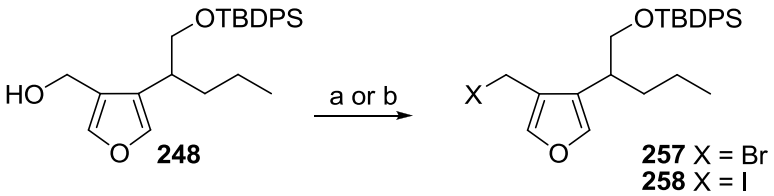


entry	R	LiCl (equiv)[a]	catalyst loading (mol%)	yield (%)
1	Bu	3.0	5	traces
2	Bu	8.0	5	5 to 32
3	Me	6.0	5	34
4	Me	8.0	7[b]	54

Table 2.1 – [a]LiCl was thoroughly flame-dried prior use; [b]4 mol% of $Pd(PPh_3)_4$ added straight, 3 mol% added to the mixture after 1.5 h.

Attempted Suzuki coupling

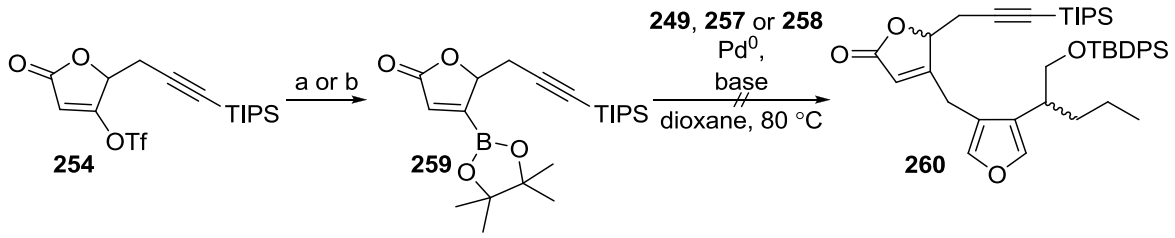
The use of toxic tin reagents is not optimal for large scale synthesis, therefore a Suzuki coupling of the two fragments was attempted as there are numerous examples of sp^2-sp^3 coupling in the literature.[101] The bromo and iodo equivalents of chloride **249** were prepared using standard conditions (Scheme 2.8).[102] Although bromide **257** was stable enough to allow characterisation, the iodo compound **258** was not and had to be used immediately on isolation.



Scheme 2.8 – Reagents & conditions: a) NBS, PPh_3, Ch_2Cl_2, rt [88%]; b) I_2, PPh_3, imidazole, THF, 0 °C [22%].

Conversion of the triflate **254** into the corresponding boronic ester **259** was accomplished following Levacher's procedure,[103] and Suzuki coupling between **259** and halides **249**, **257** and **258** was subsequently investigated (Scheme 2.9). Variation in base (K_3PO_4, $CsCO_4$, K_2CO_3) and palladium source [$Pd(PPh_3)_4$, $PdCl_2$(dppf)] in combination with halides **249**, **257** or **258** provided no evidence of cross-coupling during the reaction. The possible instability of boronic ester **259** led to its use immediately on

isolation but attempts to confirm the formation of **259** through characterisation failed. The conditions used for the conversion of the triflate could potentially lead to the formation of the corresponding dimer rather than affording boronic ester **259**. Alternative conditions were applied to form the boronic ester — for example variation in catalyst[104] — but the desired material was not isolated. Due to these results the Suzuki approach was abandoned.

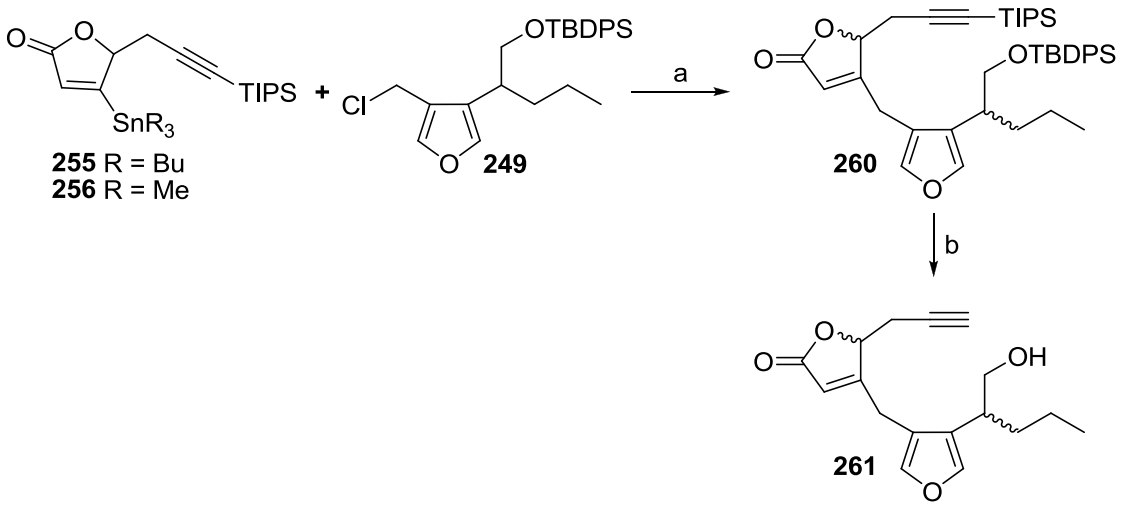


Scheme 2.9 – Reagents & conditions: a) bis(pinacolato)diboron, $Pd(PPh_3)_4$ (5 mol%), Et_3N, dioxane, 80 °C; b) bis(pinacolato)diboron, $(PPh_3)_2PdCl_2$ (5 mol%), PPh_3, K_2CO_3, dioxane, 80 °C.

2.2.3 Stille coupling and efforts towards the Nozaki-Hiyama-Kishi reaction

Stille cross-coupling

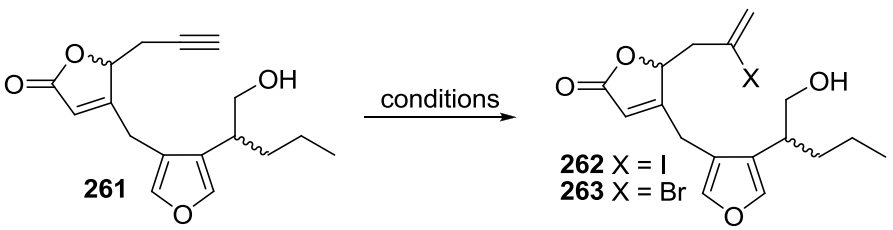
With the unsuccessful application of the Suzuki protocols, the Stille cross-coupling reaction was reconsidered. The modest yield obtained for stannane formation precedes the coupling of the two fragments, so a low yield for this process rather than after coupling is less penalising in terms of the strategy. As shown in Scheme 2.10, the cross-coupling conditions optimised by the Clark group gave compounds **260** with excellent yield when applied to substrate **249**, with no preference with regards to the stannane derivative (**255** or **256**). Coupled products **260** were obtained as an inseparable mixture of the expected diastereoisomers (*dr* 1:1). However, subsequent treatment of the mixture with TBAF to remove both silyl groups led to the decomposition of alkynes **260**, showing the lability of these compounds under basic conditions. This problem was overcome through the addition of acetic acid as a buffer, allowing access to alcohols **261** in 87% yield.[105] Interestingly, the silicon-oxygen bond was cleaved first and was followed by subsequent cleavage of the carbon-silicon bond.



Scheme 2.10 – Reagents & conditions: a) $Pd_2(dba)_3$ (6 mol%), $AsPh_3$ (24 mol%), THF, reflux [82% from **255**, 95% from **256**, *dr* 1:1]; b) *n*-Bu_4NF, AcOH, THF, 0 °C to rt [87%].

Conversion of the terminal alkyne to vinyl halide using direct methods

Conversion of the terminal alkynes **261** into their corresponding vinyl halides was considered next (Table 2.2). Standard conditions, using sodium iodide with trimethylsilyl chloride,[106] were tested (entry 1), leading only to the recovery of starting material. Entries 2 and 3 showed that the use of stronger reducing reagents like iodo- or bromo-9-BBN did not deliver the desired vinyl halides, as no reaction occurred.[107]

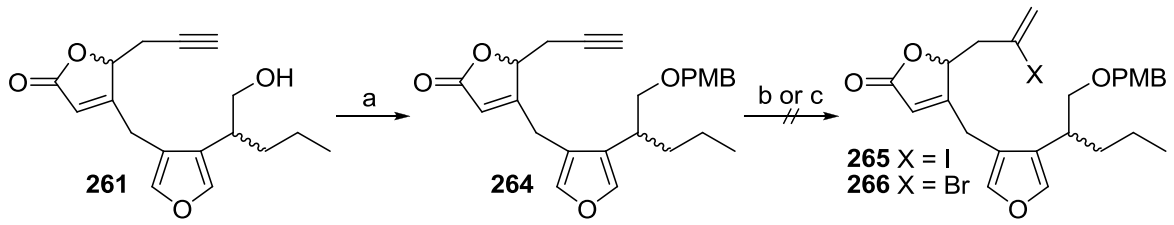


entry	conditions	temperature	result
1	NaI, TMSCl, H_2O, MeCN	rt	no reaction
2	B-iodo-9-BBN (1 M in hexane), AcOH, CH_2Cl_2	−25 °C to rt	no reaction
3	B-bromo-9-BBN, AcOH, CH_2Cl_2	0 °C to rt	no reaction

Table 2.2

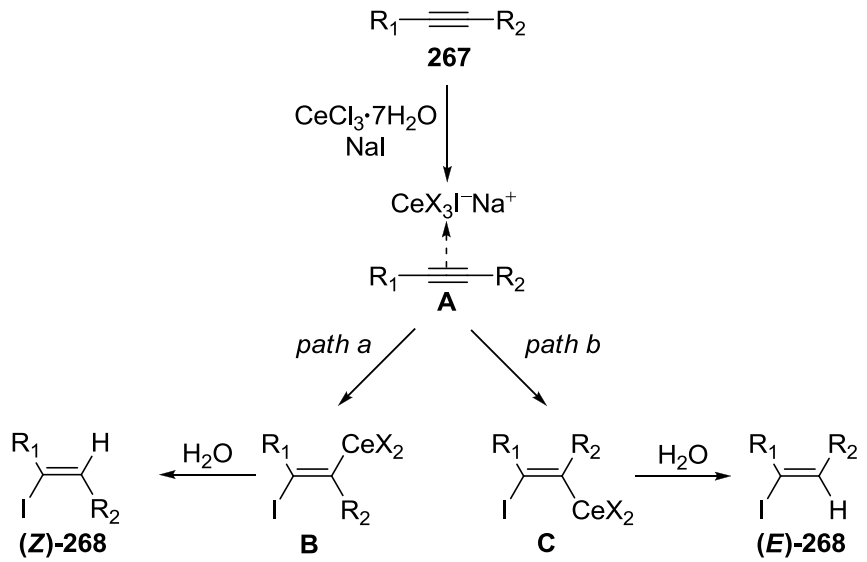
It was believed that the presence of the free hydroxyl group may be impeding the reaction, therefore the diastereoisomeric primary alcohols **261** were protected as the

corresponding PMB-ethers **264** (Scheme 2.11). Once again, the use of sodium hydride and PMBCl[108] led to decomposition (*cf*. Section 2.2.1), but acid-catalysed imidate protection allowed the formation of the desired products **264** in 81% yield.[109] Unfortunately, subsequent iodination or bromination led only to decomposition of **264**.



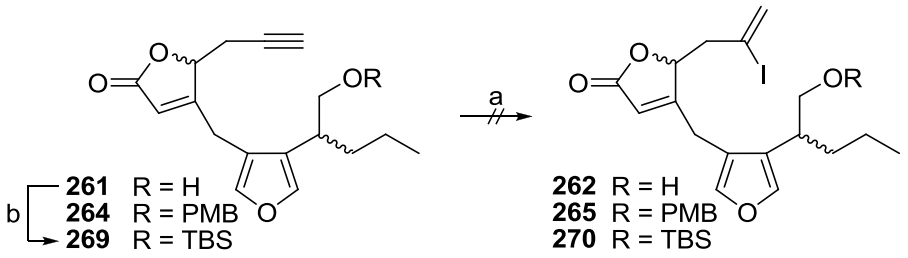
Scheme 2.11 – Reagents & conditions: a) PMBTCA, CSA (5 mol%), CH_2Cl_2, 0 ºC to rt [80%]; b) B-iodo-9-BBN (1 M in hexane), CH_2Cl_2, −20 ºC; c) B-bromo-9-BBN, CH_2Cl_2, 0 ºC.

Promising recent methodology developed by Bartoli and co-workers was then explored.[110] This work demonstrated the regio- and stereocontrolled hydroiodination of alkynes, following the proposed mechanism shown in Scheme 2.12, using sodium iodide and $CeCl_3 \cdot 7H_2O$ as a mild Lewis acid. Three steps are believed to be involved: (*i*) coordination of alkyne **267** to the Ce(III) salt to form complex **A**; (*ii*) nucleophilic attack of the iodide anion to give organocerium intermediates **B** or **C**; (*iii*) protodemetalation by coordinated water molecules to afford diastereoisomeric halo-alkenes **(*Z*)-268** or **(*E*)-268**. *Path a* is believed to occur in polar solvents, such as acetonitrile, where a slow addition of the iodide anion leads to the formation of the thermodynamically more stable *Z* isomer. In non-polar solvents, such as toluene, rapid *syn* addition following *path b* provides the *E* isomer. Interestingly, hydrated $CeCl_3$ is essential for the reaction to proceed; no product was obtained when using anhydrous $CeCl_3$.



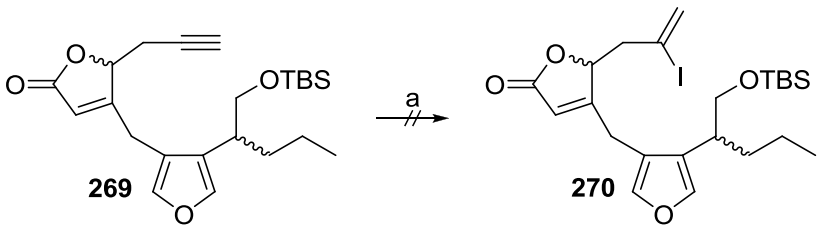
Scheme 2.12[110]

Application of this protocol to the free alkynes **261** was attempted (Scheme 2.13). After reaction a reaction time of eight hours, only starting material was isolated. After 48 hours there was complete consumption of the starting material, but no evidence for the formation of the desired vinyl iodides **262**. Reaction with PMB-ethers **264** gave comparable results, with indications of PMB cleavage. The TBS-ether equivalents **269** were synthesised, but under the reaction conditions the desired products **270** were not isolated.



Scheme 2.13 – Reagents & conditions: a) NaI, $CeCl_3 \cdot 7H_2O$, MeCN, 80 °C; b) TBSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt [54%].

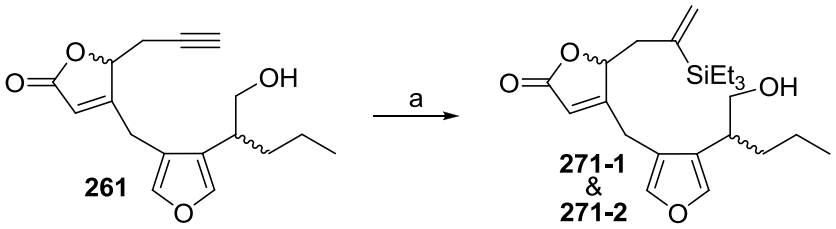
A final attempt to effect direct hydroiodination of the terminal alkynes **269** using a combination of diphenylphosphine oxide and iodine was undertaken (Scheme 2.14).[111] The substrates were submitted to the illustrated reaction conditions but were recovered unreacted. The low dilution conditions required for this reaction (1.2 M and 0.4 M) could not be reproduced on the test reactions (0.05 M), which is believed to be responsible for the failure of the reaction.



Scheme 2.14 – Reagents & conditions: a) $Ph_2P(O)H$, I_2, $CHCl_3$, rt.

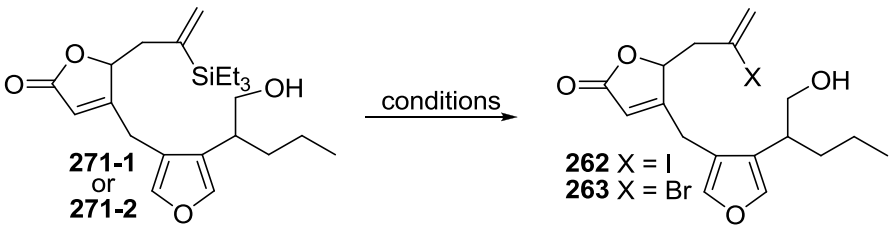
Conversion of the terminal alkyne into a vinyl halide through metal-catalysed silylation reaction

In view of the results described before, an alternative route was sought. Methodology developed by Trost[112] for the regioselective conversion of a terminal alkyne into a vinyl silane was applied to substrates **261** (Scheme 2.15). This ruthenium-catalysed hydrosilylation proceeded quickly to give only the desired proximal silanes **271-1** and **271-2** as a separable mixture of the two diastereoisomers in good yield.



Scheme 2.15 – Reagents & conditions: a) Et_3SiH, $Cp^*Ru(MeCN)_3PF_6$ (5 mol%), CH_2Cl_2, 0 ºC to rt [81%, *dr* 1:1].

Various conditions were tested for the silicon-halogen exchange of vinyl silane **271-1** or **271-2** (Table 2.3). The use of iodine, in the presence or absence of silver tetrafluoroborate led only to the recovery of the starting material (entries 1 and 2).[113] Bromine proved too reactive for the substrate, resulting in complete decomposition (entry 3).[114] Reactions using NIS (entries 4 and 5) were sluggish, with a mixture of starting material and other unidentified side-products obtained.[115] Finally iodine monochloride showed similar reactivity to bromine, leading to substrate decomposition with no traces of vinyl halide formation (entry 6).[116]

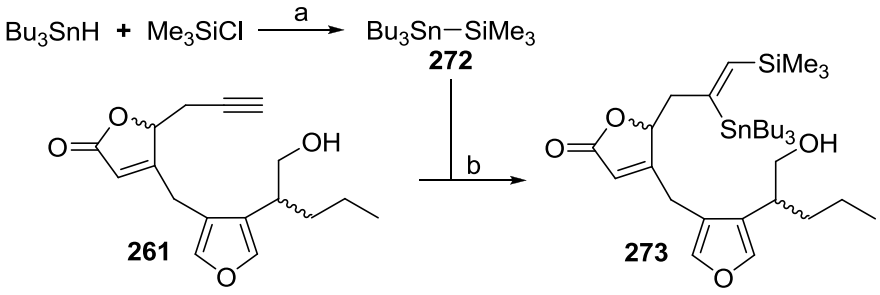


entry	substrate	conditions	temperature	result
1	**271-1**	I_2, CH_2Cl_2	0 °C to rt	no reaction
2	**271-1**	I_2, $AgBF_4$, CH_2Cl_2	0 °C to rt	no reaction
3	**271-2**	Br_2, CH_2Cl_2	−78 °C	decomposition
4	**271-1**	NIS, CH_2Cl_2	rt	decomposition
5	**271-1**	NIS, MeCN/THF	rt	decomposition
6	**271-2**	ICl, CH_2Cl_2, *n*-Bu_4NF, AcOH	−78 °C	decomposition

Table 2.3

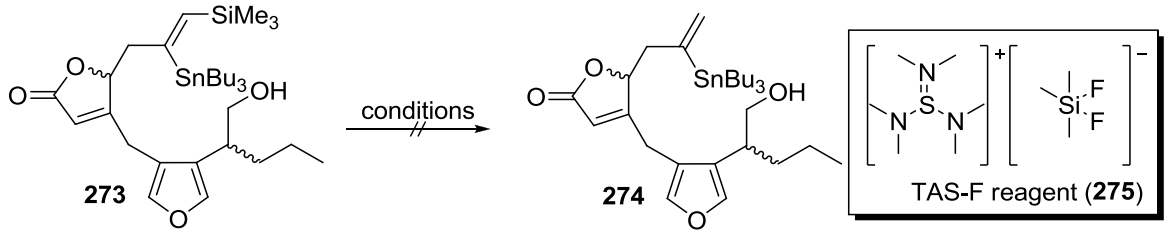
Successful conversion of the terminal alkyne to vinyl halide using tin chemistry

Considering the disappointing results obtained until this point, an alternative method of alkyne conversion to alkenyl halide was required. During his work towards the total synthesis of several amphidinolides, Fürstner reported the use of a regioselective palladium-catalysed silylstannation of a terminal alkyne with yields varying from 79 to 85%.[117] The main drawback of this approach would be the requirement for subsequent TMS group removal, which would add an additional step to the synthesis. Trimethylsilyl tri-*n*-butylstannane **272** was prepared efficiently in one step and in quantitative yield,[118] and the application of this reagent to alkynes **261**, under Paige's protocol,[119] afforded silylstannanes **273** in good yield (Scheme 2.16). From a theoretical study of the mechanism of the palladium-catalysed silylstannation reaction carried out by the group of Ito and Nakatsuji,[120] the regioselective outcome of the reaction could be the result of the insertion of the terminal alkyne into the Pd—Sn bond, due to the larger electrophilicity of Sn compared to Si, and the steric repulsion between the triphenylphosphine ligands in the palladium(II) complex and the substituents of the alkyne group.



Scheme 2.16 – Reagents & conditions: a) *i*-PrNH, *n*-BuLi, THF, −78 ºC to rt [quant.]; b) $Pd(PPh_3)_4$ (5 mol%), THF, 70 ºC [75 to 83%, *dr* 1:1].

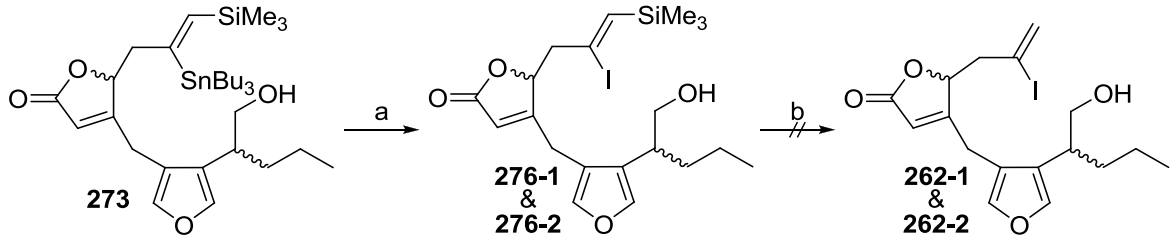
The subsequent desilylation using TBAF was attempted, with the addition of acetic acid to buffer the reaction (entry 1, Table 2.4). Unsurprisingly, no reaction occurred at rt or at reflux in THF. Substituting DMSO for THF and increasing the temperature of the reaction mixture to 80 ºC, which are the conditions reported by Fürstner and Paquette,[117,121] led to the recovery of the starting material after two hours (entry 2). It is known that the reactivity of TBAF is generally reduced when buffered with acetic acid, and so the reaction time was progressively increased. Unfortunately, heating the reaction mixture at 80 ºC for one day resulted in the complete decomposition of the starting materials **273** with no sign of the formation of vinyl stannanes **274**. Subsequently, other fluoride sources were tested. TBAT (n-$Bu_4NSiPh_3F_2$), which is known to be less basic than TBAF, was also tested with the same outcome (entry 3).[122] The use of TAS-F reagent (**275**) was investigated next, but complete product decomposition was observed when the reaction was conducted at 0 ºC (entry 4).[123] Finally, hydrogen fluoride buffered with pyridine resulted only in recovery of the starting materials **273** (entry 5).[124] It has been reported that *p*-TSA can selectively remove a TMS group in the presence of trimethylgermanium,[125] but exposure of **273** to *p*-TSA in acetonitrile or dichloromethane failed to deliver the desired product (entries 6 and 7).



entry	conditions	temperature	result
1	*n*-Bu_4NF, AcOH, THF	rt to reflux	no reaction
2	*n*-Bu_4NF, AcOH, DMSO	80 °C	decomposition
3	TBAT, THF	rt to reflux	no reaction
4	TAS-F, DMF	0 °C	decomposition
5	HF·pyridine, THF—pyridine	0 °C to rt	no reaction
6	*p*-TSA, MeCN	rt	decomposition
7	*p*-TSA, CH_2Cl_2	rt	decomposition

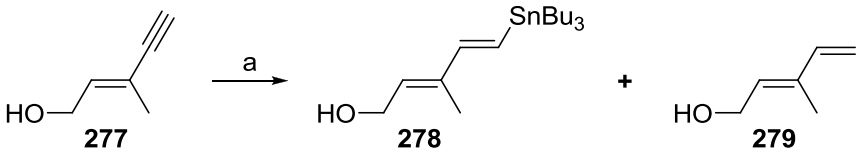
Table 2.4

It was next decided to convert the vinyl stannanes **273** into the corresponding vinyl iodides **276** (Scheme 2.17).[119] The reaction was complete in 20 minutes and the excess iodine was immediately quenched after complete consumption of the starting material to avoid subsequent iododesilylation. At this point, the diastereoisomers **276-1** and **276-2** could be separated fully. TMS removal from **276-1** and **276-2** using buffered TBAF proved unsuccessful, leading only to double elimination and recovery of the terminal alkynes **261**. Unable to remove the TMS group at this stage, it was hoped that the cleavage of the carbon—silicon bond would be possible after cyclisation.



Scheme 2.17 – Reagents & conditions: a) I_2, CH_2Cl_2, 0 °C [95%, *dr* 1:1]; b) *n*-Bu_4NF, AcOH, THF [recovery of **261**].

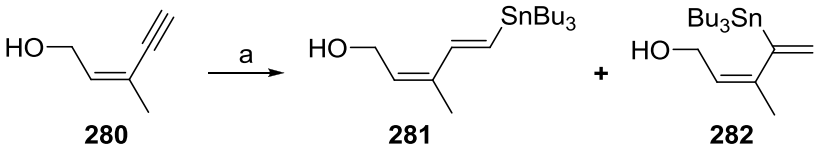
Now that the vinyl iodides **276-1** and **276-2** had been obtained, one step was remaining before the key NHK cyclisation reaction. However, during the previously described struggle to achieve the desilylation of **273** (Table 2.4), another interesting approach inspired by the research group of Pancrazi and Prunet was found.[126] Unexpected outcomes during their work towards the total synthesis of Taxol[126a] led them to further investigate the hydrostannylation of enyne systems using several methods.[126b] The palladium-catalysed hydrostannylation of enynes **277** and **280** was of particular interest (Scheme 2.18 and 2.19).



277 **278** **279**

Scheme 2.18 – Reagents & conditions: a) Bu_3SnH, $PdCl_2(PPh_3)_2$ (2 mol%), THF, 20 ºC [60% (**278**), 40% (**279**)].[126]

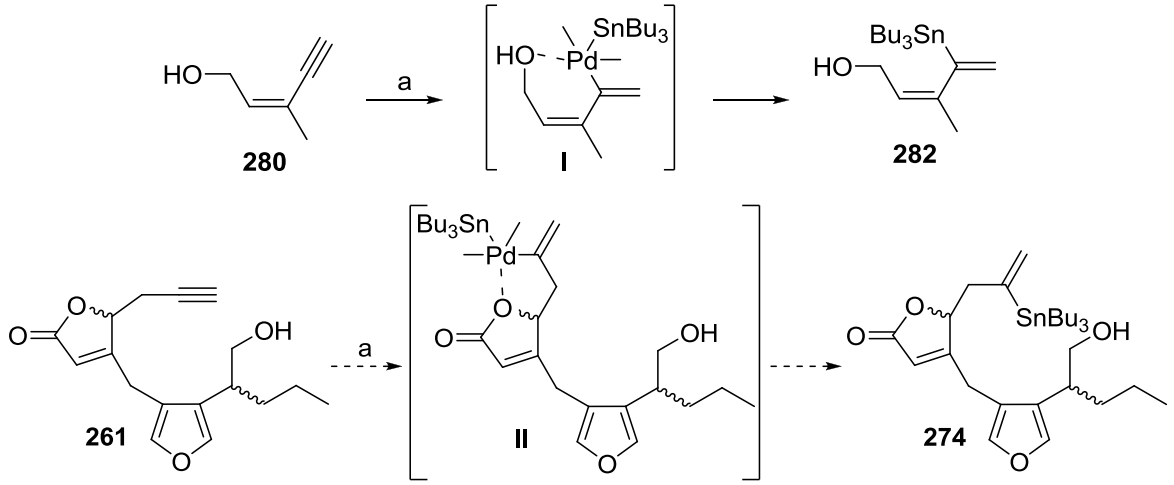
Reaction of (*E*)-enyne **277** with tributyltin hydride and palladium(II) led to the expected formation of distal stannane **278**, along with the destannylated diene derivative **279**, in a 3:2 ratio (Scheme 2.18). Interestingly with (*Z*)-enyne **280**, both distal and proximal stannane **281** and **282** were obtained in a 12:88 ratio in favour of the proximal regioisomer **282** (Scheme 2.19).



280 **281** **282**

Scheme 2.19 – Reagents & conditions: a) Bu_3SnH, $PdCl_2(PPh_3)_2$ (2 mol%), THF, 20 ºC [6% (**281**), 48% (**282**)].[126]

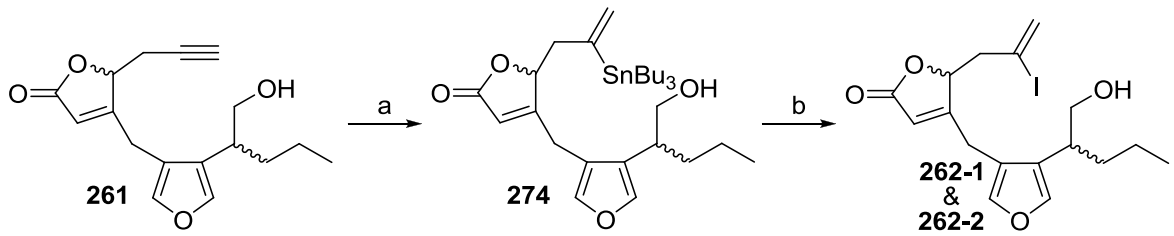
The proposed explanation for this regioselective outcome relies on the stabilisation of the intermediate palladium complex by the hydroxyl group on (*Z*)-enyne **280**, resulting in the preferential formation of proximal dienylstannane **282** (Scheme 2.20). For (*E*)-enyne **277** this stabilisation cannot occur, thus only distal stannane **278** was formed.



Scheme 2.20 – Reagents & conditions: a) Bu_3SnH, $PdCl_2(PPh_3)_2$ (2 mol%), THF, 20 °C.

It was proposed that an equivalent stabilising effect could be induced by the β-unsaturated lactone moiety of **261**, leading to the preferential formation of **274** (Scheme 2.20).

Pleasingly, when alkynes **261** were subjected to the palladium-catalysed hydrostannylation conditions (Scheme 2.21), it was clear, based on the analysis of the proton NMR of the crude mixture, that the major products formed during the reaction were the proximal vinyl stannanes **274** along with their distal regioisomers (3:1 ratio). Most of the undesired distal regioisomers could be removed by column chromatography. The subsequent metal/halogen exchange on the remaining mixture afforded vinyl iodides **262-1** and **262-2** as a separable mixture of the two diastereoisomers, in 62% yield over both steps. Following formation of the vinyl iodides **262** and **276** (*cf*. Scheme 2.17), the key NHK cyclisation reaction could be investigated.



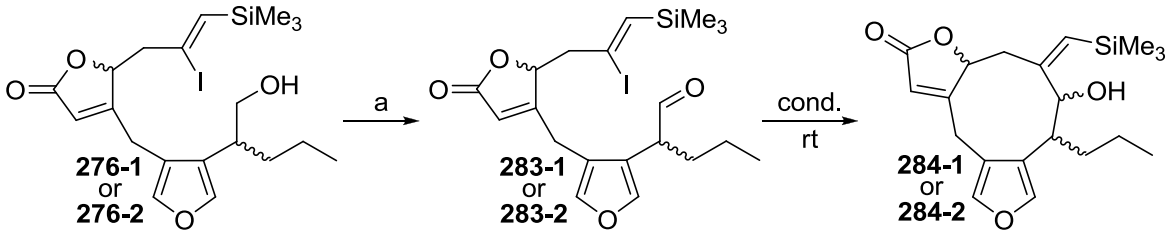
Scheme 2.21 – Reagents & conditions: a) Bu_3SnH, $Pd(PPh_3)_4$ (5 mol%), THF, rt [*rr* (proximal—distal) 3:1]; b) I_2, CH_2Cl_2, 0 °C [62% (2 steps), *dr* 1:1].

2.2.4 Nozaki-Hiyama-Kishi cyclisation

First approach of the NHK cyclisation

There are numerous examples of NHK reactions in the literature, both inter- and intramolecular, in which the variation of reaction conditions is expansive.[97,127] Reagents, chromium salts purity, catalyst loadings, nature of the solvent, concentration, the use of additives, work-up or time of reaction appear to be extremely substrate dependant. Initial investigations of the reaction conditions were conducted using the vinyl iodides **276-1** and **276-2**, bearing the TMS group (Table 2.5). At this late stage of the synthesis, the reactions were performed on a small scale, which made the isolation of products difficult. Aldehydes **283-1** and **283-2** were obtained using DMP oxidation of **276-1** and **276-2**, respectively. After a rapid purification through a plug of silica, the two aldehydes were subjected to the cyclisation conditions.

Entries 1 to 3 in Table 2.5 were adapted from the conditions optimised by Corminboeuf *et al*. during their total syntheses of the briarellins.[97] For both diastereoisomers **276-1** and **276-2**, the reaction was sluggish and the products were obtained in poor yields over the two steps. Each diastereoisomer seemed to form one product selectively and the nature of the diastereoisomer used had no effect on the isolated yield of the reaction.
In entry 3, the concentration was increased to 0.005 M but no product was isolated from this reaction. It seemed unrealistic that a minor change in the dilution of the reaction would have such a drastic effect on the yield of the reaction. The inferior quality of the batch of chromium(II) dichloride used for this reaction might offer a more reasonable explanation for the reaction's outcome, further demonstrating the importance of keeping $CrCl_2$ thoroughly anhydrous and under argon.
The loadings of the two metals were increased with no improvement on the yield of the reaction (entries 4 and 5). Entry 6 was inspired by the conditions used by Yadav in his total synthesis of amphidinolactone A.[127a] When a stoichiometric amount of $NiCl_2$ was used and the reaction mixture was seven times more concentrated than in the previous entries, the isolated yield in our case was lower. The use of DMS as an additive for intramolecular NHK reactions is widespread in the literature with no rational explanation for its actual effect in the cyclisation. Entries 6 and 7 showed that its absence was not an important factor for our substrate. Changing the solvent system to DMF[127b,127c] resulted in a decrease in the yield to 11% (entry 8). Finally, in the absence of $NiCl_2$ and using THF as solvent no products were isolated from the reaction (entry 9).[127d,127e]



entry	substrate used	$CrCl_2$[a] (equiv)	$NiCl_2$ (equiv)	solvent[b-d]	dilution (M)	reaction time	result[e,f]
1	**276-1**	10	0.1	DMSO—DMS	0.0025	3 d	31%
2	**276-2**	10	0.1	DMSO—DMS	0.0025	3 d	28%
3	**276-2**	10	0.1	DMSO—DMS	0.005	3 d	—
4	**276-2**	20	0.2	DMSO—DMS	0.0025	1.5 d	27%
5	**276-1**	30	0.3	DMSO—DMS	0.0025	3 d	26%
6	**276-1**	20	2	DMSO	0.018	1.5 d	14%
7	**276-2**	7.6	0.06	DMSO	0.005	3 d	22%
8	**276-2**	10	0.01	DMF	0.01	3 d	11%
9	**276-2**	20	0	THF	0.001	3 d	—

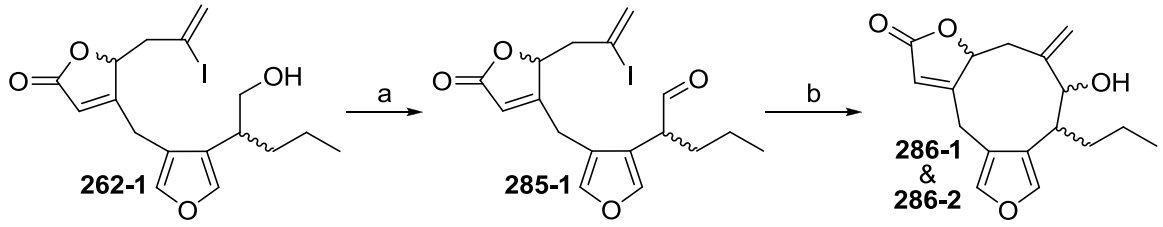
Table 2.5 – Reagents & conditions: a) DMP, CH_2Cl_2, 0 ºC to rt; [a]$CrCl_2$ was obtained from Strem Chemicals, inc. (99%) and carefully stored under argon; [b]DMSO was degassed using 3 freeze-thaw cycles; [c]DMS added as additive in a 100:1 DMSO—DMS ratio; [d]molecular sieves (4 Å) were added to the reaction in THF (entry 9); [e]isolated yield over two steps; [f]for entries 3 and 9, no products were isolated.

For most of the reactions, traces of other products could be detected, possibly dimers. Unfortunately, the low yields obtained combined with the small scale under which the reactions were performed prevented full characterisation of the reaction products. Following Kishi's report of possible improvements to the NHK reaction,[128] work-up protocols with saturated aqueous NH_4Cl or with a solution of potassium (D,L)-serinate were tested with no effect on the isolated yield obtained.

In summary, the first approach, although not as successful as expected, provided the cyclononanone core in 11 to 31% yield. It is proposed that this low yield is due to the presence of the bulky TMS group, impeding the cyclisation reaction. There is actually no literature precedent of a NHK cyclisation using a substrate bearing a trisubstituted (*Z*)-alkenyl halide.

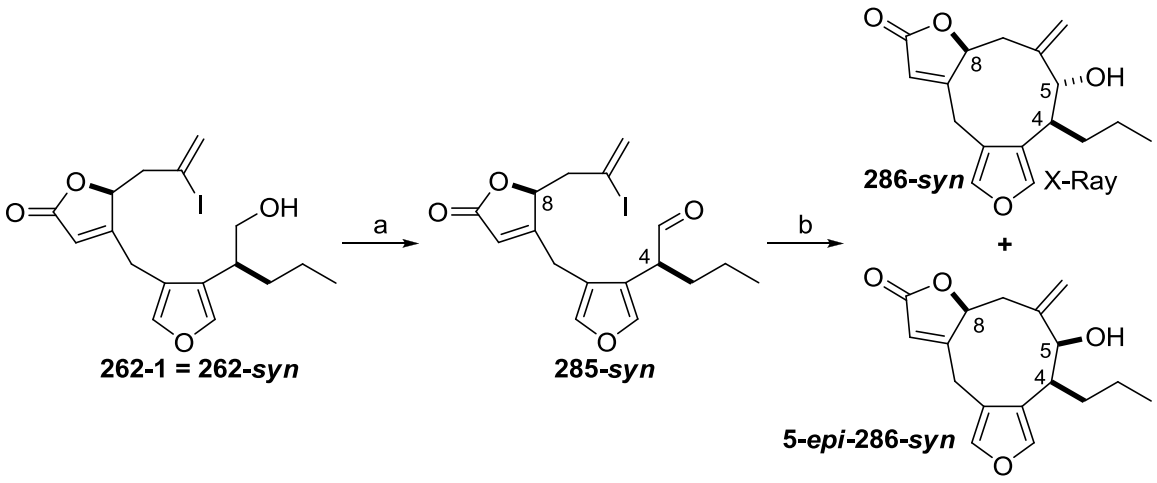
Second approach of the NHK reaction

After the relatively frustrating first study concerning the key reaction of the project, it was anticipated that the cyclisation reaction would be more successful with vinyl iodides **262-1** and **262-2**, not bearing the bulky TMS group. A first attempt was carried out on small scale with **262-1** (Scheme 2.22). The conditions previously demonstrated to be optimal (*cf*. Table 2.5, entries 1,2) were applied to aldehyde **285-1**, previously obtained from Dess-Martin oxidation of alcohol **262-1**. After purification, two separable products **286-1** and **286-2** were obtained in a 1:1.4 ratio. These two products almost certainly corresponded to the two possible diastereoisomeric products expected from the cyclisation. Further investigations of the reaction were carried out, leading to the gratifying results highlighted in Table 2.6.



Scheme 2.22 – Reagents & conditions: a) DMP, CH_2Cl_2, 0 °C to rt; b) $CrCl_2$ (10 equiv), $NiCl_2$ (10 mol%), DMSO—DMS (100:1), rt, 5 d [45% (2 steps), *dr* 1:1.4].

On scales of around 50 mg and higher reaction concentration, the products could be separated to give the two diastereoisomers in a 2.5:1 ratio, with a combined 45% yield over the two steps (Table 6, entry 1). Pleasingly, well-formed single crystals were obtained from the major isomer and X-Ray crystallography confirmed the relationship between C-4, C-5 and C-8 stereocentres (Figure 2.1). Starting from **262-*syn***, the major product **286-*syn*** of the NHK reaction bore the natural configuration at C-5. A higher concentration did not have a negative effect on the outcome of the reaction, and heating the reaction at 50 °C overnight improved the rate of the reaction and delivered an increased yield of 75% (entry 2).[98] However, using the same reaction conditions but heating the reaction at 50 °C for three days had a modest influence on the ratio between **286-*syn*** and **5-*epi*-286-*syn*** (entry 3). The 1:1 ratio obtained showed that the temperature of the reaction was an important factor on the selectivity of the reaction.



entry	concentration	reaction time, temperature	yield[a] ratio (**286-*syn*—5-*epi*-286-*syn***)[b]
1	0.007 M	3 d, rt	45% 2.5:1
2	0.01 M	1 d, rt then 15 h, 50 °C	75% 3.5:1 *(2.4:1)*
3	0.01 M	3 d, 50 °C	52% *ca* 1:1

Table 2.6 – Reagents & conditions: a) DMP, CH_2Cl_2, 0 °C to rt; b) $CrCl_2$ (10 equiv), $NiCl_2$ (10 mol%), DMSO; [a]isolated yield over two steps and sum of the two diastereoisomers obtained; [b]isolated ratio after purification, based on crude ^1H NMR analysis in brackets.

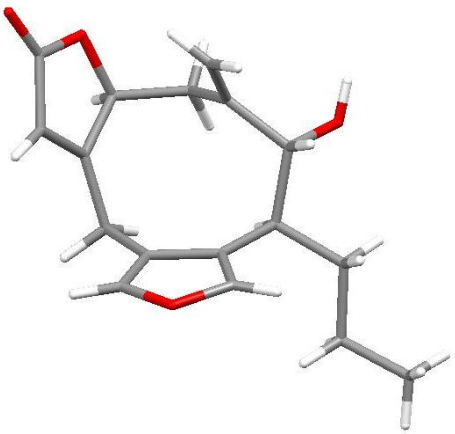
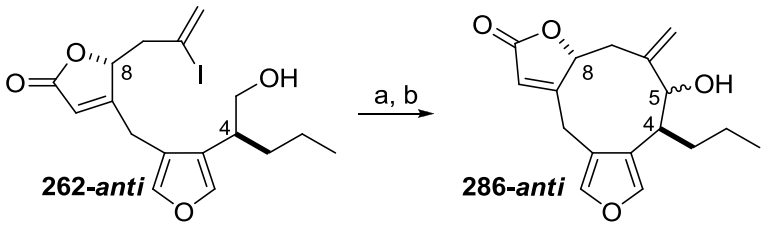


Figure 2.1 – X-Ray crystallography of the NHK product **286-*syn***.

The confirmation of the relative configuration of **286-*syn*** by X-Ray crystallography also determined that the relationship between the two stereocentres C-4 and C-8 of the aldehyde **285-*syn***, the precursor to the cyclisation, was not that found in the natural product. Alcohol **262-*anti*** bearing the natural configuration on C-4 and C-8 was oxidised

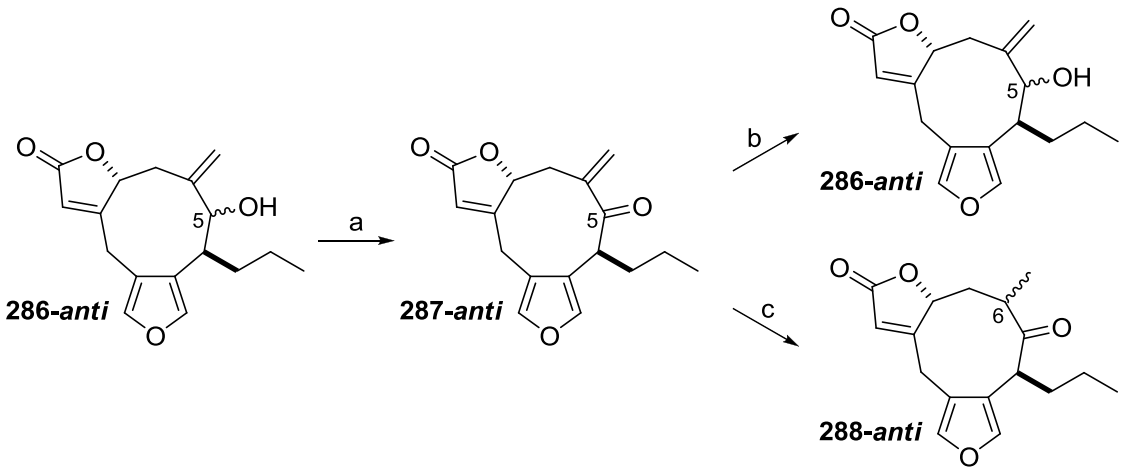
using DMP and subjected to the NHK cyclisation conditions, affording **286-*anti*** in 50% yield and 2.4:1 *dr* (Scheme 2.23). Unfortunately, despite a good overall yield the two diastereoisomers could not be separated using column chromatography. It was therefore not possible to confirm the configuration of the major diastereoisomer.



Scheme 2.23 – Reagents & conditions: a) DMP, CH_2Cl_2, 0 °C to rt; b) $CrCl_2$ (10 equiv), $NiCl_2$ (10 mol%), DMSO, 50 °C, 3 d [50% (2 steps), *dr* 2.4:1].

Oxidation — reduction sequence

In an attempt to improve the diastereoisomeric ratio obtained from the NHK reaction, a post-cyclisation oxidation—reduction sequence was undertaken on the mixture **286-*anti*** (Scheme 2.24). A similar study was published by the group of Fujiwara for the synthesis of FGHI ring system of ciguatoxins.[129] Oxidation of alcohols **286-*anti*** using DMP, then reduction under Luche conditions at −78 °C altered the diastereoisomeric ratio between the two diastereoisomers, from 2.4:1 to 3:1. When enone **287-*anti*** was reduced using L-selectride and $CeCl_3$, [1,4]-reduction occurred, yielding **288-*anti*** as two separable diastereoisomers with a ratio of 1:1. Other reduction conditions were not studied owing to a lack of material and time constraints.



Scheme 2.24 – Reagents & conditions: a) DMP, CH_2Cl_2, 0 °C to rt; b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C [quant. (2 steps), *dr* 1:3]; c) L-Selectride, $CeCl_3$, THF, −78 °C [68% (2 steps), *dr* 1.3:1].

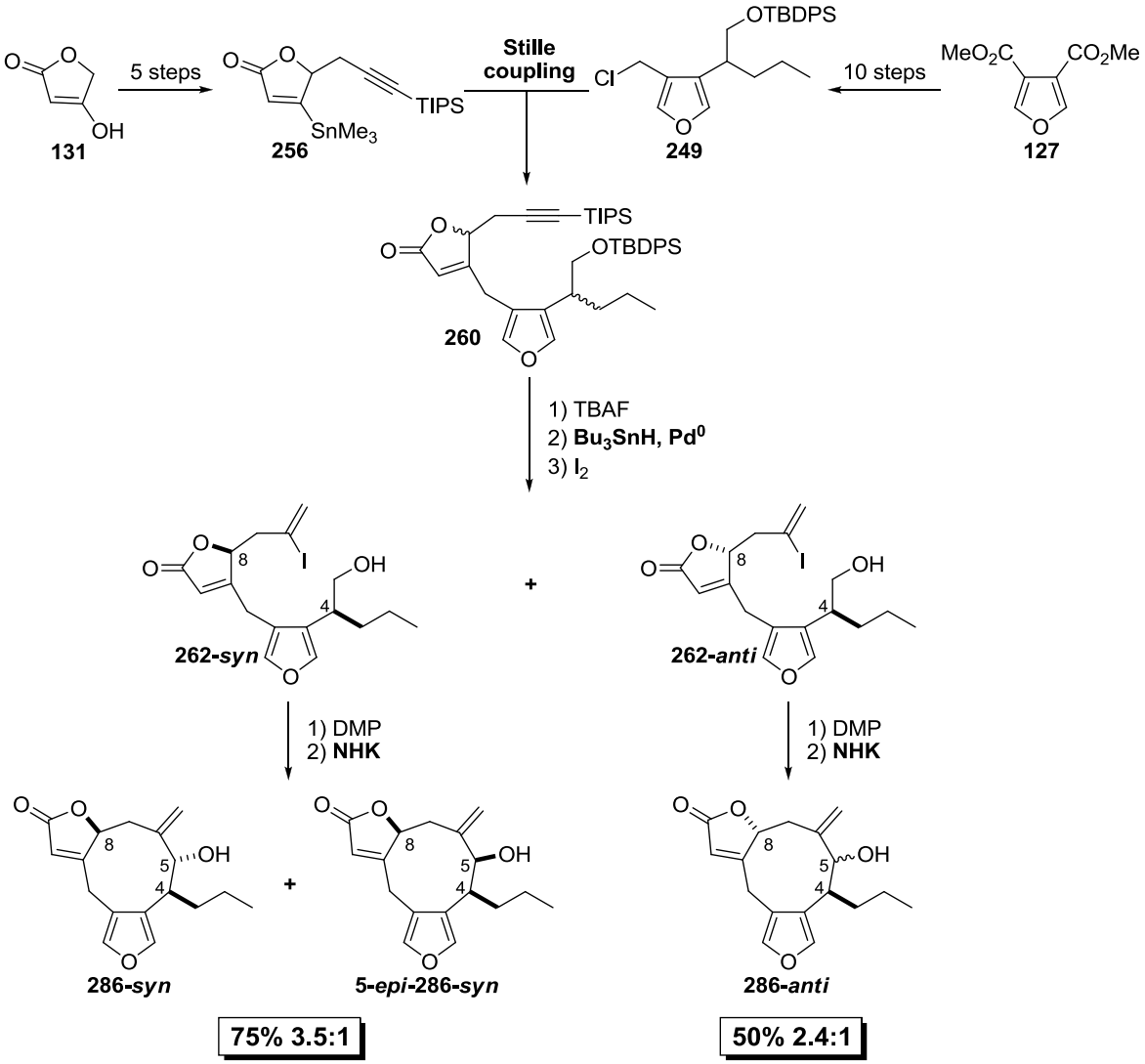
2.2.5 Approach using racemic material — key elements

In summary, the two racemic fragments were prepared and coupled using a Stille cross-coupling reaction (Scheme 2.25). The conversion of the alkyne into the corresponding vinyl iodide was accomplished using a regioselective palladium-catalysed hydrostannylation reaction. The study of the intramolecular NHK reaction on diastereoisomers **262-*syn*** and **262-*anti*** gave important insights into the reaction.

(*1*) Formation of the nine-membered ring was possible from substrates **262-*syn*** and **262-*anti***, which implied that the relationship between C-4 and C-8 was not important for the cyclisation reaction to proceed.

(*2*) The modest diastereoisomeric ratios obtained for the new C-5 stereocentre formed during the intramolecular NHK reaction suggested that there was little facial selectivity during the nucleophilic attack of the organochromium species onto the aldehyde, which was confirmed by the loss of selectivity for the NHK reaction conducted at 50 °C. Consequently, the four possible diastereoisomers obtained from the NHK cyclisation on the aldehyde of **262-*syn*** or **262-*anti*** could potentially be used to make analogues of hydroxycornexistins. More importantly, compounds possessing the natural configuration at C-5 were obtained using the NHK cyclisation reaction. This was not the case with the previous RCM strategy, and with the use of an appropriate chiral ligand, the predominant formation of the natural C-5 stereocentre might be achieved using the NHK reaction.

Finally, the oxidation—reduction sequence on the mixture of products **286-*anti*** showed that the two faces of the carbonyl group in the nine-membered ring were still accessible to reducing agents (Scheme 2.24), which was not the case with the substrates made previously in the group (*cf.* Section 1.4.4).



Scheme 2.25

At this point of the synthesis, with promising results having been obtained from the NHK cyclisation reaction, it was decided to investigate an enantioselective synthesis of hydroxycornexistin.

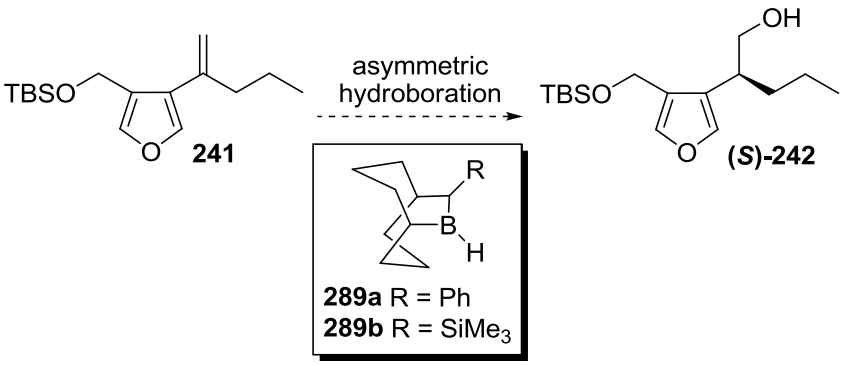
2.3 An approach to the enantioselective synthesis of hydroxycornexistin

2.3.1 Chloride fragment synthesis

Study of the asymmetric approaches for the chloride fragment

The formation of the chloride fragment **249** was initially performed to give a racemate, and enough material was synthesised to test the NHK reaction. However, an asymmetric synthesis using the same route was unlikely to deliver the desired fragment in a highly enantioselective manner, so several routes were considered.

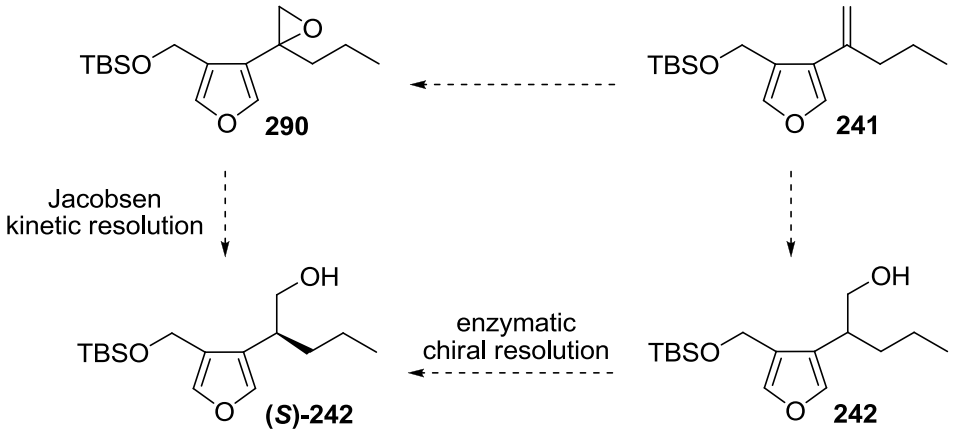
As highlighted by Aggarwal, achieving high enantioselectivity for the hydroboration of a 1,1-disubstituted alkene remains a challenge (*e.g.* **241**, Scheme 2.26).[130] Only Soderquist's organoboron reagent **289** gives enantioselectivities up to 92% for suitable systems. Unfortunately, for a similar substrate bearing a phenyl group on one side of the double bond and a methyl group on the other side, the enantiomeric excess drops to 78%.[131] It is unlikely that this methodology would afford primary alcohol (***S*)-242** with acceptable enantiopurity.



Scheme 2.26

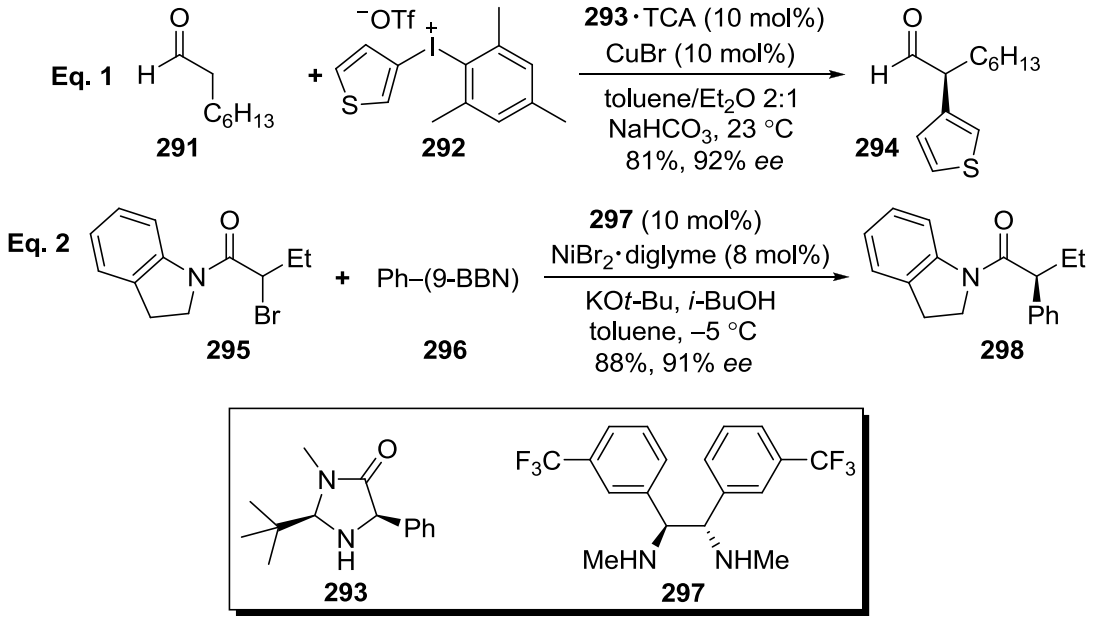
Enzymatic resolution using esterase or lipase-catalysed trans-esterification of primary alcohol **242** was also considered, but no examples could be found which matched our substrate (Scheme 2.27).[132] Acylation of **242** with (−)-menthyl chloroformate[133] to form the corresponding diasteroisomeric menthyl carbonates was considered, but the two diastereoisomers obtained could not be separated by column chromatography or recrystallisation. Conversion of the 1,1-disubstituted alkene **241** into the epoxide **290**,

followed by a kinetic resolution using Jacobsen's salen complex **211** (Figure 1.11) seemed unlikely to be an efficient process due to the presumed instability of an epoxide conjugated with the furan ring.[134]



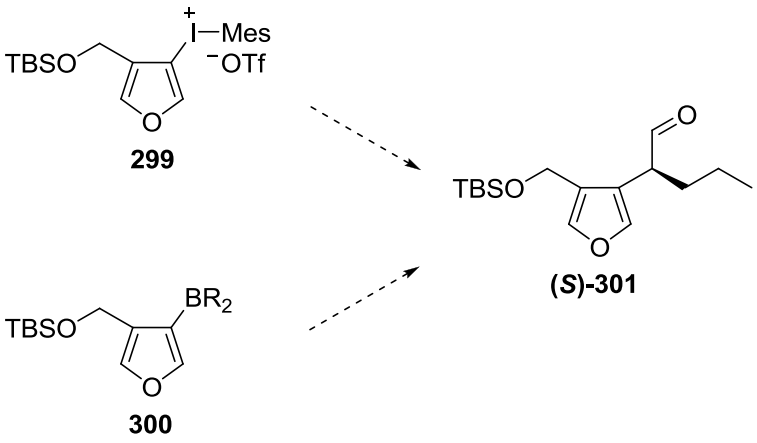
Scheme 2.27

An organocatalytic approach to the synthesis of the fragment had already been attempted in the group without success (*cf*. Section 1.4.3). Two recent reports from MacMillan[135] and Fu[136] were potentially appropriate for the asymmetric synthesis of the chloride fragment (Scheme 2.28). MacMillan obtained excellent results for the enantioselective α-arylation of aldehydes, using diaryliodonium salts, the organocatalyst **293** and copper bromide (Eq. 1, Scheme 2.28). The approach chosen by Fu proceeded through an asymmetric Suzuki cross-coupling, using racemic α-haloamides. It was found that a sub-stoichiometric amount of $NiBr_2$·diglyme combined with the chiral ligand **297** catalysed the reaction and delivered good isolated yields of the products with high enantioselectivities (Eq. 2, Scheme 2.28).



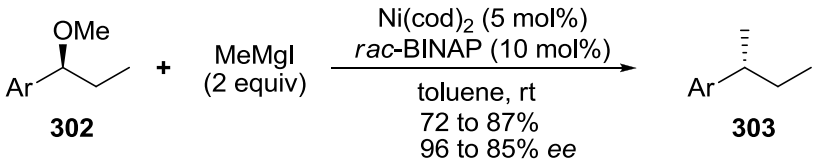
Scheme 2.28[135,136]

Applying these methodologies to the synthesis of **(*S*)-301** was attractive but the synthesis of the required starting materials **299** and **300** would be complicated (Scheme 2.29).



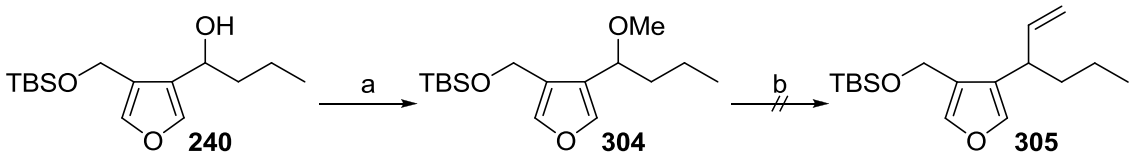
Scheme 2.29

Finally, methodology developed by Jarvo and co-workers seemed appropriate for our substrate (Scheme 2.30).[137] The published work described a stereospecific nickel-catalysed substitution reaction using a Grignard reagent, with inversion of configuration at the α-position of an aryl group.



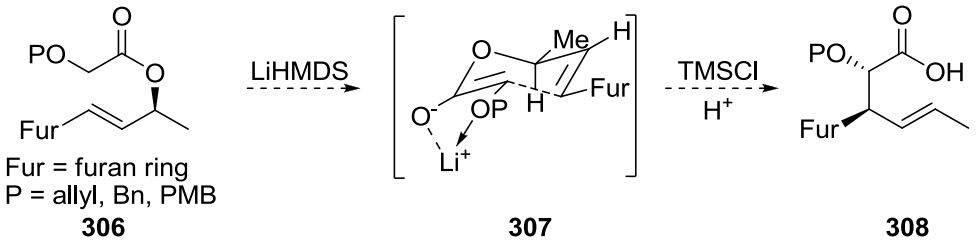
Scheme 2.30[137]

It was thought that the same methodology could be adapted for our synthesis, starting from the enantiopure version of methyl-ether **304** and using vinyl magnesium bromide instead of methyl magnesium iodide as Grignard nucleophile (Scheme 2.31). The starting material **304** was easily prepared as a racemate from alcohol **240**. Unfortunately, when applying the reported reaction conditions, no reaction occurred and only starting material was recovered. A few details are worth mentioning. The Grignard reagent used was commercially sourced and not freshly prepared, due to the difficulties associated with handling vinyl bromide. Furthermore, the protocol describes the use of a glove-box for the reaction. Without access to a glove-box, it was extremely difficult in our hands to avoid decomposition of the nickel complex, even with very careful handling. With the absence of any evidence for the formation of the new product, and the high instability of the metal source, no further efforts were made and an alternative approach was sought.



Scheme 2.31 – Reagents & conditions: a) MeI, NaH, THF, 0 °C to rt [95%]; b) vinyl magnesium bromide (1 M in THF), $Ni(cod)_2$ (5 mol%), (*S*)-BINAP (10 mol%), toluene, rt [recovery of **304**].

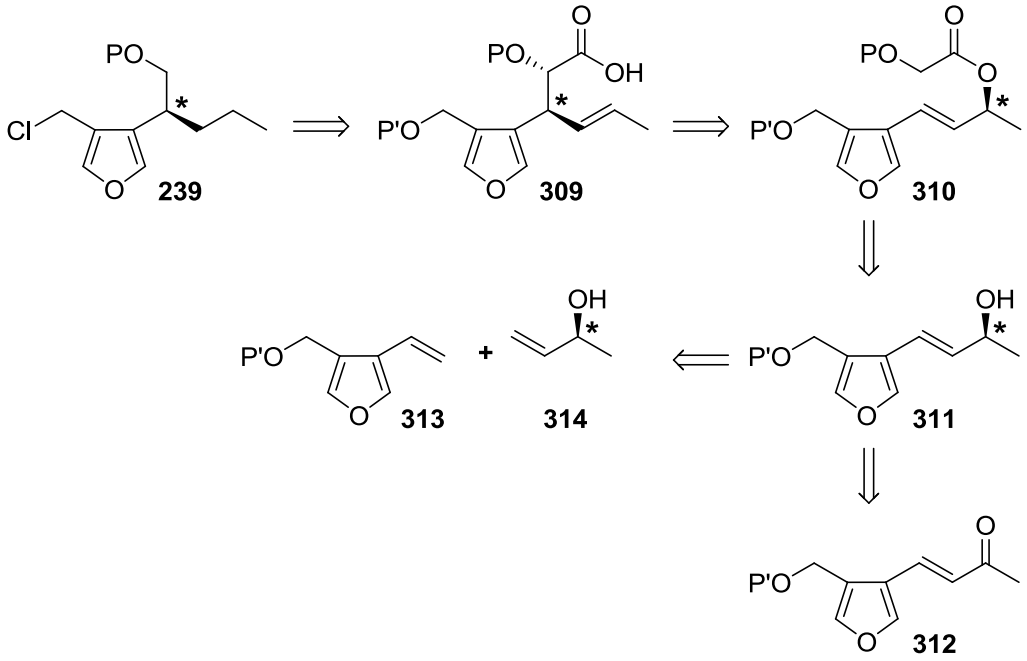
No suitable direct asymmetric approach to the synthesis of the chloride fragment seemed appropriate, so a new route was designed, involving the [3,3]-sigmatropic rearrangement reaction detailed in Scheme 2.32. From the allylic glycolate **306**, the unsaturated acid should be obtained as a single diastereoisomer by 1,3-chirality transfer through a chelation-controlled chair-like transition state, following the Buke-Fujisawa-Kallmerten modification of the Ireland-Claisen rearrangement.[138,139]



306 **307** **308**

Scheme 2.32

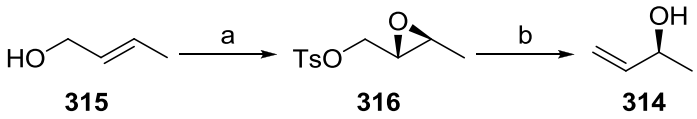
With this in mind, the new approach for the chloride fragment would begin with the addition of a carbonyl functional group to chloride **239**, leading to acid **309** (Scheme 2.33). The acid would be obtained using the [3,3]-sigmatropic rearrangement of allylic ester **310**. The ester would be derived from enantiopure allylic alcohol **311**. For the synthesis of **311**, two options could be envisaged; either an asymmetric reduction of enone **312**, or a cross metathesis reaction between vinyl furan **313** and allylic alcohol **314**. CBS-reduction[140] has been reported on a similar substrate, bearing a phenyl group instead of the furan unit, demonstrating the potential for good yields and high enantioselectivities in the reduction reaction.[141] However, the use of CBS reagent at an early stage in the synthesis seemed costly, thus the cross-coupling reaction was favoured.



Scheme 2.33

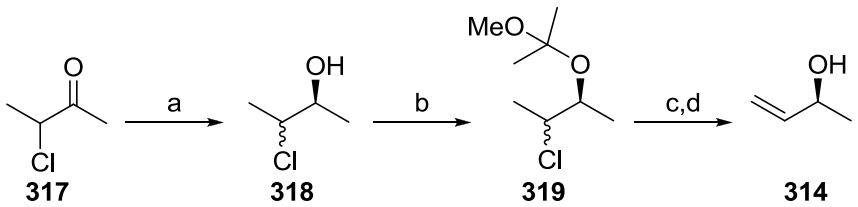
Asymmetric synthesis of allylic alcohol 314

Four main methods have been published for the synthesis of (*S*)-(+)-but-3-en-2-ol **314**. The first method used a Sharpless catalytic asymmetric epoxidation of crotyl alcohol **315** to afford the epoxy toluene-*p*-sulphonate **316** in moderate yield (Scheme 2.34).[142] Subsequent treatment with sodium iodide and zinc-copper complex in ethylene glycol allowed for the isolation of **314**, by fractional distillation. It was also mentioned that epoxide **316** was commercially available, unfortunately neither of the two possible starting materials **315** and **316** are easy to access.



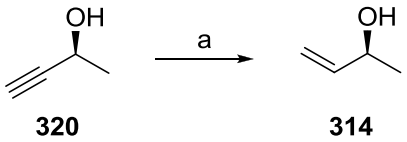
Scheme 2.34 – Reagents & conditions: a) (+)-DIPT, *t*-BuOH, MS (3 Å), Ti(O*i*-Pr)$_4$, P(OMe)$_3$, TsCl, Et$_3$N, DMAP [50-68%]; b) Zn(Cu), NaI, ethylene glycol, 70 ºC [90%].[142]

A second pathway was detailed by Ibrahim *et al.*[143] Starting from 3-chlorobutan-2-one **317**, enzymatic reduction using a specific strain of yeast provided (2*S*)-3-chlorobutan-2-ol **318** (Scheme 2.35). Etherification with 2-methoxypropene under acidic catalysis furnished acetals **319**. Allylic alcohol **314** was finally obtained after dehydrohalogenation using potassium *tert*-butoxide and acidic hydrolysis of the acetal.



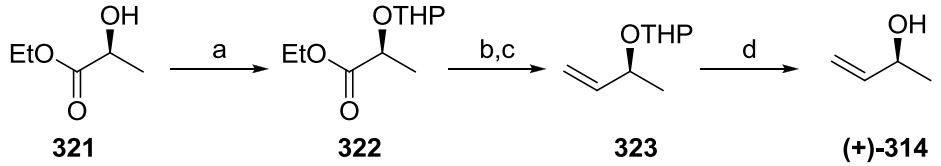
Scheme 2.35 – Reagents & conditions: a) yeast (*Saccharomyces cerevisiae*), sucrose, H_2O, 30 °C [55-64%]; b) 2-methoxypropene, oxalic acid dehydrate, Et_2O, rt [quant.]; c) KO*t*-Bu, DMF, rt [80%]; d) oxalic acid dehydrate, H_2O, rt [83%].[143]

A third option published by Höck *et al*. involves catalytic reduction of (2*S*)-but-3-yn-2-ol **320** with Lindlar's catalyst (Scheme 2.36).[144] The enantiomeric excess obtained was excellent (≥ 98% *ee*), but the rate of the reaction, the cost of the terminal alkyne **320** along with the moderate yield meant that that the method was not suitable.



Scheme 2.36 – Reagents & conditions: a) H_2, Lindlar's catalyst, diethylene glycol, rt, 13 d [50%].[144]

The chosen method involves a four-step sequence starting from ethyl-L-lactate **321** (Scheme 2.37).[145] THP-ether **322** was obtained cleanly from alcohol **321** after a simple work-up. For DIBAL-H reduction to the corresponding aldehyde, dichloromethane was chosen instead of toluene as solvent and the temperature was lowered to −78 °C instead of −40 °C to avoid potential epimerisation issues. Potassium *tert*-butoxide was used in preference to *n*-butyllithium as a base for the methylenation conditions and filtration through a plug of silica gel removed the excess unreacted ylide and the triphenylphosphine oxide formed. Special care was required for the concentration *in vacuo* after work-up and filtration because allylic ether **323** is very volatile. Finally, acid-mediated removal of the THP-ether **323** afforded (+)-but-3-en-2-ol **(+)-314** after distillation under reduced pressure, in 56% yield over the four steps. Albeit that a good overall yield was obtained, the preparation of this alcohol in large quantities was very time consuming.

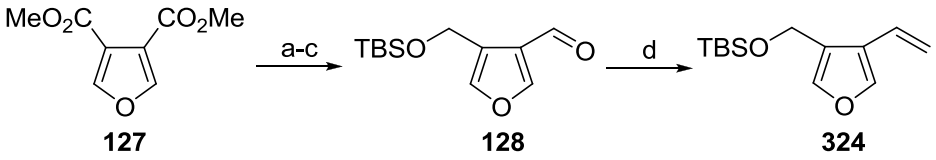


321 **322** **323** **(+)-314**

Scheme 2.37 – Reagents & conditions, **published**:[145] a) DHP, PPTS (10 mol%), CH_2Cl_2, rt [84%]; b) DIBAL-H, toluene, −40 ºC [55%]; c) PPh_3MeBr, *n*-BuLi, THF, rt [50%]; d) *p*-TSA (10 mol%), ethylene glycol, rt [64%]. Reagents & conditions, **experimental**: a) DHP, PPTS (10 mol%), CH_2Cl_2, rt; b) DIBAL-H, CH_2Cl_2, −78 ºC; c) PPh_3MeBr, KO*t*-Bu, THF, rt; d) *p*-TSA (5 mol%), ethylene glycol, rt [56% over 4 steps].

Cross-metathesis reaction using allylic alcohol (+)-314

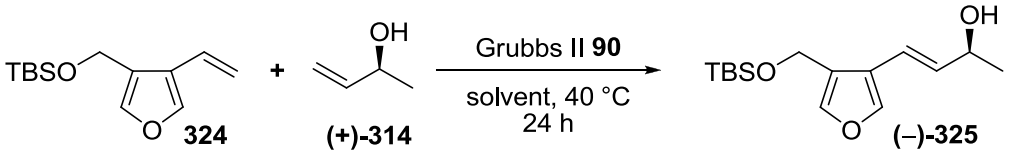
With the allylic alcohol **(+)-314** available in sufficient quantities, its cross-coupling partner **324** was prepared (Scheme 2.38). The first three steps were identical to those reported previously (*cf*. Scheme 2.2), and were followed by Wittig methylenation, providing vinyl furan **324** in 62% yield over four steps.



127 **128** **324**

Scheme 2.38 – Reagents & conditions: a) $LiAlH_4$, THF, −78 ºC to rt; b) MnO_2, CH_2Cl_2, rt; c) TBSCl, imidazole, DMAP, CH_2Cl_2, rt; d) PPh_3MeBr, KO*t*-Bu, THF, 0 ºC to rt [62% (4 steps)].

The cross-metathesis reaction between **(+)-314** and **324** was conducted as shown in Table 2.7, using Grubbs 2nd generation **90** as catalyst.[146] First, two equivalents of allylic alcohol **(+)-314** and 5 mol% of Grubbs II catalyst were used (entry 1). After 24 h at 40 ºC in 1,2-DCE, **(−)-325** was obtained in 47% yield. The catalyst loading was then increased to 10 mol% and four equivalents of the allylic alcohol were added, in DCE, CH_2Cl_2 and toluene respectively (entries 2 to 4). After 24 h at 40 ºC, the best isolated yield was obtained for the reaction performed in dichloromethane (entry 3). As a first approach, this was an encouraging result, especially as the unreacted vinyl furan **324** could be recovered from the reaction mixture. A 9:1 (*trans*/*cis*) ratio was determined by NMR analysis of the crude mixture. The minor *cis* product could be separated from the desired alcohol **(−)-325** but was not isolated. This first study showed that it was possible to use this cross-metathesis reaction for the asymmetric synthesis of **(−)-325** despite the relatively high loading of allylic alcohol **(+)-314**.

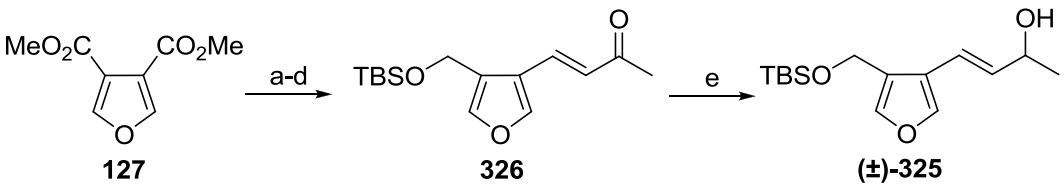


324 (+)-314 (−)-325

entry	(+)-314 loading (equiv)	solvent	cat. loading[a] (mol%)	yield[b] (%)
1	2.0	1,2-DCE	5	47 (96)
2	4.0	1,2-DCE	10	58 (73)
3	4.0	CH_2Cl_2	10	68 (80)
4	4.0	toluene	10	58 (75)

Table 2.7 – [a]5 mol% added straight, and further 5 mol% added after 5 h; [b]yield in brackets is based on the recovery of the starting material (*brsm*), **324**.

At this point, the enantiopurity of the coupled allylic alcohol **(−)-325** was considered. Racemic alcohol **(±)-325** was obtained through an alternative five-step sequence described in Scheme 2.39. Once again, a Wittig reagent provided the α,β-unsaturated ketone **326** in 57% yield over four steps, and further Luche reduction led to the formation **(±)-325** in good yield.



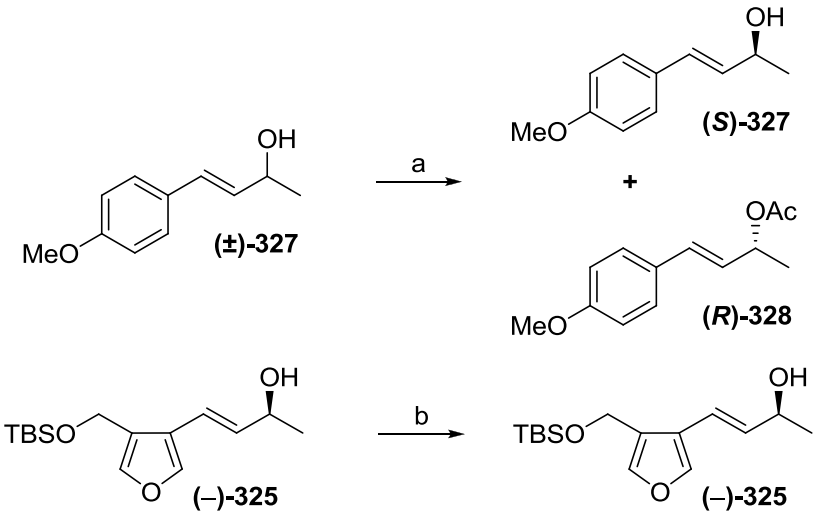
127 326 (±)-325

Scheme 2.39 – Reagents & conditions: a) $LiAlH_4$, THF, −78 ºC to rt; b) MnO_2, CH_2Cl_2, rt; c) TBSCl, imidazole, DMAP, CH_2Cl_2, rt; d) 1-(triphenylphosphoranylidene)acetone, toluene, 100 ºC [57% (4 steps)]; e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 ºC [90%].

The enantioselectivity was determined by chiral HPLC following similar conditions to those reported for a similar substrate.[141] The enantiomeric excess of alcohol **(−)-325** (Table 2.7) was determined to be 73%. This was disappointing considering that the approach chosen for the synthesis of the allylic alcohol **(+)-314** began from an enantiopure starting material. Furthermore, similar conditions had been used for the preparation of other compounds, which were obtained in excellent enantiopurities.[147] Epimerisation during the cross metathesis reaction is highly unlikely, and partial racemisation most probably occurred during the synthesis of the allylic alcohol **(+)-314**. Low purity of ethyl-L-lactate or racemisation during the DIBAL-H reduction of the ester **322** (*cf*. Scheme 2.38), the Wittig methylenation or acidic removal of the THP moiety

are all possible explanations. Only Balmer, optimising the synthesis of the alcohol **(+)-314** by Sharpless epoxidation, stated a comparable 74% *ee* measured from the Mosher ester derived from **(+)-314** (*cf*. Scheme 2.34).[142b]

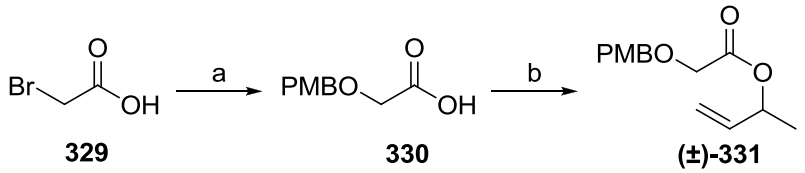
Inspired by the work of Brenna *et al*. an enzymatic resolution reaction was undertaken, in an attempt to improve the enantiopurity of the allylic alcohol **(−)-325** (Scheme 2.40).[148] Alcohol **(−)-325** was subjected to the reported reaction conditions, unfortunately no reaction seemed to occur and chiral HPLC analysis of **(−)-325**, recovered from the reaction, showed that it had exactly the same enantiomeric excess as the starting material.



Scheme 2.40 – Reagents & conditions: a) vinyl acetate, lipase PS (*Burk-holderia cepacia*), TBME, rt [**(*S*)-327** 45% (99% *ee*), **(*R*)-328** 46% (99% *ee*)];[148] b) vinyl acetate, lipase PS (*Burk-holderia cepacia*), TBME, rt [25% recovered **(−)-325** (73% *ee*)].

Alternative cross-coupling reaction

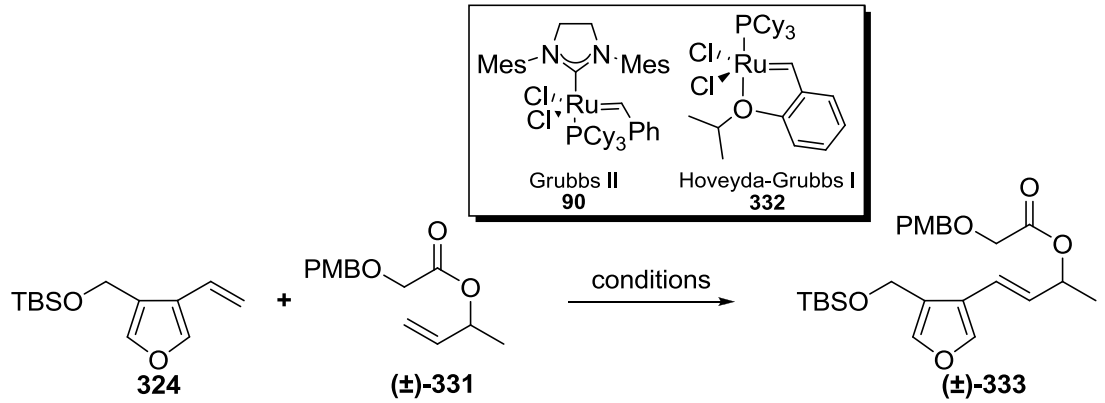
Despite this disappointing outcome, much effort had been expended during the synthesis of this fragment, so that the decision was taken to continue the synthesis. During the initial cross-metathesis reactions (*cf*. Table 2.7), the amount of allylic alcohol partner **(+)-314** was high, and the volatile alcohol proved impossible to recover after the reaction. Another approach was explored, in which the alcohol was protected as an ester (Scheme 2.41). PMB-ether **330** was easily prepared by S_N2 reaction between bromoacetic acid and *p*-anisyl alcohol.[149] Trans-esterification using commercially available alcohol **(±)-314** provided the cross metathesis partner **(±)-331**.



329 **330** **(±)-331**

Scheme 2.41 – Reagents & conditions: a) 1-bromoacetic acid, PMBOH, NaH, THF, 70 ºC [84%]; b) **(±)-314**, EDCI, DMAP, CH_2Cl_2, 0 ºC to rt [99%].

The subsequent cross-coupling reaction of **324** and **(±)-331** was examined (Table 2.8). Ester **(±)-331** was first used in excess compared to vinyl furan **324** (entry 1). Using 5 mol% of Grubbs II catalyst **90** and toluene as solvent, a complex mixture was obtained. Monitoring the reaction by ^{1}H NMR was difficult and after work-up, nearly half of the vinyl furan **324** was recovered and the metathesis product **(±)-333** proved inseparable from starting ester **(±)-331**. With equal amounts of starting materials, the result was identical using toluene or dichloromethane as solvents (entries 2 and 3). Using an excess of ester **(±)-331** allowed for the isolation of coupled ester **(±)-333** in a poor yield, after 48 h at 80 ºC (entry 4). Alternative conditions, using refluxing dichloromethane and Grubbs II or Hoveyda-Grubbs I catalysts led to a marginal improvement in the yield of the reaction (35 and 37% yield for entries 5 and 6, respectively). At such an early stage of the synthesis, the yield obtained for the cross-metathesis of **324** and **(±)-331** was unsatisfactory in comparison to the previous coupling reaction of vinyl furan **324** and allylic alcohol **(+)-314.**

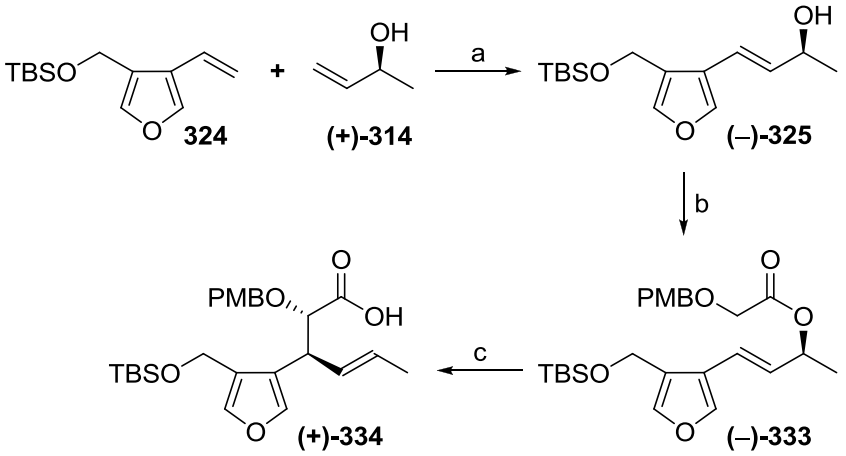


entry	**324**—**(±)-331** ratio	cat.	cat. loading (mol%)	solvent	temperature (°C)	reaction time (h)	result
1	1 : 1.5	**90**	5	toluene	80	24	complex mixture
2	1 : 1	**90**	5	toluene	80	24	complex mixture
3	1 : 1	**90**	5	CH_2Cl_2	reflux	24	complex mixture
4	1.5 : 1	**90**	10	toluene	80	48	12% yield
5	2 : 1	**90**	5	CH_2Cl_2	reflux	48	35% yield
6	2 : 1	**332**	5	CH_2Cl_2	reflux	48	37% yield

Table 2.8

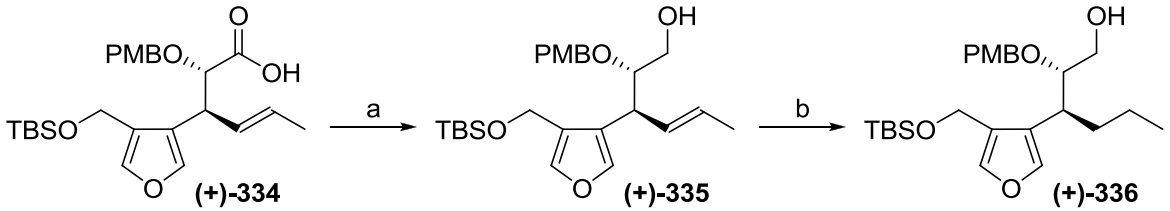
Modified Ireland-Claisen rearrangement and synthesis of the chloride fragment

The next crucial step in the revised synthetic route was the modified Ireland-Claisen rearrangement (Scheme 2.42). The coupling reaction of **324** and **(+)-314** proved to be reproducible with 73% as the best isolated yield; recovery of most of the unreacted starting furan **324** was an additional benefit. Esterification of **(−)-325** with the previously prepared acid **330** (Scheme 2.41) proceeded in good yield. Pleasingly, following a reported procedure,[150] the [3,3]-sigmatropic rearrangement took place efficiently, affording the acid **(+)-334** in 85% isolated yield.



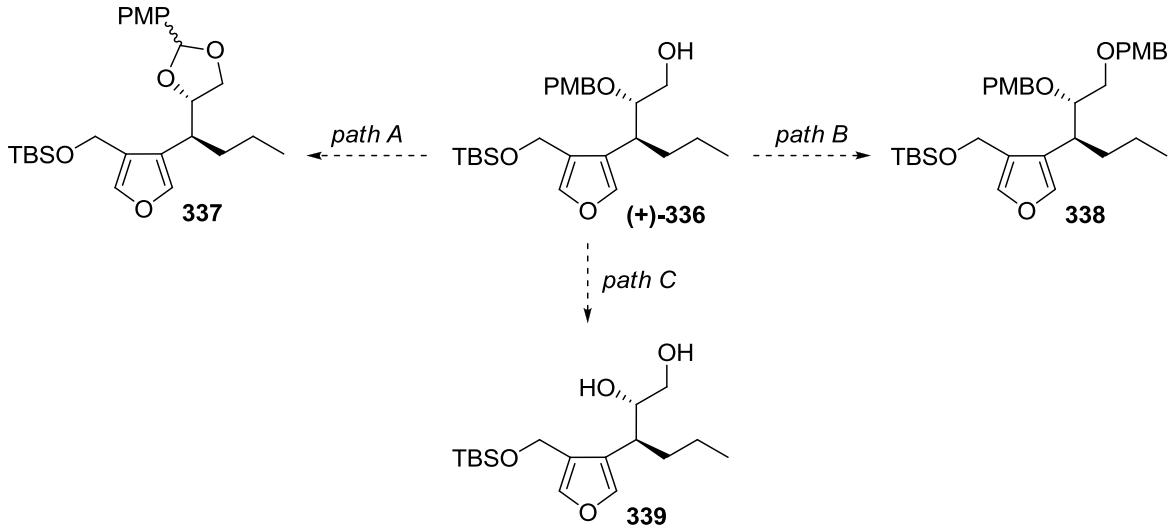
Scheme 2.42 – Reagents & conditions: a) Grubbs II (8 mol%), **(+)-314** (4 equiv), CH_2Cl_2, 45 °C [73% (91% *brsm*)]; b) **330**, EDCI, DMAP, CH_2Cl_2, 0 °C to rt [90%]; c) LiHMDS, TMSCl, THF, −78 °C to rt [85%].

The acid **(+)-334** was next reduced to the corresponding alcohol **(+)-335** using lithium aluminium hydride in diethyl ether (Scheme 2.43).[151] For the subsequent reduction of the alkene in **(+)-335**, some concerns were raised regarding the stability of either the furan or the PMB group under hydrogenation conditions.[152] Accordingly, the hydrogenation reaction was carefully monitored by ^{1}H NMR and stopped as soon as the starting material was consumed, typically after 15 to 20 minutes of reaction, affording **(+)-336** in excellent yield. No signs of competing reductions were apparent and, in fact, leaving the reaction for a longer period of time, or substituting the solvent system for protic media (ethanol or ethyl acetate) to cleave the PMB group only lowered the yield of the reaction with only traces of the diol being formed.



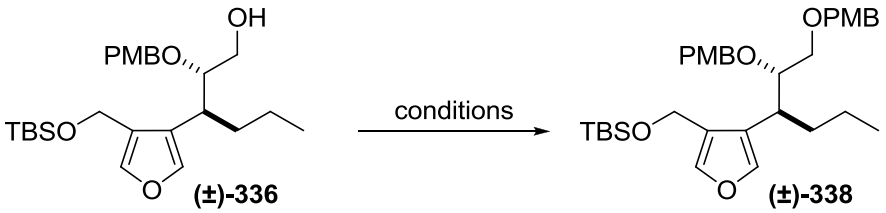
Scheme 2.43 – Reagents & conditions: a) $LiAlH_4$, Et_2O, 0 °C [95%]; b) H_2, Pd/C (10 mol%), acetone, rt [99%].

At this point, three possible routes were investigated to complete the synthesis of the chloride fragment (Scheme 2.44). The first option involved protection of alcohol **(+)-336** as a PMP-acetal (*path A*). This was briefly investigated, with the use of DDQ and molecular sieves (3 Å) in dichloromethane,[153] but these conditions led to decomposition of the starting material. This approach was abandoned due to this result and the fact that there would be no control of the new stereocentre formed in **337**.



Scheme 2.44

The formation of the *bis*-PMB ether **338** was investigated next (*path B*). Nucleophilic substitution of PMBCl under basic conditions resulted in the decomposition of the starting material **(±)-336** (Table 2.9, entry 1). The use of acid-catalysed imidate protection methodology promoted by either scandium triflate or lanthanum triflate as an acid catalyst was investigated (entries 2 and 3).[154,155] Using scandium triflate, the *bis*-PMB ether **(±)-338** was obtained in a disappointing yield (entry 2). Lanthanum triflate was a surprisingly effective catalyst, furnishing **(±)-338** in 51% yield after a reaction time of five minutes. This process could have been further optimised, but isolating the desired product was difficult because of the amounts of impurities formed.

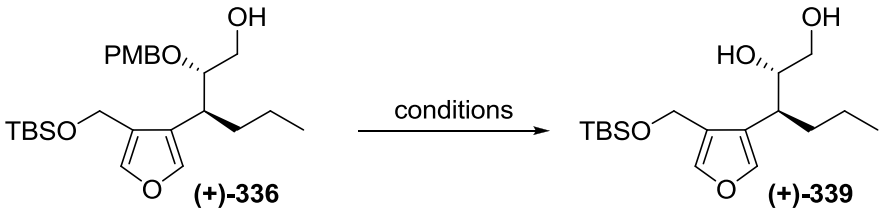


entry	conditions	result
1	NaH, PMBCl, *n*-Bu_4NI, DMF, rt	decomposition
2	PMBTCA, $Sc(OTf)_3$ (2 mol%), toluene, MeCN, 0 °C	34%
3	PMBTCA, $La(OTf)_3$ (2 mol%), toluene, rt	51%

Table 2.9

The cleavage of the PMB-ether to form diol **(+)-339** was subsequently examined (*path C*).The first results obtained using standard conditions[156] were not promising (Table

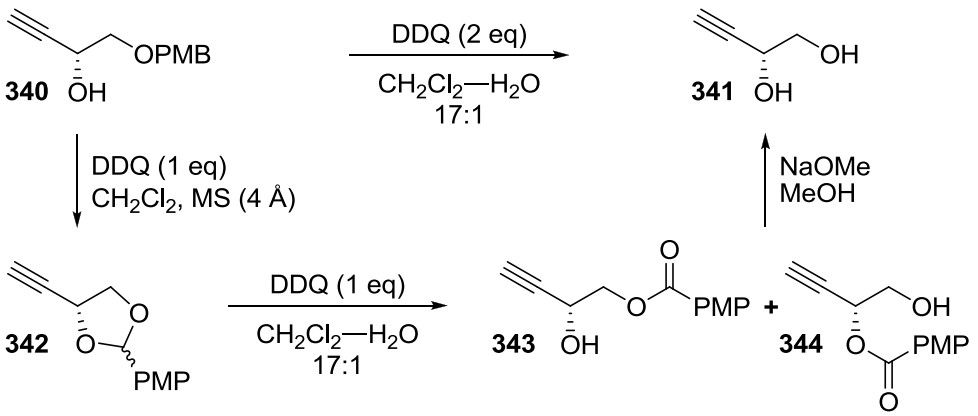
2.10). The use of DDQ in a mixture of dichloromethane and water or phosphate buffer yielded diol **(+)-339** in poor yield (entries 1 and 2). Treatment of PMB-ether **(+)-336** with triflic acid[157] at 0 ºC led to the decomposition of the starting material (entry 3). From the two unsuccessful attempts using DDQ, the complex mixtures obtained hinted that cleavage of a PMB-ether on a substrate bearing an α-hydroxyl group is difficult and is complicated by the formation of acetals and other by-products.



entry	conditions	result
1	DDQ (1.1 equiv), CH_2Cl_2—H_2O (5:1), rt	34%
2	DDQ (1.2 equiv), CH_2Cl_2—pH 7 buffer (5:1), 0 ºC	19%
3	TFA, CH_2Cl_2, H_2O, 0 ºC	decomposition

Table 2.10

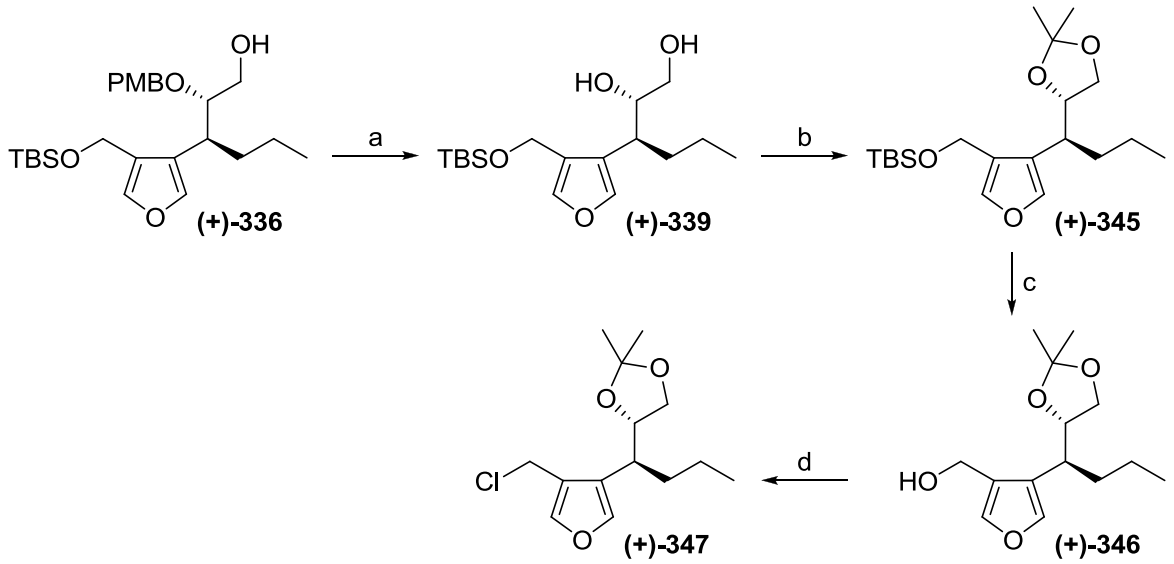
In 1988, Jadav *et al.* took advantage of this reactivity for the synthesis of propargylic alcohols (Scheme 2.45).[158] For alkyne **340**, the use of two equivalents of DDQ in a mixture of dichloromethane and water induced the formation of diol **341**, whereas using only one equivalent of DDQ in dry media produced the benzylidene derivatives **342**. Another equivalent of DDQ promoted opening of acetals, affording the mixture of esters **343** and **344**, the saponification of which furnished diol **341**.



Scheme 2.45[158]

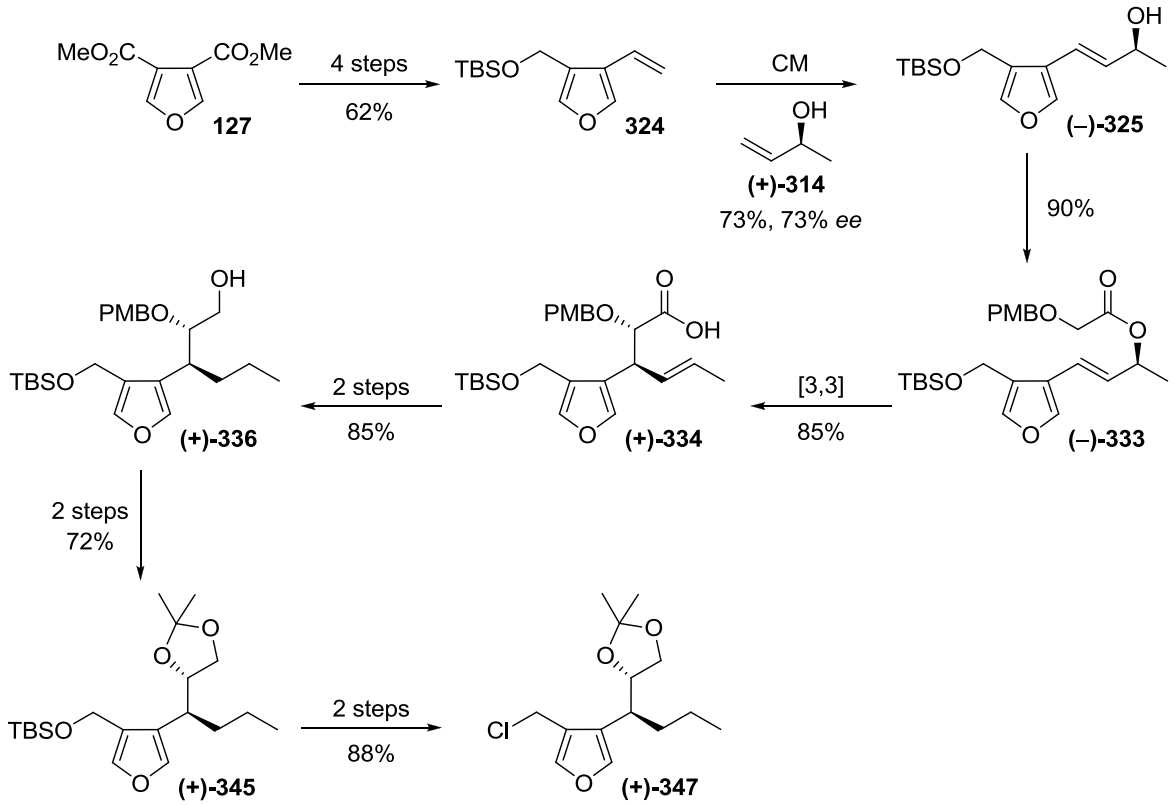
The same conditions were employed on substrate **(+)-336** with two equivalents of DDQ in a 17:1 mixture of CH_2Cl_2—H_2O (Scheme 2.46). Instead of yielding diol **(+)-339** directly, a complex mixture was obtained. Examination of the crude mixture suggested that the five potential products described by Yadav were indeed formed during the reaction. The crude mixture was therefore submitted to basic hydrolysis conditions leading to the formation of the desired diol **(+)-339** in good yield (75%). The process proved to be generally reliable, and depending on the progression of the DDQ reaction, PMP acetals and unreacted starting material could be recycled and submitted to the same conditions.

From this point, the completion of the chloride fragment synthesis was trivial. Acetonide protection[159] of the diol **(+)-339**, followed by removal of the TBS ether using TBAF and final chloride substitution of the hydroxyl group in allylic position led to chloride **(+)-347**; all three steps were achieved in excellent yield.



Scheme 2.46 – Reagents & conditions: a) (*i*) DDQ, CH_2Cl_2—H_2O (17:1), rt; (*ii*) K_2CO_3, MeOH, rt [75%]; b) 2,2-dimethoxypropane, PPTS (5 mol%), CH_2Cl_2, rt [96%]; c) *n*-Bu_4NF, THF, 0 ºC to rt [93%]; d) MsCl, Et_3N, CH_2Cl_2, 0 ºC to rt [95%].

Overall, the asymmetric synthesis of the chloride fragment was accomplished in 14 steps (longest linear sequence), 21% overall yield (86% average yield per step), and featured a cross-metathesis and [3,3]-sigmatropic rearrangement reactions as key steps in the strategy (Scheme 2.47).

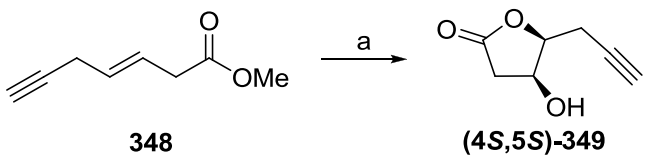


Scheme 2.47

2.3.2 Asymmetric synthesis of the stannane fragment

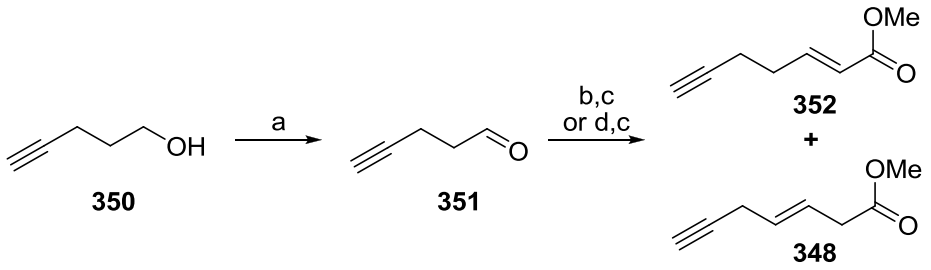
Sharpless dihydroxylation approach

Now that the new strategy for the chloride fragment had been validated, its Stille coupling partner had to be prepared. An asymmetric approach to the synthesis of the unsaturated lactone, using a chiral auxiliary in place of the pyrrolidine (*cf*. Section 1.4.3), had been attempted previously in the group with success.[41,60] An alternative approach based on the work of Harcken *et al*. to access to alkyne **349** was explored first (Scheme 2.48).[160]



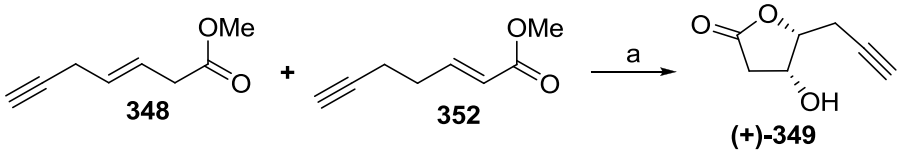
Scheme 2.48 – Reagents & conditions: a) AD mix-α, methylsulfonamide, *t*-BuOH—H_2O (1:1), 0 °C [74% (93% *ee*)].[160]

In published work it had been shown that asymmetric Sharpless dihydroxylation of β,γ-unsaturated ester **348** using AD mix-α afforded dihydrofuran **(4*S*,5*S*)-349** in good yield and with high selectivity. Accordingly, its antipode was expected to be accessible using AD mix-β. The synthesis of ester **348** is shown in Scheme 2.49. Starting from 4-pentyn-1-ol, Swern oxidation[161] afforded aldehyde **351**. Due to the volatility of this aldehyde, the crude product was used directly in the deconjugative Knoevenagel reaction using malonic acid.[162] Subsequent esterification with concentrated hydrochloric acid and methanol afforded the β,γ-unsaturated ester **348** in good yield over three steps. However, the product was inseparable from the undesired minor α,β-unsaturated ester **352**. To circumvent this issue another set of conditions was explored, using piperidinium acetate as catalyst.[162b,163] Although the reaction appeared more selective, the resulting yield of the reaction was poor.



Scheme 2.49 – Reagents & conditions: a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N, −78 °C to rt; b) malonic acid, Et_3N, 80 °C; c) HCl (conc.), MeOH, 60 °C [71% (3 steps using b), **348**—**352** (3:1), 11% (3 steps using d), only **348**]; d) malonic acid, piperidinium acetate (2 mol%), DMSO, 90 °C.

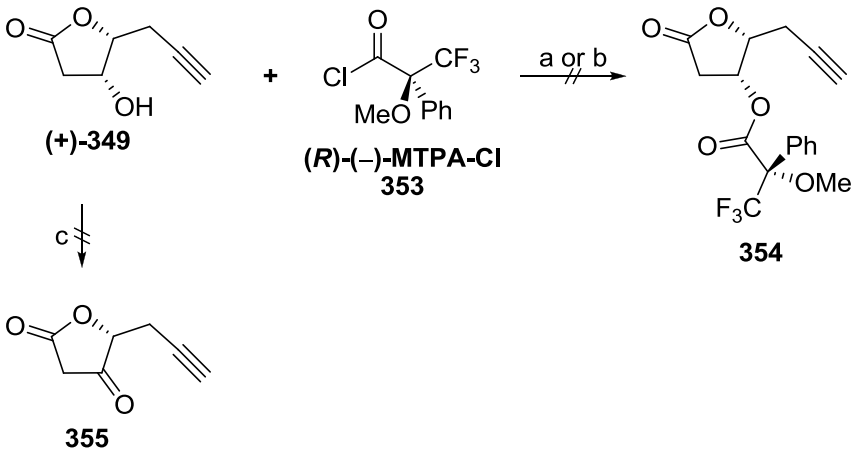
The Sharpless dihydroxylation reaction was attempted on the mixture of unsaturated esters following the procedure of Kaferer and co-workers (Scheme 2.50).[162a] After 48 h the lactone **(+)-349** was isolated in 40% yield (53% yield based upon the purity of the starting material).



Scheme 2.50 – Reagents & conditions: a) AD mix-β, methylsulfonamide, *t*-BuOH—H_2O (1:1), 0 °C [40%].

A sufficient amount of material was obtained to check the enantiopurity of the β-hydroxylactone **(+)-349** by ^{1}H NMR analysis of the corresponding Mosher ester (Scheme 2.51).[164] Two sets of conditions were applied to the synthesis of the Mosher ester **354**, in which either pyridine or triethylamine was used as the base, but both reactions led to

decomposition of starting material. Oxidation of **(+)-349** using DMP to form the tetronic acid derivative **355** was also unsuccessful. Looking through the literature, the same issue was reported by Wrobel and co-workers.[165] They suggested that these substrates were prone to undergo β-elimination or retro-aldol fragmentation. They obtained better results using Swern oxidation conditions, but it was obvious that the route was inappropriate for large scale synthesis.



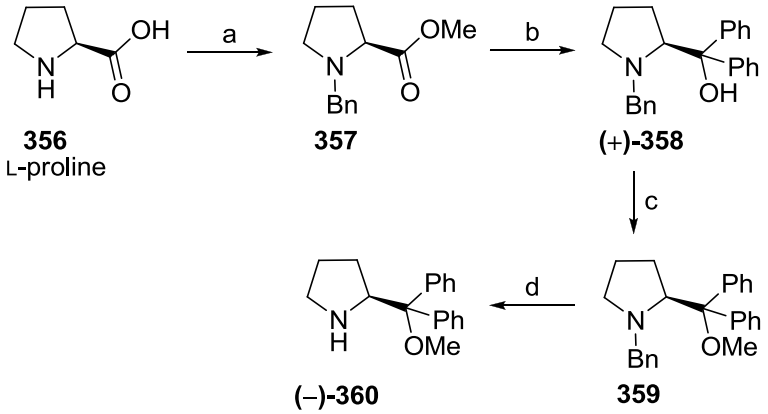
Scheme 2.51 – Reagents & conditions: a) pyridine, CH_2Cl_2, 0 °C to rt; b) Et_3N, DMAP, CH_2Cl_2, 0 °C to rt; c) DMP, CH_2Cl_2, 0 °C.

Synthesis of the chiral proline derivative

Promising results were obtained by Northall and Marlin by use of the chiral proline derivative **(−)-360** as an auxiliary (*cf*. Section 1.4.3).[41,60] Consequently, a similar outcome was expected for our synthesis, and **(−)-360** was prepared in a large scale following the original synthesis achieved by the group of Enders (Scheme 2.52).[63] It is noteworthy that the asymmetric synthesis of cornexistins requires the preparation of the auxiliary starting from D-proline. Due to the cost of the unnatural enantiomer, it was decided instead to use L-proline **356**, and investigate the asymmetric route using a model system. Once the asymmetric synthesis optimised, the steps would subsequently be repeated starting from the D-proline.

Concerning the first two reactions in one-pot (Scheme 2.52), Enders conditions for the amino-benzylation involved the use of the isourea, prepared from DCC and benzyl alcohol, with copper(I) acting as catalyst for the reaction. In our hands, the yield obtained was lower than expected, but an alternative method for this transformation,[166] using DIPEA and benzyl bromide, afforded ester **357** cleanly. The crude ester could be used directly in the next step. Grignard addition of phenyl magnesium bromide to the ester was successful, and more than 50 g of **(+)-358** could be obtained after a single

recrystallisation. After work-up of the methylation step, no further purification was required. Due to poor solubility, the hydrogenation conditions reported by Enders for *N*-benzyl cleavage were unsuccessful, but addition of concentrated hydrochloric acid to the reaction mixture allowed the salt of **(−)-360** to be isolated.[166b] The proline salt could be washed with cold diethyl ether to remove most of the organic impurities. Treatment of the salt with potassium carbonate followed by extraction with diethylether furnished the desired proline derivative **(−)-360**, without any further purification required. Pleasingly, the whole sequence was achieved without the requirement for column chromatography; the major purification step in the sequence being the recrystallisation.

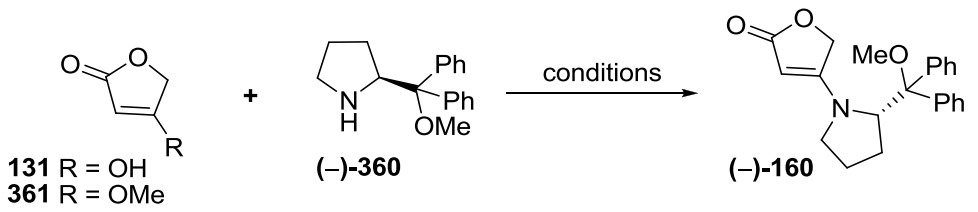


Scheme 2.52 – Reagents & conditions: a) (*i*) $SOCl_2$, MeOH, 0 °C to 65 °C; (*ii*) BnBr, *i*-Pr_2NEt, toluene, 0 °C to 65 °C; b) PhBr, Mg, I_2 (crystal), Et_2O, 0 °C to reflux [64% (3 steps)]; c) MeI, NaH, THF, 0 °C to reflux; d) H_2, Pd/C (15 mol%), HCl (conc.), EtOH, rt [90% (2 steps)].

Condensation of the proline derivative

Following the previously described condensation of pyrrolidine with tetronic acid (*cf*. Scheme 2.6), the same method was employed for the condensation of **(−)-360** (Table 2.11). Under a range of conditions, carbamate **(−)-160** was obtained, but always in a moderate yield close to 50% (entries 1 and 2). At first the stability of the product during the purification on silica gel was questioned. Neutralisation of the silica gel with triethylamine, or purification with neutral aluminium oxide did not improve the yield. Using the crude product directly in the next step was also attempted but this resulted in a poor alkylation yield. In entry 3, molecular sieves were added to force the thermodynamic equilibrium of the condensation reaction towards the product, but without success. Higher temperature and the use of Dean Stark apparatus also proved unsuccessful (entry 4). The condensation of pyrrolidine with methyl tetronate **361** has been reported by Guo *et al.*[167] Applying the reported conditions on the proline

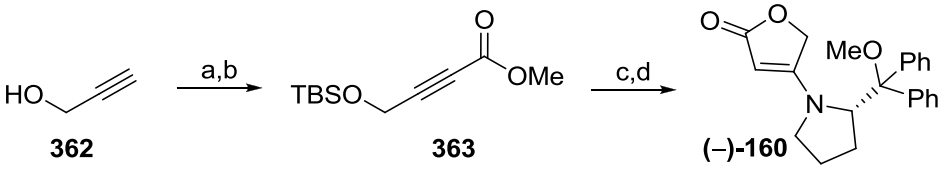
derivative **(−)-360** led only to the recovery of both starting materials (entry 5). Addition of potassium carbonate did not change the outcome of the reaction (entry 6). The same reported condensation of pyrrolidine with methyl tetronate **361** was attempted (entry 7), resulting in the expected complete conversion of **361** to the vinylogous carbamate **132**. In resignation, entry 8 was the method chosen; a mixture of toluene and ethanol was used to improve the solubility of the two starting materials, but with no major improvement in the isolated yield of the reaction.



entry	reactant	amount of **(−)-360** (equiv)	conditions	yield
1	**131**	1	toluene, 45 °C, *in vacuo*	50%
2	**131**	0.8	toluene, 45 °C, *in vacuo*	53%
3	**131**	1.1	toluene, 4 Å MS, 45 °C, *in vacuo*	42%
4	**131**	1.1	toluene, Dean Stark, 115 °C	37%
5	**361**	2.7	EtOH, 80 °C	no reaction
6	**361**	2.7	EtOH, K_2CO_3, 80 °C	no reaction
7	**361**	0	pyrrolidine, EtOH, 80 °C	quant.[a]
8	**131**	1.1	toluene, EtOH, 45 °C, *in vacuo*	53%

Table 2.11 – [a]**132** was obtained from the reaction.

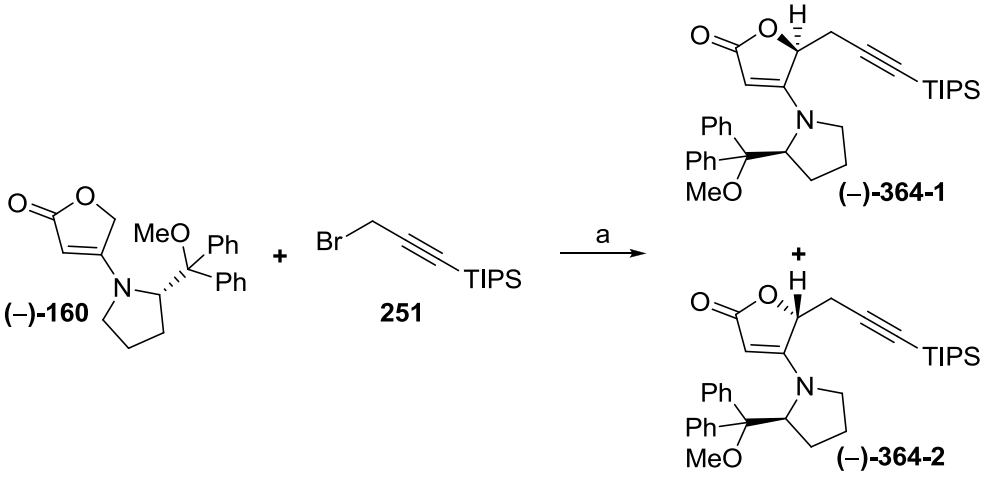
Marlin and Northall had taken a different approach to the formation of **(−)-160** (Scheme 2.53) inspired by the work of Schlessinger *et al.*[41,60,168] Initially, this approach was not adopted because of the four-step sequence required, as opposed to one step in the condensation strategy. However, owing to the difficulties encountered, this route could have been a viable alternative.



Scheme 2.53 – Reagents & conditions: a) TBSCl, imidazole, CH_2Cl_2, reflux [96%], b) *n*-BuLi, methyl chloroformate, THF, −78 °C to rt [89%]; c) **(−)-360**, *t*-BuOH, 60 °C; d) *n*-Bu_4NF, THF, rt [89% (2 steps)].[41,60,168]

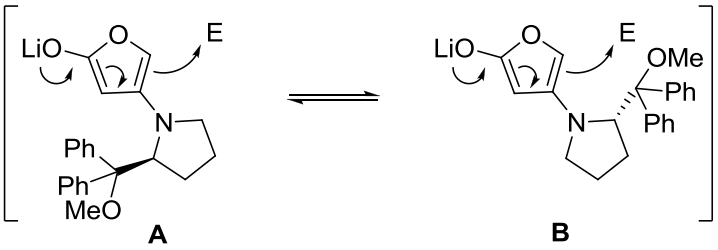
Completion of the stannane fragment

Deprotonation of vinylogous carbamate **(−)-160** with *tert*-butyllithium and subsequent nucleophilic attack of the resulting anion on propargylic bromide **251** afforded the alkylated products **(−)-364-1** and **(−)-364-2** in good yield (Scheme 2.54). Based on ^{1}H NMR analysis of the crude mixture, it was difficult to determine the diastereoisomeric ratio because the two products formed rotamers at room temperature when solvated in deuterated chloroform or benzene. The diastereoisomers were separated by flash column chromatography but the diastereoisomeric ratio obtained (4:1) was not comparable to the ratio previously reported (8:1) by Northall for his allylation step (*cf.* Section 1.4.3, Scheme 1.44).[41]



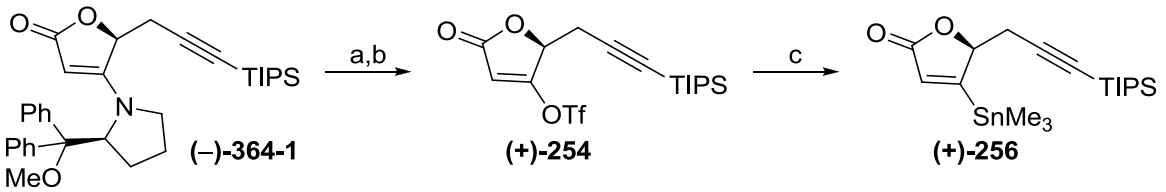
Scheme 2.54 – Reagents & conditions: a) *t*-BuLi, THF, −78 °C [**(−)-364-1** 75%, **(−)-364-2** 19%].

It is assumed that the effect of the pyrrolidine substituent depends on its proximity to the reacting carbon centre (Scheme 2.55). Assuming there is free rotation about the C-N bond, the most reactive species is expected to be **A**, with the bulky substituent situated away from the nucleophilic site. Better selectivity has been reported with larger substituents on the auxiliary, but in this case the electrophile was allyl bromide (*cf*. Section 1.4.3). The lower selectivity during the alkylation reaction using TIPS-protected propargylic bromide could be explained by the bulk of the TIPS group although it is far from the reactive site. The separation of the diastereoisomers using column chromatography and the larger scale employed seem more reasonable explanations to the different selectivity observed. The use of a C-2 symmetrical auxiliary might have given high selectivity but this approach had been unsuccessful (*cf*. Section 1.4.3, Scheme 1.42).



Scheme 2.55

Little could be done to improve the ratio of diastereoisomers, but the excellent yield obtained for this alkylation reaction allowed for the preparation of enough of the major diastereoisomer **(−)-364-1** to complete the synthesis of the fragment (Scheme 2.56). The stannane **(+)-256** was prepared using an analogous approach as in the synthesis of the racemate. Hydrochloric acid in solution with ethanol solved the solubility issue encountered originally by Northall and Marlin, so that triflate **(+)-254** was obtained in good yield. The excellent enantiopurity of triflate **(+)-254**, determined by chiral HPLC, was in agreement with previous work.[41] Ultimately, the triflate was converted into the corresponding stannane **(+)-256** in an expected yield of 52% (compared to 54% for **(±)-256**, Section 2.2.2).

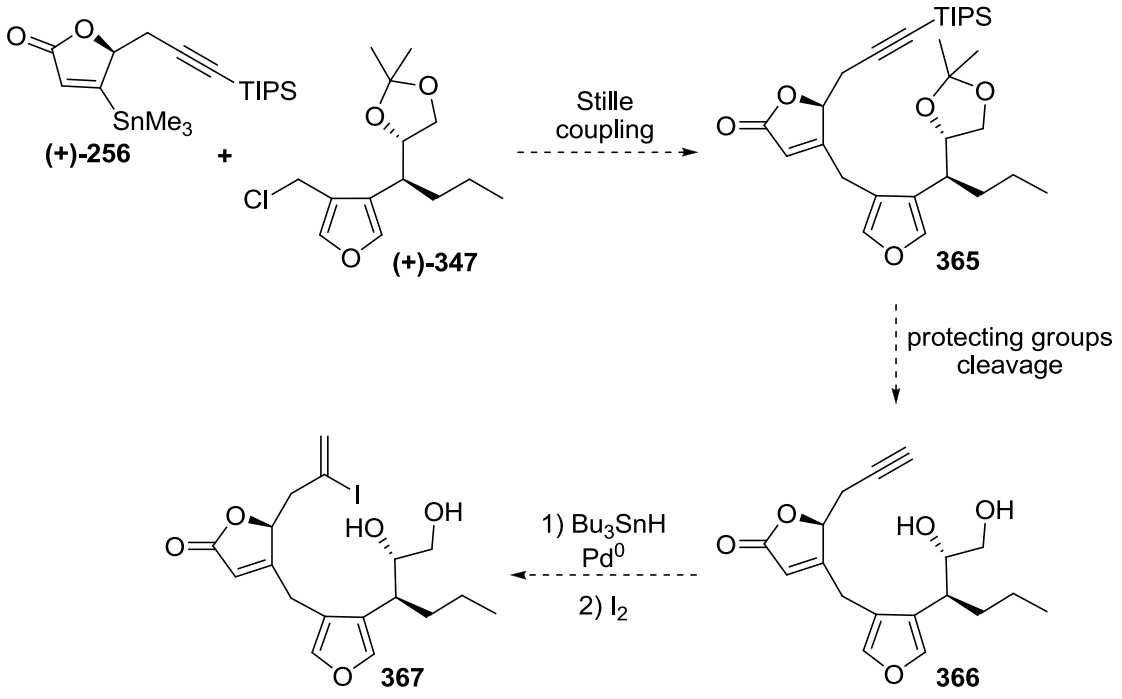


Scheme 2.56 – Reagents & conditions: a) HCl (1.26 M in EtOH), H_2O, reflux; b) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 °C [82% (2 steps), 93% *ee*]; c) $(SnMe_3)_2$, $Pd(PPh_3)_4$ (3 mol%), THF, reflux [52%].

2.3.3 Efforts toward the Nozaki-Hiyama-Kishi cyclisation

Strategy overview

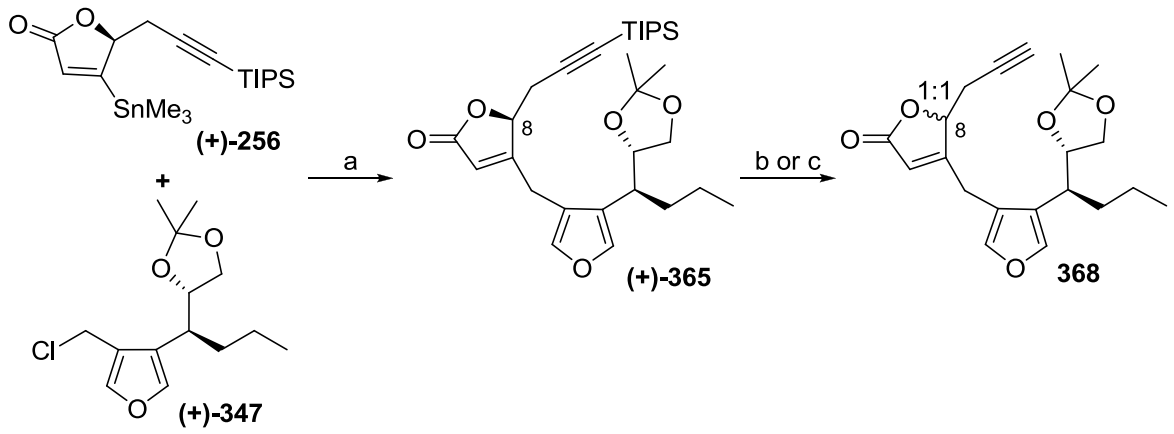
The two coupling fragments have been synthesised in an asymmetric fashion. In accordance with the synthesis of the racemate, the Stille cross-coupling was expected to afford **365** in high yield (Scheme 2.57). Deprotection of the alkyne and acetonide removal in a one-pot reaction was envisaged, due to the required buffering of TBAF with acetic acid. Regioselective palladium-catalysed hydrostannylation followed by tin-iodine exchange would provide diol **367**. Finally, oxidative cleavage would afford the precursor for the NHK reaction. After the cyclisation, it was envisaged that the previous sequence would be followed using this time the enantiomer of stannane **(+)-256**, leading to the synthesis of hydroxycornexistin (**2**). It turned out not to be that straightforward.



Scheme 2.57

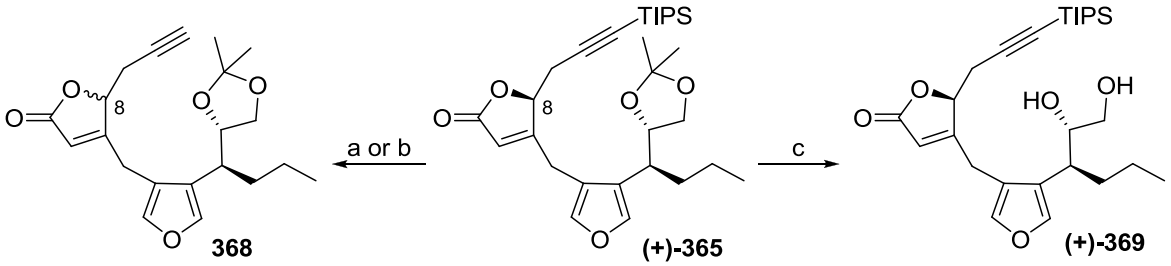
Stille coupling and epimerisation issue

The Stille coupling reaction proved highly reliable, affording **(+)-365** in 95% yield (Scheme 2.58). Given that the enantiomeric purity of the chloride fragment **(+)-347** was 73% *ee*, the diastereomeric ratio of products observed was as expected (6.4:1). The two diastereoisomers could not be separated by column chromatography on silica gel or silica gel coated with silver nitrate. Following the previous synthesis, TBAF buffered with acetic acid was employed to remove the TIPS group on alkyne **(+)-365** but in this case no reaction occurred. Depending on the quality of the TBAF used, an excess of acetic acid can reduce the reactivity of the TBAF. To avoid this problem, it was decided to attempt to remove the TIPS group using TBAF without buffer. The reaction was carefully monitored and quenched after 30 min at 0 ºC. The terminal alkyne **368** was obtained in 63% yield, but unfortunately, as a 1:1 mixture of inseparable diastereoisomers. This suggested that the unsaturated lactone moiety was sensitive to basic conditions. More importantly, the epimerisation at C-8 could not be observed in the racemic approach of the synthesis. The same result was obtained with the use of a new bottle of TBAF buffered with acetic acid, confirming the high sensitivity of the α,β-unsaturated lactone.



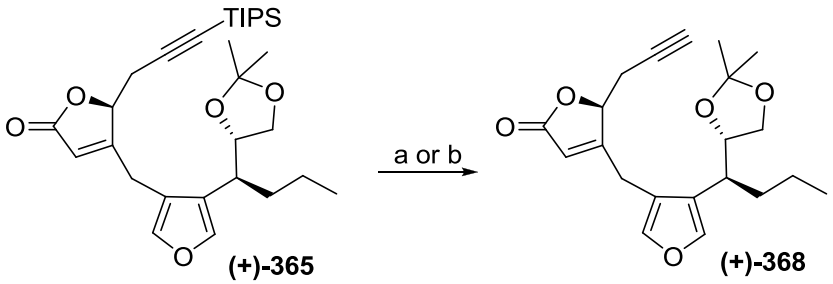
Scheme 2.58 – Reagents & conditions: a) $Pd_2(dba)_3$ (6 mol%), $AsPh_3$ (25 mol%), THF, 70 ºC [95%, *dr* 6.4:1]; b) *n*-Bu_4NF, THF, 0 ºC [63%, *dr* 1:1]; c) *n*-Bu_4NF, AcOH, 0 ºC to rt [57%, *dr* 1:1].

The TIPS-protected alkyne **(+)-365** was next subjected to alternative fluoride sources; however similar results were obtained for both TBAT and TAS-F (**275**) (Scheme 2.59). Treatment of **(+)-365** under acidic conditions, using hydrofluoric acid, cleaved the acetonide after three days without any effect on the TIPS group.



Scheme 2.59 – Reagents & conditions: a) TBAT, THF, 0 ºC to rt [*dr* 1:1 from ^{1}H NMR analysis of the crude mixture]; b) TAS-F, DMF, 0 ºC to rt [44%, *dr* 1:1]; c) HF (5% in MeCN), MeCN, 0 ºC to rt [67%].

An interesting silver(I)-catalysed protodesilylation of TMS-protected alkyne was reported by Carpita *et al*. using a catalytic amount of silver nitrate[169] and so this reaction was investigated. Unfortunately, application of this methodology to the deprotection of **(+)-365** afforded only recovered starting material (Scheme 2.60). The difficulty of cleaving a TIPS-protected acetylene using silver sources was emphasized by the studies of Kim, who reported the use of silver(I) fluoride.[170] Under these conditions, terminal alkyne **(+)-368** could be isolated without epimerisation, albeit in only 29% yield.

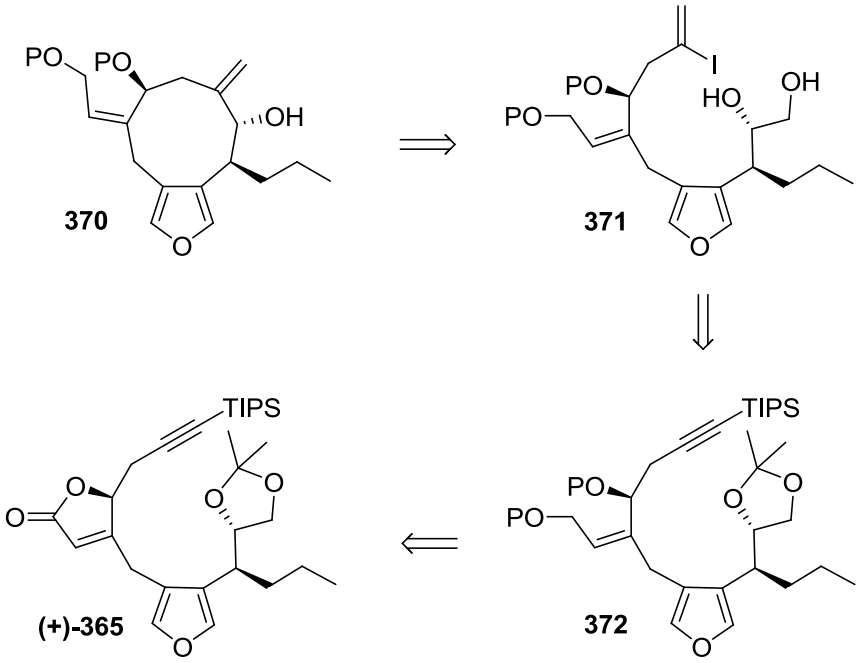


Scheme 2.60 – Reagents & conditions: a) $AgNO_3$ (10 mol%), H_2O, acetone, rt [no reaction]; b) (*i*) AgF, MeCN, rt; (*ii*) HCl (1 M), 0 ºC [29%].

Modification of the post-coupling strategy

The unsaturated lactone was highly sensitive to epimerisation, and it was therefore decided to reduce the lactone to the diol **372** prior to desilylation (Scheme 2.61). In terms of strategy, the NHK cyclisation had always been conducted in presence of the α,β-unsaturated lactone; without it, the selectivity of the NHK cyclisation would be

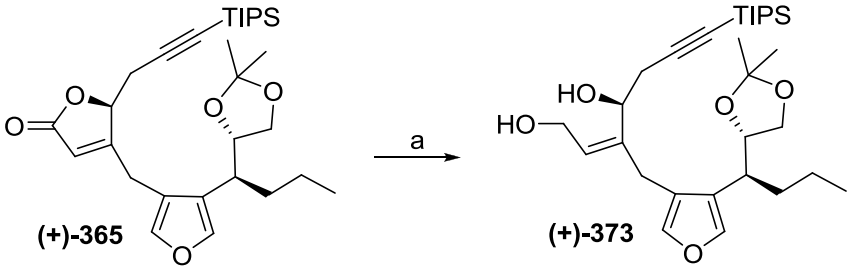
unknown. Apart from this, the overall strategy remained similar; the NHK precursor would be obtained by oxidative cleavage of diol **371**. Conversion of the vinyl iodide to protected alkyne would lead to **372**. The *bis*-protected diol **372** would be obtained *via* reduction of the α,β-unsaturated lactone and subsequent protection of the diol. From previous studies,[41] protection of both hydroxyl groups as PMB-ethers was the first choice.



Scheme 2.61

Reduction of the unsaturated lactone and protection of the diol

The reduction of similar α,β-unsaturated lactones has been described by Northall, Marlin[41,60] (*cf*. Section 1.4.2) and Masse and co-workers[58] as a difficult reaction. After significant effort to optimise the reaction conditions, the best yield was obtained by use of conditions reported by Marlin: $LiAlH_4$ and TMEDA, and warming the reaction mixture progressively from −78 to 0 °C (Scheme 2.62).



Scheme 2.62 – Reagents & conditions: a) $LiAlH_4$, TMEDA, Et_2O, −78 °C to 0 °C [53%].

A two-step reduction—protection approach could have been envisaged, but the reaction generated substantial amounts of side products. The formation of furan or acetal side-product was expected, but isolation of one of the reaction's side-products revealed the presence of the [1,4]-reduced lactone **(+)-374** which had not been reported before (Figure 2.2). Furthermore, the desired product **(+)-373** was obtained as an inseparable mixture of two products. Although the second product could not be purified for complete characterisation, it is most likely the diol **375** obtained following [1,4]-reduction. The ratio between those two products, **(+)-373** and **375**, was highly dependent on the reduction conditions, especially the temperature. Using $LiAlH_4$—TMEDA or DIBAL-H—$LiAlH_4$ protocols, the ratio (6:1) was largely in favour of the desired diol **(+)-373**. Refluxing $LiAlH_4$ in diethylether[171] decreased the ratio of the reaction to 2.2:1. The use of Red-Al in THF at 60 °C[171] even reversed the ratio to 1:2 in favour of the reduced diol **375**. Reduction with DIBAL-H followed by the addition of $NaBH_4$ could possibly lead to better results but this reaction was not explored.[172]

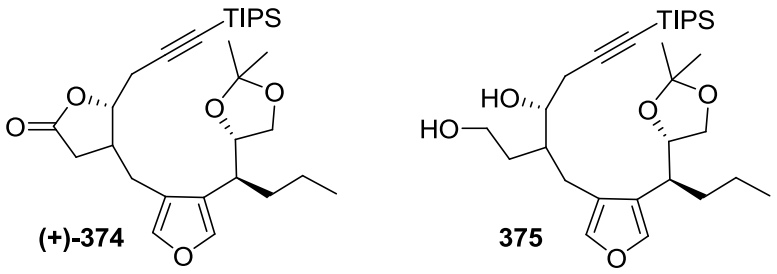
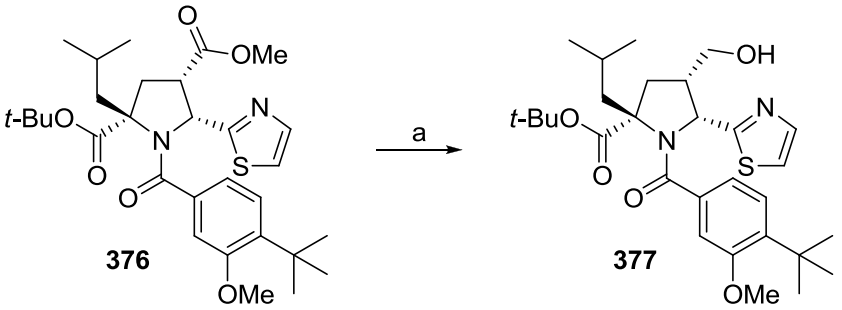


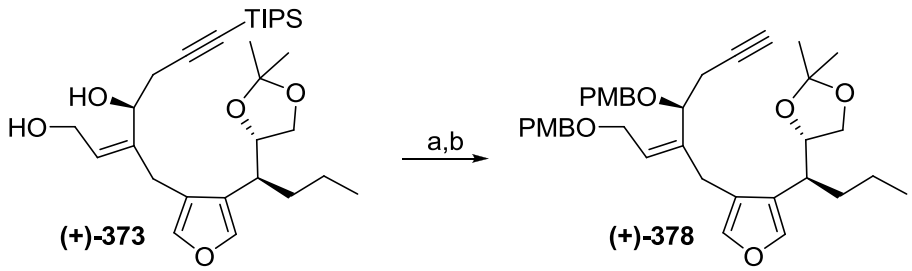
Figure 2.2

In 2008, the group of Slater and Xie at GlaxoSmithKline reported a unique set of conditions for the reduction of a methyl ester, using sodium borohydride and 5 mol% of $NaB(OAc)_3H$ (Scheme 2.63).[173] When these conditions were implemented on **(+)-365**, only starting material was recovered.



Scheme 2.63 – Reagents & conditions: a) $NaBH_4$, $NaB(OAc)_3H$ (5 mol%), MeOH, THF, 78 °C [89%].

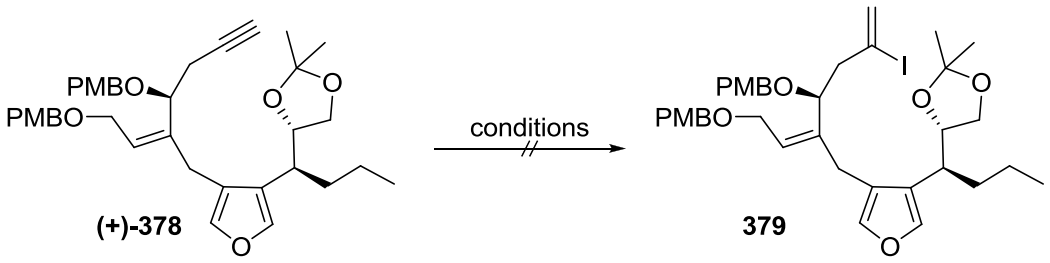
Diol **(+)-373** was then protected as the *bis*-PMB ether (Scheme 2.64) in moderate yield through nucleophilic substitution of PMBCl. Interestingly, when a large excess of sodium hydride was used in the reaction, the terminal alkyne **(+)-378** was obtained directly. This was observed on a small scale but was not reproducible. The use of TBAF resulted in removal of the TIPS-silyl group, to furnish terminal alkyne **(+)-378** in good yield.



Scheme 2.64 – Reagents & conditions: a) PMBCl, NaH, *n*-Bu_4NI (12 mol%), DMF, 0 °C to rt [55%]; b) *n*-Bu_4NF, THF, 0 °C [96%].

Conversion of the terminal alkyne to vinyl halide

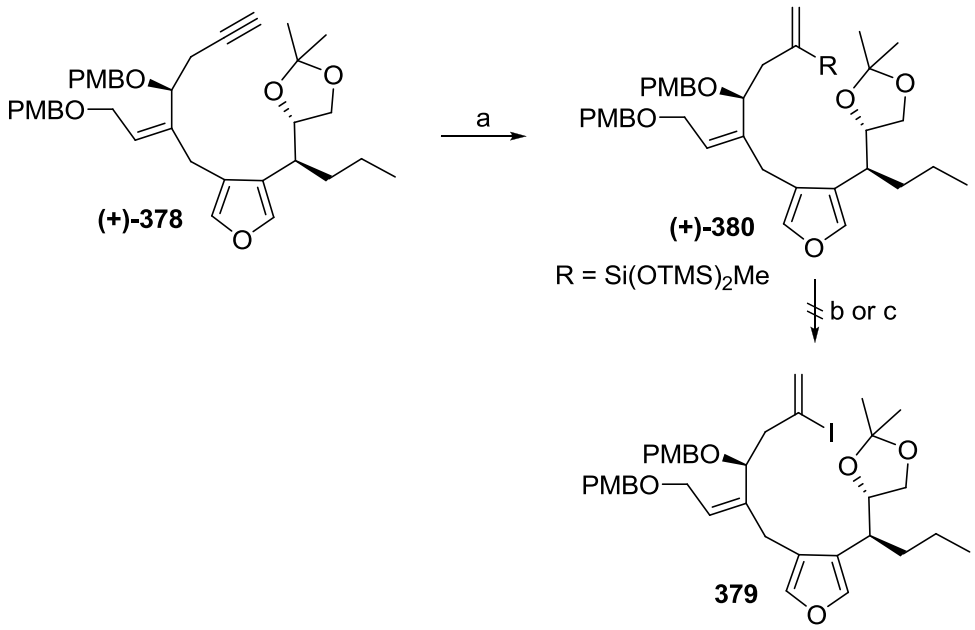
During the synthesis of the racemic NHK cyclisation precursor, the formation of the vinyl iodide unit was accomplished using a palladium-catalysed hydrostannylation reaction followed by tin-halogen exchange (*cf*. Section 2.2.3). With the reduction of the lactone and the presence of the acetonide unit, it was thought that the use of alternative methods could allow formation of the vinyl iodide from substrate **(+)-378** (Table 2.12). In agreement with the synthesis of racemic material, the hydro-iodination conditions using sodium iodide resulted in the decomposition of the starting alkyne **(+)-378** (entries 1 and 2). Acetonide cleavage, consequent to the formation of hydroiodic acid during the reaction was expected, but the PMB-ethers did not survive the reactions conditions either. Hoveyda and co-workers reported the hydroalumination of alkynes, catalysed by a nickel complex, to form the internal vinyl aluminium species.[174] The corresponding vinyl halide was obtained by the addition of NIS in the mixture. The same conditions were adopted for reaction of substrate **(+)-378**, but only starting material was recovered in this case (entry 3).



entry	conditions	result
1	NaI, TMSCl, H_2O, rt	decomposition
2	NaI, $CeCl_3 \cdot 7H_2O$, MeCN, reflux	decomposition
3	(*i*) DIBAL-H, Ni(dppp)Cl_2 (3 mol%), THF, reflux to rt; (*ii*) NIS, THF, 0 ºC	77% recovery

Table 2.12

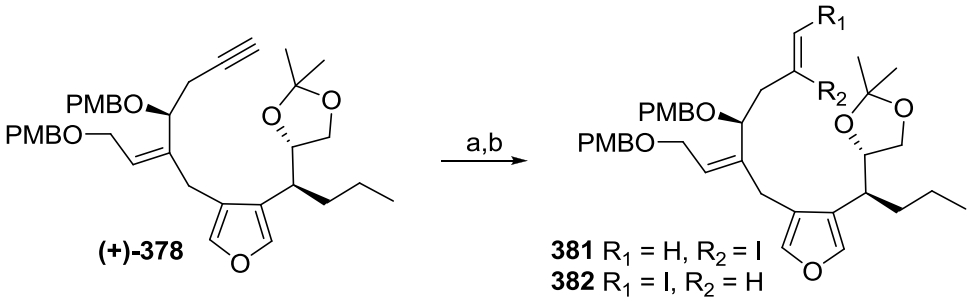
The ruthenium-catalysed hydrosilylation reaction was attempted again, using a different silyl group (Scheme 2.65).[175] Following Trost's protocol,[112b,112c] the internal silane **(+)-380** was obtained in good yield. Unfortunately, the subsequent silicon/halogen exchange reaction failed, using iodine or iodine monochloride[176] and both reactions resulted in decomposition of the vinylic silane with no evidence of vinyl iodide formation.



Scheme 2.65 – Reagents & conditions: a) $HSi(OTMS)_2Me$, $Cp^*Ru(CH_3CN)_3PF_6$ (5 mol%), CH_2Cl_2, 0 ºC to rt [68%]; b) I_2, CH_2Cl_2, 0 ºC to rt; c) ICl, THF, 0 ºC to rt.

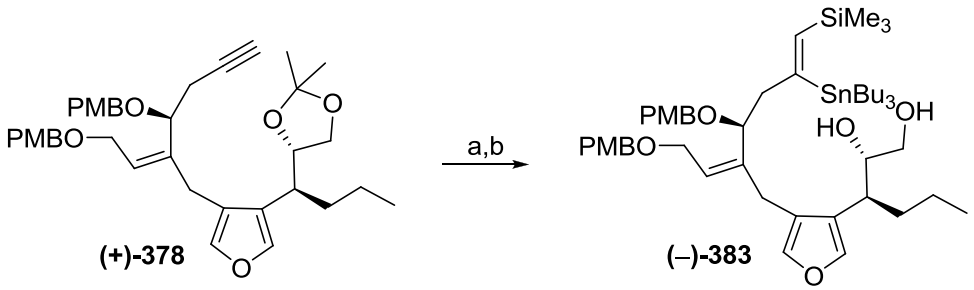
Conversion of the terminal alkyne to vinyl iodide using palladium-catalysed stannylation reactions

The palladium-catalysed hydrostannylation reaction, having proved high-yielding and regioselective previously (*cf*. Scheme 2.21), was applied to alkyne **(+)-378** (Scheme 2.66). After the hydrostannylation reaction, the ratio between the internal and external regioisomers was difficult to determine. The subsequent metal halogen exchange reaction was attempted, using iodine in dichloromethane on the mixture of isomers. However, even when the reaction mixture was maintained at 0 ºC, the PMB-ether groups and acetonide were not stable, and only small amounts of **381** and **382** could be isolated, as an inseparable mixture. Based on ^1H NMR analysis, equimolar amounts of the two regioisomers were produced at this stage.



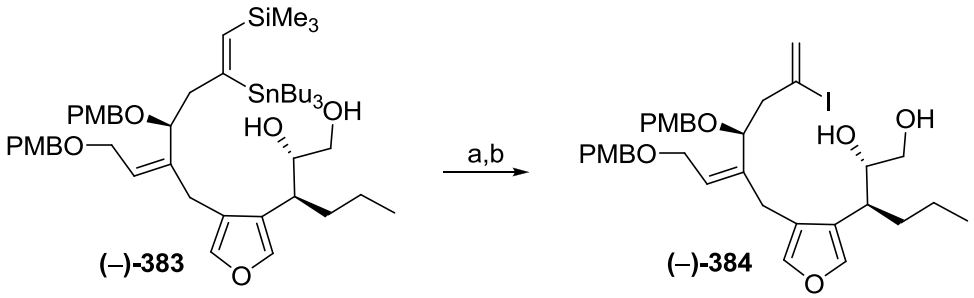
Scheme 2.66 – Reagents & conditions: a) Bu_3SnH, $Pd(PPh_3)_4$ (5 mol%), THF, rt; b) I_2, CH_2Cl_2, 0 ºC [<9%, **381**—**382** (1:1)].

Reduction of the unsaturated lactone had a dramatic impact on the regioselectivity of the palladium-catalysed hydrostannylation reaction. However, the sequence of palladium-catalysed silylstannylation followed by TMS removal using TBAF that had been unsuccessful during the synthesis of racemic material due to the presence of the unsaturated lactone could now be attempted (*cf*. Section 2.2.3, Table 2.4). The acetonide was cleaved using *p*-TSA[177] to afford the 1,2-diol and subsequent palladium-catalysed silylstannylation furnished **(−)-383** in 66% yield (Scheme 2.67).



Scheme 2.67 – Reagents & conditions: a) *p*-TSA, MeOH, rt [95%]; b) **272**, $Pd(PPh_3)_4$ (5 mol%), THF, 70 ºC [66%].

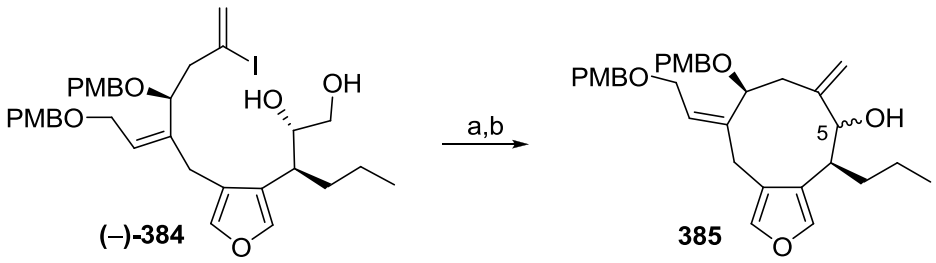
This time, using Fürstner's conditions,[117] desilylation of **(−)-383** using TBAF was accomplished without decomposition of the molecule (Scheme 2.68). However, the reaction required careful monitoring to minimise the formation of the destannylated product. The vinyl iodide **(−)-384** was subsequently formed at −78 ºC using NIS,[178] again with no sign of decomposition.



Scheme 2.68 – Reagents & conditions: a) *n*-Bu_4NF, DMSO, 80 ºC [77%]; b) NIS, CH_2Cl_2, −78 ºC [96%].

At this stage only a small amount of material was available for the intramolecular NHK reaction, and only one attempt to perform the reaction could be made. Oxidative cleavage of diol **(−)-384** provided the corresponding aldehyde smoothly and in a good yield (Scheme 2.69).[179] The conditions previously demonstrated to be optimal (*cf*. Section 2.2.4) for the NHK reaction were applied to the aldehyde, providing a mixture that was difficult to purify, especially due to the small scale of the reaction. Around

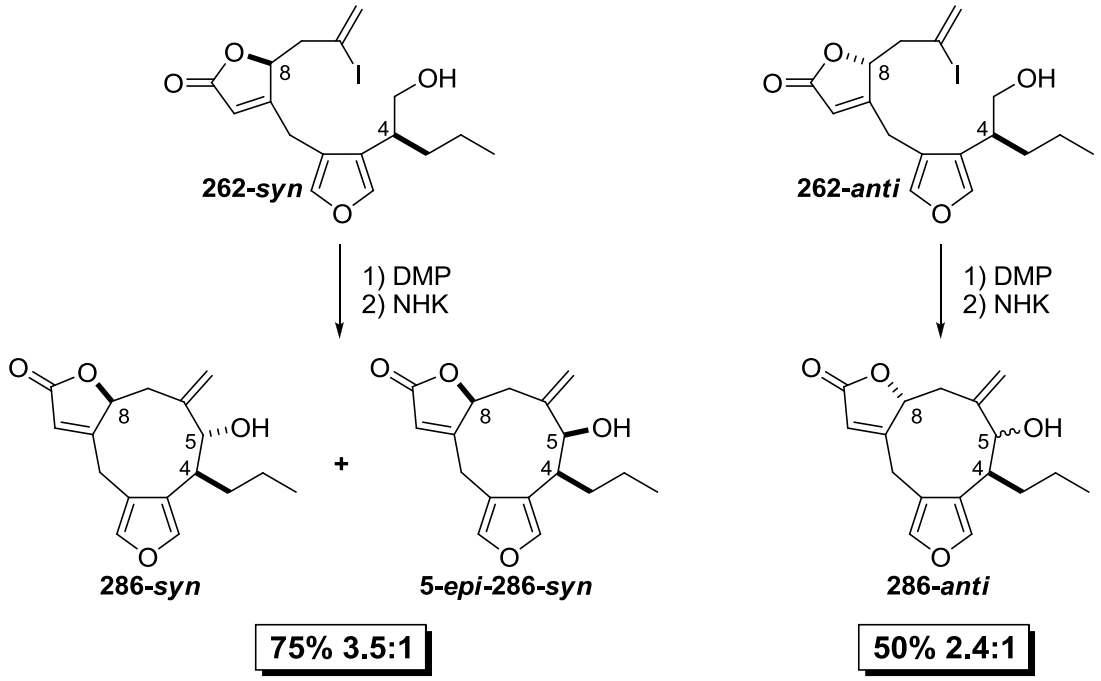
25% yield of the desired cyclised product could be isolated as an inseparable mixture of two diastereoisomers **385** (*dr* 3:1). The presence of homocoupled aldehyde in the mixture suggested that performing the reaction at lower concentration would have probably been beneficial. Unfortunately, there was insufficient quantity of substrate to permit a comprehensive study of this reaction.



Scheme 2.69 – Reagents & conditions: a) $NaIO_4$, MeOH, H_2O, 0 ºC [73%]; b) $CrCl_2$ (10 equiv), $NiCl_2$ (10 mol%), DMSO (0.007 M), 25 ºC [*ca* 25%, *dr* 3:1].

2.4 Summary and Future work

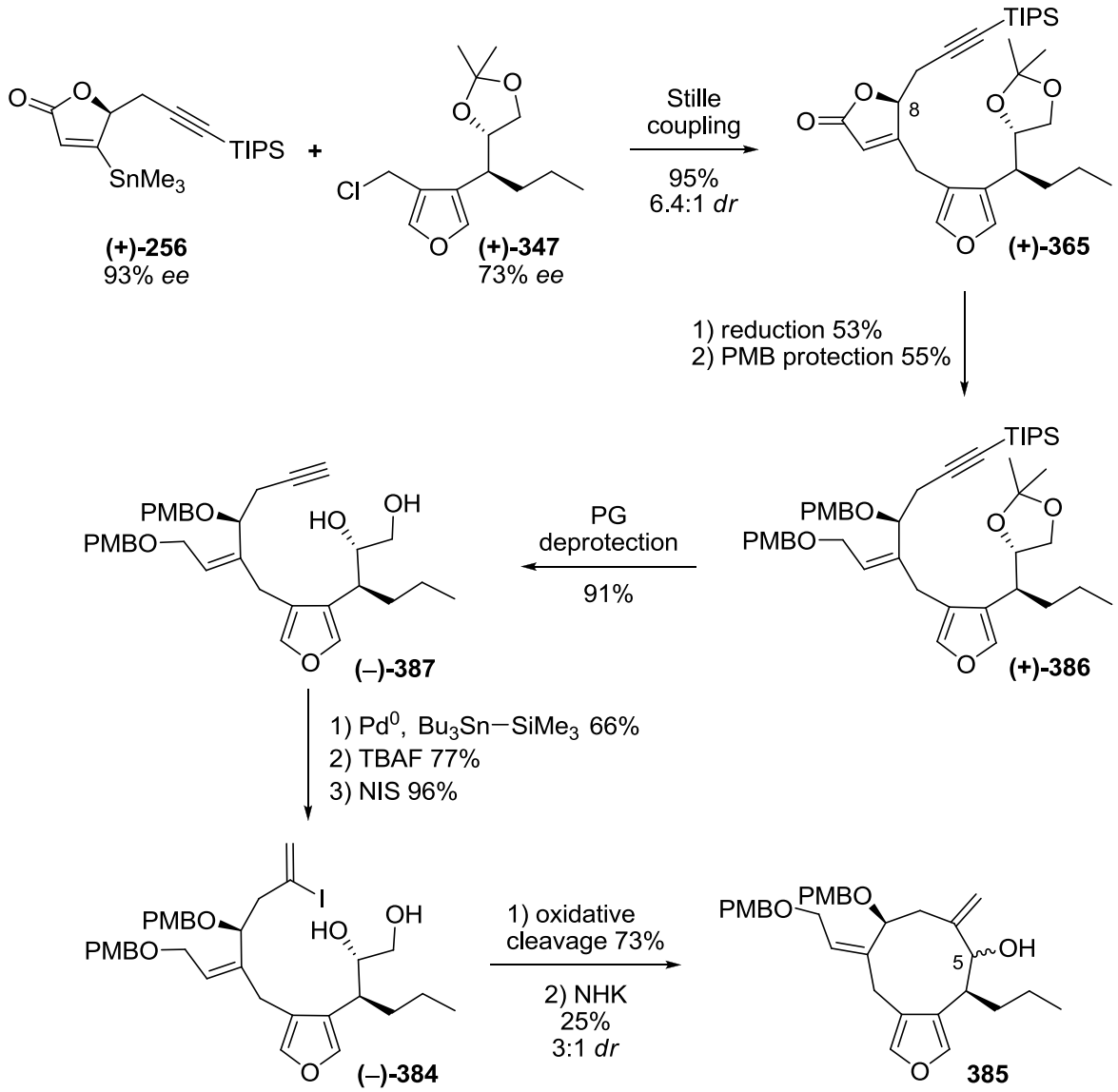
There has been an abundance of work from several research groups concerning the synthesis of the cornexistins and despite their apparent simple structure, the first total synthesis remains elusive. The first generation synthesis showed that the formation of the nine-membered ring could be achieved by NHK coupling (Scheme 2.70). The formation of the nine-membered ring was possible from **262-*syn*** and **262-*anti***, and the diastereoisomeric mixture obtained proved that the natural C-5 configuration of cornexistins could be installed.



Scheme 2.70

An asymmetric synthesis was also investigated (Scheme 2.71). The strength of the enantioselective strategy is the possible large scale synthesis of both chloride and stannane fragments, followed by their union through an efficient Stille coupling reaction. Epimerisation problems at C-8 necessitated a change in the post-coupling strategy, with reduction of the α,β-unsaturated lactone and protection of the diol to form **(+)-386**. After protecting group removal, a palladium-catalysed silylstannylation reaction, followed by TMS removal using TBAF, and tin-halogen exchange allowed formation of vinyl iodide **(−)-384**. Finally, a first approach to the intramolecular NHK reaction could be attempted on the aldehyde derived from **(−)-384**, and the ratio of diastereoisomers obtained from the reaction seemed to indicate a similar behaviour to that of the corresponding racemic intermediate. However, ending the project at such

an exciting stage is deeply frustrating. Improvements and a proposed strategy for the completion of the synthesis will be described briefly in the following section.



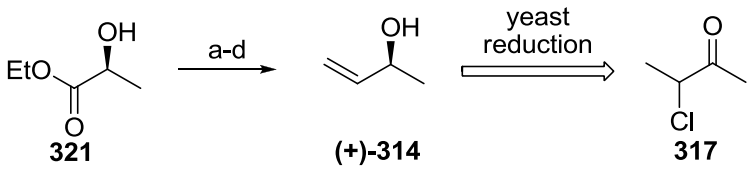
Scheme 2.71

2.4.1 Improvements to the syntheses of the chloride and stannane fragments

Asymmetric allylic alcohol synthesis

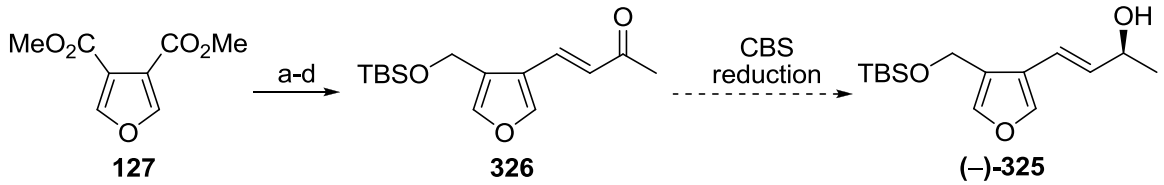
Although the chloride fragment synthesis was high-yielding, the method for the asymmetric synthesis of allylic alcohol **(+)-314** was difficult and unsatisfactory in terms of purity (Scheme 2.72). Accordingly, the method optimized by Ibrahim *et al.*[143] using a

specific strain of yeast to reduce selectively 3-chlorobutan-2-one **317** would certainly allow for an easier access to alcohol **(+)-314**, with improved purity.



Scheme 2.72 – a) DHP, PPTS (10 mol%), CH_2Cl_2, rt; b) DIBAL-H, CH_2Cl_2, −78 ºC; c) PPh_3MeBr, KO*t*-Bu, THF, rt; d) *p*-TSA (5 mol%), ethylene glycol, rt [56% over 4 steps];

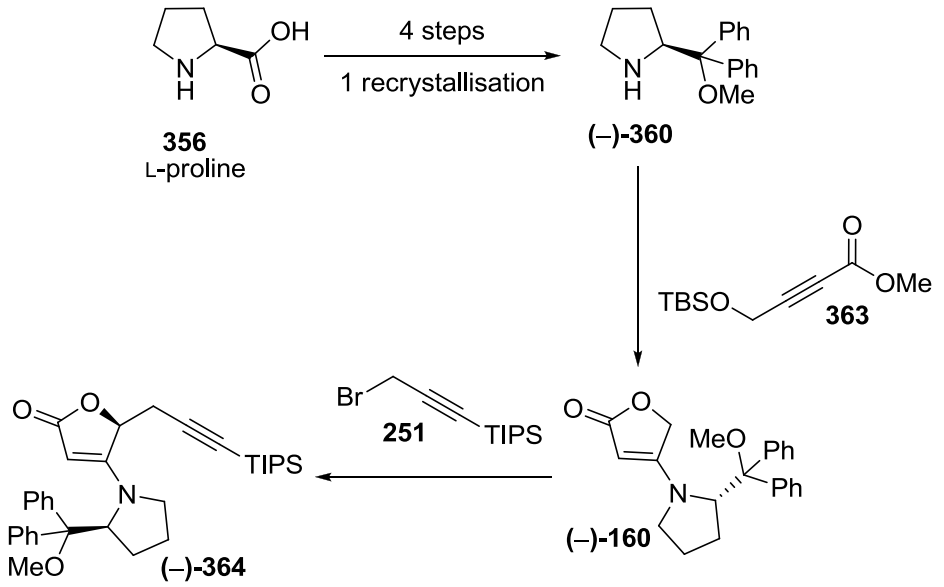
Alternatively, enone **326** is easily accessible and CBS reduction of this compound could be envisaged to introduce the desired stereocentre (Scheme 2.73).[140-141]



Scheme 2.73 – Reagents & conditions: a) $LiAlH_4$, THF, −78 ºC to rt; b) MnO_2, CH_2Cl_2, rt; c) TBSCl, imidazole, DMAP, CH_2Cl_2, rt; d) 1-(triphenylphosphoranylidene)acetone, toluene, 100 ºC [57% (4 steps)].

Asymmetric stannane synthesis

Considering the work done so far, the use of a chiral auxiliary offered an efficient approach to the enantioselective synthesis of hydroxycornexistin. Its preparation could be conducted on large scale with a single purification step (Scheme 2.74). Direct condensation of the proline derivative proved to be less efficient than the method previously described by Northall and Marlin,[41,60] which should be the method of choice. The subsequent alkylation was not as highly selective as it could have been in the case of a C-2 symmetrical auxiliary, but the yield was high, and the diastereoisomers obtained were separable.

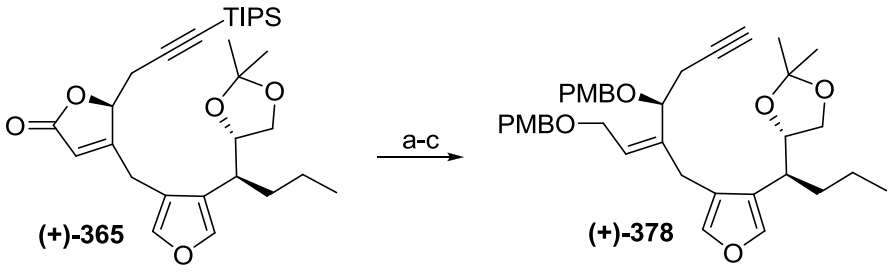


Scheme 2.74

2.4.2 Coupled fragments and future work

Improvement of the reduction—protection sequence

The reduction—protection sequence remains to be improved (Scheme 2.75). Although lactone reduction with lithium aluminium hydride and TMEDA gave respectable results, milder conditions like DIBAL-H—$NaBH_4$ might avoid the formation of the undesired 1,4-reduction products.[180]

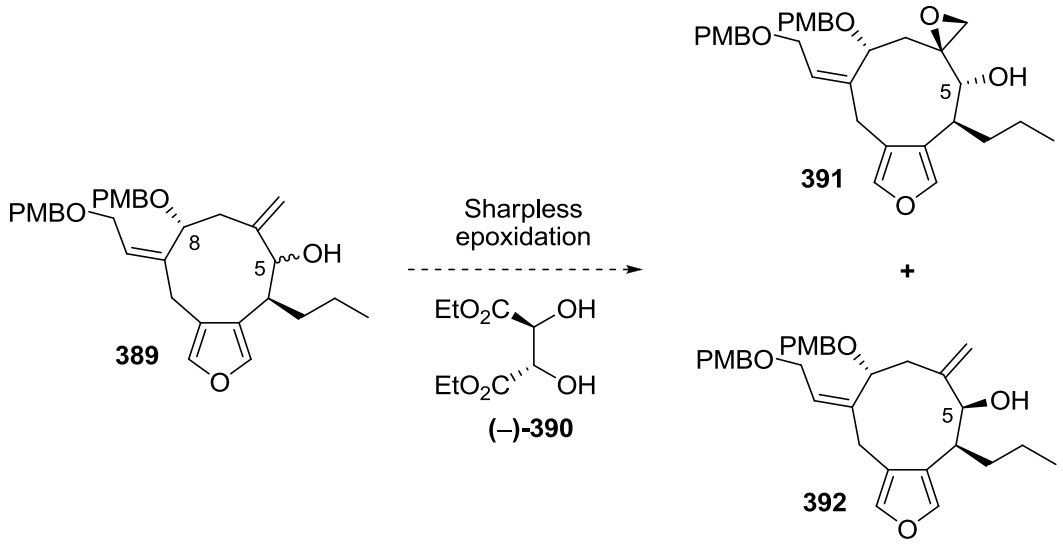


Scheme 2.75 – Reagents & conditions: a) $LiAlH_4$, TMEDA, Et_2O, −78 °C to 0 °C [53%]; b) PMBCl, NaH, *n*-Bu_4NI (12 mol%), DMF, 0 °C to rt [55%]; b) TBAF, THF, 0 °C [96%].

Diastereoselectivity of the NHK

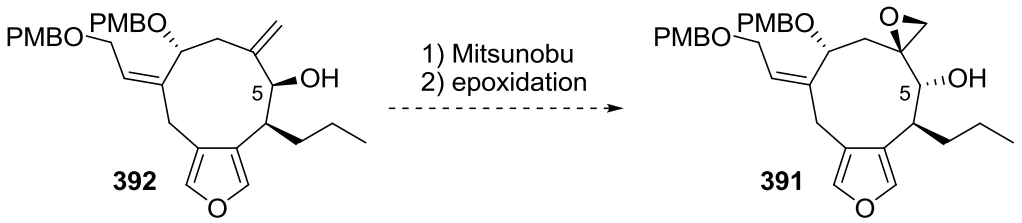
For the NHK cyclisation, a closer study of the dilution factor is needed to improve the yield of the reaction. If the yield of the cyclisation reaction is actually improved for the

model substrate, a similar yield could be obtained with the desired C-8 isomer **389** (Scheme 2.76), and its synthesis could be accomplished. This would require starting from the more expensive D-proline, but all the steps in the reaction sequence leading to the NHK are operational. The diastereoselectivity of the NHK reaction could be improved using a chiral ligand, or by further investigating an oxidation—reduction sequence analogous to that attempted during the first generation synthesis (*cf*. Scheme 2.24). For the completion of the target, Sharpless epoxidation should be a suitable method for the kinetic resolution of the mixture (Scheme 2.76). The use of diethyl tartrate **(−)-390** would furnished the desired epoxide **391**,[181] and the undesired diastereoisomer **392** could be recovered and converted to the desired diastereoisomer *via* a Mitsunobu inversion sequence.



Scheme 2.76

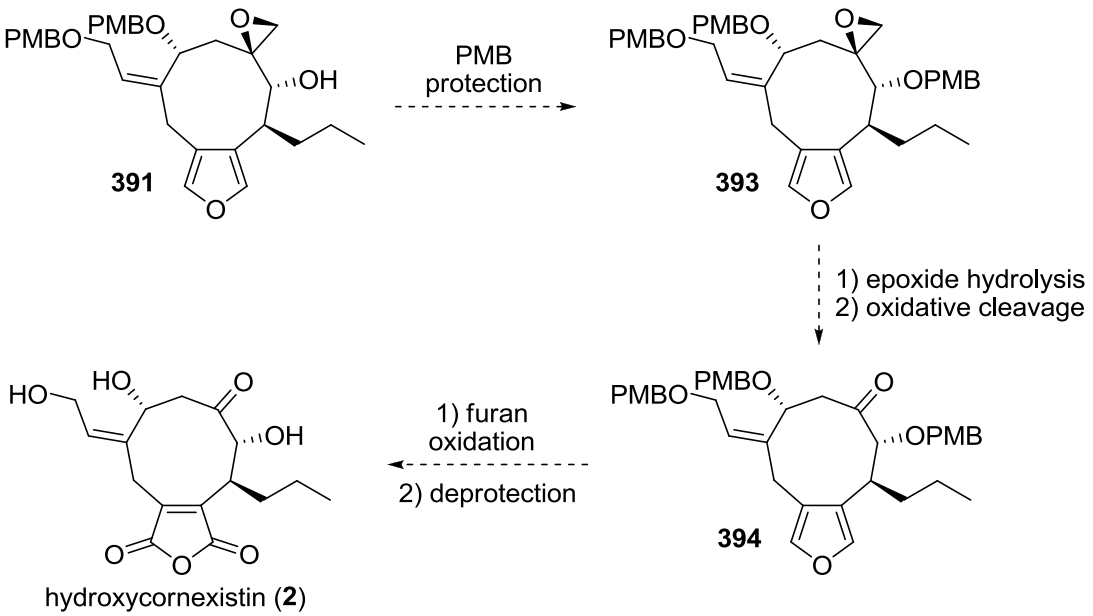
Although the inversion of the C-5 stereocentre has been attempted by Northall and found to be problematic, the substrates are different (*cf*. Section 1.4.4).[41] In this case, the alcohol **392** is allylic and there is a literature precedent for inversion of configuration in related systems.[182] Using *p*-nitrobenzoic acid and DIAD, the C-5 stereocentre could be inverted to provide **391** after epoxidation (Scheme 2.77).



Scheme 2.77

Completion of the total synthesis of hydroxycornexistin

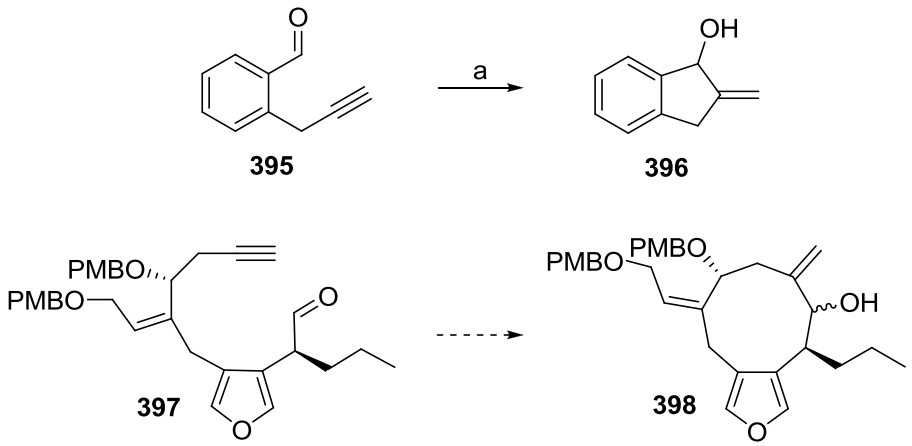
The final steps of the synthesis are proposed below (Scheme 2.78). There is a precedent in the literature for the PMB protection of an alcohol in the presence of an epoxide, followed by basic epoxide hydrolysis.[183] Subsequent oxidative cleavage of the diol would deliver ketone **394**. Finally, the furan oxidation—deprotection sequence has already been achieved by Northall during his synthesis of 5-*epi*-hydroxycornexistin.[41,51b]



Scheme 2.78

Alternative to the NHK cyclisation

In 2006, the group of Takai reported the hydrochromination of alkynes using a nickel catalyst. The reductive couplings of alkynes and aldehydes shown were mostly intermolecular aside from the reaction shown in Scheme 2.79.[184] The substrate **398** presents a considerable challenge (nine-membered ring) when compared with the reported example **396** (five-membered ring) but this approach is worth considering, given the efficiency that would be achieved.



Scheme 2.79 – Reagents & conditions: a) $CrCl_2$, H_2O, $NiCl_2$ (cat.), PPh_3 (cat.), DMF, 25 °C [64%].[184]

Part III: Experimental part

General remarks

Air and/or moisture sensitive reactions were performed under an atmosphere of Argon in flame dried apparatus. Organic solvents were dried using a Pure Solv™ solvent purification system (SPS). All reagents were purchased from commercial suppliers and used without further purification, unless otherwise stated. All reactions were monitored by thin layer chromatography using Merck silica gel 60 covered alumina plates F^{254}. Thin layer chromatography plates were viewed under UV light or were visualised using either potassium permanganate solution or acidic ethanolic anisaldehyde solution. Column chromatography was performed under pressure using silica gel (Fluorochem LC60A, 35-70 micron, 60 Å) as solid support and HPLC-graded solvents as eluent. Petroleum ether used for column chromatography was 40—60 °C fraction.

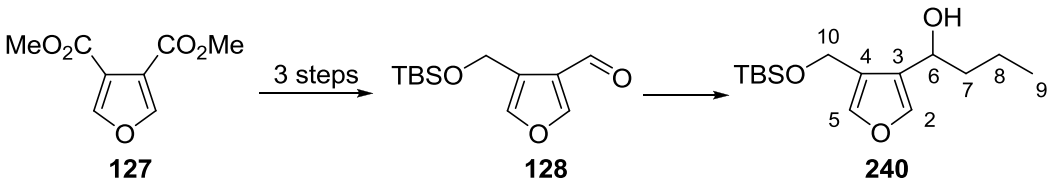
IR spectra were recorded using a type IIa diamond single reflection element on a Shimadzu FTIR-8400 instrument. The IR spectrum of the compound (solid or liquid) was directly detected as a thin layer at ambient temperature.

^{1}H NMR spectra were recorded on a Bruker 400 MHz or 500 MHz Spectrospin spectrometer at ambient temperature. IUPAC numbering is used for the molecule names. Numbers assigned for the molecule characterisations are not related to the name of the molecule. Data are reported as follows: chemical shift in ppm relative to $CDCl_3$ (7.26) on the δ scale, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad, app = apparent or a combination of these), coupling constant(s) *J* (Hz) and assignment. ^{13}C NMR spectra were recorded on a Bruker 400 MHz or 500 MHz Spectrospin spectrometer at 101 MHz or 126 MHz at ambient temperature and multiplicities were obtained using a DEPT sequence. Data are reported as follows: chemical shift in ppm relative to $CHCl_3$ (77.16) on the δ scale and assignment. High resolution mass spectra (HRMS) were obtained under EI, FAB, CI and ESI conditions by the analytical services of the University of Glasgow on a Jeol MStation JMS-700 instrument. Low resolution mass spectra (LRMS) were carried out on the same instrument; the intensity of each peak is quoted as a percentage of the largest, where this information was available.

Elemental analyses were carried out on an Exeter Analytical Elemental Analyser EA 440.

Melting points were recorded with an Electrothermal IA 9100 apparatus.

1-[4-(*tert*-Butyldimethylsilyloxy)methylfuran-3-yl]butan-1-ol (240)



To a suspension of $LiAlH_4$ (4.74 g, 125 mmol, 2.30 equiv) in THF (200 mL) at −78 °C was added a solution of diester **127** (10.0 g, 54.3 mmol) in THF (200 mL) over 20 min at −78 °C. The solution was gently warmed to rt over 2 h and stirred overnight. The reaction was cooled to 0 °C and quenched carefully with successively water (4.7 mL), aqueous NaOH (1 M, 4.7 mL) and water (13 mL). After warming up to rt and stirring for 1 h, a cloudy white suspension was formed. $MgSO_4$ (*ca* 15 g) was added and the mixture was filtered through a pad of Celite and washed with EtOAc (1 L). After concentration *in vacuo*, the pale yellow oil obtained was used directly for the next step.

To a solution of the crude oil obtained (6.95 g, ~54.3 mmol) in CH_2Cl_2 (450 mL) was added activated MnO_2 (28.3 g, 326 mmol, 6.00 equiv) at rt. The mixture was stirred vigorously for 2.5 h and MnO_2 (9.50 g, 108 mmol, 2.00 equiv) was added 3 times at regular intervals. The black suspension was then filtered through a pad of Celite and washed with CH_2Cl_2 (1.5 L). After concentration *in vacuo*, the crude yellow oil was separated in two fractions: **A** (3.46 g) and **B** (3.72 g) and used in the next step without any further purification.

To a solution of the crude aldehyde **A** (3.46 g, ~27.5 mmol) in CH_2Cl_2 (250 mL), imidazole (2.24 g, 33.0 mmol, 1.20 equiv), DMAP (336 mg, 2.75 mmol, 0.100 equiv) and TBSCl (4.55 g, 30.2 mmol, 1.10 equiv) were added sequentially. The solution was stirred for 20 min at rt, before water (60 mL) was added. The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 60 mL) and the organic extracts were combined, washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The pale yellow oil was used immediately in the next step.

To a solution of the silylated aldehyde **128** (~27.5 mmol) in THF (250 mL) at −78 °C was added dropwise *n*-propylmagnesium chloride (23.3 mL of a 1.0 M solution in THF, 46.7 mmol, 1.70 equiv). The solution was stirred at −78 °C for 1.5 h, warmed to 0 °C and the reaction was quenched with saturated aqueous NH_4Cl (35 mL). Water (35 mL) and Et_2O (60 mL) were added and the phases separated. The aqueous phase was extracted with Et_2O (2 × 60 mL), the organic extracts washed with brine (120 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (PE—Et_2O, 9:1) to give the desired colourless oil.

The same procedure was adapted for aldehyde **B**, affording once combined 10.7 g (69% over 4 steps) of the corresponding alcohol **240**.

$C_{15}H_{28}O_3Si$ **Molecular weight: 284.47 g·mol^{-1}**

R_f = 0.34 (PE—Et_2O, 9:1);

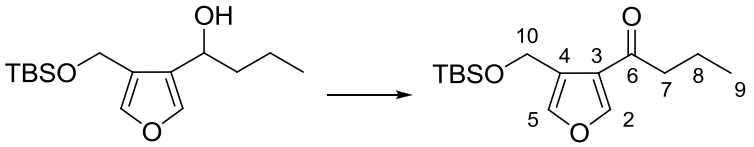
IR ν_{max} 3349, 2955, 2929, 2858, 1749, 1521 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, s, CH-C2 and CH-C5), 4.65 (1H, d, *J* = 12.2 Hz, CH_2-C10), 4.61 (1H, d, *J* = 12.2 Hz, CH_2-C10), 4.60 (1H, dt, *J* = 7.9, 5.6 Hz, CH-C6), 3.58 (1H, d, *J* = 5.6 Hz, OH), 1.84 (1H, dddd, *J* = 13.4, 9.8, 7.9, 5.5 Hz, CH_2-C7), 1.73 (1H, dddd, *J* = 13.4, 9.8, 5.9, 5.6 Hz, CH_2-C7), 1.57—1.48 (1H, m, CH_2-C8), 1.43—1.34 (1H, m, CH_2-C8), 0.96 (3H, t, *J* = 7.4 Hz, CH_3-C9), 0.91 (9H, s, 3×CH_3-*t*Bu), 0.12 (3H, s, CH_3-SiMe_2), 0.12 (3H, s, CH_3-SiMe_2);

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6 (CH-C2 or CH-C5), 140.1 (CH-C2 or CH-C5), 128.5 (C-C3 or C-C4), 123.7 (C-C3 or C-C4), 65.8 (CH-C6), 56.8 (CH_2-C10), 38.5 (CH_2-C7), 26.0 (3×CH_3-*t*Bu), 19.5 (CH_2-C8), 18.4 (C-*t*Bu), 14.1 (CH_3-C9), −5.2 (CH_3-SiMe_2), −5.2 (CH_3-SiMe_2);

LRMS (CI, Me_3CH): *m/z* (*int*) 267 (31), 135 (49), 107 (9), 89 (100), 69 (20). HRMS (CI, Me_3CH) calculated for $C_{15}H_{27}O_2Si$ [M−OH]$^+$: 267.1780, found 267.1775, Δ −1.9 ppm.

1-[4-(*tert*-Butyldimethylsilyloxy)methylfuran-3-yl]butan-1-one (399)



To a solution of alcohol **240** (522 mg, 1.94 mmol) in CH_2Cl_2 (20 mL) was added activated MnO_2 (3.43 g, 38.9 mmol, 20.0 equiv). The mixture was stirred at rt for 2 h, then 2 h at reflux, and stirred overnight at rt. The suspension was filtered through a pad of Celite and washed with CH_2Cl_2 (500 mL). The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography (PE—Et_2O, 95:5), affording the desired ketone **399** (468 mg, 86%) as a colourless oil.

$C_{15}H_{26}O_3Si$ **Molecular weight: 282.45 g·mol^{-1}**

R_f = 0.63 (PE—Et_2O, 9:1);

IR ν_{max} 2957, 2929, 2885, 2858, 2361, 1676, 1535, 1464 cm^{-1};

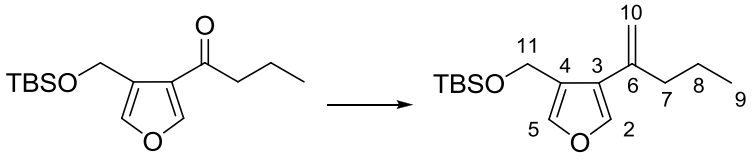
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (1H, d, *J* = 1.7 Hz, CH-C2), 7.40 (1H, dd, *J* = 1.7, 1.7 Hz, CH-C5), 4.87 (2H, d, *J* = 1.7 Hz, CH_2-C10), 2.69 (2H, t, *J* = 7.3 Hz, CH_2-C7), 1.72 (2H, qt, *J* = 7.4, 7.3 Hz, CH_2-C8), 0.97 (3H, t, *J* = 7.4 Hz, CH_3-C9), 0.93 (9H, s, 3×CH_3-*t*Bu), 0.10 (6H, s, 2×CH_3-SiMe_2);

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.3 (C-C6), 148.5 (CH-C2 or CH-C5), 141.6 (CH-C2 or CH-C5), 127.1 (C-C3 or C-C4), 125.4 (C-C3 or C-C4), 58.8 (CH_2-C10), 42.3 (CH_2-C7), 26.1

(3×CH_3-*t*Bu), 18.5 (C-*t*Bu), 17.9 (CH_2-C8), 14.0 (CH_3-C9), −5.3 (CH_3-SiMe_2), −5.3 (CH_3-SiMe_2);

LRMS (CI, Me_3CH): *m/z* (*int*) 283 (46), 225 (8), 89 (100), 69 (10). HRMS (CI, Me_3CH) calculated for $C_{15}H_{27}O_3Si$ $[M+H]^+$: 283.1729, found 283.1732, Δ +0.7 ppm.

tert-Butyldimethyl[4-(pent-1-en-2-yl)furan-3-yl]methoxysilane (241)



To a suspension of methyltriphenylphosphonium bromide (2.87 g, 8.03 mmol, 5.00 equiv) in THF (7.5 mL) at 0 °C was added dropwise a solution of NaHMDS (6.4 mL of a 1.0 M solution in THF, 6.4 mmol, 4.0 equiv). The bright yellow suspension was warmed to rt and stirred for 1 h, before being cooled down to 0 °C. A solution of ketone **399** (453 mg, 1.60 mmol) in THF (7 mL) was added dropwise and the mixture was stirred for 1 h at rt. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and the mixture was diluted with Et_2O (30 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE—Et_2O, 99:1) to give the corresponding 1,1-disubstituted alkene **241** (426 mg, 95%) as a colourless oil.

$C_{16}H_{28}O_2Si$ **Molecular weight: 280.48 g·mol^{-1}**

R_f = 0.91 (PE—Et_2O, 95:5);

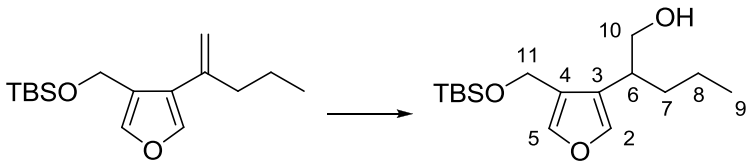
IR ν_{max} 2957, 2930, 2857, 1636, 1585, 1535, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, s, CH-C2), 7.34 (1H, s, CH-C5), 5.12 (1H, s, CH_2-C10), 5.00 (1H, d, *J* = 0.9 Hz, CH_2-C10), 4.63 (2H, s, CH_2-C11), 2.29 (2H, t, *J* = 7.4 Hz, CH_2-C7), 1.51 (2H, qt, *J* = 7.4, 7.4 Hz, CH_2-C8), 0.94—0.89 (12H, m, CH_3-C9 and 3×CH_3-*t*Bu), 0.08 (6H, s, 2×CH_3-SiMe_2);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4 (CH-C5), 140.5 (CH-C2), 139.8 (C-C6), 125.7 (C-C3 or C-C4), 124.7 (C-C3 or C-C4), 112.6 (CH_2-C10), 57.6 (CH_2-C11), 38.6 (CH_2-C7), 26.0 (3×CH_3-*t*Bu), 21.5 (CH_2-C8), 18.5 (C-*t*Bu), 14.0 (CH_3-C9), −5.1 (2×CH_3-SiMe_2);

HRMS (ESI) calculated for $C_{16}H_{28}NaO_2Si$ $[M+Na]^+$: 303.1751, found 303.1744, Δ −2.2 ppm.

2-[4-(*tert*-Butyldimethylsilyloxymethyl)furan-3-yl]pentan-1-ol (242)



241 **242**

To a solution of 1,1-disubstituted alkene **241** (1.07 g, 3.83 mmol) in THF (4 mL), cooled to 0 °C, was added dropwise a solution of 9-BBN (23.0 mL of a 0.5 M solution in THF, 11.5 mmol, 3.01 equiv). The reaction was then warmed to 65 °C for 75 min, cooled to 0 °C before careful addition of EtOH (18 mL) and aqueous NaOH (3 M, 11.5 mL). After 15 min, aqueous H_2O_2 (30%, 18 mL) was added. The mixture was heated at reflux for 1 h, cooled to rt before the addition of Et_2O (60 mL) and water (20 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 50 mL). The organic extracts were combined and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 9:1) to give the desired primary alcohol **242** (1.01 g, 88%) as a colourless oil.

$C_{16}H_{30}O_3Si$ **Molecular weight: 298.49 g·mol^{-1}**

R_f = 0.18 (PE—Et_2O, 9:1);

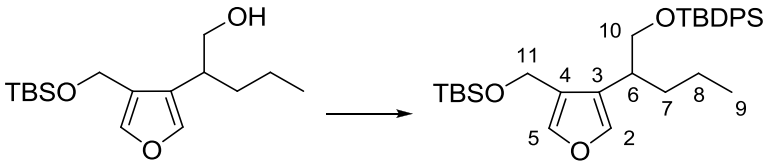
IR ν_{max} 3381, 2955, 2929, 2858, 1602, 1541, 1471, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, d, *J* = 1.6 Hz, CH-C5), 7.23 (1H, d, *J* = 1.6 Hz, CH-C2), 4.55 (2H, d, *J* = 1.0 Hz, CH_2-C11), 3.73 (1H, ddd, *J* = 10.8, 6.6, 4.9 Hz, CH_2-C10), 3.61 (1H, ddd, *J* = 10.8, 7.3, 6.0 Hz, CH_2-C10), 2.83—2.75 (1H, m, CH-C6), 2.17 (1H, dd, *J* = 6.3, 6.0 Hz, OH), 1.67—1.57 (1H, m, CH_2-C7), 1.56—1.48 (1H, m, CH_2-C7), 1.38—1.27 (2H, m, CH_2-C8), 0.91 (9H, s, 3×CH_3-*t*Bu), 0.89 (3H, t, *J* = 5.9 Hz, CH_3-C9), 0.10 (6H, s, 2×CH_3-SiMe_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1 (CH-C5), 140.6 (CH-C2), 125.6 (C-C3 or C-C4), 124.9 (C-C3 or C-C4), 66.8 (CH_2-C10), 56.5 (CH_2-C11), 38.1 (CH-C6), 33.8 (CH_2-C7), 26.0 (3×CH_3-*t*Bu), 20.8 (CH_2-C8), 18.5 (C-*t*Bu), 14.2 (CH_3-C9), −5.2 (2×CH_3-SiMe_2);

HRMS (ESI) calculated for $C_{16}H_{30}NaO_3Si$ $[M+Na]^+$: 321.1856, found 321.1846, Δ −3.1 ppm.

tert-Butyl-[4-(1-_tert_-butyldiphenylsilyloxypentan-2-yl)furan-3-yl]methoxy-dimethylsilane (245)



242 **245**

To a solution of alcohol **242** (1.72 g, 5.78 mmol) in CH_2Cl_2 (58 mL), DMAP (203 mg, 2.98 mmol, 0.500 equiv), TBDPSCl (2.26 mL, 8.67 mmol, 1.50 equiv) and Et_3N (1.37 mL, 9.83 mmol, 1.70 equiv) were successively added at 0 °C. The solution was stirred overnight at rt and quenched with saturated aqueous NH_4Cl (20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The organic extracts were combined and washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—CH_2Cl_2, 9:1) affording product **245** (2.81 g, 91%) as a colourless oil.

$C_{32}H_{48}O_3Si_2$ **Molecular weight: 536.89 g·mol^{-1}**

R_f = 0.50 (PE—CH_2Cl_2, 8:2);

IR ν_{max} 3073, 3049, 2955, 2930, 2857, 1589, 1541, 1471, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (4H, ddd, *J* = 7.9, 4.9, 1.5 Hz, 4×CH-Ar), 7.44—7.33 (6H, m, 6×CH-Ar), 7.27 (1H, d, *J* = 0.8 Hz, CH-C5), 7.17 (1H, d, *J* = 0.8 Hz, CH-C2), 4.45 (2H, s, CH_2-C11), 3.67 (1H, dd, *J* = 10.1, 5.8 Hz, CH_2-C10), 3.63 (1H, dd, *J* = 10.1, 6.4 Hz, CH_2-C10), 2.75 (1H, dddd, *J* = 8.6, 6.4, 6.1, 5.8 Hz, CH-C6), 1.78 (1H, app ddt, *J* = 13.3, 9.7, 6.1 Hz, CH_2-C7), 1.54—1.44 (1H, m, CH_2-C7), 1.35—1.20 (2H, m, CH_2-C8), 1.02 (9H, s, 3×CH_3-*t*Bu), 0.90—0.84 (12H, m, 3×CH_3-*t*Bu and CH_3-C9), 0.04 (3H, s, CH_3-$SiMe_2$), 0.03 (3H, s, CH_3-$SiMe_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4 (CH-C5 or CH-C2), 140.0 (CH-C2 or CH-C5), 135.8 (2×CH-Ar), 135.7 (2×CH-Ar), 133.9 (2×C-Ar), 129.7 (CH-Ar), 129.7 (CH-Ar), 127.7 (4×CH-Ar), 125.6 (C-C4 or C-C3), 125.5 (C-C4 or C-C3), 67.3 (CH_2-C10), 56.9 (CH_2-C11), 37.5 (CH-C6), 34.0 (CH_2-C7), 27.0 (3×CH_3-*t*Bu), 26.0 (3×CH_3-*t*Bu), 20.5 (CH_2-C8), 19.4 (C-*t*Bu), 18.4 (C-*t*Bu), 14.4 (CH_3-C9), −5.2 (2×CH_3-$SiMe_2$);

LRMS (CI, Me_3CH): *m/z* (*int*) 537 (5), 461 (27), 447 (12), 405 (100), 133 (13). HRMS (CI, Me_3CH) calculated for $C_{32}H_{49}O_3Si_2$ $[M+H]^+$: 537.3220, found 537.3221, Δ +0.1 ppm.

2-(4-Hydroxymethylfuran-3-yl)pentan-1-ol (246)

245 **246**

To a solution of the silylated product **245** (388 mg, 0.724 mmol) in MeOH (7 mL) was added CSA (50.4 mg, 0.217 mmol, 0.300 equiv) at rt and the mixture was stirred for 2 h at rt. K_2CO_3 (*ca* 100 mg) was added and the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (PE—Et_2O, 5:5 to 2:8) to give diol **246** (40.0 mg, 30%) as a colourless oil.

$C_{10}H_{16}O_3$ **Molecular weight: 184.23 g·mol^{-1}**

R_f = 0.25 (PE—Et_2O, 2:8);

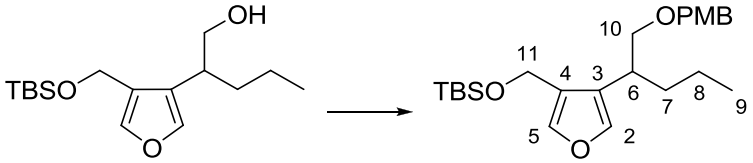
IR ν_{max} 3294, 2957, 2931, 2872, 2360, 1600, 1541, 1465 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (1H, d, *J* = 1.5 Hz, CH-C5), 7.23 (1H, d, *J* = 1.5 Hz, CH-C2), 4.46 (2H, s, CH_2-C11), 3.79 (1H, dd, *J* = 10.2, 4.5 Hz, CH_2-C10), 3.55 (1H, dd, *J* = 10.2, 8.5 Hz, CH_2-C10), 3.18 (1H, br s, OH), 2.79 (1H, tdd, *J* = 8.5, 6.1, 4.5 Hz, CH-C6), 2.67 (1H, br s, OH), 1.63—1.49 (2H, m, CH_2-C7), 1.38—1.27 (2H, m, CH_2-C8), 0.89 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4 (CH-C5), 140.3 (CH-C2), 126.3 (C-C3 or C-C4), 125.5 (C-C3 or C-C4), 67.9 (CH_2-C10), 54.9 (CH_2-C11), 37.6 (CH-C6), 33.7 (CH_2-C7), 20.8 (CH_2-C8), 14.2 (CH_3-C9);

HRMS (ESI) calculated for $C_{10}H_{16}NaO_3$ $[M+Na]^+$: 207.0992, found 207.0995, Δ −1.4 ppm.

***tert*-Butyl{4-[1-(4-methoxyphenyl)methoxypentan-2-yl]furan-3-yl}methoxydimethylsilane (247)**



242 **247**

To a solution of alcohol **242** (54.8 mg, 0.184 mmol) in CH_2Cl_2 (1.8 mL) at rt was added freshly prepared PMBTCA (118 mg, 0.414 mmol, 2.25 equiv) and CSA (4.0 mg, 0.02 mmol, 0.09 equiv). The mixture was stirred at rt for 48 h and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). Et_2O (15 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

The crude product was purified by flash column chromatography (PE—Et_2O, 95:5) affording PMB-ether **247** (26.9 mg, 35%) as a colourless oil.

$C_{24}H_{38}O_4Si$ **Molecular weight: 418.64 g·mol^{-1}**

R_f = 0.93 (PE—Et_2O, 8:2);

IR ν_{max} 2955, 2929, 2857, 2362, 2332, 1612, 1514, 1464 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (1H, t, *J* = 0.9 Hz, CH-C5), 7.22 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 7.18 (1H, d, *J* = 1.6 Hz, CH-C2), 6.87 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 4.53 (2H, d, *J* = 0.9 Hz, CH_2-C11), 4.42 (2H, s, CH_2-PMB), 3.80 (3H, s, CH_3-PMB), 3.51 (1H, dd, *J* = 9.1, 5.5 Hz, CH_2-C10), 3.44 (1H, dd, *J* = 9.1, 7.0 Hz, CH_2-C10), 2.83 (1H, app ddt, *J* = 9.0, 7.0, 5.5 Hz, CH-C6), 1.74 (1H, app ddt, *J* = 13.3, 10.1, 5.5 Hz, CH_2-C7), 1.49 (1H, app ddt, *J* = 13.3, 9.0, 5.2 Hz, CH_2-C7), 1.35—1.20 (2H, m, CH_2-C8), 0.91 (9H, s, 3×CH_3-*t*Bu), 0.87 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.06 (6H, s, 2×CH_3-SiMe_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2 (C-PMB), 140.2 (CH-C2 or CH-C5), 140.2 (CH-C2 or CH-C5), 130.8 (C-PMB), 129.3 (2×CH-PMB), 125.6 (C-C3 or C-C4), 125.5 (C-C3 or C-C4), 113.9 (2×CH-PMB), 74.0 (CH_2-C10), 72.8 (CH_2-PMB), 57.0 (CH_2-C11), 55.4 (CH_3-PMB), 35.6 (CH-C6), 34.6 (CH_2-C7), 26.1 (3×CH_3-*t*Bu), 20.6 (CH_2-C8), 18.5 (C-*t*Bu), 14.3 (CH_3-C9), −5.2 (2×CH_3-SiMe_2);

HRMS (ESI) calculated for $C_{24}H_{38}NaO_4Si$ $[M+Na]^+$: 441.2432, found 441.2417, Δ +1.4 ppm.

[4-(1-*tert*-Butyldiphenylsilyloxypentan-2-yl)furan-3-yl]methanol (248)

245 **248**

To a solution of silylated furan **245** (2.81 g, 5.24 mmol) in EtOH (18 mL) was added PPTS (660 mg, 2.62 mmol, 0.506 equiv) and the mixture was stirred overnight at 40 ºC. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and ethanol was removed *in vacuo*. The residue was diluted in Et_2O (20 mL), the phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The organic extracts were combined and washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 9:1) to give the desired alcohol **248** (2.09 g, 95%) as a colourless oil.

$C_{26}H_{34}O_3Si$ **Molecular weight: 422.63 g·mol^{-1}**

R_f = 0.20 (PE—Et_2O, 9:1);

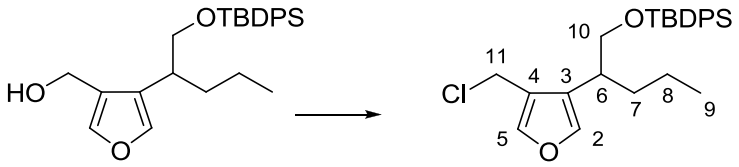
IR ν_{max} 3366, 2042, 2893, 2866, 1757, 1600, 1541, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62—7.53 (4H, m, 4×CH-Ar), 7.45—7.34 (7H, m, CH-C5, 6×CH-Ar), 7.19 (1H, d, *J* = 1.5 Hz, CH-C2), 4.42 (2H, d, *J* = 5.4 Hz, CH_2-C11), 3.72 (1H, dd, *J* = 9.8, 5.7 Hz, CH_2-C10), 3.63 (1H, dd, *J* = 9.8, 7.0 Hz, CH_2-C10), 2.81 (1H, ddt, *J* = 9.1, 6.8, 5.7 Hz, CH-C6), 1.95 (1H, t, *J* = 5.4 Hz, OH), 1.69 (1H, dddd, *J* = 13.1, 9.5, 6.4, 5.7 Hz, CH_2-C7), 1.54—1.42 (1H, m, CH_2-C7), 1.37—1.20 (2H, m, CH_2-C8), 1.02 (9H, s, 3×CH_3-*t*Bu), 0.87 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5 (CH-C5 or CH-C2), 140.5 (CH-C2 or CH-C5), 135.8 (2×CH-Ar), 135.7 (2×CH-Ar), 133.4 (C-Ar), 133.4 (C-Ar), 129.8 (2×CH-Ar), 127.8 (2×CH-Ar),127.7 (2×CH-Ar), 126.1 (C-C4 or C-C3), 125.4 (C-C4 or C-C3), 68.7 (CH_2-C10), 55.5 (CH_2-C11), 37.3 (CH-C6), 34.0 (CH_2-C7), 26.9 (3×CH_3-*t*Bu), 20.6 (CH_2-C8), 19.3 (C-*t*Bu), 14.3 (CH_3-C9);

LRMS (CI, Me_3CH): *m/z* (*int*) 405 (34), 365 (6), 341 (5), 265 (100), 237 (12), 217 (75) 135 (9). HRMS (CI, Me_3CH) calculated for $C_{26}H_{33}O_2Si$ [M−OH]$^+$: 405.2250, found 405.2252, Δ +0.5 ppm.

***tert*-Butyl[2-(4-chloromethylfuran-3-yl)pentyloxy]diphenylsilane (249)**



248 **249**

To a solution of allylic alcohol **248** (1.47 g, 3.48 mmol) in CH_2Cl_2 (12 mL) cooled to 0 °C, Et_3N (870 µL, 6.24 mmol, 1.80 equiv) and MsCl (405 µL, 5.21 mmol, 1.50 equiv), both freshly distilled, were successively added. The mixture was warmed to rt, stirred overnight and quenched with saturated aqueous NH_4Cl (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—CH_2Cl_2, 9:1) affording chloride **249** (1.38 g, 90%) as a colourless oil.

$C_{26}H_{33}ClO_2Si$ **Molecular weight: 441.08 g·mol^{-1}**

R_f = 0.40 (PE—CH_2Cl_2, 9:1);

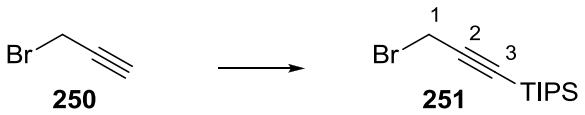
IR ν_{max} (cm^{-1}) 3071, 2943, 2910, 2862, 1589, 1543, 1460 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61—7.57 (4H, m, 4×CH-Ar), 7.44—7.33 (7H, m, CH-C2, 6×CH-Ar), 7.20 (1H, d, *J* = 1.5 Hz, CH-C5), 4.35 (2H, s, CH_2-C11), 3.67 (2H, d, *J* = 5.8 Hz, CH_2-C10), 2.82 (1H, dtd, *J* = 9.0, 5.8, 5.7 Hz, CH-C6), 1.81 (1H, dddd, *J* = 13.2, 9.3, 6.5, 5.7 Hz, CH_2-C7), 1.59—1.46 (1H, m, CH_2-C7), 1.37—1.25 (2H, m, CH_2-C8), 1.03 (9H, s, 3×CH_3-*t*Bu), 0.90 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5 (CH-C2), 140.9 (CH-C5), 135.8 (2×CH-Ar), 135.7 (2×CH-Ar), 133.8 (C-Ar), 133.7 (C-Ar), 129.8 (CH-Ar), 129.7 (CH-Ar), 127.8 (4×CH-Ar), 126.1 (C-C3 or C-C4), 122.5 (C-C3 or C-C4), 67.8 (CH_2-C10), 37.2 (CH-C6), 36.4 (CH_2-C11), 34.1 (CH_2-C7), 27.0 (3×CH_3-*t*Bu), 20.6 (CH_2-C8), 19.4 (C-*t*Bu), 14.3 (CH_3-C9);

LRMS (CI, Me_3CH): *m/z* (*int*) 441 (60), 405 (98), 363 (72), 241 (61), 227 (77), 185 (100), 149 (45), 91 (31). HRMS (CI, Me_3CH) calculated for $C_{26}H_{34}{}^{35}ClO_2Si$ $[M+H]^+$: 441.2017, found 441.2015, Δ −0.4 ppm. Analytic. calculated for $C_{26}H_{33}ClO_2Si$: C, 70.80; H, 7.54. Found: C, 70.96; H, 7.59.

1-Bromo-3-(triisopropylsilyl)-2-propyne (251)



To a solution of propargyl bromide **250** (3.0 mL of an 80% solution in toluene, 27 mmol) in THF (130 mL) at −78 °C was added dropwise LiHMDS (32 mL of a 1.0 M solution in THF, 32 mmol, 1.2 equiv). The solution was stirred for 15 minutes before the addition of TIPSCl (7.5 mL, 35 mmol, 1.3 equiv). After 3 h at −78 °C, the solution was allowed to warm up to rt. The reaction was quenched with saturated aqueous NH_4Cl (40 mL) and diluted with EtOAc (100 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The organic extracts were combined and washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE) to give the desired TIPS-protected propargyl bromide **251** (7.19 g, 97%) as a colourless oil.

$C_{12}H_{23}BrSi$ **Molecular weight: 275.30 g·mol^{-1}**

R_f = 0.80 (PE—CH_2Cl_2, 95:5);

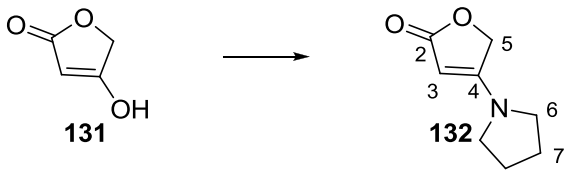
IR ν_{max} 2943, 2866, 2176, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (2H, s, CH_2-C1), 1.07 (21H, br s, 3×*i*Pr);

^{13}C NMR (101 MHz, $CDCl_3$) δ 102.0 (C-C2), 89.3 (C-C3), 18.7 (6×CH_3-*i*Pr), 15.2 (CH_2-C1), 11.5 (3×CH-*i*Pr);

LRMS (CI, Me_3CH): *m*/*z* (*int*) 277 (4), 275 (2), 239 (9), 197 (100), 155 (31), 107 (30), 71 (89).

4-(Pyrrolidin-1-yl)furan-2(5*H*)-one (132)[41]



To a solution of tetronic acid **131** (500 mg, 5.00 mmol) in toluene (25 mL) was added pyrrolidine (2.50 mL, 30.0 mmol, 6.00 equiv) at 0 °C. The reaction was stirred for 30 min before concentration *in vacuo*. The residue was re-dissolved in toluene (25 mL), and the process was repeated twice. The residue was then dried at 50 °C under high vacuum for 3 h. A solid was formed which was filtered through a pad of neutral aluminium oxide (Brockmann I, PE—EtOAc, 5:5) to give **132** (622 mg, 81%) as a colourless solid. The data obtained matches that reported previously.[41]

$C_8H_{11}NO_2$ **Molecular weight: 153.18 g·mol^{-1}**

mp. 120—123 °C;

R_f = 0.26 (PE—EtOAc, 1:9);

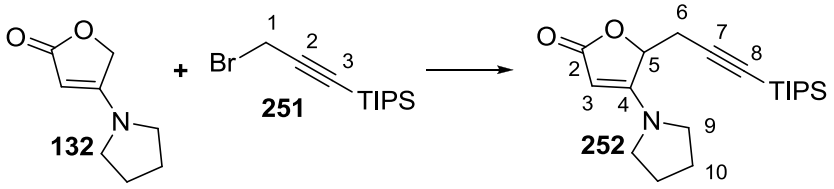
IR ν_{max} 2929, 2870, 1712, 1602, 1431 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (2H, s, CH_2-C5), 4.52 (1H, s, CH-C3), 3.27 (4H, t, *J* = 6.7 Hz, 2×CH_2-C6), 2.02 (4H, p, *J* = 6.7 Hz, 2×CH_2-C7);

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8 (C-C2), 166.2 (C-C4), 80.7 (CH-C3), 67.1 (CH_2-C5), 49.4 (CH_2-C6), 47.4 (CH_2-C6), 25.8 (CH_2-C7), 25.0 (CH_2-C7);

LRMS (EI+): *m/z* (*int*) 153 (100), 124 (19), 108 (16), 95 (50), 70 (22), 43 (43). HRMS (EI+) calculated for $C_8H_{11}NO_2$ $[M]^+$: 153.0790, found 153.0792, Δ +1.3 ppm.

4-(Pyrrolidin-1-yl)-5-(3-triisopropylsilylprop-2-ynyl)furan-2(5*H*)-one (252)



To a solution of **132** (653 mg, 4.27 mmol) in THF (6 mL) at −78 °C was carefully added a solution of *t*-BuLi (4.0 mL of a 1.6 M solution in hexane, 6.4 mmol, 1.5 equiv). The reaction was stirred for 30 min before a solution of the protected propargyl bromide **251** (5.88 g, 21.4 mmol, 5.00 equiv) in THF (8 mL) cooled to −78 °C was carefully added. After 3 h, the reaction was allowed to warm up to rt over 45 min, and the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and diluted with EtOAc (20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The organic extracts were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—EtOAc, 7:3) to give the desired product **252** (1.34 g, 90%) as a colourless solid.

$C_{20}H_{33}NO_2Si$ **Molecular weight: 347.57 g·mol^{-1}**

mp. 122—125 °C;

R_f = 0.23 (PE—EtOAc, 5:5);

IR ν_{max} 2941, 2865, 2179, 1721, 1610, 1673, 1462 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (1H, dd, *J* = 4.5, 3.5 Hz, CH-C5), 4.55 (1H, s, CH-C3), 3.32 (4H, br s, 2×CH_2-C9), 3.00 (1H, dd, *J* = 17.8, 3.5 Hz, CH_2-C6), 2.80 (1H, dd, *J* = 17.8, 4.5 Hz, CH_2-C6), 2.12—2.02 (2H, m, CH_2-C10), 1.99—1.90 (2H, m, CH_2-C10), 1.03 (21H, s, 3×*i*Pr);

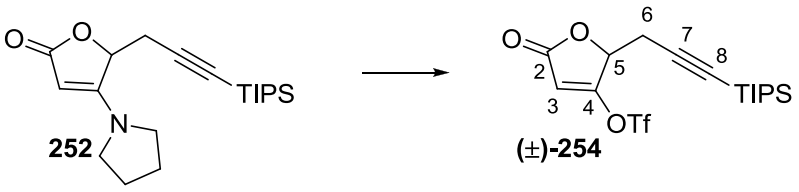
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9 (C-C2), 167.1 (C-C4), 100.6 (C-C7), 84.5 (C-C8), 83.3 (CH-C3), 76.0 (CH-C5), 24.2 (CH_2-C6), 18.7 (6×CH_3-*i*Pr), 11.3 (3×CH-*i*Pr);

Carbon peaks not appearing:

- CH_2-C9, CH_2-C10;

LRMS (CI, Me_3CH): *m/z* (*int*) 348 (98), 137 (61), 121 (51), 89 (94). HRMS (CI, Me_3CH) calculated for $C_{20}H_{34}NO_2Si$ $[M+H]^+$: 348.2359, found 348.2364, Δ +1.4 ppm. Analytic. calculated for $C_{20}H_{33}NO_2Si$: C, 69.11; H, 9.57; N, 4.03. Found: C, 69.07; H, 9.65; N, 4.09.

5-Oxo-2-{3-[*tris*(propan-2-yl)silyl]prop-2-yn-1-yl}-2,5-dihydrofuran-3-yl trifluoromethanesulfonate ((±)-254)



To a solution of **252** (1.83 mg, 5.27 mmol) was added a solution of hydrochloric acid in EtOH (1.2 M, 30 mL, 38 mmol, 7.1 equiv) at 0 °C followed by water (3.00 mL). The mixture was heated at 78 °C for 5 h, cooled to rt and diluted with water (10 mL) and Et_2O (40 mL). The phases were separated, the aqueous phase was extracted with Et_2O (2 × 20 mL) and the organic extracts washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. After azeotropic removal of water with toluene (3 × 50 mL), the orange residue was directly used in the next step.

To a solution of the crude acid in CH_2Cl_2 (53 mL) at −78 °C was added dropwise freshly distilled DIPEA (1.40 mL, 7.98 mmol, 1.51 equiv), and after 5 min triflic anhydride (1.15 mL, 6.84 mmol, 1.30 equiv). The dark red solution was stirred for 1 h at −78 °C, then diluted with CH_2Cl_2 (30 mL) and warmed to rt. The reaction was quenched with water (20 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), the organic extracts were combined, washed with brine (50 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 9:1 to 8:2) to afford triflate **(±)-254** (1.82 g, 81% over two steps) as a colourless solid.

$C_{17}H_{25}F_3O_5SSi$ **Molecular weight: 426.52 g·mol^{-1}**

mp. 42—43 °C;

R_f = 0.81 (PE—Et_2O, 5:5);

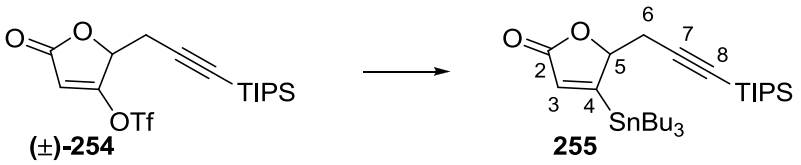
IR ν_{max} 2947, 2870, 2176, 1767, 1643, 1435 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (1H, d, *J* = 1.2 Hz, CH-C3), 5.07 (1H, ddd, *J* = 4.8, 3.5, 1.2 Hz, CH-C5), 3.09 (1H, dd, *J* = 17.7, 4.8 Hz, CH_2-C6), 2.84 (1H, dd, *J* = 17.7, 3.5 Hz, CH_2-C6), 1.03 (21H, s, 3×*i*Pr);

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8 (C-C2), 167.2 (C-C4), 118.6 (q, *J* = 322 Hz, CF_3), 104.8 (CH-C3), 97.3 (C-C8), 87.1 (C-C7), 76.3 (CH-C5), 23.0 (CH_2-C6), 18.6 (6×CH_3-*i*Pr), 11.2 (3×CH-*i*Pr);

LRMS (CI, Me_3CH): *m/z* (*int*) 427 (26), 334 (11), 279 (32), 276 (21), 235 (15), 181 (11), 133 (27), 97 (35), 71 (100). HRMS (CI, Me_3CH) calculated for $C_{17}H_{26}F_3O_5SSi$ $[M+H]^+$: 427.1222, found 427.1223, Δ +0.1 ppm. Analytic. calculated for $C_{17}H_{25}F_3O_5SSi$: C, 47.87; H, 5.91. Found: C, 47.79; H, 5.96.

5-(3-Triisopropylsilylprop-2-ynyl)-4-(tributylstannyl)furan-2(5*H*)-one (255)



To triflate **(±)-254** (492 mg, 1.15 mmol) in THF (12 mL) was added thoroughly flame-dried LiCl (360 mg, 8.49 mmol, 7.36 equiv) and $Pd(PPh_3)_4$ (64 mg, 0.055 mmol, 0.048 equiv). After 5 min, bis(tributyl)ditin (758 µL, 1.50 mmol, 1.30 equiv) was added and the mixture was heated at 60 °C for 4 h then cooled to 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and the mixture was diluted with Et_2O (30 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, washed with brine (50 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 9:1 to 8:2) to give stannane **255** (207 mg, 32%) as a pale yellow oil.

$C_{28}H_{52}O_2SiSn$ **Molecular weight: 567.51 g·mol^{-1}**

R_f = 0.53 (PE—Et_2O, 8:2);

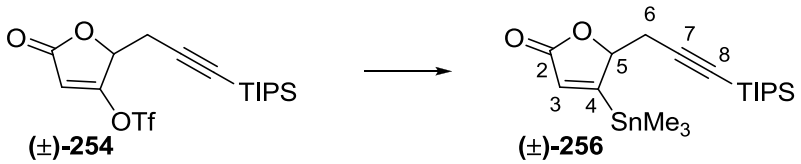
IR ν_{max} 2924, 2866, 2176, 1751, 1612, 1642, 1420 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (1H, d, *J* = 1.8 Hz, CH-C3), 5.19 (1H, ddd, *J* = 4.8, 3.9, 1.8 Hz, CH-C5), 3.06 (1H, dd, *J* = 17.3, 4.8 Hz, CH_2-C6), 2.59 (1H, dd, *J* = 17.3, 3.9 Hz, CH_2-C6), 1.57—1.47 (6H, m, 3×CH_2-$SnBu_3$), 1.38—1.28 (6H, m, 3×CH_2-$SnBu_3$), 1.13—1.07 (6H, m, 3×CH_2-$SnBu_3$), 1.02 (21H, br s, 3×*i*Pr), 0.91 (9H, t, *J* = 7.3 Hz, 3×CH_3-$SnBu_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9 (C-C2), 172.6 (C-C4), 131.4 (CH-C3), 100.5 (C-C8), 86.3 (CH-C5 and C-C7), 29.1 (3×CH_2-$SnBu_3$), 27.4 (3×CH_2-$SnBu_3$), 25.2 (CH_2-C6), 18.7 (6×CH_3-*i*Pr), 13.7 (3×CH_2-$SnBu_3$), 11.3 (3×CH-*i*Pr), 10.1 (3×CH_3-$SnBu_3$);

LRMS (CI, Me_3CH): *m/z* (*int*) 569 (14), 513 (25), 279 (100), 69 (98). HRMS (CI, Me_3CH) calculated for $C_{28}H_{53}O_2Si^{120}Sn$ $[M+H]^+$: 569.2842, found 569.2831, Δ −1.1 ppm.

4-Trimethylstannyl-5-{3-[*tris*(propan-2-yl)silyl]prop-2-yn-1-yl}-2,5-dihydrofuran-2-one ((±)-256)



In a 50 mL 3-necked flask containing thoroughly flame-dried LiCl (600 mg, 14.2 mmol, 8.00 equiv) and $Pd(PPh_3)_4$ (80.1 mg, 0.0692 mmol, 0.0391 equiv) was added THF (5 mL). A solution of triflate **(±)-254** (755 mg, 1.77 mmol) in THF (17 mL) was added. After 5 min hexamethylditin (480 µL, 2.31 mmol, 1.31 equiv) was added and the mixture was heated at reflux for 1.5 h. Further $Pd(PPh_3)_4$ (67.8 mg, 0.0586 mmol, 0.0331 equiv) was then added and the mixture was stirred for 1.5 h. The mixture was cooled to 0 °C and the reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL) and diluted with Et_2O (40 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 30 mL). The organic extracts were combined, washed with brine (40 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 95:5 to 8:2) to give the corresponding stannane **(±)-256** (419 mg, 54%) as a pale yellow solid.

$C_{19}H_{34}O_2SiSn$ **Molecular weight: 441.27 g·mol^{-1}**

mp. 69—72 °C;

R_f = 0.21 (PE—Et_2O, 8:2);

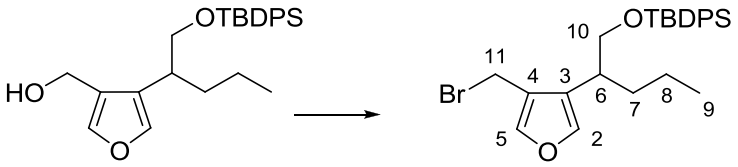
IR ν_{max} 2940, 2863, 2176, 1751, 1643, 1466 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (1H, d, *J* = 1.9 Hz, CH-C3), 5.21 (1H, ddd, *J* = 5.3, 3.6, 1.9 Hz, CH-C5), 3.04 (1H, dd, *J* = 17.3, 5.3 Hz, CH_2-C6), 2.65 (1H, dd, *J* = 17.3, 3.6 Hz, CH_2-C6), 1.01 (21H, br s, 3×*i*Pr), 0.36 (9H, s, $SnMe_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4 (C-C4), 172.4 (C-C2), 131.1 (CH-C3), 100.4 (C-C8), 85.8 (CH-C5), 85.5 (C-C7), 25.1 (CH_2-C6), 18.7 (6×CH_3-*i*Pr), 11.3 (3×CH-*i*Pr), −9.2 (3×CH_3-$SnMe_3$);

LRMS (CI, Me_3CH): *m/z* (*int*) 443 (76), 441 (57), 337 (11), 279 (48), 257 (15), 235 (12), 113 (20), 69 (100). HRMS (CI, Me_3CH) calculated for $C_{19}H_{35}O_2Si^{120}Sn$ $[M+H]^+$: 443.1431, found 443.1424, Δ −1.1 ppm.

[2-(4-Bromomethylfuran-3-yl)pentyloxy]*tert*-butyldiphenylsilane (257)



248 **257**

To a solution of alcohol **248** (204 mg, 0.483 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C, PPh_3 (187 mg, 0.713 mmol, 1.48 equiv) and NBS (127 mg, 0.714 mmol, 1.48 equiv) were added successively. The mixture was stirred for 1 h at 0 °C, diluted with CH_2Cl_2 (5 mL), washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—CH_2Cl_2, 95:5) to give the desired bromide **257** (220 mg, 94%) as a pale yellow oil.

$C_{26}H_{33}BrO_2Si$ **Molecular weight: 485.53 g·mol^{-1}**

R_f = 0.52 (PE—CH_2Cl_2, 95:5);

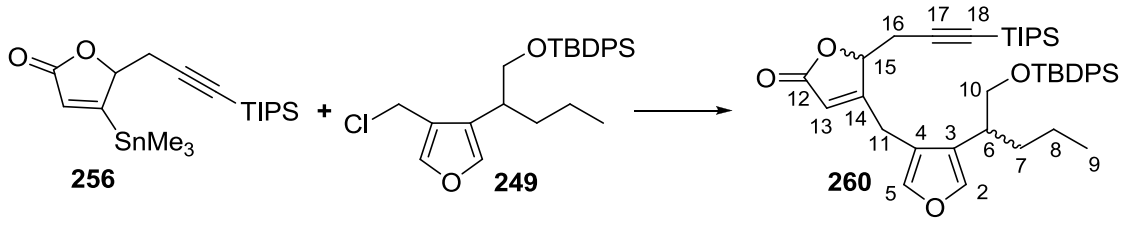
IR ν_{max} 3071, 3051, 2955, 2931, 2859, 1589, 1543, 1466 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61—7.57 (4H, m, 4×CH-Ar), 7.44—7.33 (7H, m, CH-C2, 6×CH-Ar), 7.20 (1H, d, *J* = 1.3 Hz, CH-C5), 4.25 (2H, s, CH_2-C11), 3.66 (1H, dd, *J* = 9.8, 6.2 Hz, CH_2-C10), 3.66 (1H, dd, *J* = 9.8, 5.8 Hz, CH_2-C10), 2.84 (1H, app dq, *J* = 9.1, 5.8 Hz, CH-C6), 1.82 (1H, dddd, *J* = 12.8, 9.1, 6.5, 5.6 Hz, CH_2-C7), 1.58—1.49 (1H, m, CH_2-C7), 1.39—1.25 (2H, m, CH_2-8), 1.03 (9H, s, 3×CH_3-*t*Bu), 0.91 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6 (CH-C2), 140.9 (CH-C5), 135.8 (2×CH-Ar), 135.7 (2×CH-Ar), 133.8 (C-Ar), 133.7 (C-Ar), 129.8 (CH-Ar), 129.7 (CH-Ar), 127.8 (4×CH-Ar), 126.2 (C-C3 or C-C4), 122.6 (C-C3 or C-C4), 67.8 (CH_2-C10), 37.1 (CH-C6), 34.2 (CH_2-C7), 27.0 (3×CH_3-*t*Bu), 23.0 (CH_2-C11), 20.6 (CH_2-C8), 19.4 (C-*t*Bu), 14.4 (CH_3-C9);

LRMS (CI, Me_3CH): *m/z* (*int*) 487 (19), 463 (39), 405 (100), 349 (12), 231 (15), 207 (18), 151 (27), 97 (18), 79 (42). HRMS (CI, Me_3CH) calculated for $C_{26}H_{34}{}^{81}BrO_2Si$ $[M+H]^+$: 487.1495, found 487.1492, Δ +0.1 ppm.

4-[4-(1-*tert*-Butyldiphenylsilyloxypentan-2-yl)furan-3-yl]methyl-5-[3-*tris*(propan-2-yl)silylprop-2-yn-1-yl]-2,5-dihydrofuran-2-one (260)



To a solution of chloride **249** (449 mg, 1.02 mmol, 1.07 equiv) in THF (2 mL) was added $Pd_2(dba)_3$ (57 mg, 0.063 mmol, 0.066 equiv) and triphenylarsine (106 mg, 0.346 mmol, 0.364 equiv). The purple to yellow mixture was stirred for 5 min at rt before a solution of stannane **256** (419 mg, 0.950 mmol, 1.00 equiv) in THF (9 mL) was added. The mixture was heated at 65 °C overnight, cooled to rt and then diluted with Et_2O (30 mL) and H_2O (10 mL). The phases were separated, the aqueous phase was extracted with Et_2O (2 × 20 mL) and the organic extracts were combined, washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 95:5 to 92:8) to give the corresponding product **260** (605 mg, 93%) as a pale yellow oil and an inseparable mixture (1:1) of diastereoisomers.

$C_{42}H_{58}O_4Si_2$ **Molecular weight: 683.08 g·mol^{-1}**

R_f = 0.69 (PE—Et_2O, 7:3);

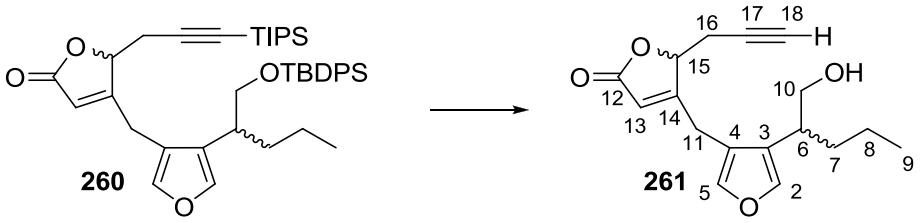
IR ν_{max} 3071, 2931, 2862, 2175, 1759, 1643, 1589, 1543, 1466 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58—7.54 (8H, m, 8×CH-Ar), 7.45—7.33 (12H, m, 12×CH-Ar), 7.25 (1H, d, *J* = 1.6 Hz, CH-C2), 7.24—7.23 (2H, m, CH-C2 and CH-C5), 7.22 (1H, d, *J* = 1.5 Hz, CH-C5), 5.72 (1H, d, *J* = 1.3 Hz, CH-C13), 5.67 (1H, d, *J* = 1.5 Hz, CH-C13), 4.82 (1H, app t, *J* = 5.0 Hz, CH-C15), 4.80 (1H, app t, *J* = 5.0 Hz, CH-C15), 3.62—3.59 (4H, m, 2×CH_2-C10), 3.52 (1H, d, *J* = 17.7 Hz, CH_2-C11), 3.43 (1H, d, *J* = 18.4 Hz, CH_2-C11), 3.24 (1H, dd, *J* = 17.7, 1.5 Hz, CH_2-C11), 3.20 (1H, d, *J* = 18.4 Hz , CH_2-C11), 2.90 (1H, dd, *J* = 5.1, 2.0 Hz, CH_2-C16), 2.86 (1H, dd, *J* = 5.1, 2.0 Hz, CH_2-C16), 2.67 (1H, dd, *J* = 5.1, 4.0 Hz, CH_2-C16), 2.63 (1H, dd, *J* = 5.1, 3.9 Hz, CH_2-C16), 2.54 (1H, dq, *J* = 9.0, 5.8 Hz, CH-C6), 2.49 (1H, dq, *J* = 8.7, 5.8 Hz, CH-C6), 1.79—1.69 (2H, m, CH_2-C7), 1.51—1.38 (2H, m, CH_2-C7), 1.30—1.16 (4H, m, 2×CH_2-C8), 1.05—0.98 (60H, m, 6×*i*Pr and 6×CH_3-*t*Bu), 0.86 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.87 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9 (2×C-C12), 169.7 (C-C14), 169.5 (C-C14), 140.8 (CH-C2 or CH-C5), 140.7 (CH-C2 or CH-C5), 140.4 (CH-C2 or CH-C5), 140.3 (CH-C2 or CH-C5), 135.7 (4×CH-Ar), 135.6 (4×CH-Ar), 133.6 (2×C-Ar), 133.5 (2×C-Ar), 129.9 (2×CH-Ar), 129.8 (2×CH-Ar), 127.8 (8×CH-Ar), 126.2 (2×C-C3 or 2×C-C4), 119.4 (2×C-C3 or 2×C-C4), 118.4 (2×CH-C13), 99.7 (C-C17), 99.6 (C-C17), 85.4 (2×C-C18), 80.5 (CH- C15), 80.4 (CH-C15), 67.9 (CH_2-C10), 67.8 (CH_2-C10), 37.5 (2×CH-C6), 34.2 (CH_2-C7), 34.1 (CH_2-C7),

27.0 (6×CH_3-*t*Bu), 23.6 (CH_2-C16), 23.5 (CH_2-C16), 23.1 (CH_2-C11), 23.0 (CH_2-C11), 20.7 (2×CH_2-C9), 19.4 (2×C-*t*Bu), 18.7 (12×CH_3-*i*Pr), 14.4 (2×CH_3-C9), 11.3 (6×CH-*i*Pr);
LRMS (FAB): *m/z* (*int*) 705 (100), 605 (67), 427 (9), 197 (40), 135 (73), 59 (42). HRMS (FAB) calculated for $C_{42}H_{58}NaO_4Si_2$ [M+Na]$^+$: 705.3771, found 705.3763, Δ −1.1 ppm.

4-[4-(1-Hydroxypentan-2-yl)furan-3-yl]methyl-5-(prop-2-yn-1-yl)-2,5-dihydrofuran-2-one (261)



To a solution of **260** (1.23 g, 1.80 mmol) in THF (31 mL) was added at 0 °C concentrated AcOH (400 µL, 6.99 mmol, 3.88 equiv) and TBAF (7.4 mL of a 1 M solution in THF, 7.4 mmol, 4.1 equiv). The mixture was warmed slowly to rt, stirred for 24 h and then diluted with water (10 mL) and EtOAc (30 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 30 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 5:5 to 2:8) to give the corresponding unprotected alcohols **261** (461 mg, 89%) as a pale yellow oil and a partially separable 1:1 mixture of diastereoisomers.

$C_{17}H_{20}O_4$ **Molecular weight: 288.34 g·mol^{-1}**

R_f = 0.44 and 0.42 (PE—Et_2O, 2:8);

IR ν_{max} 3446, 2954, 2933, 2869, 2360, 1742, 1645, 1417 cm^{-1};

Less polar diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, s, CH-C2 and CH-C5), 5.78 (1H, ddd, *J* = 1.5, 1.5, 1.2 Hz, CH-C13), 5.03 (1H, ddd, *J* = 5.6, 4.2, 1.2 Hz, CH-C15), 3.68—3.60 (2H, m, CH_2-C10), 3.59 (1H, dd, *J* = 18.3, 1.5 Hz, CH_2-C11), 3.45 (1H, dd, J = 18.3, 1.5 Hz, CH_2-C11), 2.85 (1H, ddd, *J* = 17.3, 5.6, 2.6 Hz, CH_2-C16), 2.73 (1H, ddd, *J* = 17.3, 4.2, 2.7 Hz, CH_2-C16), 2.59 (1H, dq, *J* = 8.6, 5.9 Hz, CH-C6), 2.07 (1H, dd, *J* = 2.7, 2.6 Hz, CH-C18), 1.69—1.59 (1H, m, CH_2-C7), 1.52—1.41 (1H, m, CH_2-C7), 1.36—1.23 (2H, m, CH_2-C8), 0.89 (3H, t, *J* = 7.3 Hz, CH_3-C10);

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C-C12), 169.9 (C-C14), 141.0 (CH-C2 or CH-C5), 140.5 (CH-C2 or CH-C5), 126.0 (C-C3 or C-C4), 119.5 (C-C3 or C-C4), 118.5 (CH-C13), 80.3 (CH-C15), 76.6 (C-C17), 72.6 (CH-C18), 66.7 (CH_2-C10), 37.5 (CH-C6), 34.5 (CH_2-C7), 23.2 (CH_2-C11), 22.6 (CH_2-C16), 20.7 (CH_2-C8), 14.3 (CH_3-C9);

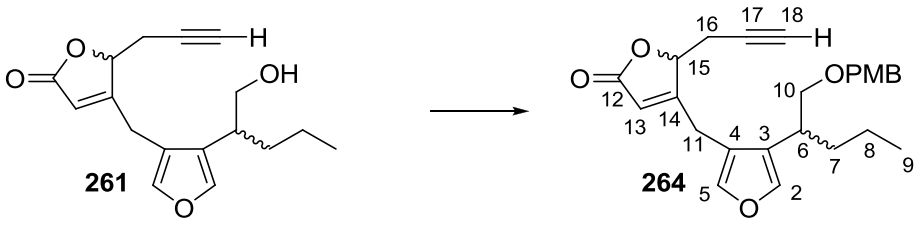
More polar diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, s, CH-C2 and CH-C5), 5.81 (1H, ddd, *J* = 1.6, 1.6, 1.5 Hz, CH-C13), 5.00 (1H, ddd, *J* = 6.3, 4.6, 1.5 Hz, CH-C15), 3.70—3.59 (2H, m, CH_2-C10), 3.59 (1H, dd, *J* = 18.3, 1.6 Hz, CH_2-C11), 3.44 (1H, dd, *J* = 18.2, 1.6 Hz, CH_2-C11), 2.87 (1H, ddd, *J* = 17.3, 6.3, 2.5 Hz, CH_2-C16), 2.74 (1H, ddd, *J* = 17.3, 4.6, 2.5 Hz, CH_2-C16), 2.68—2.55 (1H, m, CH-C6), 2.08 (1H, t, *J* = 2.5 Hz, CH-C18), 1.69—1.58 (1H, m, CH_2-C7), 1.52—1.40 (1H, m, CH_2-C7), 1.36—1.27 (2H, m, CH_2-C8), 0.89 (3H, t, *J* = 7.3 Hz, CH_3-C10);

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C-C12), 169.7 (C-C14), 141.1 (CH-C2 or CH-C5), 140.6 (CH-C2 or CH-C5), 126.0 (C-C3 or C-C4), 119.4 (C-C3 or C-C4), 118.5 (CH-C13), 80.2 (CH-C15), 76.5 (C-C17), 72.7 (CH-C18), 66.9 (CH_2-C10), 37.5 (CH-C6), 34.2 (CH_2-C7), 23.2 (CH_2-C11), 22.6 (CH_2-C16), 20.6 (CH_2-C8), 14.3 (CH_3-C9);

LRMS (CI, Me_3CH): *m/z* (*int*) 289 (100), 71 (13). HRMS (CI, Me_3CH) calculated for $C_{17}H_{21}O_4$ $[M+H]^+$: 289.1440, found 289.1442, Δ +0.7 ppm.

4-{4-[1-(4-Methoxyphenylmethoxy)pentan-2-yl]furan-3-yl}methyl-5-(prop-2-yn-1-yl)-2,5-dihydrofuran-2-one (264)



To a solution of alkynes **261** (18.3 mg, 0.0635 mmol) in CH_2Cl_2 (0.5 mL) were added freshly prepared PMBTCA (56.7 mg, 0.199 mmol, 3.13 equiv) and CSA (8.2 mg, 0.035 mmol, 0.56 equiv). The mixture was stirred for 8 h at rt and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (10 mL), the organic extracts were combined and washed with brine (15 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—CH_2Cl_2, 1:9). Crystallisation of acetimidate impurities using PE and Et_2O helped to give the desired products **264** (20.9 mg, 81%) as an inseparable mixture (1:1) of diastereoisomers.

$C_{25}H_{28}O_5$ **Molecular weight: 408.49 g·mol^{-1}**

R_f = 0.55 (PE—Et_2O, 4:6);

IR ν_{max} 3288, 2957, 2926, 2859, 1755, 1643, 1612, 1585, 1512, 1464, 1417 cm^{-1};

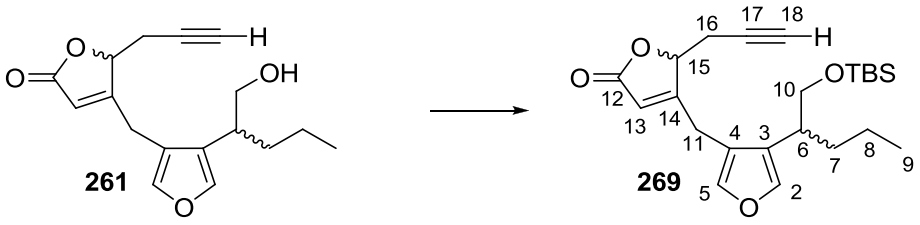
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, s, 2×CH-C2), 7.24 (2H, s, 2×CH-C5), 7.18 (4H, d, *J* = 8.6 Hz, 4×CH-PMB), 6.86 (4H, d, *J* = 8.6 Hz, 4×CH-PMB), 5.77 (1H, ddd, *J* = 1.6, 1.6, 1.5 Hz, CH-C13), 5.76 (1H, ddd, *J* = 1.6, 1.6, 1.5 Hz, CH-C13), 4.92 (1H, app td, *J* = 5.5,

1.5 Hz, CH-C15), 4.91 (1H, app td, *J* = 5.5, 1.5 Hz, CH-C15), 4.42—4.34 (4H, m, 2×CH_2-PMB), 3.81 (6H, s, 2×CH_3-PMB), 3.63—3.31 (8H, m, 2×CH_2-C10 and 2×CH_2-C11), 2.82—2.73 (2H, m, 2×CH_2-C16), 2.68—2.58 (4H, m, 2×CH_2-C16, 2×CH-C6), 2.03 (2H, t, *J* = 2.6 Hz, 2×CH-C18), 1.72—1.61 (2H, m, 2×CH_2-C7), 1.50—1.39 (2H, m, 2×CH_2-C7),1.34—1.18 (4H, m, CH_2-C8), 0.87 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.86 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 (2×C-C12), 170.0 (C-C14), 169.9 (C-C14), 159.3 (2×C-PMB), 140.5 (2×CH-C2 or 2×CH-C5), 140.4 (CH-C2 or CH-C5), 140.3 (CH-C2 or CH-C5), 130.5 (C-PMB), 130.4 (C-PMB), 129.4 (2×CH-PMB), 129.3 (2×CH-PMB), 126.8 (C-C3 or C-C4), 126.7 (C-C3 or C-C4), 119.6 (C-C3 or C-C4), 119.5 (C-C3 or C-C4), 118.4 (2×CH-C13), 113.9 (4×CH-PMB), 80.3 (CH-C15), 80.2 (CH-C15), 76.6 (2×C-C17), 74.8 (CH_2-C10), 74.4 (CH_2-C10), 73.0 (2×CH-C18), 72.5 (CH_2-PMB), 55.4 (2×CH_3-PMB), 35.5 (CH-C6), 35.4 (CH-C6), 35.0 (CH_2-C7), 34.7 (CH_2-C7), 23.3 (CH_2-C11), 23.2 (CH_2-C11), 22.5 (2×CH_2-C16), 20.7 (CH_2-C8), 20.7 (CH_2-C8), 14.3 (2×CH_3-C9);

LRMS (CI, Me_3CH): *m/z* (*int*) 409 (26), 289 (41), 121 (100). HRMS (CI, Me_3CH) calculated for $C_{25}H_{29}O_5$ $[M+H]^+$: 409.2015, found 409.2017, Δ +0.5 ppm.

4-{[4-(1-*tert*-Butyldimethylsilyloxy-pentan-2-yl)furan-3-yl]methyl}-5-(prop-2-yn-1-yl)-2,5-dihydrofuran-2-one (269)



To a solution of alkynes **261** (22.2 mg, 0.0770 mmol) in CH_2Cl_2 (1 mL) at 0 ºC were successively added freshly distilled Et_3N (18 µL, 0.13 mmol, 1.7 equiv), DMAP (2.7 mg, 0.022 mmol, 0.040 equiv) and TBSCl (15.4 mg, 0.102 mmol, 1.33 equiv). The mixture was warmed to rt and stirred overnight. More Et_3N (18 µL, 0.13 mmol, 1.7 equiv) and TBSCl (10 mg, 0.067 mmol, 0.87 equiv) were added and the reaction was stirred for a further 8 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and diluted with CH_2Cl_2 (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 6:4) to afford the desired products **269** (16.8 mg, 54%) as an inseparable mixture (1:1) of diastereoisomers, and recovered alcohols **261** (7.3 mg).

$C_{23}H_{34}O_4Si$ **Molecular weight: 402.60 g·mol^{-1}**

R_f = 0.29 (PE—Et_2O, 6:4);

IR ν_{max} 3309, 2955, 2929, 2857, 1755, 1643, 1541, 1464, 1417 cm^{-1};

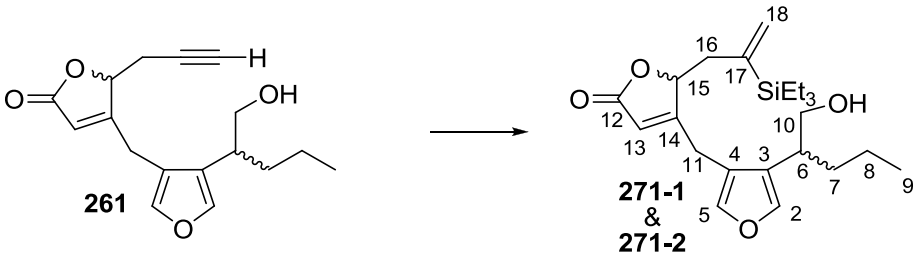
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28—7.23 (4H, m, 2×CH-C2, 2×CH-C5), 5.79 (1H, ddd, *J* = 1.6, 1.6, 1.4 Hz, CH-C13), 5.76 (1H, ddd, *J* = 1.7, 1.7, 1.4 Hz, CH-C13), 5.01 (1H, ddd, *J* = 5.6, 4.1, 1.4 Hz, CH-C15), 4.97 (1H, ddd, *J* = 5.5, 4.3, 1.4 Hz, CH-C15), 3.64 (1H, dd, *J* = 18.1, 1.6 Hz, CH_2-C11), 3.60—3.52 (5H, m, 2×CH_2-C10, CH_2-C11), 3.44 (1H, dd, *J* = 18.1, 1.7 Hz, CH_2-C11), 3.40 (1H, dd, *J* = 18.1, 1.7 Hz, CH_2-C11), 2.86 (1H, ddd, *J* = 17.2, 5.6, 2.6 Hz, CH_2-C16), 2.84 (1H, ddd, *J* = 17.2, 5.5, 2.6 Hz, CH_2-C16), 2.72 (1H, ddd, *J* = 17.2, 4.3, 2.6 Hz, CH_2-C16), 2.71 (1H, ddd, *J* = 17.2, 4.1, 2.6 Hz, CH_2-C16), 2.56—2.46 (2H, m, 2×CH-C6), 2.06 (1H, t, *J* = 2.6 Hz, CH-C18), 2.06 (1H, t, *J* = 2.6 Hz, CH-C18), 2.05 (1H, t, *J* = 2.6 Hz, CH-C18), 1.71—1.61 (2H, m, 2×CH_2-C7), 1.45—1.34 (2H, m, 2×CH_2-C7), 1.34—1.18 (4H, m, CH_2-C8), 0.88 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.87 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.86 (9H, s, 3×CH_3-*t*Bu), 0.85 (9H, s, 3×CH_3-*t*Bu), −0.02 (3H, s,CH_3-SiMe_2), −0.02 (6H, s, 2×CH_3-SiMe_2), −0.03 (3H, s, CH_3-SiMe_2);

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C-C12), 171.9 (C-C12), 170.1 (C-C14), 169.9 (C-C14), 140.5 (2×CH-C2 or 2×CH-C5), 140.3 (CH-C2 or CH-C5), 140.3 (CH-C2 or CH-C5), 126.7 (C-C3 or C-C4), 126.7 (C-C3 or C-C4), 119.5 (C-C3 or C-C4), 119.5 (C-C3 or C-C4), 118.4 (CH-C13), 118.4 (CH-C13), 80.3 (CH-C15), 80.2 (CH-C15), 76.6 (C-C17), 76.5 (C-C17),

72.6 (2×CH-C18), 67.7 (CH_2-C10), 67.4 (CH_2-C10), 37.4 (CH-C6), 37.4 (CH-C6), 34.7 (CH_2-C7), 34.3 (CH_2-C7), 26.0 (3×CH_3-*t*Bu), 26.0 (3×CH_3-*t*Bu), 23.3 (CH_2-C11), 23.2 (CH_2-C11), 22.6 (CH_2-C16), 22.6 (CH_2-C16), 20.7 (CH_2-C8), 20.7 (CH_2-C8), 18.5 (2×C-*t*Bu), 14.4 (2×CH_3-C9), −5.4 (2×CH_3-SiMe_2), −5.4 (2×CH_3-SiMe_2);

LRMS (CI, Me_3CH): *m/z* (*int*) 403 (100), 378 (8), 345 (14), 271 (36), 133 (11), 85 (33). HRMS (CI, Me_3CH) calculated for $C_{23}H_{35}O_4Si$ $[M+H]^+$: 403.2305, found 403.2303, Δ −0.4 ppm.

4-[4-(1-Hydroxypentan-2-yl)furan-3-yl]methyl-5-(2-triethylsilylprop-2-en-1-yl)-2,5-dihydrofuran-2-one (271-1 and 271-2)



To a solution of alkynes **261** (63.7 mg, 0.221 mmol) in CH_2Cl_2 (1 mL) was added freshly distilled triethylsilane (43 µL, 0.27 mmol, 1.2 equiv) and Cp*Ru(MeCN)$_3$PF$_6$ (5.6 mg, 0.011 mmol, 0.050 equiv). The mixture was stirred for 1 h at rt and directly concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 5:5 to 4:6) to give **271-1** and **271-2** as two separable diastereoisomers: 32.7 mg (37%) of the less polar diastereoisomer **271-1** and 34.6 mg (39%) of the more polar diastereoisomer **271-2**, both colourless oils.

$C_{23}H_{36}O_4Si$ Molecular weight: 404.62 g·mol^{-1}

Less polar diastereoisomer 271-1

R_f = 0.45 (PE—Et_2O, 4:6);

IR ν_{max} 3458, 2955, 2933, 2912, 2874, 2361, 1749, 1637, 1541, 1458, 1417 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (1H, d, *J* = 1.4 Hz, CH-C2), 7.28 (1H, s, CH-C5), 5.87 (1H, dt, *J* = 2.0, 0.9 Hz, CH_2-C18), 5.73 (1H, ddd, *J* = 1.5, 1.5, 1.5 Hz, CH-C13), 5.52 (1H, dt, *J* = 2.0, 1.2 Hz, CH_2-C18), 5.02 (1H, ddd, *J* = 9.7, 3.1, 1.5 Hz, CH-C15), 3.69—3.57 (2H, m, CH_2-C10), 3.53 (1H, dd, *J* = 18.1, 1.5 Hz, CH_2-C11), 3.41 (1H, dd, *J* = 18.1, 1.5 Hz, CH_2-C11), 2.65 (1H, ddd, *J* = 15.2, 3.1, 1.2 Hz, CH_2-C16), 2.56 (1H, dq, *J* = 8.5, 6.0 Hz, CH-C6), 2.23 (1H, ddd, *J* = 15.2, 9.7, 0.9 Hz, CH_2-C16), 1.67—1.57 (1H, m, CH_2-C7), 1.52—1.41 (1H, m, CH_2-C7), 1.37 (1H, dd, *J* = 6.2, 5.5 Hz, OH), 1.34—1.23 (2H, m, CH_2-C8), 0.93 (9H, t, *J* = 7.9 Hz, 3×CH_3-SiEt_3), 0.89 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.62 (6H, q, *J* = 8.0 Hz, 3×CH_2-SiEt_3);

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6 (C-C12), 171.4 (C-C14), 143.2 (C-C17), 140.9 (CH-C2 or CH-C5), 140.6 (CH-C2 or CH-C5), 129.6 (CH_2-C18), 126.0 (C-C4 or C-C3), 119.6 (C-C4

or C-C3), 117.6 (CH-C13), 83.0 (CH-C15), 66.8 (CH_2-C10), 39.4 (CH_2-C16), 37.5 (CH-C6), 34.2 (CH_2-C7), 23.4 (CH_2-C11), 20.7 (CH_2-C8), 14.3 (CH_3-C9), 7.4 (3×CH_3-$SiEt_3$), 3.0 (3×CH_2-$SiEt_3$);

LRMS (CI, Me_3CH): *m/z* (*int*) 405 (100), 389 (10), 289 (11), 251 (16), 133 (10), 85 (12), 71 (15). HRMS (CI, Me_3CH) calculated for $C_{23}H_{37}O_4Si$ $[M+H]^+$: 405.2461, found 405.2455, Δ −1.6 ppm.

More polar diastereoisomer 271-2

R_f = 0.34 (PE—Et_2O, 4:6);

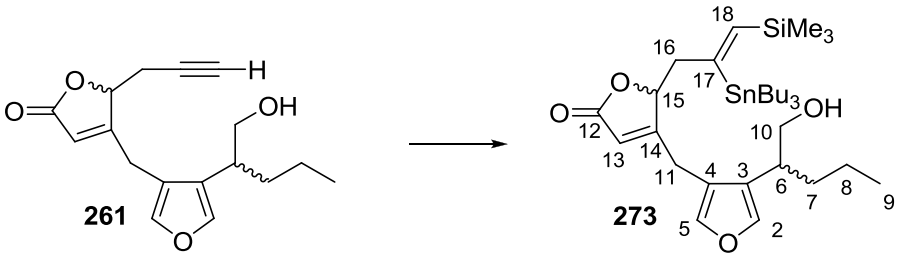
IR ν_{max} 3449, 2955, 2878, 2360, 1743, 1643, 1543, 1458, 1419 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (1H, d, *J* = 1.4 Hz, CH-C2), 7.28 (1H, s, CH-C5), 5.87 (1H, dt, *J* = 2.0, 1.2 Hz, CH_2-C18), 5.75 (1H, ddd, *J* = 1.5, 1.4, 1.4 Hz, CH-C13), 5.52 (1H, dt, *J* = 2.0, 0.9 Hz, CH_2-C18), 4.97 (1H, ddd, *J* = 9.7, 3.1, 1.5 Hz, CH-C15), 3.68—3.60 (2H, m, CH_2-C10), 3.59 (1H, dd, *J* = 17.8, 1.4 Hz, CH_2-C11), 3.40 (1H, dd, *J* = 17.8, 1.4 Hz, CH_2-C11), 2.67 (1H, ddd, *J* = 15.1, 3.1, 1.2 Hz, CH_2-C16), 2.57 (1H, dq, *J* = 8.5, 6.0 Hz, CH-C6), 2.22 (1H, ddd, *J* = 15.1, 9.7, 0.9 Hz, CH_2-C16), 1.67—1.57 (1H, m, CH_2-C7), 1.51—1.40 (2H, m, CH_2-C7 and OH), 1.34—1.21 (2H, m, CH_2-C8), 0.93 (9H, t, *J* = 7.9 Hz, 3×CH_3-$SiEt_3$), 0.88 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.62 (6H, q, *J* = 8.0 Hz, 3×CH_2-$SiEt_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (C-C12), 171.4 (C-C14), 143.2 (C-C17), 141.0 (CH-C2 or CH-C5), 140.6 (CH-C2 or CH-C5), 129.7 (CH_2-C18), 126.0 (C-C4 or C-C3), 119.6 (C-C4 or C-C3), 117.7 (CH-C13), 83.0 (CH-C15), 66.8 (CH_2-C10), 39.5 (CH_2-C16), 37.6 (CH-C6), 34.2 (CH_2-C7), 23.5 (CH_2-C11), 20.7 (CH_2-C8), 14.3 (CH_3-C9), 7.4 (3×CH_3-$SiEt_3$), 3.0 (3×CH_2-$SiEt_3$);

LRMS (CI, Me_3CH): *m/z* (*int*) 405 (100), 97 (10), 81 (24). HRMS (CI, Me_3CH) calculated for $C_{23}H_{37}O_4Si$ $[M+H]^+$: 405.2461, found 405.2460, Δ −0.2 ppm.

4-[4-(1-Hydroxypentan-2-yl)furan-3-yl]methyl-5-[(2*Z*)-2-(tributylstannyl)-3-(trimethylsilyl)prop-2-en-1-yl]-2,5-dihydrofuran-2-one (273)



To a solution of alkynes **261** (325 mg, 1.13 mmol) in THF (2.3 mL) was added $Pd(PPh_3)_4$ (69.8 mg, 0.0604 mmol, 0.0536 equiv) and stannane **272** (600 µL, 1.69 mmol, 1.50 equiv) previously prepared in quantitative yield following the literature.[118] The mixture was warmed to 70 °C for 3 h and then cooled to rt. Saturated aqueous NH_4Cl

(20 mL) and Et_2O (50 mL) were added. The phases were separated and the aqueous phase was extracted with Et_2O (30 mL). The organic extracts were combined, washed with brine (40 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 6:4 to 5:5) to give the corresponding stannanes **273** (550 mg, 75%) as a pale yellow oil and partially separable mixture (1:1) of two diastereoisomers.

$C_{32}H_{56}O_4SiSn$ Molecular weight: 651.58 g·mol^{-1}

R_f = 0.73 and 0.64 (PE—Et_2O, 7:3);

IR ν_{max} 3440, 2955, 2923, 2871, 2854, 1745, 1637, 1541, 1464 cm^{-1};

Less polar diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (1H, s, CH-C2 or CH-C5), 7.28 (1H, s, CH-C2 or CH-C5), 6.56 (1H, s, CH-C18), 5.69 (1H, d, *J* = 1.0 Hz, CH-C13), 4.91 (1H, ddd, *J* = 8.7, 4.0, 1.0 Hz, CH-C15), 3.68—3.59 (2H, m, CH_2-C10), 3.49 (1H, d, *J* = 18.2 Hz, CH_2-C11), 3.37 (1H, d, *J* = 18.2 Hz, CH_2-C11), 2.80 (1H, dd, *J* = 14.1, 4.0 Hz, CH_2-C16), 2.57—2.54 (1H, m, CH-C6), 2.49 (1H, dd, *J* = 14.1, 8.7 Hz, CH_2-C16), 1.67—1.59 (1H, m, CH_2-C7), 1.53—1.45 (7H, m, CH_2-C7, 3×CH_2-$SnBu_3$), 1.39—1.27 (8H, m, CH_2-C8, 3×CH_2-$SnBu_3$), 1.0—0.95 (6H, m, 3×CH_2-$SnBu_3$), 0.91—0.86 (12H, m, CH_3-C9, 3×CH_3-$SnBu_3$), 0.12 (9H, s, 3×CH_3-$SiMe_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (C-C12), 171.5 (C-C14), 158.9 (C-C17), 149.0 (CH-C18), 141.0 (CH-C2 or CH-C5), 140.5 (CH-C2 or CH-C5), 125.9 (C-C3 or C-C4), 119.6 (C-C3 or C-C4), 117.6 (CH-C13), 84.2 (CH-C15), 66.8 (CH_2-C10), 49.5 (CH_2-C16), 37.6 (CH-C6), 34.2 (CH_2-C7), 29.3 (3×CH_2-$SnBu_3$), 27.6 (3×CH_2-$SnBu_3$), 23.5 (CH_2-C11), 20.7 (CH_2-C8), 14.3 (CH_3-C9), 13.8 (3×CH_3-$SnBu_3$), 11.7 (3×CH_2-$SnBu_3$), 0.2 (3×CH_3-$SiMe_3$);

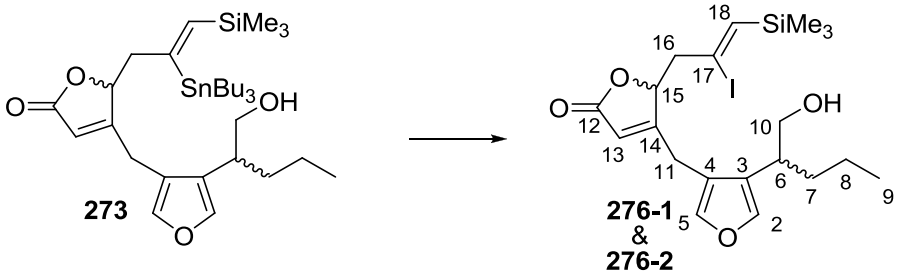
More polar diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (1H, s, CH-C2 or CH-C5), 7.28 (1H, s, CH-C2 or CH-C5), 6.55 (1H, s, CH-C18), 5.68 (1H, d, *J* = 1.5 Hz, CH-C13), 4.88 (1H, ddd, *J* = 9.1, 3.6, 1.0 Hz, CH-C15), 3.68—3.59 (2H, m, CH_2-C10), 3.53 (1H, d, *J* = 18.0 Hz, CH_2-C11), 3.35 (1H, d, *J* = 18.0 Hz, CH_2-C11), 2.83—2.77 (1H, m, CH_2-C16), 2.58—2.53 (1H, m, CH-C6), 2.52—2.44 (1H, m, CH_2-C16), 1.67—1.59 (1H, m, CH_2-C7), 1.53—1.45 (7H, m, CH_2-C7, 3×CH_2-$SnBu_3$), 1.39—1.27 (8H, m, CH_2-C8, 3×CH_2-$SnBu_3$), 1.0—0.95 (6H, m, 3×CH_2-$SnBu_3$), 0.91—0.86 (12H, m, CH_3-C9, 3×CH_3-$SnBu_3$), 0.12 (9H, s, 3×CH_3-$SiMe_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4 (C-C12), 171.5 (C-C14), 158.9 (C-C17), 148.9 (CH-C18), 141.0 (CH-C2 or CH-C5), 140.5 (CH-C2 or CH-C5), 125.8 (C-C3 or C-C4), 119.6 (C-C3 or C-C4), 117.6 (CH-C13), 84.1 (CH-C15), 66.7 (CH_2-C10), 49.3 (CH_2-C16), 37.6 (CH-C6), 34.2 (CH_2-C7), 29.3 (3×CH_2-$SnBu_3$), 27.6 (3×CH_2-$SnBu_3$), 23.4 (CH_2-C11), 20.7 (CH_2-C8), 14.3 (CH_3-C9), 13.8 (3×CH_3-$SnBu_3$), 11.7 (3×CH_2-$SnBu_3$), 0.2 (3×CH_3-$SiMe_3$);

LRMS (CI, Me_3CH): *m/z* (*int*) 653 (4), 595 (17), 593 (14), 403 (28), 363 (100), 361 (36), 291 (28), 289 (22), 73 (18). HRMS (CI, Me_3CH) calculated for $C_{32}H_{57}O_4Si^{120}Sn$ $[M+H]^+$: 653.3054, found 653.3060, Δ +1.8 ppm.

4-[4-(1-Hydroxypentan-2-yl)furan-3-yl]methyl-5-((2*Z*)-2-iodo-3-trimethylsilylprop-2-en-1-yl)-2,5-dihydrofuran-2-one (276-1 and 276-2)



To a solution of stannanes **273** (533 mg, 0.818 mmol) in CH_2Cl_2 (8.5 mL) at 0 °C was added I_2 (230 mg, 0.906 mmol, 1.11 equiv). The reaction was stirred for 15 min, quenched with saturated aqueous $Na_2S_2O_3$ (20 mL) and diluted with CH_2Cl_2 (30 mL). After 10 min, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were combined, washed with brine (40 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 7:3) to give the corresponding vinyl iodides **276-1** and **276-2** (388 mg, 97%) as two separable diastereoisomers in a 1:1 ratio, both colourless oils.

$C_{20}H_{29}IO_4Si$ Molecular weight: 488.43 g·mol^{-1}

Less polar diastereoisomer 276-1

R_f = 0.48 (PE—Et_2O, 3:7);

IR ν_{max} 3460, 2955, 2929, 2899, 2872, 2360, 1747, 1637, 1597, 1541, 1464 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (2H, br s, CH-C2 and CH-C5), 6.61 (1H, d, *J* = 0.7 Hz, CH-C18), 5.72 (1H, ddd, *J* = 1.6, 1.0, 1.0 Hz, CH-C13), 5.21 (1H, ddd, *J* = 8.9, 3.4, 1.6 Hz, CH-C15), 3.66—3.55 (2H, m, CH_2-C10), 3.52 (1H, dd, *J* = 18.2, 1.0 Hz, CH_2-C11), 3.44 (1H, dd, *J* = 18.2, 1.0 Hz, CH_2-C11), 3.06 (1H, ddd, *J* = 15.0, 3.4, 0.7 Hz, CH_2-C16), 2.73 (1H, dd, *J* = 15.0, 8.9 Hz, CH_2-C16), 2.54 (1H, dq, *J* = 8.6, 5.9 Hz, CH-C6), 1.70 (1H, br s, OH), 1.62 (1H, ddt, *J* = 13.2, 9.9, 5.9 Hz, CH_2-C7), 1.49—1.40 (1H, m, CH_2-C7), 1.34—1.21 (2H, m, CH_2-C8), 0.87 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.19 (9H, s, 3×CH_3-$SiMe_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (C-C12), 170.5 (C-C14), 143.1 (C-C18), 141.0 (CH-C2 or CH-C5), 140.5 (CH-C2 or CH-C5), 125.9 (C-C17), 119.3 (C-C3 or C-C4), 118.0 (CH-C13), 112.4 (C-C3 or C-C4), 82.1 (CH-C15), 66.7 (CH_2-C10), 53.3 (CH_2-C16), 37.5 (CH-C6), 34.4 (CH_2-C7), 23.3 (CH_2-C11), 20.7 (CH_2-C8), 14.3 (CH_3-C9), −1.3 (3×CH_3-$SiMe_3$);

LRMS (CI, Me_3CH): *m/z* (*int*) 489 (100), 361 (68), 345 (7). HRMS (CI, Me_3CH) calculated for $C_{20}H_{30}IO_4Si$ $[M+H]^+$: 489.0958, found 489.0959, Δ +0.3 ppm.

More polar diastereoisomer 276-2

R_f = 0.40 (PE—Et_2O, 3:7);

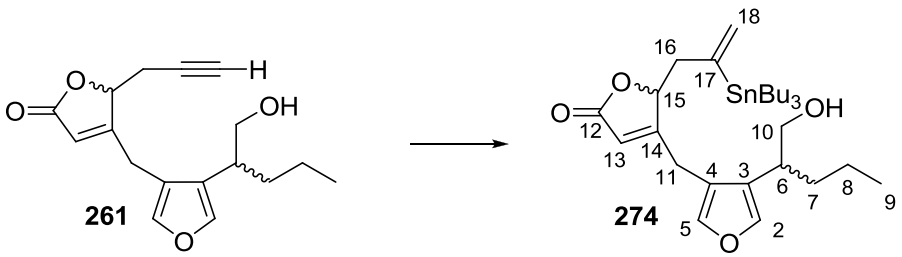
IR ν_{max} 3458, 2955, 2928, 2872, 2359, 2340, 1751, 1637, 1597, 1466 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (2H, s, CH-C2 and CH-C5), 6.62 (1H, dd, *J* = 1.0, 0.7 Hz, CH-C18), 5.77 (1H, ddd, *J* = 1.4, 1.4, 1.4 Hz, CH-C13), 5.19 (1H, ddd, *J* = 9.0, 3.5, 1.4 Hz, CH-C15), 3.67 (1H, dd, *J* = 10.5, 5.8 Hz , CH_2-C10), 3.59 (1H, dd, *J* = 18.0, 1.4 Hz, CH_2-C11), 3.59 (1H, dd, *J* = 10.5, 6.8 Hz, CH_2-C10), 3.43 (1H, dd, *J* = 18.0, 1.4 Hz, CH_2-C11), 3.08 (1H, ddd, *J* = 14.8, 3.5, 1.0 Hz, CH_2-C16), 2.73 (1H, ddd, *J* = 14.8, 9.0, 0.7 Hz, CH_2-C16), 2.57 (1H, dddd, *J* = 8.6, 6.8, 6.7, 5.8 Hz, CH-C6), 1.67—1.58 (1H, m, CH_2-C7), 1.51—1.42 (2H, m, CH_2-C7, OH), 1.33—1.25 (2H, m, CH_2-C8), 0.89 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.21 (9H, s, 3×CH_3-$SiMe_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (C-C12), 170.3 (C-C14), 143.3 (C-C18), 141.1 (CH-C2 or CH-C5), 140.6 (CH-C2 or CH-C5), 125.9 (C-C17), 119.4 (C-C3 or C-C4), 118.1 (CH-C13), 112.5 (C-C3 or C-C4), 82.1 (CH-C15), 67.0 (CH_2-C10), 53.5 (CH_2-C16), 37.6 (CH-C6), 34.2 (CH_2-C7), 23.4 (CH_2-C11), 20.8 (CH_2-C8), 14.3 (CH_3-C9), −1.2 (3×CH_3-$SiMe_3$);

LRMS (CI, Me_3CH): *m/z* (*int*) 489 (100), 361 (37), 345 (5). HRMS (CI, Me_3CH) calculated for $C_{20}H_{30}IO_4Si$ $[M+H]^+$: 489.0958, found 489.0955, Δ −0.7 ppm.

4-[4-(1-Hydroxypentan-2-yl)furan-3-yl]methyl-5-[2-(tributylstannyl)prop-2-en-1-yl]-2,5-dihydrofuran-2-one (274)

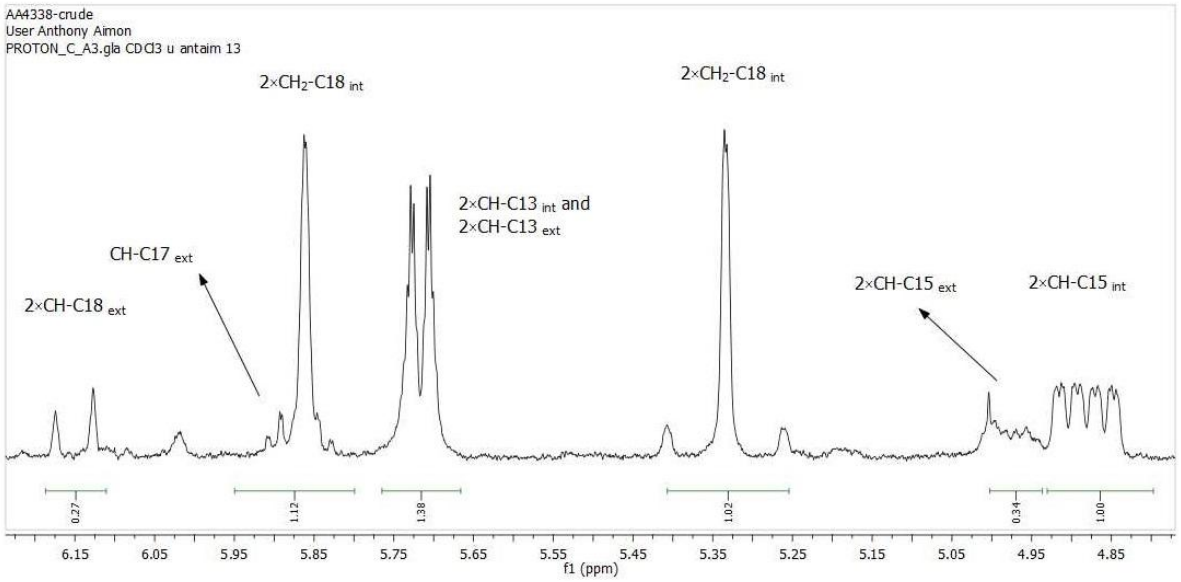


To a solution of alkynes **261** (419 mg, 1.45 mmol) in THF (6.6 mL) at rt were added successively $Pd(PPh_3)_4$ (60.1 mg, 0.0520 mmol, 0.0358 equiv) and tributyltin hydride (425 µL, 1.60 mmol, 1.10 equiv). The mixture was stirred for 20 min and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was diluted with Et_2O (10 mL) and the phases were then separated. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the organic extracts were combined, washed with brine (20 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 5:5 to 4:6) to give a partially separable mixture (1:3.2) in favour of the proximal stannane *versus* stannane in distal position. Most of the proximal stannanes **274** (572 mg) were isolated and taken straight to the next step for better characterisation.

$C_{29}H_{48}O_4Sn$ **Molecular weight: 579.40 g·mol^{-1}**

R_f = 0.68 and 0.76 (PE—Et_2O, 2:8);

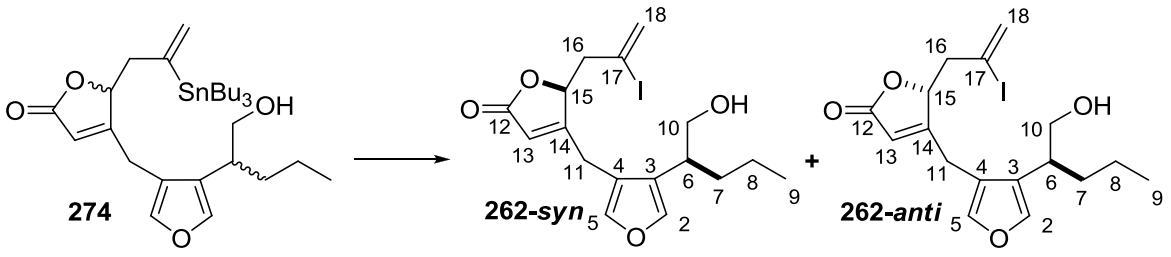
^1H NMR of the crude product showing the alkenyl regions for the internal—external ratio determination.



(5*S)-4-[4-((2*S**)-1-Hydroxypentan-2-yl)furan-3-yl]methyl-5-(2-iodoprop-2-en-1-yl)-2,5-dihydrofuran-2-one (262-*syn*)**

and

(5*S)-4-[4-((2*R**)-1-Hydroxypentan-2-yl)furan-3-yl]methyl-5-(2-iodoprop-2-en-1-yl)-2,5-dihydrofuran-2-one (262-*anti*)**



To a solution of stannanes **274** (572 mg, 0.988 mmol) in CH_2Cl_2 (10 mL) at 0 ºC was added I_2 (289 mg, 1.14 mmol, 1.15 equiv). The mixture was stirred for 20 min and the reaction was then quenched with saturated aqueous $Na_2S_2O_3$ (15 mL). The mixture was diluted with CH_2Cl_2 (20 mL) and after 10 min, the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the organic extracts were combined, washed with brine (30 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 55:45) to give the corresponding vinyl iodides (378 mg, 62%) as separable diastereoisomers **262-*syn*** and **262-*anti***; both colourless oils.

$C_{17}H_{21}IO_4$ **Molecular weight: 416.25 g·mol^{-1}**

Less polar diastereoisomer 262-*syn*

R_f = 0.36 (PE—Et_2O, 2:8);

IR ν_{max} 3446, 2955, 2929, 2870, 1743, 1637, 1618, 1541, 1466 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, s, CH-C2 and CH-C5), 6.25 (1H, d, *J* = 1.7 Hz, CH_2-C18), 5.91 (1H, d, *J* = 1.7 Hz, CH_2-C18), 5.75 (1H, ddd, *J* = 1.4, 1.1, 1.1 Hz, CH-C13), 5.16 (1H, ddd, *J* = 8.7, 3.6, 1.4 Hz, CH-C15), 3.65 (1H, dd, *J* = 10.5, 5.6 Hz, CH_2-C10), 3.59 (1H, dd, *J* = 10.5, 6.8 Hz, CH_2-C10), 3.55 (1H, dd, *J* = 17.8, 1.1 Hz, CH_2-C11), 3.46 (1H, dd, *J* = 17.8, 1.1 Hz, CH_2-C11), 2.94 (1H, dd, *J* = 15.0, 3.6 Hz, CH_2-C16), 2.64 (1H, dd, *J* = 15.0, 8.7 Hz, CH_2-C16), 2.56 (1H, dddd, *J* = 8.5, 6.8, 5.9, 5.6 Hz, CH-C6), 1.69—1.58 (2H, m, CH_2-C7 and OH), 1.51—1.40 (1H, m, CH_2-C7), 1.36—1.23 (2H, m, CH_2-C8), 0.89 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C-C12), 170.2 (C-C14), 141.0 (CH-C2 or CH-C5), 140.5 (CH-C2 or CH-C5), 130.5 (CH_2-C18), 126.0 (C-C3 or C-C4), 119.4 (C-C3 or C-C4), 118.3 (CH-C13), 102.1 (C-C17), 81.9 (CH-C15), 66.8 (CH_2-C10), 48.2 (CH_2-C16), 37.6 (CH-C6), 34.4 (CH_2-C7), 23.4 (CH_2-C11), 20.7 (CH_2-C8), 14.3 (CH_3-C9);

LRMS (EI+): *m/z* (*int*) 416 (100), 385 (10), 289 (56), 271 (20), 215 (33), 161 (35), 119 (21), 91 (45), 77 (20), 55 (10). HRMS (EI+) calculated for $C_{17}H_{21}IO_4$ $[M]^+$: 416.0485, found 416.0488, Δ +0.8 ppm.

More polar diastereoisomer 262-*anti*

R_f = 0.31 (PE—Et_2O, 2:8);

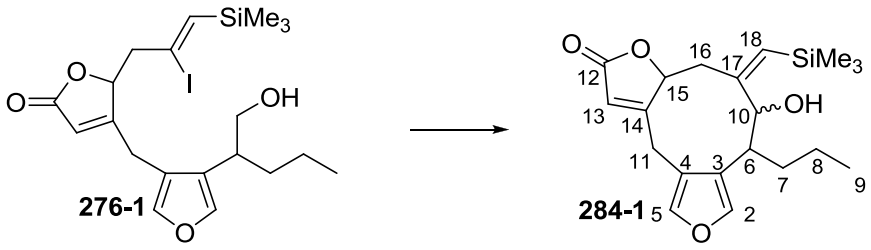
IR ν_{max} 3446, 2955, 2928, 2869, 1746, 1638, 1618, 1539, 1465 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, s, CH-C2 and CH-C5), 6.26 (1H, dd, *J* = 1.7, 0.8 Hz, CH_2-C18), 5.91 (1H, d, *J* = 1.7 Hz, CH_2-C18), 5.78 (1H, ddd, *J* = 1.5, 1.4, 1.1 Hz, CH-C13), 5.13 (1H, ddd, *J* = 8.6, 3.6, 1.5 Hz, CH-C15), 3.67 (1H, dd, *J* = 10.5, 5.5 Hz, CH_2-C10), 3.60 (1H, dd, *J* = 18.1, 1.1 Hz, CH_2-C11), 3.59 (1H, dd, *J* = 10.5, 6.9 Hz, CH_2-C10), 3.44 (1H, dd, *J* = 18.1, 1.4 Hz, CH_2-C11), 2.95 (1H, dd, *J* = 15.0, 3.6 Hz, CH_2-C16), 2.63 (1H, ddd, *J* = 15.0, 8.6, 0.8 Hz, CH_2-C16), 2.57 (1H, dddd, *J* = 8.6, 6.9, 5.6, 5.5 Hz, CH-C6), 1.63 (1H, dddd, *J* = 13.1, 9.6, 6.1, 5.5 Hz, CH_2-C7), 1.55 (1H, br s, OH), 1.51—1.41 (1H, m, CH_2-C7), 1.36—1.22 (2H, m, CH_2-C8), 0.89 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C-C12), 170.1 (C-C14), 141.0 (CH-C2 or CH-C5), 140.6 (CH-C2 or CH-C5), 130.5 (CH_2-C18), 126.0 (C-C3 or C-C4), 119.4 (C-C3 or C-C4), 118.3 (CH-C13), 102.2 (C-C17), 81.8 (CH-C15), 67.0 (CH_2-C10), 48.2 (CH_2-C16), 37.6 (CH-C6), 34.2 (CH_2-C7), 23.4 (CH_2-C11), 20.7 (CH_2-C8), 14.3 (CH_3-C9);

LRMS (CI, Me_3CH): *m/z* (*int*) 417 (69), 291 (100), 273 (46), 251 (10), 97 (13), 71 (28). HRMS (CI, Me_3CH) calculated for $C_{17}H_{22}IO_4$ $[M+H]^+$: 417.0563, found 417.0564, Δ +0.3 ppm.

(10*Z*)-9-Hydroxy-8-propyl-10-(trimethylsilyl)methylidene-5,13-dioxatricyclo[10.3.0.0^{3,7}]pentadeca-1(15),3,6-trien-14-one (284-1)



To a solution of vinyl iodide **276-1** (12.5 mg, 0.0256 mmol) in CH_2Cl_2 (0.5 mL) was added DMP (31 mg, 0.073 mmol, 2.9 equiv) and the mixture was stirred at rt for 2.5 h, then cooled to 0 °C. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (3 mL) and the mixture diluted with water (5 mL) and CH_2Cl_2 (5 mL). After 10 min, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined, washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was quickly purified by passage through small plug of silica (PE—Et_2O, 8:2) to give the corresponding aldehyde (11.8 mg, 95%) as a colourless oil.

To a solution of the aldehyde (11.8 mg, 0.0242 mmol) in degassed DMSO (three freeze-thaw cycles, 9.5 mL) were successively added DMS (97 µL), $CrCl_2$ (61.8 mg, 0.505 mmol, 20.8 equiv) and $NiCl_2$ (0.9 mg, 0.007 mmol, 0.3 equiv). The dark green mixture was stirred at rt for 35 h and then cooled to 0 °C. The reaction was quenched with a solution of serinate (0.5 g of serine diluted in 10 mL H_2O, buffered to pH = 8 with Na_2CO_3) and the mixture diluted with EtOAc (10 mL). The biphasic mixture was stirred for 40 min, the phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 6:4) to give the corresponding tricyclic product **284-1** (2.7 mg, 29% over two steps) as a colourless oil. One diastereoisomer only was isolated.

$C_{20}H_{28}O_4Si$ **Molecular weight: 360.52 g·mol^{-1}**

R_f = 0.35 (PE—Et_2O, 4:6);

IR ν_{max} 3451, 2955, 2934, 2872, 2359, 1753, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, d, *J* = 1.2 Hz, CH-C2 or CH-C5), 7.23 (1H, d, *J* = 1.5 Hz, CH-C2 or CH-C5), 5.93 (1H, s, CH-C18), 5.84 (1H, s, CH-C13), 4.84 (1H, dd, *J* = 11.7, 3.0 Hz, CH-C15), 4.41 (1H, dd, *J* = 5.2, 2.6 Hz, CH-C10), 3.69 (1H, d, *J* = 15.0 Hz, CH_2-C11), 3.47 (1H, d, *J* = 15.0 Hz, CH_2-C11), 2.98—2.92 (2H, m, CH-C6 and CH_2-C16), 2.34 (1H, dd, *J* = 13.8, 11.7 Hz, CH_2-C16), 1.90 (1H, dddd, *J* = 11.8, 8.8, 6.8, 5.2 Hz,

CH_2-C7), 1.75 (1H, d, *J* = 5.2 Hz, OH), 1.55—1.46 (1H, m, CH_2-C7), 1.30—1.20 (2H, m, CH_2-C8), 0.91 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.15 (9H, s, 3×CH_3-$SiMe_3$);

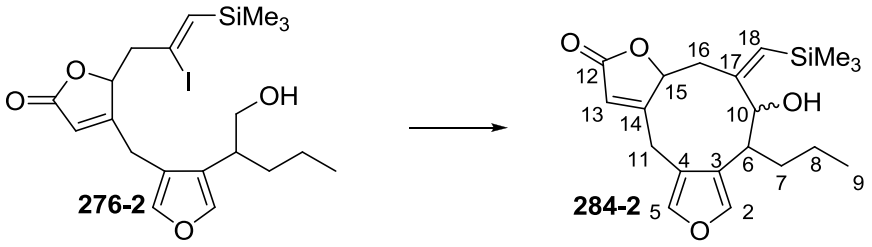
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8 (C-C12), 172.6 (C-C14), 154.7 (C-C17), 142.7 (CH-C2 or CH-C5), 142.2 (CH-C2 or CH-C5), 133.1 (CH-C18), 123.2 (C-C3 or C-C4), 120.0 (C-C3 or C-C4), 114.9 (CH-C13), 77.4 (CH-C10), 42.9 (CH-C6), 23.7 (CH_2-C11), 21.1 (CH_2-C8), 14.1 (CH_3-C9), 0.1 (3×CH_3-$SiMe_3$);

Carbon peaks missing:

- From HSQC: CH-C15 (*ca* 83);
- CH_2-C7, CH_2-C16;

LRMS (CI, Me_3CH): *m/z* (*int*) 361 (100), 343 (12), 237 (11), 213 (32), 133 (10), 85 (28), 69 (29). HRMS (CI, Me_3CH) calculated for $C_{20}H_{29}O_4Si$ $[M+H]^+$: 361.1835, found 361.1836, Δ +0.2 ppm.

(10*Z*)-9-Hydroxy-8-propyl-10-(trimethylsilyl)methylidene-5,13-dioxatricyclo[10.3.0.0^{3,7}]pentadeca-1(15),3,6-trien-14-one (284-2)



To a solution of vinyl iodide **276-2** (52.6 mg, 0.108 mmol) in CH_2Cl_2 (2.2 mL) was added DMP (132 mg, 0.311 mmol, 2.89 equiv). The mixture was stirred at rt for 2.5 h and then cooled to 0 °C. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (5 mL) and the mixture was diluted with water (5 mL) and CH_2Cl_2 (5 mL). After 10 min, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined and washed with brine (10 mL), then dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was quickly purified by passage through a small plug of silica (PE—Et_2O, 8:2) to give the corresponding aldehyde (41.5 mg, 79%) as a colourless oil.

To a solution of the aldehyde (41.5 mg, 0.0853 mmol) in degassed DMSO (three freeze-thaw cycles, 24 mL) were successively added DMS (240 µL), $CrCl_2$ (211 mg, 1.72 mmol, 20.2 equiv) and $NiCl_2$ (5.5 mg, 0.042 mmol, 0.50 equiv). The dark green mixture was stirred at rt for 35 h and then cooled to 0 °C. The reaction was quenched with a solution of serinate (3.0 g of serine diluted in 30 mL H_2O, buffered to pH = 8 with Na_2CO_3) and the mixture diluted with EtOAc (30 mL). The biphasic mixture was stirred for 40 min, the phases were separated and the aqueous phase was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, washed with brine (50 mL), dried over

$MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 6:4) to give the corresponding tricyclic product **284-2** (8.4 mg, 22% over two steps) as a colourless oil. One diastereoisomer only was isolated.

$C_{20}H_{28}O_4Si$ **Molecular weight: 360.52 g·mol^{-1}**

R_f = 0.35 (PE—Et_2O, 4:6);

IR ν_{max} 3458, 2958, 2928, 2868, 2359, 1751, 1629, 1606, 1541, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (1H, d, *J* = 1.5 Hz, CH-C2 or CH-C5), 7.16 (1H, d, *J* = 1.5 Hz, CH-C2 or CH-C5), 5.87 (1H, app ddd, *J* = 1.6, 1.3, 1.3 Hz, CH-C13), 5.49 (1H, s, CH-C18), 4.68 (1H, d, *J* = 9.4 Hz, CH-C15), 3.99 (1H, d, *J* = 9.4 Hz , CH-C10), 3.83 (1H, d, *J* = 18.0 Hz, CH_2-C11), 3.63 (1H, d, *J* = 18.0 Hz, CH_2-C11), 2.82 (1H, app dt, *J* = 15.5, 1.5 Hz, CH_2-C16), 2.56 (1H, ddd, *J* = 11.6, 9.4, 3.4 Hz, CH-C6), 2.50 (1H, dd, *J* = 15.5, 9.4 Hz, CH_2-C16), 2.11 (1H, dddd, *J* = 13.2, 9.9, 6.4, 3.4 Hz, CH_2-C7), 1.80 (1H, s, OH), 1.55—1.43 (1H, m, CH_2-C7), 1.35—1.16 (2H, m, CH_2-C8), 0.89 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.08 (9H, s, 3×CH_3-$SiMe_3$);

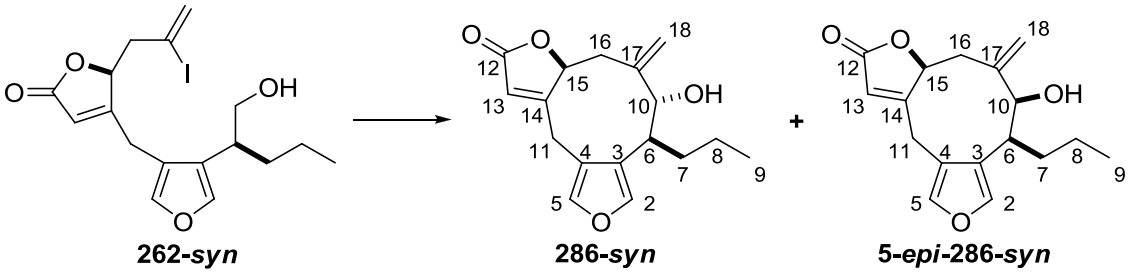
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (C-C12), 172.2 (C-C14), 154.4 (C-C17), 141.1 (CH-C2 or CH-C5), 140.2 (CH-C2 or CH-C5), 134.1 (CH-C18), 125.3 (C-C3 or C-C4), 119.3 (C-C3 or C-C4), 115.9 (CH-C13), 86.2 (CH-C10), 85.8 (CH-C15), 39.4 (CH-C6), 35.7 (CH_2-C7), 31.7 (CH_2-C16), 22.6 (CH_2-C11), 21.0 (CH_2-C8), 14.3 (CH_3-C9), −0.3 (3×CH_3-$SiMe_3$);

LRMS (CI, Me_3CH): *m/z* (*int*) 361 (100), 160 (22), 85 (32), 71 (35). HRMS (CI, Me_3CH) calculated for $C_{20}H_{29}O_4Si$ $[M+H]^+$: 361.1835, found 361.1833, Δ −0.5 ppm.

(8*S,9*,12*S**)-9-Hydroxy-10-methylidene-8-propyl-5,13-dioxatricyclo[10.3.0.0^{3,7}]pentadeca-1(15),3,6-trien-14-one (286-*syn*)**

and

(8*S,9*S**,12*S**)-9-Hydroxy-10-methylidene-8-propyl-5,13-dioxatricyclo[10.3.0.0^{3,7}]pentadeca-1(15),3,6-trien-14-one (5-*epi*-286-*syn*)**



262-*syn* **286-*syn*** **5-*epi*-286-*syn***

To a solution of vinyl iodide **262-*syn*** (59.2 mg, 0.142 mmol) in CH_2Cl_2 (2.8 mL) was added DMP (132 mg, 0.279 mmol, 1.96 equiv). The mixture was stirred at rt for 2 h and then cooled to 0 ºC. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (5 mL) and the mixture diluted with water (5 mL) and CH_2Cl_2 (5 mL). After 10 min, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), the organic

extracts were combined and washed with brine (10 mL), then dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was quickly purified by passage through a small plug of silica (PE—Et_2O, 8:2) to afford the corresponding aldehyde (50.1 mg, 85%) as a colourless oil.

To a solution of $CrCl_2$ (200 mg, 1.63 mmol, 13.5 equiv) and $NiCl_2$ (1.6 mg, 0.012 mmol, 0.10 equiv) in previously degassed DMSO (three freeze-thaw cycles, 6 mL) was added a solution of aldehyde (50.1 mg, 0.121 mmol) in degassed DMSO (three freeze-thaw cycles, 6 mL) at rt. The dark green mixture was stirred for 24 h at rt and for 16 h at 50 °C. The reaction was quenched with saturated aqueous NH_4Cl (15 mL) and the mixture diluted with EtOAc (30 mL). The biphasic mixture was stirred for 30 min, the phases were separated and the aqueous phase was extracted with EtOAc (3 × 30 mL). The organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 45:55) allowing the separation of minor diastereoisomer **5-*epi*-286-*syn*** (5.5 mg, 13% over two steps) as a colourless oil and major diastereoisomer **286-*syn*** (20.2 mg, 49% over two steps) as a colourless solid. The crystal structure of the major diastereoisomer was obtained, confirming its structure (*cf*. Annexe 15).

$C_{17}H_{20}O_4$ **Molecular weight: 288.34 g·mol^{-1}**

Less polar diastereoisomer 5-*epi*-286-*syn*

mp. 140—143 °C;

R_f = 0.53 (PE—Et_2O, 2:8);

IR ν_{max} 3454, 2955, 2930, 2870, 2366, 1743, 1635, 1537, 1456 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (1H, d, *J* = 1.5 Hz, CH-C5), 7.23 (1H, d, *J* = 1.5 Hz, CH-C2), 5.89 (1H, ddd, *J* = 1.6, 1.1, 1.1 Hz, CH-C13), 5.23 (1H, ddd, *J* = 3.6, 2.7, 1.6 Hz, CH-C15), 4.97 (1H, s, CH_2-C18), 4.94 (1H, s, CH_2-C18), 4.12 (1H, d, *J* = 1.5 Hz, CH-C10), 3.68 (1H, dd, *J* = 14.7, 1.1 Hz, CH_2-C11), 3.01 (1H, dd, *J* = 14.7, 1.1 Hz, CH_2-C11), 2.97 (1H, ddd, *J* = 8.6, 6.5, 1.5 Hz, CH-C6), 2.91 (1H, dd, *J* = 16.4, 2.7 Hz, CH_2-C16), 2.45 (1H, dd, *J* = 16.4, 3.6 Hz, CH_2-C16), 1.84—1.65 (2H, m, CH_2-C7), 1.57 (1H, br s, OH), 1.40—1.29 (2H, m, CH_2-C8), 0.92 (3H, t, *J* = 7.4 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6 (C-C12), 170.3 (C-C14), 143.2 (C-C17), 140.8 (CH-C2), 140.5 (CH-C5), 122.5 (C-C3 or C-C4), 122.0 (C-C3 or C-C4), 120.0 (CH-C13), 113.5 (CH_2-C18), 83.9 (CH-C15), 74.8 (CH-C10), 38.0 (CH-C6), 30.5 (CH_2-C16), 30.2 (CH_2-C7), 21.5 (CH_2-C11), 21.1 (CH_2-C8), 14.1 (CH_3-C9);

LRMS (CI, Me_3CH): *m/z* (*int*) 289 (72), 273 (12), 137 (13), 113 (68), 97 (68), 81 (73), 71 (100). HRMS (CI, Me_3CH) calculated for $C_{17}H_{21}O_4$ $[M+H]^+$: 289.1440, found 289.1438, Δ −0.7 ppm.

More polar diastereoisomer 286-*syn*

mp. 140—142 °C;

R_f = 0.44 (PE—Et_2O, 2:8);

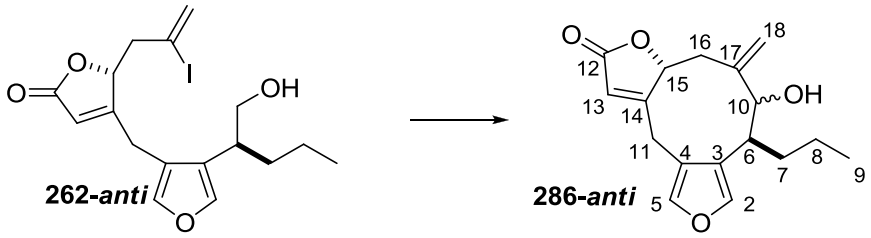
IR ν_{max} 3400, 2957, 2928, 2872, 1744, 1636, 1537, 1444 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (1H, s, CH-C5), 7.23 (1H, s, CH-C2), 5.93 (1H, s, CH-C13), 5.15 (1H, s, CH-C15), 4.92 (1H, s, CH_2-C18), 4.87 (1H, s, CH_2-C18), 3.90 (1H, d, *J* = 4.3 Hz, CH-C10), 3.68 (1H, d, *J* = 16.0 Hz, CH_2-C11), 3.27 (1H, br s, CH_2-C11), 2.81—2.71 (2H, m, CH-C6 and CH_2-C16), 2.55 (1H, br s, CH_2-C16), 1.85 (2H, br s, CH_2-C7 and OH), 1.55—1.44 (1H, m, CH_2-C7), 1.39—1.28 (1H, m, CH_2-C8), 1.27—1.14 (1H, m, CH_2-C8), 0.89 (3H, t, *J* = 7.4 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8 (C-C12), 170.4 (C-C14), 141.9 (C-C17), 141.5 (CH-C2), 140.0 (CH-C5), 123.3 (C-C3 or C-C4), 121.1 (C-C3 or C-C4), 119.7 (CH-C13), 118.6 (CH_2-C18), 83.2 (CH-C15), 81.5 (CH-C10), 39.7 (CH-C6), 32.7 (CH_2-C7), 28.9 (CH_2-C16), 22.8 (CH_2-C11), 20.9 (CH_2-C8), 14.2 (CH_3-C9);

LRMS (EI+): *m/z* (*int*) 288 (100), 270 (43), 259 (36), 219 (64), 173 (51), 129 (39), 91 (81), 77 (47), 43 (47). HRMS (EI+) calculated for $C_{17}H_{20}O_4$ $[M]^+$: 288.1362, found 288.1360, Δ −0.6 ppm.

(8*S,12*R**)-9-Hydroxy-10-methylidene-8-propyl-5,13-dioxatricyclo[10.3.0.0^{3,7}]pentadeca-1(15),3,6-trien-14-one (286-*anti*)**



To a solution of vinyl iodide **262-*anti*** (59.2 mg, 0.123 mmol) in CH_2Cl_2 (2.5 mL) was added DMP (80.2 mg, 0.189 mmol, 1.54 equiv). The mixture was stirred at rt for 40 min, cooled to 0 °C and the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (5 mL). The mixture was diluted with water (5 mL) and CH_2Cl_2 (5 mL) and after 10 min, the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), the organic extracts were combined and washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was quickly purified by passage through a small plug of silica (PE—Et_2O, 8:2) to afford the corresponding aldehyde (50.9 mg, 100%) as a colourless oil.

To a solution of $CrCl_2$ (215 mg, 1.76 mmol, 14.3 equiv) and $NiCl_2$ (2.5 mg, 0.019 mmol, 0.16 equiv) in degassed DMSO (three freeze-thaw cycles, 6 mL) was added a solution of aldehyde (50.9 mg, 0.123 mmol) in degassed DMSO (three freeze-thaw cycles, 6.5 mL) at rt. The dark green mixture was stirred for 48 h at 50 °C. The reaction was quenched

with saturated aqueous NH_4Cl (15 mL) and the mixture diluted with EtOAc (30 mL). The biphasic mixture was stirred for 30 min and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the organic extracts were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 45:55) to give an inseparable mixture (1:2.4 based on ^1H NMR) of the two diastereoisomers **286-*anti*** (17.8 mg, 50%).

$C_{17}H_{20}O_4$ **Molecular weight: 288.34 g·mol^{-1}**

R_f = 0.25 (PE—Et_2O, 4:6);

IR ν_{max} 3448, 2957, 2928, 2872, 2360, 1748, 1633, 1541, 1465 cm^{-1};

Minor diastereoisomer

^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (1H, d, *J* = 1.4 Hz, CH-C5), 7.32 (1H, d, *J* = 1.4 Hz, CH-C2), 6.02 (1H, dd, *J* = 1.1, 0.8 Hz, CH-C13), 5.14 (1H, s, CH_2-C18), 5.05 (1H, s, CH_2-C18), 4.98 (1H, ddd, *J* = 4.5, 3.6, 1.0 Hz, CH-C15), 4.14 (1H, s, CH-C10), 3.76 (1H, dd, *J* = 18.0, 0.8 Hz, CH_2-C11), 3.67 (1H, d, *J* = 18.0 Hz, CH_2-C11), 2.60—2.48 (2H, m, CH-C6 and CH_2-C16), 2.05 (1H, app ddd, *J* = 15.2, 3.6, 1.3 Hz, CH_2-C16), 2.11 (1H, br s, CH_2-C7), 1.92 (1H, br s, OH), 1.56—1.49 (1H, m, CH_2-C7), 1.37—1.24 (1H, m, CH_2-C8), 1.23—1.11 (1H, m, CH_2-C8), 0.87 (3H, t, *J* = 7.4 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6 (C-C12), 171.4 (C-C14), 146.4 (C-C17), 142.1 (CH-C2), 140.4 (CH-C5), 123.7 (C-C3 or C-C4), 119.5 (CH_2-C18), 119.4 (C-C3 or C-C4), 119.2 (CH-C13), 82.6 (CH-C15), 77.8 (CH-C10), 39.6 (CH-C6), 35.2 (CH_2-C7), 30.9 (CH_2-C16), 24.2 (CH_2-C11), 20.7 (CH_2-C8), 14.0 (CH_3-C9);

Major diastereoisomer

^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (1H, s, CH-C5), 7.23 (1H, d, *J* = 1.5 Hz, CH-C2), 5.90 (1H, s, CH-C13), 5.13 (1H, s, CH_2-C18), 5.05 (1H, s, CH_2-C18), 4.75 (1H, br s, CH-C15), 3.98 (1H, d, *J* = 7.4 Hz, CH-C10), 3.83—3.73 (1H, m, CH_2-C11), 3.61 (1H, d, *J* = 17.9 Hz, CH_2-C11), 2.60—2.48 (2H, m, CH-C6 and CH_2-C16), 2.39 (1H, d, *J* = 15.4 Hz, CH_2-C16), 1.92 (1H, br s, OH), 1.78—1.61 (2H, m, CH_2-C7), 1.37—1.24 (1H, m, CH_2-C8), 1.23—1.11 (1H, m, CH_2-C8), 0.87 (3H, t, *J* = 7.4 Hz, CH_3-C9);

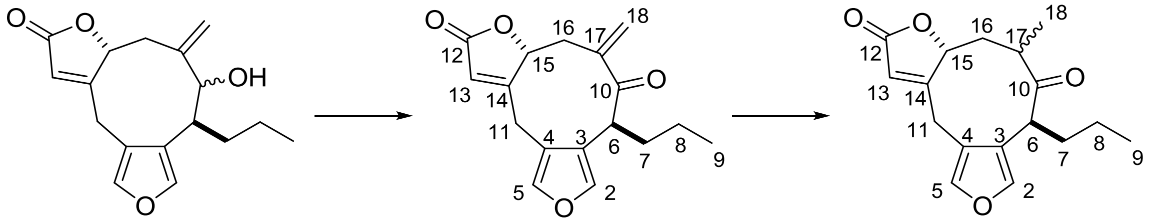
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5 (C-C12), 168.6 (C-C14), 143.4 (C-C17), 141.2 (CH-C2), 140.4 (CH-C5), 123.7 (C-C3 or C-C4), 119.1 (C-C3 or C-C4), 116.9 (CH_2-C18), 116.4 (CH-C13), 86.2 (CH-C15), 81.5 (CH-C10), 40.0 (CH-C6), 37.1 (CH_2-C7), 31.1 (CH_2-C16), 22.5 (CH_2-C11), 20.8 (CH_2-C8), 14.2 (CH_3-C9);

LRMS (CI, Me_3CH): *m/z* (*int*) 289 (100), 271 (24), 137 (10), 71 (13). HRMS (CI, Me_3CH) calculated for $C_{17}H_{21}O_4$ $[M+H]^+$: 289.1440, found 289.1436, Δ −1.4 ppm.

(8*S,12*R**)-10-Methylidene-8-propyl-5,13-dioxatricyclo[10.3.0.0^{3,7}]pentadeca-1(15),3,6-triene-9,14-dione (287-*anti*)**

and

(8*S,12*R**)-10-Methyl-8-propyl-5,13-dioxatricyclo[10.3.0.0^{3,7}]pentadeca-1(15),3,6-triene-9,14-dione (288-*anti*)**



286-*anti* **287-*anti*** **288-*anti***

To a solution of the diastereoisomeric mixture **286-*anti*** (7.1 mg, 0.025 mmol) in CH_2Cl_2 (1 mL) was added DMP (15.6 mg, 0.0368 mmol, 1.49 equiv). The solution was stirred at rt for 1 h and then cooled to 0 °C. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (5 mL) and the mixture diluted with water (5 mL) and CH_2Cl_2 (5 mL). After 10 min, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined and washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by passage through a small plug of silica (PE—Et_2O, 5:5) to give 7.0 mg (99%) of a colourless oil. ^{1}H NMR confirmed that one enone **287-*anti*** was obtained from the mixture of the two diastereoisomers **286-*anti***.

To a solution of the enone **287-*anti*** (7.0 mg, 0.024 mmol) in THF (2.4 mL) at −78 °C were successively added $CeCl_3$ (12 mg, 0.049 mmol, 2.0 equiv) and L-selectride (29 μL of a 1 M solution in THF, 0.029 mmol, 1.2 equiv). The mixture was stirred for 1 h and more L-selectride (29 μL of a 1 M solution in THF, 0.029 mmol, 1.2 equiv) was added. After a further 30 min, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and the mixture was warmed to rt. Et_2O (10 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the organic extracts were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 6:4) to give **288-*anti*** as two separable diastereoisomers: 2.7 mg (38%, 2 steps) of the less polar diastereoisomer, 2.1 mg (30%, 2 steps) of the more polar diastereoisomer, both colourless oils.

287-*anti*

$C_{17}H_{18}O_4$ **Molecular weight: 286.32 g·mol^{-1}**

R_f = 0.50 (PE—Et_2O, 2:8);

IR ν_{max} 3153, 3099, 2958, 2932, 2872, 2355, 1755, 1687, 1633, 1534, 1464 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (1H, d, *J* = 1.2 Hz, CH-C2 or CH-C5), 7.28 (1H, s, CH-C2 or CH-C5), 5.88 (1H, td, *J* = 1.9, 1.3 Hz, CH-C13), 5.74 (1H, d, *J* = 1.2 Hz, CH_2-C18), 5.70 (1H, d, *J* = 1.2 Hz, CH_2-C18), 4.81 (1H, ddd, *J* = 8.6, 5.2, 1.3 Hz, CH-C15), 4.09 (1H, ddd, *J* = 10.3, 4.2, 1.2 Hz, CH_2-C6), 3.62 (2H, d, *J* = 1.9 Hz, CH_2-C11), 3.46 (1H, dd, *J* = 13.9, 5.2 Hz, CH_2-C16), 2.42 (1H, dd, *J* = 13.9, 8.6 Hz, CH_2-C16), 2.19—2.12 (1H, m, CH_2-C7), 1.75 (1H, dddd, *J* = 13.0, 8.5, 7.7, 4.2 Hz, CH_2-C7), 1.39 (2H, app tq, *J* = 7.3, 7.3 Hz, CH_2-C8), 0.99 (3H, t, *J* = 7.3 Hz, CH_3-C9);

288-*anti*

$C_{17}H_{20}O_4$ **Molecular weight: 288.34 g·mol^{-1}**

Less polar diastereoisomer

R_f = 0.35 (PE—Et_2O, 4:6);

IR ν_{max} 2963, 2931, 2870, 2337, 1759, 1705, 1636, 1543, 1458 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (1H, app t, *J* = 1.3 Hz, CH-C2), 7.33 (1H, s, CH-C5), 5.84 (1H, app t, *J* = 1.9 Hz, CH-C13), 4.55 (1H, dd, *J* = 9.3, 3.8 Hz, CH-C15), 3.73 (1H, d, *J* = 17.4 Hz, CH_2-C11), 3.55 (1H, ddd, *J* = 9.6, 5.5, 1.3 Hz, CH-C6), 3.34 (1H, dd, *J* = 17.4, 1.9 Hz, CH_2-C11), 2.87—2.79 (1H, m, CH-C17), 2.06—2.00 (2H, m, CH_2-C16), 1.97—1.90 (1H, m, CH_2-C7), 1.89—1.81 (1H, m, CH_2-C7), 1.50—1.33 (2H, m, CH_2-C8), 1.13 (3H, d, *J* = 6.9 Hz, CH_3-C18), 0.99 (3H, t, *J* = 7.4 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 216.0 (C-C10), 171.9 (C-C12), 170.7 (C-C14), 142.5 (CH-C5), 140.5 (CH-C2), 122.5 (C-C3 or C-C4), 119.3 (C-C3 or C-C4), 116.7 (CH-C13), 82.9 (CH-C15), 50.5 (CH-C6), 39.2 (CH-C17), 38.4 (CH_2-C16), 31.7 (CH_2-C7), 22.4 (CH_2-C11), 21.2 (CH_3-C18), 20.6 (CH_2-C8), 14.0 (CH_3-C9);

LRMS (CI, Me_3CH): *m/z* (*int*) 289 (100), 113 (14), 85 (26), 73 (47). HRMS (CI, Me_3CH) calculated for $C_{17}H_{21}O_4$ $[M+H]^+$: 289.1440, found 289.1438, Δ −0.7 ppm.

More polar diastereoisomer

R_f = 0.20 (PE—Et_2O, 4:6);

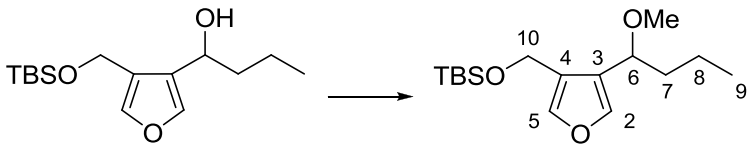
IR ν_{max} 2962, 2924, 2360, 1751, 1712, 1635, 1535, 1458 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (1H, s, CH-C2 or CH-C5), 7.26 (1H, s, CH-C2 or CH-C5), 5.92 (1H, s, CH-C13), 4.91 (1H, dd, *J* = 5.3, 3.5 Hz, CH-C15), 3.67 (1H, dd, *J* = 8.7, 5.6 Hz, CH-C6), 3.61 (1H, dd, *J* = 17.3, 1.3 Hz, CH_2-C11), 3.28 (1H, d, *J* = 17.3 Hz, CH_2-C11), 2.80 (1H, dqd, *J* = 9.5, 6.8, 2.5 Hz, CH-C17), 2.30 (1H, ddd, *J* = 14.9, 9.5, 3.5 Hz, CH_2-C16), 2.08 (1H, ddd, *J* = 14.9, 5.3, 2.5 Hz, CH_2-C16), 1.94—1.85 (1H, m, CH_2-C7), 1.76—1.67 (1H, m, CH_2-C7), 1.39—1.29 (2H, m, CH_2-C8), 1.14 (3H, d, *J* = 6.8 Hz, CH_3-C18), 0.95 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 216.8 (C-C10), 170.0 (C-C12), 170.0 (C-C14), 141.3 (CH-C2 or CH-C5), 141.2 (CH-C2 or CH-C5), 124.2 (C-C3 or C-C4), 119.8 (C-C3 or C-C4), 118.8 (CH-C13), 81.8 (CH-C15), 49.9 (CH-C6), 42.1 (CH-C17), 37.4 (CH_2-C16), 33.9 (CH_2-C7), 23.6 (CH_2-C11), 21.2 (CH_2-C8), 18.3 (CH_3-C18), 14.4 (CH_3-C9);

LRMS (CI, Me_3CH): *m/z* (*int*) 289 (82), 113 (18), 89 (100), 85 (42), 73 (55), 69 (59). HRMS (CI, Me_3CH) calculated for $C_{17}H_{21}O_4$ $[M+H]^+$: 289.1440, found 289.1444, Δ +1.5 ppm.

tert-Butyl[4-(1-methoxybutyl)furan-3-yl]methoxydimethylsilane (304)



240 **304**

To a solution of alcohol **240** (1.14 g, 4.01 mmol, 1.00 equiv) in THF (41 mL) at 0 °C was added NaH (257 mg of a 60% dispersion in mineral oil, 6.43 mmol, 1.60 equiv) portionwise. After 5 min, iodomethane (520 µL, 8.35 mmol, 2.08 equiv) was added and the mixture was warmed to rt and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the mixture diluted with Et_2O (40 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 20 mL). The organic extracts were combined and washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE—Et_2O, 95:5) to give the desired product **304** (1.14 g, 95%) as a colourless oil.

$C_{16}H_{30}O_3Si$ **Molecular weight: 298.49 g·mol^{-1}**

R_f = 0.90 (PE—Et_2O, 9:1);

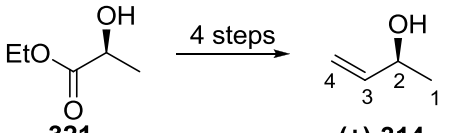
IR ν_{max} 2957, 2930, 2859, 2819, 2339, 1544, 1472, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, dd, *J* = 1.3, 1.3 Hz, CH-C5), 7.28 (1H, d, *J* = 1.7 Hz, CH-C2), 4.63 (1H, dd, *J* = 13.4, 1.3 Hz, CH_2-C10), 4.59 (1H, dd, *J* = 13.4, 1.3 Hz, CH_2-C10), 4.16 (1H, dd, *J* = 7.3, 6.8 Hz, CH-C6), 3.22 (3H, s, CH_3-OMe), 1.77 (1H, dddd, *J* = 13.5, 10.0, 7.3, 5.6 Hz, CH_2-C7), 1.63 (1H, dddd, *J* = 13.5, 9.8, 6.8, 6.8 Hz, CH_2-C7), 1.45—1.25 (2H, m, CH_2-C8), 0.92 (9H, s, 3×CH_3-*t*Bu), 0.91 (3H, t, *J* = 7.4 Hz, CH_3-C9), 0.09 (3H, s, CH_3-$SiMe_2$), 0.08 (3H, s, CH_3-$SiMe_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1 (CH-C2 or CH-C5), 141.0 (CH-C2 or CH-C5), 125.1 (C-C3 or C-C4), 124.6 (C-C3 or C-C4), 75.9 (CH-C6), 57.2 (CH_2-C10), 56.2 (CH_3-OMe), 38.2 (CH_2-C7), 26.1 (3×CH_3-*t*Bu), 19.2 (CH_2-C8), 18.5 (C-*t*Bu), 14.1 (CH_3-C9), −5.2 (2×CH_3-$SiMe_2$);

LRMS (CI, Me_3CH): *m/z* (*int*) 299 (21), 267 (76), 241 (10), 193 (33), 179 (21), 135 (100), 87 (12). HRMS (CI, Me_3CH) calculated for $C_{16}H_{31}O_3Si$ $[M+H]^+$: 299.2042, found 299.2043, Δ +0.3 ppm.

(*S*)-But-3-en-2-ol ((+)-314)[145,143]



321 **(+)-314**

To a solution of (−)-Ethyl-L-lactate **321** (15.0 mL, 132 mmol) in CH_2Cl_2 (130 mL), DHP (14.5 mL, 159 mmol, 1.20 equiv) and PPTS (3.3 g, 13 mmol, 0.10 equiv) were added to the solution at rt. The mixture was stirred overnight and the reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL). The two phases were separated and the aqueous phase was extracted with PE (2 × 60 mL). The organic extracts were combined, washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

To a solution of the crude ester **322** in CH_2Cl_2 (660 mL) at −78 °C, DIBAL-H (134 mL of a 1 M solution in hexane, 134 mmol, 1.01 equiv) was added dropwise over 25 min at −78 °C. The mixture was stirred for 1 h and the reaction was quenched with MeOH (10 mL). The solution was stirred for 10 min and poured onto a saturated solution of Rochelle salt (1 L) at 0 °C. Et_2O (1.5 L) was added and the solution was warmed to rt and stirred vigorously until clear separation of the phases (typically 1 to 1.5 h). Once the phases had separated, the aqueous phase was extracted with Et_2O (2 × 500 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*, delivering the aldehyde that was used directly without further purification.

To a suspension of methyltriphenylphosphonium bromide (142 g, 397 mmol, 3.01 equiv) in THF (660 mL) at 0 °C was added portionwise potassium *tert*-butoxide (37.1 g, 331 mmol, 2.50 equiv). The bright yellow suspension was warmed to rt and stirred for 1 h, before being cooled to 0 °C and slowly added to a solution of crude aldehyde in THF (660 mL). The addition of the ylide was stopped when the colour of the mixture remained bright yellow. The mixture was stirred then warmed to rt and stirred for 30 min before being quenched with a saturated solution of NH_4Cl (300 mL), and diluted with Et_2O (800 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 500 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was filtered through a plug of silica (PE—Et_2O, 95:5) to remove the triphenylphosphonium oxide and the volatile colourless oil was used for the next step immediately.

Alkene **323** was diluted in ethylene glycol (40 mL) and *p*-TSA (1.3 g, 6.8 mmol, 0.05 equiv) was added. The mixture was stirred at rt for 2 days. The product was obtained from the solution by distillation (46 mbar, 80 to 95 °C) to afford allylic alcohol **(+)-314** (5.35 g, 56% over 4 steps) as a colourless oil.

C_4H_8O **Molecular weight: 72.11 g·mol^{-1}**

bp. 97 °C (1 bar);

R_f = 0.4 (PE—Et_2O, 5:5);

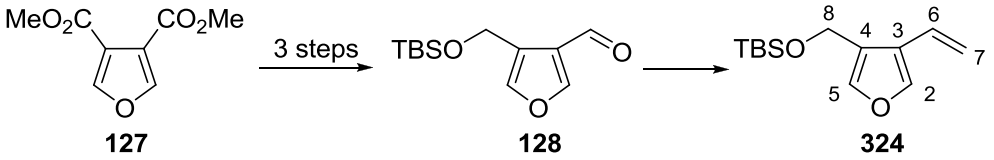
$[\alpha]_D^{24}$ +16.7 (c = 1.12, $CHCl_3$) {Lit.[145] $[\alpha]_D^{20}$ +31.5 (neat), Lit.[143] $[\alpha]_D^{24}$ +25.9 (c = 1.2, Et_2O)};

IR ν_{max} 3331, 2974, 2929, 2874, 1645, 1452, 1422 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (1H, dddd, *J* = 17.2, 10.4, 6.0, 0.8 Hz, CH-C3), 5.21 (1H, ddd, *J* = 17.2, 2.4, 1.2 Hz, CH_2-C4), 5.06 (1H, ddd, *J* = 10.4, 2.4, 1.2 Hz, CH_2-C4), 4.30 (1H, qdd, *J* = 6.4, 6.0, 1.2 Hz, CH-C2), 1.67—1.57 (1H, m, OH), 1.27 (3H, d, *J* = 6.4 Hz, CH_3-C1);

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5 (CH-C3), 113.8 (CH_2-C4), 69.2 (CH-C2), 23.2 (CH_3-C1).

tert-Butyl(4-ethenylfuran-3-yl)methoxydimethylsilane (324)



To a suspension of methyltriphenylphosphonium bromide (68.5 g, 192 mmol, 4.00 equiv) in THF (300 mL) at 0 °C was added potassium *tert*-butoxide (16.1 g, 144 mmol, 3.00 equiv). The bright yellow suspension was warmed to rt, stirred for 1 h and cooled to 0 °C. A solution of the crude, previously prepared aldehyde **128** (13.0 g, ~54.3 mmol) in THF (140 mL) was added slowly to the solution. The mixture was stirred for 1 h at rt and the reaction was quenched with saturated aqueous NH_4Cl (60 mL). The mixture was diluted with Et_2O (200 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 60 mL) and the organic extracts were combined, washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE—Et_2O, 95:5 to 9:1) to deliver the corresponding alkene **324** (8.14 g, 62% over 4 steps) as a colourless oil.

$C_{13}H_{22}O_2Si$ **Molecular weight: 238.40 g·mol^{-1}**

R_f = 0.95 (PE—Et_2O, 8:2);

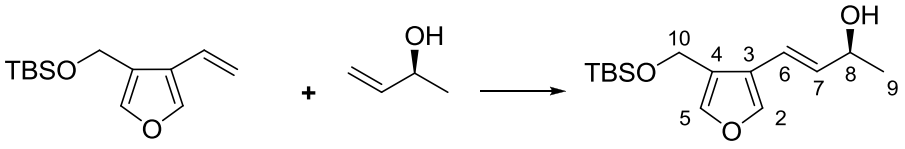
IR ν_{max} 2955, 2932, 2886, 2859, 1643, 1582, 1535, 1470 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (1H, d, *J* = 1.5 Hz, CH-C2), 7.32 (1H, app d, *J* = 1.1 Hz, CH-C5), 6.53 (1H, dd, *J* = 17.8, 11.3 Hz, CH-C6), 5.47 (1H, dd, *J* = 17.8, 1.5 Hz, CH_2-C7), 5.17 (1H, dd, *J* = 11.3, 1.5 Hz, CH_2-C7), 4.66 (2H, d, *J* = 1.1 Hz, CH_2-C8), 0.92 (9H, s, 3×CH_3-*t*Bu), 0.09 (6H, s, 2×CH_3-$SiMe_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5 (CH-C2), 141.2 (CH-C5), 126.6 (CH-C6), 124.5 (C-C4), 123.7 (C-C3), 114.9 (CH_2-C7), 57.2 (CH_2-C8), 26.0 (3×CH_3-*t*Bu), 18.5 (C-*t*Bu), −5.2 (2×CH_3-$SiMe_2$);

LRMS (CI, Me_3CH): *m*/*z* (*int*) 239 (32), 230 (9), 181 (30), 163 (9), 137 (9), 107 (100), 81 (30). HRMS (CI, Me_3CH) calculated for $C_{13}H_{23}O_2Si$ $[M+H]^+$: 239.1467, found 239.1468, Δ +0.1 ppm. Analytic. calculated for $C_{13}H_{22}O_2Si$: C, 65.50; H, 9.30. Found: C, 65.61; H, 9.45.

(2*S*,3*E*)-4-(4-*tert*-Butyldimethylsilyloxymethylfuran-3-yl)but-3-en-2-ol ((−)-325)



324 **(+)-314** **(−)-325**

To a solution of vinyl furan **324** (1.01 g, 4.24 mmol) in CH_2Cl_2 (22 mL) was added allylic alcohol **(+)-314** (1.5 mL, 17 mmol, 4.1 equiv) and Grubbs II catalyst (180 mg, 0.212 mmol, 0.0500 equiv). The solution was stirred at reflux for 48 h; two further portions of Grubbs II catalyst (57.2 mg, 0.674 mmol, 0.0159 equiv and 60.4 mg, 0.0711 mmol, 0.0168 equiv) were added at 12 h intervals. The mixture was concentrated *in vacuo* and purified by flash column chromatography (PE—Et_2O, 92:8 to 9:1) to give the colourless oil **(−)-325** (878 mg, 73%) and unreacted vinyl furan **324** (200 mg, 20%). Enantiomeric purity was 73%, as determined by normal phase chiral HPLC analysis.[141]

$C_{15}H_{26}O_3Si$ **Molecular weight: 282.45 g·mol^{-1}**

R_f = 0.30 (PE—Et_2O, 7:3);

$[\alpha]_D^{26}$ −9.8 (c = 1.11, $CHCl_3$);

IR ν_{max} 3562, 2958, 2929, 2857, 2361, 1667, 1538, 1472 cm^{-1};

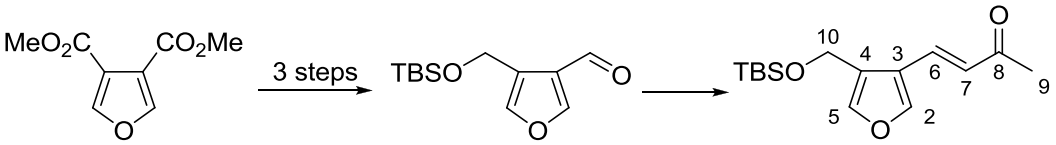
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (1H, d, *J* = 1.6 Hz, CH-C2), 7.30 (1H, app d, *J* = 1.1 Hz, CH-C5), 6.40 (1H, d, *J* = 16.1 Hz, CH-C6), 6.05 (1H, dd, *J* = 16.1, 6.4 Hz, CH-C7), 4.64 (2H, d, *J* = 1.1 Hz, CH_2-C10), 4.41 (1H, dqd, *J* = 6.4, 6.4, 0.8 Hz, CH-C8), 1.57 (1H, br s, OH), 1.34 (3H, d, *J* = 6.4 Hz, CH_3-C9), 0.91 (9H, s, CH_3-*t*Bu), 0.08 (3H, s, CH_3-$SiMe_2$), 0.08 (3H, s, CH_3-$SiMe_2$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.4 (CH-C2 or CH-C5), 141.3 (CH-C2 or CH-C5), 134.5 (CH-C7), 124.3 (C-C3 or C-C4), 122.6 (C-C3 or C-C4), 119.1 (CH-C6), 69.4 (CH-C8), 57.0 (CH_2-C10), 26.0 (CH_3-*t*Bu), 23.6 (CH_3-C9), 18.4 (C-*t*Bu), −5.1 (2×CH_3-$SiMe_2$);

LRMS (FAB): *m*/*z* (*int*) 265 (100), 253 (10), 237 (10), 195 (13), 133 (26), 121 (92), 105 (20), 73 (83). HRMS (FAB) calculated for $C_{15}H_{25}O_2Si$ $[M-OH]^+$: 265.1624, found 265.1619, Δ −2.0 ppm.

HPLC analysis : t_R (*R* enantiomer) = 27.9 min, t_R (*S* enantiomer) = 35.3 min, Chiracel OD-H, 2.5% propan-2-ol in *n*-hexane, flowrate 1.00 mL.min^{-1}, detection 254 nm, temperature oven 20 °C (*cf*. Annexes 16 and 17).

(3*E*)-4-[4-(*tert*-Butyldimethylsilyloxymethyl)furan-3-yl]but-3-en-2-one (326)



127 **128** **326**

Crude aldehyde **128** (1.30 g, ~5.42 mmol), prepared according to previously reported protocols, and 1-(triphenylphosphoranylidene)acetone[185] (5.16 g, 16.2 mmol, 3.00 equiv) were dissolved in toluene (54 mL). The resulting mixture was heated at 100 °C and stirred at this temperature for 5 h. The solution was concentrated *in vacuo* and purified by flash column chromatography (PE—Et_2O, 9:1) to give the desired unsaturated ketone **326** (871 mg, 57% over 4 steps) as a colourless oil.

$C_{15}H_{24}O_3Si$ **Molecular weight: 280.43 g·mol^{-1}**

R_f = 0.39 (PE—Et_2O, 8:2);

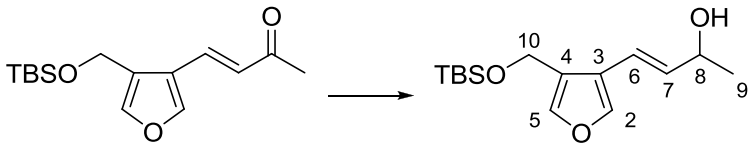
IR ν_{max} 2955, 2929, 2857, 1667, 1615 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (1H, d, *J* = 1.4 Hz, CH-C2), 7.43 (1H, d, *J* = 16.4 Hz, CH-C7), 7.38 (1H, t, *J* = 0.8 Hz, CH-C5), 6.55 (1H, d, *J* = 16.4 Hz, CH-C6), 4.68 (2H, d, *J* = 0.8 Hz, CH_2-C10), 2.32 (3H, s, CH_3-C9), 0.91 (9H, s, 3×CH_3-*t*Bu), 0.09 (6H, s, 2×CH_3-$SiMe_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (C-C8), 145.9 (CH-C2), 142.2 (CH-C5), 133.4 (CH-C7), 127.8 (CH-C6), 124.5 (C-C3 or C-C4), 121.8 (C-C3 or C-C4), 56.8 (CH_2-C10), 27.7 (CH_3-C9), 26.0 (3×CH_3-*t*Bu), 18.4 (C-*t*Bu), −5.1 (2×CH_3-$SiMe_2$);

LRMS (CI, Me_3CH): *m/z* (*int*) 281 (98), 223 (13), 149 (32). HRMS (CI, Me_3CH) calculated for $C_{15}H_{25}O_3Si$ $[M+H]^+$: 281.1573, found 281.1575, Δ +0.6 ppm.

(3*E*)-4-[4-(*tert*-Butyldimethylsilyloxymethyl)furan-3-yl]but-3-en-2-ol ((±)-325)



326 **(±)-325**

To a solution of the unsaturated ketone **326** (1.09 g, 3.89 mmol) in MeOH (40 mL) at 0 °C were successively added $CeCl_3·7H_2O$ (2.90 g, 7.78 mmol, 2.00 equiv) and $NaBH_4$ (176 mg, 4.67 mmol, 1.20 equiv). The solution was stirred for 1 h at 0 °C and the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was diluted with Et_2O (50 mL) and water (10 mL), the phases were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The organic extracts were combined and washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated

in vacuo. The residue was purified by flash column chromatography (PE—Et_2O, 8:2) to give the desired alcohol **(±)-325** (991 mg, 90%) as a colourless oil.

$C_{15}H_{26}O_3Si$ **Molecular weight: 282.45 g·mol^{-1}**

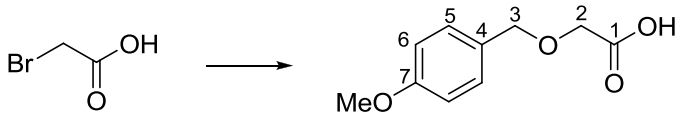
R_f = 0.38 (PE—Et_2O, 7:3);

IR ν_{max} (cm^{-1}) 3356, 2955, 2928, 2827, 1472 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (1H, d, *J* = 1.6 Hz, CH-C2), 7.31 (1H, t, *J* = 1.2 Hz, CH-C5), 6.40 (1H, d, *J* = 16.1 Hz, CH-C6), 6.05 (1H, dd, *J* = 16.1, 6.4 Hz, CH-C7), 4.64 (2H, d, *J* = 1.2 Hz, CH_2-C10), 4.41 (1H, qdd, *J* = 6.4, 6.4, 3.9 Hz, CH-C8), 1.50 (1H, d, *J* = 3.9 Hz, OH), 1.34 (3H, d, *J* = 6.4 Hz, CH_3-C9), 0.91 (9H, s, 3×CH_3-*t*Bu), 0.08 (6H, s, 2×CH_3-SiMe_2);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5 (CH-C2), 141.3 (CH-C5), 134.5 (CH-C7), 124.3 (C-C4 or C-C3), 122.6 (C-C4 or C-C3), 119.1 (CH-C6), 69.4 (CH-C8), 57.0 (CH_2-C10), 26.0 (3×CH_3-*t*Bu), 23.6 (CH_3-C9), 18.4 (C-*t*Bu), −4.9 (2×CH_3-SiMe_2).

2-(4-Methoxybenzyloxy)acetic acid (330)[149]



To a solution of 1-bromoacetic acid **329** (1.2 g, 8.6 mmol, 1.0 equiv) and *p*-methoxybenzyl alcohol (1.1 mL, 8.8 mmol, 1.0 equiv) in THF (15 mL) at 0 °C was added portionwise NaH (827 mg of a 60% dispersion in mineral oil, 20.7 mmol, 2.40 equiv). For a better suspension, THF (10 mL) was added. The resulting suspension was heated at reflux overnight. The reaction was quenched with MeOH (5 mL) and the mixture was concentrated and partitioned between Et_2O (20 mL) and water (20 mL). The organic phase was extracted with water (3 × 20 mL) and the aqueous phase was acidified with aqueous HCl until pH = 3 (1 M, 15 mL) and then extracted with CH_2Cl_2 (3 × 70 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was crystallised with PE, and re-crystallised with PE and EtOAc to give the desired acid **330** (1.43 g, 84%) as a colourless solid. The data obtained for this compound matches that published in the literature.[149]

$C_{10}H_{12}O_4$ **Molecular weight: 196.20 g·mol^{-1}**

mp. 53—54 °C;

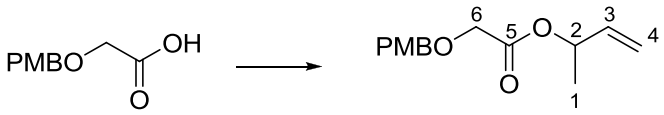
R_f = 0.05 (PE—EtOAc, 5:5);

IR ν_{max} (cm^{-1}) 3127, 1757, 1725, 1512 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (1H, br s, OH), 7.29 (2H, d, *J* = 8.7 Hz, 2×CH-C6), 6.90 (2H, d, *J* = 8.7 Hz, 2×CH-C5), 4.58 (2H, s, CH_2-C2), 4.11 (2H, s, CH_2-C3), 3.81 (3H, s, CH_3-OMe);

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (C-C1), 130.0 (2×CH-C6), 128.6 (C-C4 or C-C7), 128.6 (C-C4 or C-C7), 114.1 (2×CH-C5), 73.3 (CH_2-C2), 66.4 (CH_2-C3), 55.4 (CH_3-OMe);
LRMS (EI+): *m/z* (*int*) 196 (25), 137 (88), 121 (98), 109 (15), 82 (44), 77 (24). HRMS (EI+) calculated for $C_{10}H_{12}O_4$ $[M]^+$: 196.0736, found 196.0733, Δ −1.3 ppm.

But-3-en-2-yl-2-(4-methoxyphenyl)methoxyacetate ((±)-331)



330 **(±)-331**

To a solution of but-3-en-2-ol (270 µL, 3.14 mmol, 1.00 equiv) and carboxylic acid **330** (803 mg, 4.10 mmol, 1.31 equiv) in CH_2Cl_2 (10.5 mL) at 0 °C were successively added DMAP (534 mg, 7.85 mmol, 2.50 equiv) and EDCI (1.50 g, 7.82 mmol, 2.49 equiv). The mixture was warmed to rt and stirred overnight. The reaction was quenched with addition of water (15 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE—Et_2O, 80:20) to give the desired ester **(±)-331** as a colourless oil (780 mg, 99%).

$C_{14}H_{18}O_4$ **Molecular weight: 250.29 g·mol^{-1}**

R_f = 0.85 (PE—Et_2O, 5:5);

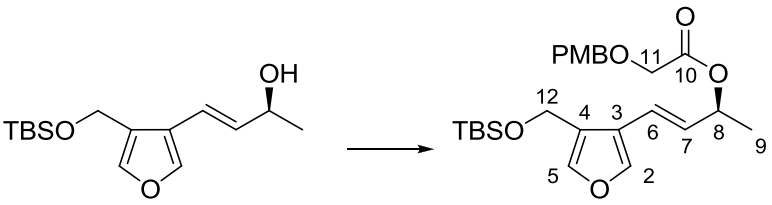
IR ν_{max} (cm^{-1}) 2982, 2934, 2900, 2837, 2359, 1749, 1732, 1612, 1586, 1513, 1464 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 6.88 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 5.85 (1H, ddd, *J* = 17.3, 10.5, 6.0 Hz, CH-C3), 5.45 (1H, qdt, *J* = 6.5, 6.0, 1.2 Hz, CH-C2), 5.26 (1H, dt, *J* = 17.3, 1.2 Hz, CH_2-C4), 5.16 (1H, dt, *J* = 10.5, 1.2 Hz, CH_2-C4), 4.57 (2H, s, CH_2-PMB), 4.06 (2H, s, CH_2-C6), 3.81 (3H, s, CH_3-PMB), 1.34 (3H, d, *J* = 6.5 Hz, CH_3-C1);

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9 (C-C5), 159.6 (C-PMB), 137.4 (CH-C3), 129.9 (2×CH-PMB), 129.3 (C-PMB), 116.5 (CH_2-C4), 114.0 (2×CH-PMB), 73.1 (CH_2-PMB), 71.8 (CH-C2), 67.1 (CH_2-C6), 55.4 (CH_3-PMB), 20.1 (CH_3-C1);

LRMS (EI+): *m/z* (*int*) 250 (11), 195 (80), 137 (91), 121 (100), 91 (10), 78 (15), 55 (18). HRMS (EI+) calculated for $C_{14}H_{18}O_4$ $[M]^+$: 250.1205, found 250.1204, Δ −0.3 ppm.

(2*S*,3*E*)-4-(4-*tert*-Butyldimethylsilyloxymethylfuran-3-yl)but-3-en-2-yl 2-(4-methoxyphenylmethoxy)acetate ((−)-333)



To a solution of the allylic alcohol **(−)-325** (6.51 g, 23.9 mmol, 1.00 equiv) and carboxylic acid **330** (6.85 g, 34.9 mmol, 1.50 equiv) in CH_2Cl_2 (78 mL) at 0 °C were successively added DMAP (3.97 g, 58.2 mmol, 2.50 equiv) and EDCI (11.2 g, 58.2 mmol, 2.50 equiv). The mixture was warmed to rt and stirred for 2 h. The reaction was quenched by the addition of water (50 mL), the phases separated and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE—Et_2O, 9:1 to 85:15) to give the desired ester **(−)-333** as a colourless oil (9.52 g, 90%).

$C_{25}H_{36}O_6Si$ **Molecular weight: 460.64 g·mol^{-1}**

R_f = 0.51 (PE—Et_2O, 7:3);

$[\alpha]_D^{26}$ −32.7 (c = 1.06, $CHCl_3$);

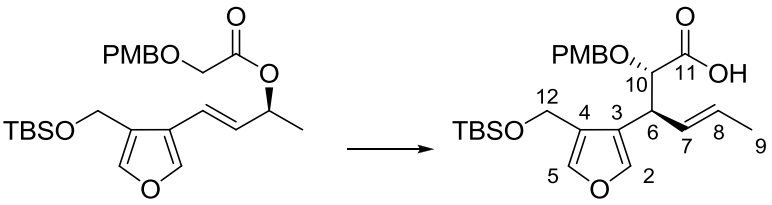
IR ν_{max} 2949, 2929, 2857, 1752, 1613, 1513, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, d, *J* = 1.6 Hz, CH-C2), 7.31 (1H, d, *J* = 1.6 Hz, CH-C5), 7.30 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 6.88 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 6.46 (1H, d, *J* = 16.1 Hz, CH-C6), 6.02 (1H, dd, *J* = 16.1, 7.0 Hz, CH-C7), 5.56 (1H, dqd, *J* = 7.0, 6.5, 0.9 Hz, CH-C8), 4.61 (2H, d, *J* = 0.9 Hz, CH_2-C12), 4.57 (2H, s, CH_2-C11), 4.06 (2H, s, CH_2-PMB), 3.80 (3H, s, CH_3-PMB), 1.40 (3H, d, *J* = 6.5 Hz, CH_3-C9), 0.90 (9H, s, CH_3-*t*Bu), 0.08 (6H, s, 2×CH_3-SiMe_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9 (C-C10), 159.6 (C-PMB), 142.1 (CH-C2), 141.5 (CH-C5), 129.9 (2×CH-PMB), 129.4 (C-PMB), 129.2 (CH-C7), 124.1 (C-C3 or C-C4), 122.5 (C-C3 or C-C4), 121.9 (CH-C6), 114.0 (2×CH-PMB), 73.1 (CH_2-C11), 72.2 (CH-C8), 67.2 (CH_2-PMB), 56.8 (CH_2-C12), 55.4 (CH_3-PMB), 26.0 (CH_3-*t*Bu), 20.6 (CH_3-C9), 18.4 (C-*t*Bu), −5.1 (2×CH_3-SiMe_2);

LRMS (CI, Me_3CH): *m/z* (*int*) 461 (8), 321 (65), 265 (78), 133 (56), 121 (100). HRMS (CI, Me_3CH) calculated for $C_{25}H_{37}O_6Si$ $[M+H]^+$: 461.2359, found 461.2356, Δ −0.8 ppm.

(2*S*,3*S*,4*E*)-3-(4-*tert*-Butyldimethylsilyloxymethylfuran-3-yl)-2-(4-methoxyphenylmethoxy)hex-4-enoic acid ((+)-334)



(–)-333 **(+)-334**

To a solution of LiHMDS (31 mL of a 1 M solution in THF, 31 mmol, 1.5 equiv) in THF (200 mL) at −78 °C was slowly added a solution of ester **(−)-333** (9.28 g, 20.1 mmol) in THF (210 mL) over 15 min. The solution was stirred for 1.5 h at −78 °C before dropwise addition of freshly distilled TMSCl (10.4 mL, 81.4 mmol, 4.05 equiv). The mixture was stirred for 1 h at −78 °C then allowed to slowly warm up to rt over 1 h. The reaction was quenched with saturated aqueous NH_4Cl (200 mL) and the mixture was diluted with Et_2O (600 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 200 mL). The organic extracts were combined and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE—Et_2O, 85:15) to give the desired acid **(+)-334** as a colourless oil (7.91 g, 85%).

$C_{25}H_{36}O_6Si$ **Molecular weight: 460.64 g·mol^{-1}**

R_f = 0.13 (PE—Et_2O, 7:3);

$[\alpha]_D^{23}$ +9.3 (c = 1.01, $CHCl_3$);

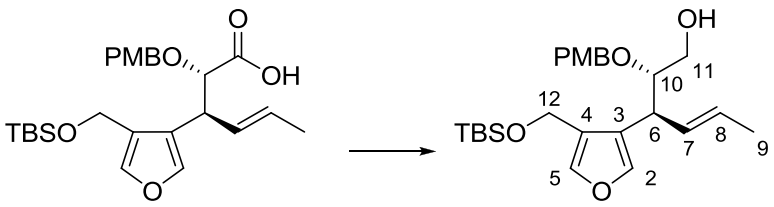
IR ν_{max} 3100, 2999, 2955, 2929, 2883, 2857, 2368, 1719, 1612, 1514 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (1H, br s, COOH), 7.34 (1H, d, *J* = 1.5 Hz, CH-C2), 7.27 (1H, dt, *J* = 1.5, 0.9 Hz, CH-C5), 7.23 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 6.88 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 5.59—5.46 (2H, m, CH-C7 and CH-C8), 4.71 (1H, d, *J* = 11.3 Hz, CH_2-PMB), 4.52 (1H, dd, *J* = 12.9, 0.9 Hz, CH_2-C12), 4.48 (1H, dd, *J* = 12.9, 0.9 Hz, CH_2-C12), 4.41 (1H, d, *J* = 11.3 Hz, CH_2-PMB), 4.13 (1H, d, *J* = 5.0 Hz, CH-C10), 3.81 (3H, s, CH_3-PMB), 3.77 (1H, dd, *J* = 5.0, 5.0 Hz, CH-C6), 1.65 (3H, d, *J* = 4.7 Hz, CH_3-C9), 0.90 (9H, s, CH_3-*t*Bu), 0.05 (3H, s, CH_3-$SiMe_2$), 0.04 (3H, s, CH_3-$SiMe_2$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0 (C-C11), 159.6 (C-PMB), 141.4 (CH-C2), 140.1 (CH-C5), 129.9 (2×CH-PMB), 129.6 (CH-C7 or CH-C8), 129.2 (C-CPMB), 127.9 (CH-C7 or CH-C8), 125.3 (C-C3 or C-C4), 121.6 (C-C3 or C-C4), 113.9 (2×CH-PMB), 81.0 (CH-C10), 73.1 (CH_2-PMB), 56.9 (CH_2-C12), 55.4 (CH_3-PMB), 41.8 (CH-C6), 26.0 (CH_3-*t*Bu), 18.5 (C-*t*Bu), 17.9 (CH_3-C9), −5.3 (2×CH_3-$SiMe_2$);

LRMS (CI, Me_3CH): *m/z* (*int*) 461 (84), 385 (14), 329 (72), 265 (12), 221 (32), 209 (26), 163 (12), 121 (100). HRMS (CI, Me_3CH) calculated for $C_{25}H_{37}O_6Si$ $[M+H]^+$: 461.2359, found 461.2351, Δ −1.9 ppm.

(2*S*,3*S*,4*E*)-3-(4-*tert*-Butyldimethylsilyloxymethylfuran-3-yl)-2-(4-methoxyphenylmethoxy)hex-4-en-1-ol ((+)-335)



(+)-334 **(+)-335**

To a solution of acid **(+)-334** (7.61 g, 16.5 mmol) in Et_2O (170 mL) at 0 ºC was added $LiAlH_4$ (1.40 g, 36.9 mmol, 2.23 equiv) portionwise. The suspension was allowed to warm to rt and stirred for 2.5 h. The reaction was quenched by dropwise addition of water (1.4 mL), aqueous NaOH (1 M, 1.4 mL) and water (2.8 mL) at 0 ºC. The resulting suspension was warmed to rt and stirred for 0.5 h before the addition of $MgSO_4$ (10 g). The mixture was then filtered through a pad of Celite and washed with Et_2O (800 mL). After concentration *in vacuo* the resulting colourless oil could be used without purification (6.99 g, 95%). A small portion was purified by flash column chromatography (PE—Et_2O, 7:3) for characterisation purpose.

$C_{25}H_{38}O_5Si$ **Molecular weight: 446.65 g·mol^{-1}**

R_f = 0.53 (PE—Et_2O, 5:5);

$[\alpha]_D^{23}$ +19.5 (c = 1.00, $CHCl_3$);

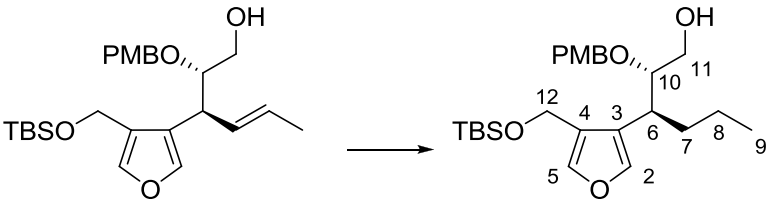
IR ν_{max} 3451, 2953, 2930, 2857, 1612, 1514, 1513, 1464 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (1H, s, CH-C5), 7.29 (1H, d, *J* = 1.3 Hz, CH-C2), 7.19 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 6.86 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 5.60 (1H, ddd, *J* = 15.2, 8.0, 1.1 Hz, CH-C7), 5.53 (1H, dq, *J* = 15.2, 5.9 Hz, CH-C8), 4.55 (1H, d, *J* = 12.6 Hz, CH_2-C12), 4.51 (1H, d, *J* = 12.6 Hz, CH_2-C12), 4.49 (1H, d, *J* = 11.1 Hz, CH_2-PMB), 4.46 (1H, d, *J* = 11.1 Hz, CH_2-PMB), 3.80 (3H, s, CH_3-PMB), 3.70—3.62 (1H, m, CH-C10), 3.62—3.54 (2H, m, CH-C6 and CH_2-C11), 3.53—3.46 (1H, m, CH_2-C11), 2.47 (1H, t, *J* = 6.7 Hz, OH), 1.67 (3H, d, *J* = 5.9 Hz, CH_3-C9), 0.91 (9H, s, CH_3-*t*Bu), 0.09 (3H, s, CH_3-$SiMe_2$), 0.08 (3H, s, CH_3-$SiMe_2$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4 (C-PMB), 141.2 (CH-C2), 140.3 (CH-C5), 131.0 (CH-C7), 130.7 (C-PMB), 129.5 (2×CH-PMB), 126.9 (CH-C8), 125.1 (C-C3), 123.3 (C-C4), 113.9 (2×CH-PMB), 82.3 (CH-C10), 72.6 (CH_2-PMB), 62.2 (CH_2-C11), 56.7 (CH_2-C12), 55.4 (CH_3-PMB), 40.2 (CH-C6), 26.1 (CH_3-*t*Bu), 18.6 (C-*t*Bu), 18.1 (CH_3-C9), −5.1 (CH_3-$SiMe_2$), −5.2 (CH_3-$SiMe_2$);

LRMS (EI+): *m/z* (*int*) 446 (8), 386 (53), 329 (72), 314 (10), 265 (100), 237 (10), 121 (100), 105 (18), 73 (24). HRMS (EI+) calculated for $C_{25}H_{38}O_5Si$ $[M]^+$: 446.2489, found 446.2495, Δ +1.4 ppm.

(2*S*,3*S*)-3-(4-*tert*-Butyldimethylsilyloxymethylfuran-3-yl)-2-(4-methoxyphenylmethoxy)hexan-1-ol ((+)-336)



(+)-335 **(+)-336**

To a solution of alcohol **(+)-335** (6.90 g, 15.4 mmol) in acetone (300 mL) was added Pd/C (1.6 g, 1.5 mmol, 0.10 equiv). The reaction vessel was purged twice with H_2 and the mixture was stirred for 30 min under H_2 atmosphere at rt. The heterogeneous mixture was then filtered twice through a pad of Celite washing with Et_2O. The filtrate was concentrated *in vacuo* and the resulting colourless oil (6.85 g, 99%) was used in the next step without any further purification.

A small portion was purified by flash column chromatography (PE—Et_2O, 7:3) for characterisation purpose.

$C_{25}H_{40}O_5Si$ **Molecular weight: 448.67 g·mol^{-1}**

R_f = 0.58 (PE—Et_2O, 5:5);

$[\alpha]_D^{23}$ +0.2 (c = 1.00, $CHCl_3$);

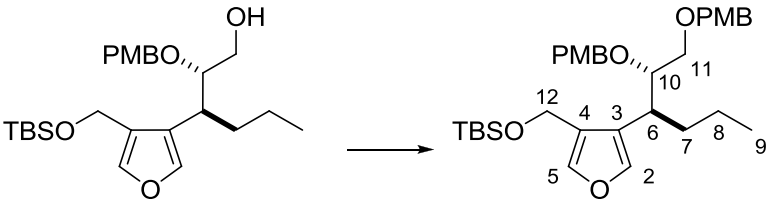
IR ν_{max} 3441, 2955, 2929, 2856, 1612, 1587, 1541, 1514, 1465 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (1H, d, *J* = 1.4 Hz, CH-C5), 7.28 (1H, d, *J* = 1.4 Hz, CH-C2), 7.25 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 6.88 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 4.55 (1H, d, *J* = 11.3 Hz, CH_2-PMB), 4.54 (1H, d, *J* = 12.5 Hz, CH_2-C12), 4.51 (1H, d, *J* = 11.3 Hz, CH_2-PMB), 4.51 (1H, d, *J* = 12.5 Hz, CH_2-C12), 3.81 (3H, s, CH_3-PMB), 3.63 (1H, ddd, *J* = 7.3, 5.7, 3.7 Hz, CH-C10), 3.54 (1H, ddd, *J* = 11.6, 6.9, 5.7 Hz, CH_2-C11), 3.33 (1H, ddd, *J* = 11.6, 7.3, 6.9 Hz, CH_2-C11), 2.98 (1H, t, *J* = 6.9 Hz, OH), 2.93 (1H, ddd, *J* = 9.4, 6.6, 3.7 Hz, CH-C6), 1.66—1.59 (2H, m, CH_2-C7), 1.31—1.17 (2H, m, CH_2-C8), 0.91 (9H, s, CH_3-*t*Bu), 0.86 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.11 (3H, s, CH_3-SiMe_2), 0.10 (3H, s, CH_3-SiMe_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3 (C-PMB), 141.8 (CH-C2), 140.2 (CH-C5), 131.0 (C-PMB), 129.4 (2×CH-PMB), 125.3 (C-C4), 123.8 (C-C3), 113.9 (2×CH-PMB), 81.4 (CH-C10), 72.6 (CH_2-PMB), 61.5 (CH_2-C11), 56.5 (CH_2-C12), 55.4 (CH_3-PMB), 35.8 (CH-C6), 35.6 (CH_2-C7), 26.1 (CH_3-*t*Bu), 21.1 (CH_2-C8), 18.7 (C-*t*Bu), 14.4 (CH_3-C9), −5.1 (CH_3-SiMe_2), −5.2 (CH_3-SiMe_2);

LRMS (CI, Me_3CH): *m*/*z* (*int*) 449 (6), 317 (13), 289 (10), 197 (10), 137 (16), 133 (24), 113 (35), 97 (30), 73 (100). HRMS (CI, Me_3CH) calculated for $C_{25}H_{41}O_5Si$ $[M+H]^+$: 449.2723, found 449.2729, Δ +1.4 ppm.

{4-[(2*S,3*S**)-1,2-*bis*(4-Methoxyphenylmethoxy)hexan-3-yl]furan-3-yl}methoxy-*tert*-butyldimethylsilane ((±)-338)**



(±)-336 **(±)-338**

To a solution of alcohol **(±)-336** (43.4 mg, 96.7 µmol) in toluene (2.4 mL) were added PMBTCA (31 µL, 0.15 mmol, 1.5 equiv) and $La(OTf)_3$ (1.1 mg, 0.0019 mmol, 0.019 equiv) at rt. The mixture was stirred for 10 min, concentrated *in vacuo* and purified by flash column chromatography (PE—Et_2O, 92:8) to afford the desired product **(±)-338** (28.2 mg, 51%) as a colourless oil.

$C_{33}H_{48}O_6Si$ **Molecular weight: 568.82 g·mol^{-1}**

R_f = 0.49 (PE—Et_2O, 7:3);

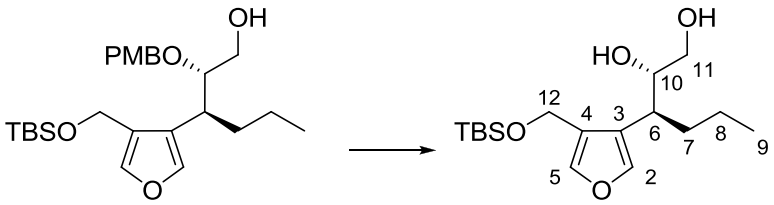
IR ν_{max} 2953, 2929, 2856, 1613, 1512, 1464 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30—7.26 (2H, m, CH-C2 and CH-C5), 7.23 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 7.22 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 6.87 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 6.86 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 4.66 (1H, d, *J* = 11.2 Hz, CH_2-PMB), 4.53 (1H, dd, *J* = 13.0, 0.9 Hz, CH_2-C12), 4.49 (1H, dd, *J* = 13.0, 0.9 Hz, CH_2-C12), 4.48 (1H, d, *J* = 11.2 Hz, CH_2-PMB), 4.40 (1H, d, *J* = 12.0 Hz, CH_2-PMB), 4.37 (1H, d, *J* = 12.0 Hz, CH_2-PMB), 3.81 (3H, s, CH_3-PMB), 3.81 (3H, s, CH_3-PMB), 3.72 (1H, ddd, *J* = 6.0, 4.9, 3.9 Hz, CH-C10), 3.48 (1H, dd, *J* = 9.9, 6.0 Hz, CH_2-C11), 3.39 (1H, dd, *J* = 9.9, 4.9 Hz, CH_2-C11), 2.79 (1H, ddd, J = 9.4, 5.9, 3.9 Hz, CH-C6), 1.66—1.50 (2H, m, CH_2-C7), 1.30—1.16 (2H, m, CH_2-C8), 0.90 (9H, s, CH_3-*t*Bu), 0.84 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.03 (3H, s, CH_3-$SiMe_2$), 0.03 (3H, s, CH_3-$SiMe_2$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3 (C-PMB), 159.1 (C-PMB), 141.4 (CH-C2 or CH-C5), 139.8 (CH-C2 or CH-C5), 131.4 (C-PMB), 130.6 (C-PMB), 129.4 (2×CH-PMB), 129.3 (2×CH-PMB), 126.2 (C-C3 or C-C4), 123.6 (C-C3 or C-C4), 113.9 (2×CH-PMB), 113.8 (2×CH-PMB), 80.1 (CH-C10), 73.1 (CH_2-PMB), 72.8 (CH_2-PMB), 71.8 (CH_2-C11), 57.3 (CH_2-C12), 55.4 (2×CH_3-PMB), 37.5 (CH-C6), 34.9 (CH_2-C7), 26.1 (CH_3-*t*Bu), 21.0 (CH_2-C8), 18.5 (C-*t*Bu), 14.3 (CH_3-C9), −5.2 (2×CH_3-$SiMe_2$);

LRMS (CI, Me_3CH): *m/z* (*int*) 569 (4), 137 (17), 121 (100), 69 (11). HRMS (ESI) calculated for $C_{33}H_{48}NaO_6Si$ $[M+Na]^+$: 591.3097, found 591.3112, Δ +2.6 ppm.

(2*S*,3*S*)-3-(4-*tert*-Butyldimethylsilyloxymethylfuran-3-yl)hexane-1,2-diol ((+)-339)



(+)-336 **(+)-339**

To a solution of alcohol **(+)-336** (6.83 g, 15.2 mmol) in a mixture of CH_2Cl_2/H_2O (17:1, 152 mL) was added DDQ (7.27 g, 32.0 mmol, 2.11 equiv) at rt. The resulting dark biphasic mixture was stirred vigorously for 1.5 h and the reaction was then quenched with saturated aqueous Na_2CO_3 (150 mL). The phases were separated following the addition of CH_2Cl_2 (500 mL) and a large volume of water (*ca* 1 L). The aqueous phase was extracted with CH_2Cl_2 (3 × 300 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The yellow residue was diluted with MeOH (153 mL) and K_2CO_3 (3.9 g, 28 mmol, 1.8 equiv) was added. The mixture was stirred at rt for 2 h and the reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL). The mixture was diluted in Et_2O (300 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (4 × 200 mL) and the organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (PE—Et_2O, 8:2 to 6:4) to afford the desired diol **(+)-339** (3.54 g, 71%) as a colourless oil. From a recovered mixture of starting material and uncharacterised acetals (1.5 g of mixture), the same procedure was used to give a further 222 mg (4%) of product.

$C_{17}H_{32}O_4Si$ **Molecular weight: 328.52 g·mol^{-1}**

R_f = 0.28 (PE—Et_2O, 5:5);

$[\alpha]_D^{23}$ +2.5 (c = 1.13, $CHCl_3$);

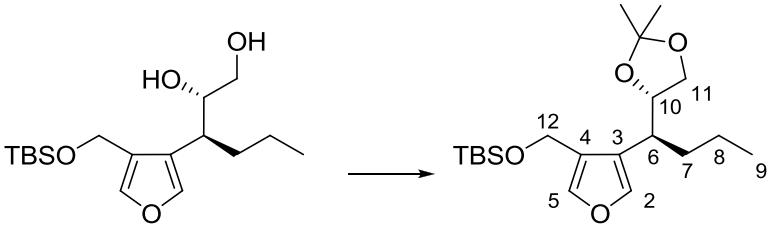
IR ν_{max} 3341, 2955, 2929, 2858, 1539, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, d, *J* = 1.4 Hz, CH-C5), 7.26 (1H, br s, CH-C2), 4.56 (1H, d, *J* = 12.2 Hz, CH_2-C12), 4.51 (1H, d, *J* = 12.2 Hz, CH_2-C12), 3.76 (1H, dddd, *J* = 6.6, 6.4, 4.9, 4.7 Hz, CH-C10), 3.55 (1H, ddd, *J* = 11.3, 7.6, 4.7 Hz, CH_2-C11), 3.47 (1H, ddd, *J* = 11.3, 6.4, 5.4 Hz, CH_2-C11), 2.80 (1H, d, *J* = 6.6 Hz, OH), 2.77 (1H, ddd, *J* = 9.1, 5.6, 4.7 Hz, CH-C6), 2.52 (1H, dd, *J* = 7.6, 5.4 Hz, OH), 1.66—1.57 (2H, m, CH_2-C7), 1.31—1.20 (2H, m, CH_2-C8), 0.92 (9H, s, CH_3-*t*Bu), 0.87 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.13 (6H, s, 2×CH_3-SiMe_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.5 (CH-C5), 141.4 (CH-C2), 124.5 (C-C3 or C-C4), 123.7 (C-C3 or C-C4), 74.3 (CH-C10), 65.3 (CH_2-C11), 56.4 (CH_2-C12), 38.1 (CH-C6), 35.0 (CH_2-C7), 26.0 (CH_3-*t*Bu), 20.9 (CH_2-C8), 18.6 (C-*t*Bu), 14.2 (CH_3-C9), −5.2 (2×CH_3-SiMe_2);

LRMS (CI, Me_3CH): *m*/*z* (*int*) 329 (10), 253 (14), 197 (100), 179 (25), 165 (15), 133 (16). HRMS calculated for $C_{17}H_{32}NaO_4Si$ $[M+Na]^+$: 351.1960, found 351.1962, Δ +0.5 ppm.

tert-Butyl{4-[(1*S*)-1-((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butyl]furan-3-yl}methoxydimethylsilane ((+)-345)



To a solution of diol **(+)-339** (1.70 g, 5.17 mmol) in a mixture of CH_2Cl_2 (10 mL) and 2,2-dimethoxypropane (17 mL) was added PPTS (65 mg, 0.26 mmol, 0.050 equiv). The mixture was stirred at rt for 1 h and Na_2CO_3 (*ca* 60 mg) was then added. The heterogeneous mixture was concentrated *in vacuo* and purified by flash column chromatography (PE—Et_2O, 96:4) to afford the desired product **(+)-345** (1.83 g, 96%) as a colourless oil.

$C_{20}H_{36}O_4Si$ **Molecular weight: 368.58 g·mol^{-1}**

R_f = 0.61 (PE—Et_2O, 9:1);

$[\alpha]_D^{23}$ +16.95 (c = 1.00, $CHCl_3$);

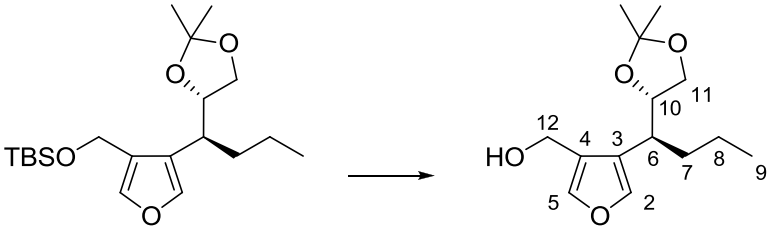
IR ν_{max} 2983, 2955, 2929, 2858, 1541, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (1H, br s, CH-C5), 7.25 (1H, d, *J* = 1.6 Hz, CH-C2), 4.55 (2H, d, *J* = 0.6 Hz, CH_2-C12), 4.24 (1H, ddd, *J* = 7.9, 6.3, 6.0 Hz, CH-C10), 3.94 (1H, dd, *J* = 7.9, 6.3 Hz, CH_2-C11), 3.55 (1H, t, *J* = 7.9 Hz, CH_2-C11), 2.74 (1H, ddd, *J* = 9.5, 6.0, 5.5 Hz, CH-C6), 1.61—1.54 (2H, m, CH_2-C7), 1.37 (3H, s, CH_3-CMe_2), 1.33 (3H, s, CH_3-CMe_2),1.35—1.20 (2H, m, CH_2-C8), 0.91 (9H, s, CH_3-*t*Bu), 0.87 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.08 (6H, s, 2×CH_3-SiMe_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7 (CH-C2), 140.1 (CH-C5), 125.8 (C-C4), 123.9 (C-C3), 109.0 (C-CMe_2), 78.8 (CH-C10), 67.6 (CH_2-C11), 56.9 (CH_2-C12), 37.6 (CH-C6), 34.4 (CH_2-C7), 26.7 (CH_3-CMe_2), 26.1 (3×CH_3-*t*Bu), 25.6 (CH_3-CMe_2), 20.8 (CH_2-C8), 18.5 (C-*t*Bu), 14.3 (CH_3-C9), −5.2 (2×CH_3-SiMe_2);

LRMS (CI, Me_3CH): *m*/*z* (*int*) 369 (38), 311 (11), 237 (100), 179 (18), 133 (10). HRMS (CI, Me_3CH) calculated for $C_{20}H_{36}O_4Si$ $[M]^+$: 369.2461, found 369.2463, Δ +0.5 ppm.

[4-(1*S*)-1-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)butylfuran-3-yl]methanol ((+)-346)



(+)-345 **(+)-346**

To a solution of acetonide **(+)-345** (1.81 g, 4.91 mmol) in THF (49 mL), TBAF (7.4 mL of a 1 M solution in THF, 7.4 mmol, 1.5 equiv) was added dropwise at 0 °C. The mixture was warmed to rt and stirred for 40 min. Water (20 mL) and Et_2O (60 mL) were added and the phases separated. The aqueous phase was extracted with Et_2O (3 × 40 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE—Et_2O, 7:3) to afford the desired allylic alcohol **(+)-346** (1.16 g, 93%) as a colourless oil.

$C_{14}H_{22}O_4$ **Molecular weight: 254.32 g·mol^{-1}**

R_f = 0.32 (PE—Et_2O, 5:5);

$[\alpha]_D^{23}$ +34.75 (c = 1.00, $CHCl_3$);

IR ν_{max} 3428, 2983, 2957, 2934, 2873, 1541, 1456 cm^{-1};

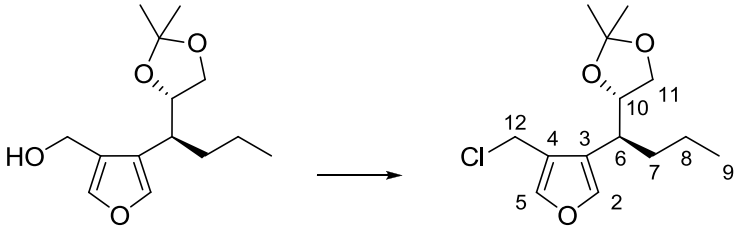
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, d, *J* = 1.5 Hz, CH-C5), 7.24 (1H, d, *J* = 1.5 Hz, CH-C2), 4.46 (1H, dd, *J* = 12.7, 4.7 Hz, CH_2-C12), 4.43 (1H, dd, *J* = 12.7, 6.4 Hz, CH_2-C12), 4.09 (1H, ddd, *J* = 7.6, 7.5, 5.9 Hz, CH-C10), 4.05 (1H, dd, *J* = 7.5, 5.9 Hz, CH_2-C11), 3.60 (1H, t, *J* = 7.5 Hz, CH_2-C11), 3.03 (1H, dd, *J* = 6.4, 4.7 Hz, OH), 2.69 (1H, ddd, *J* = 11.1, 7.6, 3.9 Hz, CH-C6), 1.60 (1H, dddd, *J* = 12.9, 11.1, 9.6, 5.4 Hz, CH_2-C7), 1.44 (1H, m, CH_2-C7), 1.37 (3H, s, CH_3-CMe_2), 1.38—1.28 (1H, m, CH_2-C8), 1.30 (3H, s, CH_3-CMe_2), 1.28—1.14 (1H, m, CH_2-C8), 0.86 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1 (CH-C5), 140.6 (CH-C2), 125.8 (C-C3 or C-C4), 124.8 (C-C3 or C-C4), 109.4 (C-CMe_2), 80.7 (CH-C10), 68.7 (CH_2-C11), 55.1 (CH_2-C12), 38.4 (CH-C6), 34.3 (CH_2-C7), 26.5 (CH_3-CMe_2), 25.7 (CH_3-CMe_2), 20.6 (CH_2-C8), 14.0 (CH_3-C9);

LRMS (EI+): *m/z* (*int*) 254 (23), 239 (12), 161 (13), 154 (10), 101 (100), 73 (11), 42 (14).

HRMS (EI+) calculated for $C_{14}H_{22}O_4$ $[M]^+$: 254.1518, found 254.1520, Δ +0.7 ppm.

(4*S*)-4-(1*S*)-1-(4-Chloromethylfuran-3-yl)butyl-2,2-dimethyl-1,3-dioxolane ((+)-347)



(+)-346 **(+)-347**

To a solution of allylic alcohol **(+)-346** (1.02 g, 4.01 mmol) in CH_2Cl_2 (16 mL) cooled to 0 °C, Et_3N (840 µL, 6.03 mmol, 1.51 equiv) and MsCl (410 µL, 5.29 mmol, 1.32 equiv), both freshly distilled, were successively added. The mixture was warmed to rt, stirred for 15 h and quenched with saturated aqueous NH_4Cl (20 ml). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined and dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 95:5) to give 1.03 g (95%) of the desired chloride **(+)-347** as a colourless oil.

$C_{14}H_{21}ClO_3$ **Molecular weight: 272.77 g·mol^{-1}**

R_f = 0.72 (PE—Et_2O, 5:5);

$[\alpha]_D^{26}$ +32.3 (c = 1.00, $CHCl_3$);

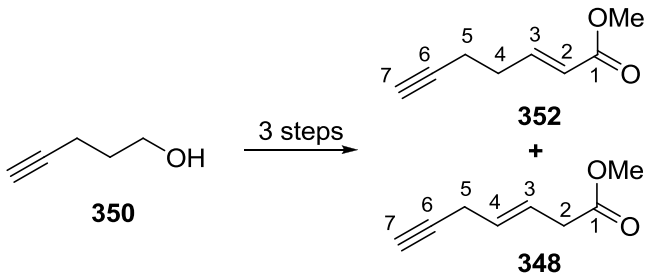
IR ν_{max} 2984, 2959, 2934, 2872, 1541, 1456 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (1H, d, *J* = 1.5 Hz, CH-C5), 7.29 (1H, d, *J* = 1.5 Hz, CH-C2), 4.54 (1H, d, *J* = 12.1 Hz, CH_2-C12), 4.48 (1H, d, *J* = 12.1 Hz, CH_2-C12), 4.19 (1H, ddd, *J* = 8.1, 6.0, 6.0 Hz, CH-C10), 4.00 (1H, dd, *J* = 8.0, 6.0 Hz, CH_2-C11), 3.54 (1H, dd, *J* = 8.1, 8.0 Hz, CH_2-C11), 2.79 (1H, ddd, *J* = 9.3, 6.0, 5.7 Hz, CH-C6), 1.63—1.53 (2H, m, CH_2-C7), 1.37 (3H, s, CH_3-CMe_2), 1.33 (3H, s, CH_3-CMe_2), 1.36—1.24 (2H, m, CH_2-C8), 0.89 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.6 (CH-C5), 141.3 (CH-C2), 124.3 (C-C3 or C-C4), 122.8 (C-C3 or C-C4), 109.1 (C-CMe_2), 79.3 (CH-C10), 68.0 (CH_2-C11), 37.5 (CH-C6), 36.6 (CH_2-C12), 35.0 (CH_2-C7), 26.6 (CH_3-CMe_2), 25.7 (CH_3-CMe_2), 20.7 (CH_2-C8), 14.2 (CH_3-C9);

LRMS (EI+): *m/z* (*int*) 274 (5), 272 (10), 101 (100), 73 (15), 43 (16). HRMS (EI+) calculated for $C_{14}H_{21}{}^{35}ClO_3$ $[M]^+$: 272.1179, found 272.1182, Δ +0.9 ppm; Analytic. calculated for $C_{14}H_{21}ClO_3$: C, 61.65; H, 7.76. Found: C, 61.73; H, 7.85.

(*E*)-Methyl hept-3-en-6-ynoate (348) and **(*E*)-Methyl hept-2-en-6-ynoate (352)**[186]



A solution of oxalyl chloride (5.8 mL, 68 mmol, 1.5 equiv) in CH_2Cl_2 (60 mL) was cooled to −78 °C before dropwise addition (20 min) of a solution of DMSO (8.00 mL, 113 mmol, 2.49 equiv) in CH_2Cl_2 (30 mL). After 20 min, a solution of 4-pentyn-1-ol (4.2 mL, 45 mmol) in CH_2Cl_2 (60 mL) was added carefully over 10 min. The mixture was stirred at −78 °C for 1.5 h before dropwise addition of Et_3N (38.0 mL, 273 mmol, 6.04 equiv). The solution was then warmed to rt over 1 h. The mixture was diluted with CH_2Cl_2 (60 mL) and washed with aqueous HCl (1 M, 2 × 80 mL), water (80 mL) and brine (80 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was used directly in the next step.

The crude aldehyde was dissolved in Et_3N (19.0 mL, 136 mmol, 3.02 equiv) and malonic acid (6.85 g, 67.8 mmol, 1.50 equiv) was added. The mixture was warmed to 80 °C and stirred overnight. The mixture was then cooled down to rt, diluted with Et_2O (100 mL) and the reaction was quenched with aqueous HCl (1 M, 100 mL). The phases were separated and the organic phase was washed with aqueous HCl (1 M, 50 mL), brine (80 mL) and then dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was used in the next step without any further purification.

To the crude acid in MeOH (20 mL) was added concentrated HCl (500 µL). The mixture was heated at reflux for 2 h, cooled to rt and the reaction was quenched with saturated aqueous $NaHCO_3$ (25 mL). The mixture was diluted with EtOAc (50 mL), the phases were separated and the organic phase was washed with brine (50 mL) and dried over $MgSO_4$. After filtration, the solution was carefully concentrated *in vacuo* and purified by flash column chromatography (PE—Et_2O, 98:2) yielding an inseparable mixture (3:1) of β,γ-unsaturated ester **348** and minor α,β-unsaturated ester **352** (4.41 g, 71% over 3 steps) as a colourless and volatile oil.

$C_8H_{10}O_2$ **Molecular weight: 138.16 g·mol^{-1}**

R_f = 0.71 (PE—Et_2O, 5:5);

IR ν_{max} 3292, 3001, 2953, 2908, 1732, 1660, 1435, 1422 cm^{-1};

Major isomer 348

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (1H, dtt, *J* = 15.3, 7.0, 1.8 Hz, CH-C3), 5.57 (1H, dtt, *J* = 15.3, 5.6, 1.3 Hz, CH-C4), 3.69 (3H, s, OMe), 3.09 (2H, ddt, *J* = 7.0, 1.3, 1.3 Hz, CH_2-C2), 2.98—2.95 (2H, m, CH_2-C5), 2.11 (1H, t, *J* = 2.7 Hz, CH-C7);

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2 (C-C1), 127.9 (CH-C4), 124.1 (CH-C3), 81.3 (C-C6), 70.5 (CH-C7), 52.0 (CH_3-OMe), 37.7 (CH_2-C2), 21.8 (CH_2-C5);

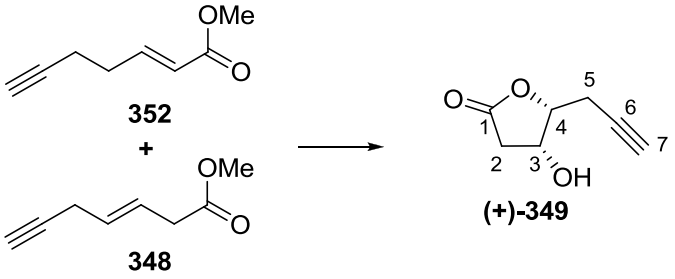
Minor isomer 352

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (1H, dt, *J* = 15.7, 6.6 Hz, CH-C3), 5.91 (1H, dt, *J* = 15.7, 1.6 Hz, CH-C2), 3.74 (3H, s, OMe), 2.44 (2H, tdd, *J* = 6.6, 6.6, 1.6 Hz, CH_2-C4), 2.35 (2H, td, *J* = 6.6, 2.6 Hz, CH_2-C5), 2.00 (1H, t, *J* = 2.6 Hz, CH-C7);

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9 (C-C1), 146.8 (CH-C3), 122.3 (CH-C2), 82.8 (C-C6), 69.6 (CH-C7), 51.7 (CH_3-OMe), 31.2 (CH_2-C4), 17.6 (CH_2-C5);

LRMS (CI, Me_3CH): *m/z* (*int*) 139 (95), 129 (100), 113 (52), 101 (34), 85 (59), 73 (95), 71 (75). HRMS (CI, Me_3CH) calculated for $C_8H_{11}O_2$ $[M+H]^+$: 139.0759, found 139.0760, Δ +0.5 ppm.

(4*R*,5*R*)-4-Hydroxy-5-(prop-2-yn-1-yl)oxolan-2-one ((+)-349)[160]



AD-mix β (4.0 g, 1.4 g/mmol of starting material) and methanesulfonamide (306 mg, 2.89 mmol, 1.00 equiv) were dissolved at rt in a 1:1 mixture of *t*-BuOH/water (20 mL). The mixture was stirred for 5 min at rt and cooled to 0 ºC before dropwise addition of a solution of esters **348** and **352** (399 mg, 2.89 mmol) in a 1:1 mixture of *t*-BuOH/water (8 mL). The mixture was stirred vigorously at 0 ºC for 48 h and the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (25 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 6:4) to give ester **(+)-349** (164 mg, 40%) as a colourless oil.

$C_7H_8O_3$ **Molecular weight: 140.14 g·mol^{-1}**

R_f = 0.27 (PE—Et_2O, 5:5);

$[\alpha]_D^{22}$ +3.1 (c = 1.05, $CHCl_3$);

IR ν_{max} 3419, 3286, 2929, 1755, 1406, 1348, 1149 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (1H, ddd, *J* = 5.9, 4.4, 1.0 Hz, CH-C3), 4.55 (1H, ddd, *J* = 9.1, 5.9, 3.8 Hz, CH-C4), 2.87—2.78 (2H, m, CH_2-C2, CH_2-C5), 2.74 (1H, ddd, *J* = 16.6, 9.1, 2.7 Hz, CH_2-C5), 2.62 (1H, dd, *J* = 17.9, 1.0 Hz, CH_2-C2), 2.39 (1H, d, *J* = 4.4 Hz, OH), 2.10 (1H, t, *J* = 2.7 Hz, CH-C7);

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9 (C-C1), 81.4 (CH-C4), 78.4 (C-C6), 71.6 (CH-C7), 68.4 (CH-C3), 38.6 (CH_2-C2), 18.8 (CH_2-C5);
LRMS (ESI): *m/z* (*int*) 163 (100), 153 (10). HRMS (ESI) calculated for $C_7H_8NaO_3$ $[M+Na]^+$: 163.0361, found 163.0366, Δ +3.0 ppm.

((2*S*)-1-Benzylpyrrolidin-2-yl)diphenylmethanol ((+)-358)[63,166b]

356 **(+)-358**

L-Proline **356** (30.0 g, 261 mmol) was dissolved in MeOH (500 mL). The solution was cooled to 0 °C before dropwise addition of $SOCl_2$ (23.0 mL, 317 mmol, 1.22 equiv). The mixture was then warmed to rt and heated at reflux for 2 h. After concentration *in vacuo*, the residue was diluted in toluene (50 mL) and concentrated *in vacuo*. The residue was used in the next step without further purification.
To a solution of the salt in toluene (260 mL) at 0 °C, DIPEA (202 mL, 1.16 mol, 4.45 equiv) was added slowly. The slurry was warmed to rt and upon cessation of gas evolution, the reaction was cooled to 0 °C and benzyl bromide (34.5 mL, 290 mmol, 1.11 equiv) was added. The mixture was heated to reflux and stirred for 20 h. The mixture was allowed to cool to rt and the reaction was quenched with saturated aqueous NH_4Cl (300 mL). The mixture was diluted with EtOAc (400 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 300 mL) and the organic extracts were combined, washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The remaining orange oil was used in the next step without further purification.
To a suspension of magnesium turnings (17.9 g, 736 mmol, 2.83 equiv) in Et_2O (260 mL) was added bromobenzene (75.5 ml, 730 mmol, 2.80 equiv) dropwise. When the reflux generated from the reaction had slowed, the mixture was heated at reflux and stirred for a further 2 h. It was then cooled to 0 °C and a solution of the crude ester in Et_2O (200 mL) was added slowly. The heterogeneous mixture was stirred at rt and heated gently back to reflux during 3 h. The reaction was then quenched with the addition of saturated aqueous NH_4Cl (500 mL) and the mixture was diluted with Et_2O (600 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 600 mL). The organic extracts were combined, washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then re-crystallised in a 9:1 mixture of PE—EtOAc (1 L) at −30 °C for 16 h, to afford the desired tertiary alcohol **(+)-358** (56.9 g, 64%) as a colourless solid.

$C_{24}H_{25}NO$ **Molecular weight: 343.46 g·mol^{-1}**

R_f = 0.47 (PE—Et_2O, 9:1);

mp. 114—116 °C {Lit.[166b] mp. 118—119 °C, Lit.[63] mp. 113—115 °C};

$[\alpha]_D^{18}$ +98.4 (c = 1.23, $CHCl_3$), $[\alpha]_D^{24}$ +86.0 (c = 1.05, $CHCl_3$) {Lit.[166b] $[\alpha]_D^{20}$ +86.6 (c = 1.00, $CHCl_3$), Lit.[63] $[\alpha]_D^{20}$ +76.2 (c = 1.60, CH_2Cl_2)};

IR ν_{max} 3333, 3088, 3059, 2968, 2874, 2800, 2364, 1597, 1495 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* = 8.4 Hz, 2×CH-Ar), 7.61 (2H, d, *J* = 8.4 Hz, 2×CH-Ar), 7.35—7.17 (8H, m, 8×CH-Ar), 7.12 (1H, t, *J* = 7.3 Hz, CH-Ar), 7.07 (2H, d, *J* = 7.1 Hz, 2×CH-Ar), 4.97 (1H, s, OH), 4.00 (1H, dd, *J* = 9.1, 4.3 Hz, CH-C2), 3.25 (1H, d, *J* = 12.6 Hz, CH_2-Bn), 3.05 (1H, d, *J* = 12.6 Hz, CH_2-Bn), 2.94 (1H, ddd, *J* = 9.2, 5.9, 3.3 Hz, CH_2-C5), 2.38 (1H, ddd, *J* = 9.6, 9.2, 7.0 Hz, CH_2-C5), 2.04—1.95 (1H, m, CH_2-C3), 1.82—1.76 (1H, m, CH_2-C3), 1.71—1.61 (2H, m, CH_2-C4);

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2 (C-Ar), 146.8 (C-Ar), 139.8 (C-Ar), 128.7 (2×CH-Ar), 128.3 (2×CH-Ar), 128.3 (2×CH-Ar), 128.2 (2×CH-Ar), 127.0 (CH-Ar), 126.5 (CH-Ar), 126.4 (CH-Ar), 125.8 (2×CH-Ar), 125.7 (2×CH-Ar), 78.1 (C-C6), 70.8 (CH-C2), 60.7 (CH_2-Bn), 55.7 (CH_2-C5), 27.9 (CH_2-C3), 24.3 (CH_2-C4);

HRMS (ESI) calculated for $C_{24}H_{26}NO$ $[M+H]^+$: 344.2009, found 344.2003, Δ +1.8 ppm. HRMS (ESI) calculated for $C_{24}H_{25}NaNO$ $[M+Na]^+$: 366.1828, found 366.1816, Δ +3.5 ppm.

(2*S*)-2-(Methoxydiphenylmethyl)pyrrolidine ((−)-360)[63,60]

(+)-358 **(−)-360**

To a solution of alcohol **(+)-358** (59.9 g, 166 mmol) in THF (500 mL) at 0 °C was added NaH (8.60 g of a 60% dispersion in mineral oil, 215 mmol, 1.30 equiv) portionwise. After 5 min, iodomethane (14.5 mL, 233 mmol, 1.41 equiv) was added and the mixture was slowly heated to reflux, with an outlet allowing the release of the hydrogen formed during the reaction, and stirred overnight. The mixture was cooled to 0 °C and the reaction was quenched with saturated aqueous NH_4Cl (200 mL). The mixture was diluted with Et_2O (500 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 400 mL) and the organic extracts were combined, washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Without further purification the residue was then diluted in EtOH (166 mL). Concentrated HCl (20 mL) was added and the mixture was stirred vigorously at 50 °C until the solid was completely solubilised. The solution was cooled to rt and Pd/C (1.8 g, 17 mmol, 0.10 equiv) was added. The reaction vessel was purged 3 times with H_2 and the mixture was stirred

vigorously under H_2 atmosphere for 14 h. Further Pd/C (0.90 g, 0.05 equiv) was added and the mixture was stirred under H_2 atmosphere for a further 24 h. The heterogeneous mixture was then filtered through a pad of Celite washing with Et_2O (500 mL). After concentration *in vacuo*, the salt was washed with cold Et_2O (200 mL). The salt was then suspended in Et_2O (500 mL) and saturated aqueous K_2CO_3 (300 mL) added. After stirring for 1 h, the phases were separated, the aqueous phase was extracted with Et_2O (2 × 300 mL) and the combined organic extracts washed with brine and dried over $MgSO_4$. Concentration *in vacuo* gave the desired product as a colourless oil **(−)-360** (39.8 g, 90% over two steps). The filtrate was concentrated *in vacuo*, diluted with Et_2O (100 mL) and a saturated aqueous solution of K_2CO_3 (100 mL) added and stirred for 1 h. The phases were separated, the aqueous phase was extracted with Et_2O (2 × 100 mL), the combined organic extracts were washed with brine and dried over $MgSO_4$. The organic extracts were concentrated *in vacuo* and purification by flash column chromatography (PE—EtOAc, 6:4) gave a further 2.0 g (4%) of the desired product.

$C_{18}H_{21}NO$ **Molecular weight: 267.37 g·mol^{-1}**

R_f = 0.29 (PE—EtOAc, 5:5);

$[\alpha]_D^{26}$ −10.9 (c = 1.05, $CHCl_3$) {Lit.[60] $[\alpha]_D^{22}$ 1.1 (c = 1.0, $CHCl_3$), Lit.[63] $[\alpha]_D^{22}$ −110.2 (c = 1.23, $CHCl_3$)};

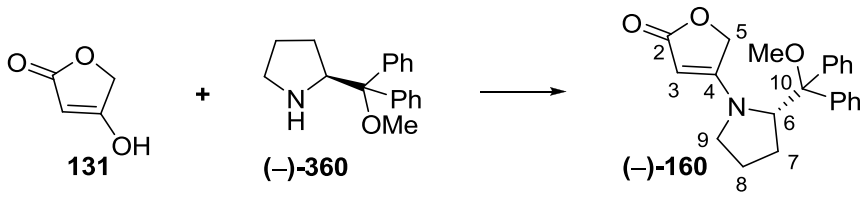
IR ν_{max} 3352, 3057, 2941, 2872, 1957, 1890, 1817, 1493, 1446 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45—7.38 (4H, m, 4×CH-Ph), 7.33—7.26 (6H, m, 6×CH-Ph), 4.15 (1H, t, *J* = 7.4 Hz, CH-C2), 3.08 (3H, s, CH_3-OMe), 2.74 (1H, dt, *J* = 10.4, 7.1 Hz, CH_2-C5), 2.56 (1H, ddd, *J* = 10.4, 7.2, 5.6 Hz, CH_2-C5), 2.27 (1H, br s, NH), 1.87 (1H, dddd, *J* = 13.4, 8.0, 7.4, 5.8 Hz, CH_2-C3), 1.64 (1H, dddd, *J* = 13.4, 8.7, 7.4, 7.1 Hz, CH_2-C3), 1.59—1.49 (1H, m, CH_2-C4), 1.13—1.02 (1H, m, CH_2-C4);

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.9 (C-Ph), 141.9 (C-Ph), 129.4 (2×CH-Ph), 129.2 (2×CH-Ph), 127.8 (2×CH-Ph), 127.6 (2×CH-Ph), 127.3 (CH-Ph),127.3 (CH-Ph), 85.4 (C-C6), 62.3 (CH-C2), 51.5 (CH_3-OMe), 47.0 (CH_2-C5), 27.6 (CH_2-C3), 25.5 (CH_2-C4);

LRMS (CI, Me_3CH): *m/z* (*int*) 268 (42), 236 (100), 183 (45), 70 (38). HRMS (CI, Me_3CH) calculated for $C_{18}H_{22}NO$ $[M+H]^+$: 268.1701, found 268.1697, Δ −1.6 ppm.

4-[(2*S*)-2-(Methoxydiphenylmethyl)pyrrolidin-1-yl]-2,5-dihydrofuran-2-one ((−)-160)[41]



Tetronic acid (4.19 g, 41.8 mmol, 1.00 equiv) and pyrrolidine derivative **(−)-360** (12.3 g, 46.1 mmol, 1.10 equiv) were diluted in EtOH (10 mL) and toluene (20 mL). The solvents were removed *in vacuo* using a rotary evaporator at 45 °C and the residue was dried under vaccum pump for 30 min. The residue was diluted with the same amount of EtOH and toluene and the process was repeated 5 times. The residue was purified by flash column chromatography (PE—EtOAc, 6:4) to afford the desired product **(−)-160** (7.73 g, 53%) as a colourless foam.

$C_{22}H_{23}NO_3$ **Molecular weight: 349.42 g·mol^{-1}**

R_f = 0.36 (PE—EtOAc, 5:5);

$[\alpha]_D^{18}$ −126.0 (c = 1.07, $CHCl_3$) {Lit.[41] $[\alpha]_D^{20}$ −135.2 (c = 0.50, $CHCl_3$)};

IR ν_{max} 2970, 2935, 2359, 1724, 1593, 1492 cm^{-1};

^{1}H NMR (400 MHz, C_6D_6, 65 °C) δ 7.30—7.10 (10H, m, 10×CH-Ph), 4.89 (1H, d, *J* = 15.0 Hz, CH_2-C5), 4.72 (1H, s, CH-C3), 4.50 (1H, d, *J* = 15.0 Hz, CH_2-C5), 4.43 (1H, dd, *J* = 9.2, 2.1 Hz, CH-C6), 2.54 (3H, s, CH_3-OMe), 2.54—2.48 (1H, m, CH_2-C9), 1.86—1.70 (2H, m, CH_2-C9, CH_2-C7), 1.60—1.52 (1H, m, CH_2-C7), 1.15—1.03 (1H, m, CH_2-C8), 0.72—0.58 (1H, m, CH_2-C8);

^{13}C NMR (101 MHz, C_6D_6, 65 °C) δ 174.6 (C-C2), 168.8 (C-C4), 138.3 (C-Ph), 137.7 (C-Ph), 130.2 (2×CH-Ph), 130.1 (2×CH-Ph), 128.4 (2×CH-Ph), 128.2 (2×CH-Ph), 128.0 (2×CH-Ph), 88.6 (C-C10), 84.7 (CH-C3), 68.7 (CH-C6), 68.4 (CH_2-C5), 51.1 (CH_3-OMe), 50.8 (CH_2-C9), 28.2 (CH_2-C7), 22.6 (CH_2-C8);

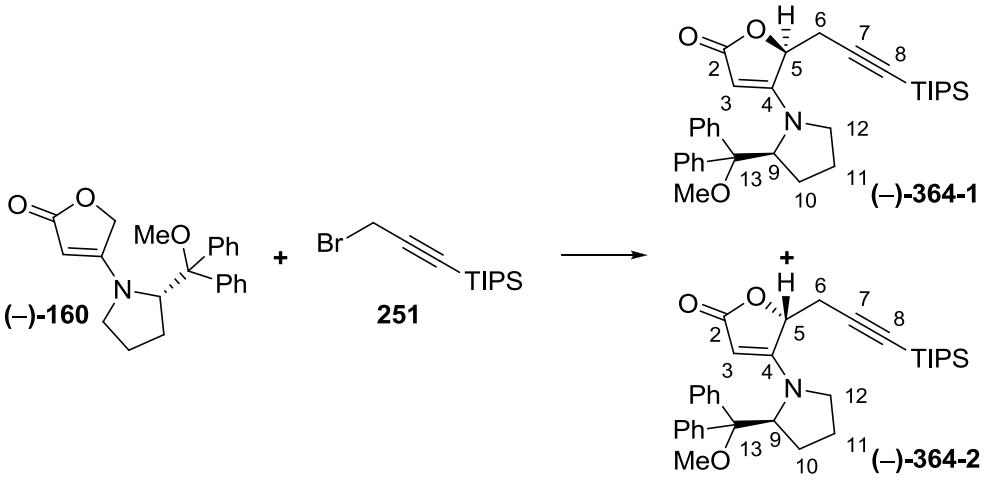
HRMS (ESI) calculated for $C_{22}H_{24}NO_3$ $[M+H]^+$: 350.1751, found 350.1738, Δ +3.7 ppm.

HRMS (ESI) calculated for $C_{22}H_{23}NaNO_3$ $[M+Na]^+$: 372.1570, found 372.1588, Δ −4.9 ppm.

(5*S*)-4-[(2*S*)-2-(Methoxydiphenylmethyl)pyrrolidin-1-yl]-5-{3-[*tris*(propan-2-yl)silyl]prop-2-yn-1-yl}-2,5-dihydrofuran-2-one ((−)-364-1)

and

(5*R*)-4-[(2*S*)-2-(Methoxydiphenylmethyl)pyrrolidin-1-yl]-5-{3-[*tris*(propan-2-yl)silyl]prop-2-yn-1-yl}-2,5-dihydrofuran-2-one ((−)-364-2)



To a solution of furanone **(−)-160** (7.67 g, 22.0 mmol) in THF (110 mL) at −78 °C was added a solution of *t*-BuLi (14.4 mL of a 1.6 M solution in hexane, 23.0 mmol, 1.05 equiv) dropwise. The reaction was stirred for 1 h before the protected propargylic bromide **251** (6.40 g, 34.4 mmol, 1.50 equiv) was added dropwise over 15 min. After 2 h the reaction was quenched with saturated aqueous NH_4Cl (30 mL). The mixture was diluted with EtOAc (100 mL) and allowed to warm to rt over 45 min. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The organic extracts were combined and washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—EtOAc, 8:2 to 75:25) to give the diastereoisomers **(−)-364-1** (8.89 g, 75%) and **(−)-364-2** (2.21 g, 19%), both colourless foams.

$C_{34}H_{45}NO_3Si$ **Molecular weight: 543.81 g·mol^{-1}**

Major diastereoisomer (−)-364-1

R_f = 0.52 (PE—EtOAc, 5:5);

$[\alpha]_D^{18}$ −103.8 (c = 1.02, $CHCl_3$);

IR ν_{max} 2941, 2864, 2363, 1734, 1606, 1462 cm^{-1};

^{1}H NMR (400 MHz, C_6D_6, 70 °C) δ 7.33—7.11 (10H, m, 10×CH-Ph), 4.99 (2H, br s, CH-C3 and CH-C5), 4.62 (1H, d, *J* = 6.7 Hz, CH-C9), 2.79 (1H, br d, *J* = 17.3 Hz, CH_2-C6), 2.63 (3H, s, CH_3-OMe), 2.61—2.48 (2H, m, CH_2-C6 and CH_2-C12), 1.84—1.73 (1H, m, CH_2-C10), 1.73—1.64 (1H, m, CH_2-C12), 1.58 (1H, dddd, *J* = 8.9, 6.7, 5.3, 3.8 Hz, CH_2-C10), 1.25—1.21 (21H, m, 3×*i*Pr), 1.20—1.04 (1H, m, CH_2-C11), 0.88—0.73 (1H, m, CH_2-C11);

^{13}C NMR (101 MHz, C_6D_6, 70 °C) δ 172.4 (C-C2), 168.8 (C-C4), 138.6 (C-Ph), 137.5 (C-Ph), 130.3 (2×CH-Ph), 130.1 (2×CH-Ph), 128.4 (CH-Ph), 128.2 (2×CH-Ph), 128.1 (CH-Ph),

127.9 (2×CH-Ph), 103.3 (C-C7), 89.2 (CH-C3), 87.9 (CH-C13), 84.5 (C-C8), 76.6 (CH-C5), 68.8 (CH-C9), 51.4 (CH_3-OMe), 50.8 (CH_2-C12), 28.1 (CH_2-C10), 25.6 (CH_2-C6), 23.1 (CH_2-C11), 19.0 (6×CH_3-*i*Pr), 12.0 (3×CH-*i*Pr);

HRMS (ESI) calculated for $C_{34}H_{46}NO_3Si$ $[M+H]^+$: 544.3241, found 544.3229, Δ +2.3 ppm. HRMS (ESI) calculated for $C_{34}H_{45}NaNO_3Si$ $[M+Na]^+$: 566.3061, found 566.3054, Δ +1.3 ppm.

Minor diastereoisomer (−)-364-2

R_f = 0.66 (PE—EtOAc, 5:5);

$[\alpha]_D^{18}$ −128.9 (c = 1.01, $CHCl_3$);

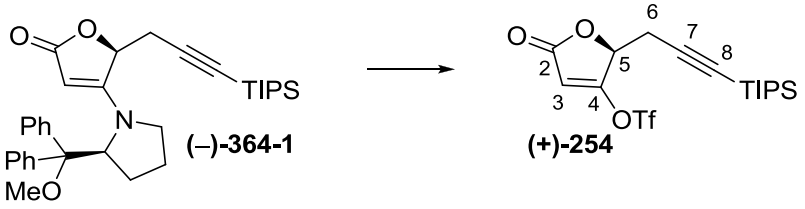
IR ν_{max} 2941, 2864, 2363, 1734, 1604, 1464 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45—7.33 (10H, m, 10×CH-Ph), 5.24 (1H, s, CH-C3), 4.86 (1H, dd, *J* = 4.2, 3.1 Hz, CH-C5), 4.72 (1H, dd, *J* = 9.3, 3.9 Hz, CH-C9), 3.08 (1H, ddd, *J* = 10.7, 8.2, 3.9 Hz, CH_2-C12), 2.94 (1H, dd, *J* = 17.9, 3.1 Hz, CH_2-C6), 2.79 (3H, s, CH_3-OMe), 2.77 (1H, dd, *J* = 17.9, 4.2 Hz, CH_2-C6), 2.09 (1H, dddd, *J* = 13.7, 9.7, 9.3, 5.8 Hz, CH_2-C10), 1.89—1.81 (1H, m, CH_2-C10), 1.70 (1H, dt, *J* = 10.7, 8.0 Hz, CH_2-C12), 1.53—1.42 (1H, m, CH_2-C11), 1.25—1.15 (1H, m, CH_2-C11), 1.07—1.01 (21H, m, 3×*i*Pr);

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5 (C-C2), 168.8 (C-C4), 137.8 (C-Ph), 137.0 (C-Ph), 129.9 (2×CH-Ph), 129.6 (2×CH-Ph), 128.3 (CH-Ph), 128.1 (2×CH-Ph), 128.0 (CH-Ph), 127.8 (2×CH-Ph), 101.0 (C-C7), 88.7 (C-C13), 87.9 (CH-C3), 84.4 (C-C8), 76.4 (CH-C5), 70.5 (CH-C9), 51.3 (CH_3-OMe), 49.1 (CH_2-C12), 28.1 (CH_2-C10), 25.3 (CH_2-C6), 23.6 (CH_2-C11), 18.6 (6×CH_3-*i*Pr), 11.2 (3×CH-*i*Pr);

HRMS (ESI) calculated for $C_{34}H_{45}NO_3Si$ $[M+H]^+$: 544.3241, found 544.3227, Δ +2.6 ppm. HRMS (ESI) calculated for $C_{34}H_{45}NaNO_3Si$ $[M+Na]^+$: 566.3061, found 566.3050, Δ +2.0 ppm.

(2*S*)-5-Oxo-2-{3-[*tris*(propan-2-yl)silyl]prop-2-yn-1-yl}-2,5-dihydrofuran-3-yl trifluoromethanesulfonate ((+)-254)



(−)-364-1 (8.36 g, 15.4 mmol) was dissolved in HCl (98 mL of a 1.25 M solution in EtOH, 123 mmol, 7.97 equiv) at rt followed by the addition of water (9.80 ml, 544 mmol, 35.4 equiv). The mixture was heated at 78 °C overnight, HCl (12.4 mL of a 1.25 M solution in EtOH, 15.5 mmol, 1.01 equiv) and water (1.20 mL, 66.7 mmol, 4.34 equiv) were added. The mixture was heated at 78 °C for a further 8 h, cooled to rt and diluted with water (60 mL) and Et_2O (500 mL). The phases were separated, the aqueous phase was

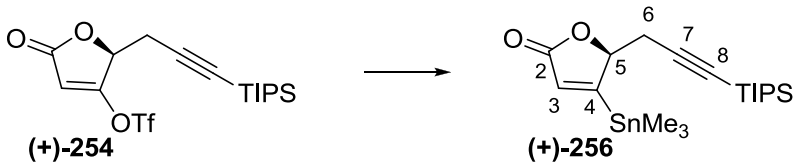
extracted with Et_2O (2 × 50 mL) and the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After azeotropic removal of water with toluene (3 × 50 mL), the orange residue was directly used in the next step.

To a solution of the crude enol lactone in CH_2Cl_2 (153 mL) at −78 °C was added dropwise freshly distilled DIPEA (4.1 mL, 23 mmol, 1.5 equiv). After 5 min triflic anhydride (3.4 mL, 20 mmol, 1.3 equiv) was added and the solution was stirred for 1 h at −78 °C. The reaction was quenched with water (30 mL) and the mixture was diluted with CH_2Cl_2 (100 mL) and slowly warmed to rt over 50 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), the organic extracts were combined, washed with brine (50 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 9:1 to 8:2) affording triflate **(+)-254** (5.35 g, 82%) as a colourless solid. Enantiomeric purity was 93% as determined by normal-phase chiral HPLC analysis. (*S*)-Configuration for **(+)-254** was assigned by comparison with previous studies on similar substrates.[41,187] The data of **(+)-254** matches with triflate **(±)-254** reported previously. Additional data are described below.

$[\alpha]_D^{23}$ +57.2 (c = 1.04, $CHCl_3$);

HPLC analysis: t_R (*R* enantiomer) = 8.4 min, t_R (*S* enantiomer) = 10.9 min, Chiracel AD-H, 2.0% propan-2-ol in *n*-hexane, flowrate 0.50 mL.min^{-1}, detection 220 nm, temperature oven 20 °C (*cf*. Annexes 18 and 19).

(5*S*)-4-Trimethylstannyl-5-{3-[*tris*(propan-2-yl)silyl]prop-2-yn-1-yl}-2,5-dihydrofuran-2-one ((+)-256)

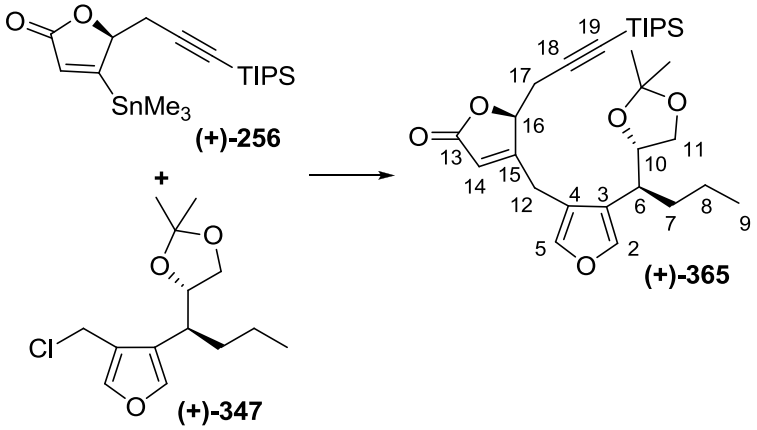


In a 250 mL flask containing thoroughly flame-dried LiCl (3.49 g, 82.3 mmol, 6.56 equiv) and $Pd(PPh_3)_4$ (349 mg, 0.302 mmol, 0.02 equiv) was added a solution of triflate **(+)-254** (5.35 g, 12.5 mmol) in THF (126 mL) followed by hexamethylditin (3.65 mL, 17.6 mmol, 1.40 equiv). The mixture was heated at reflux for 40 min. When the solution turned darker, further $Pd(PPh_3)_4$ (52.4 mg, 0.045 mmol, 0.004 equiv) was added and the mixture was stirred for 40 min at reflux. Further $Pd(PPh_3)_4$ (66.7 mg, 0.058 mmol, 0.005 equiv) was added and the mixture was stirred at reflux for a further 1 h and cooled to 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL) and the mixture was diluted with Et_2O (200 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The organic extracts were combined, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by

flash column chromatography (PE—Et_2O, 9:1 to 8:2) to give the corresponding stannane **(+)-254** (2.85 g, 52 %) as a pale yellow solid. The data of **(+)-256** matches with stannane **(±)-256** described previously. Additional data are described below.

$[\alpha]_D^{23}$ +57.2 (c = 1.04, $CHCl_3$).

(5*S*)-4-{4-[(1*S*)-1-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)butyl]furan-3-yl}methyl-5-{3-[*tris*(propan-2-yl)silyl]prop-2-yn-1-yl}-2,5-dihydrofuran-2-one ((+)-365)



To a solution of chloride **(+)-347** (73% *ee*, 840 mg, 3.08 mmol, 1.01 equiv) in THF (10 mL) were added $Pd_2(dba)_3$ (168 mg, 0.184 mmol, 0.0604 equiv) and $AsPh_3$ (232 mg, 0.758 mmol, 0.249 equiv). The mixture was stirred for 5 min at rt before a solution of stannane **(+)-365** (1.34 g, 3.04 mmol, 1.00 equiv) in THF (22 mL) was added. The mixture was heated at reflux and stirred at this temperature for 24 h and then cooled to rt. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and the mixture was diluted with Et_2O (40 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 92:8 to 6:4) to afford the coupled product **(+)-365** (1.49 g, 95%) as a colourless oil and as an inseparable mixture (6.4:1) of diastereoisomers.

$C_{30}H_{46}O_5Si$ **Molecular weight: 514.77 g·mol^{-1}**

R_f = 0.17 (PE—Et_2O, 7:3);

$[\alpha]_D^{25}$ +84.8 (c = 1.23, $CHCl_3$);

IR ν_{max} 2942, 2864, 2357, 2332, 2177, 1755, 1643, 1541, 1464 cm^{-1};

Major diastereoisomer

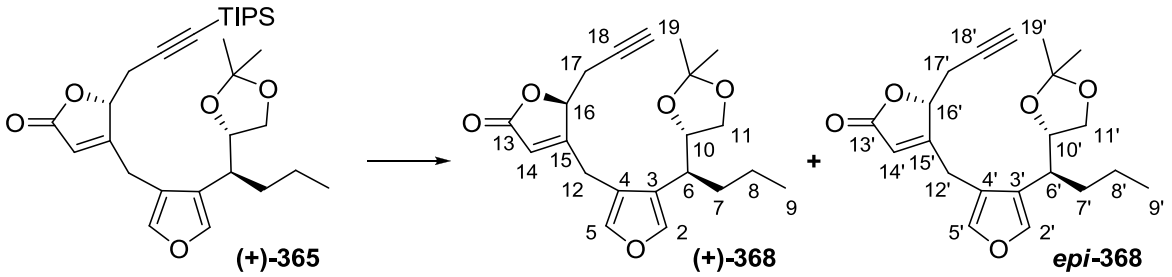
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (1H, d, *J* = 1.5 Hz, CH-C2), 7.16 (1H, s, CH-C5), 5.80 (1H, d, *J* = 1.1 Hz, CH-C14), 5.01 (1H, ddd, *J* = 5.3, 3.9, 1.1 Hz, CH-C16), 4.06 (1H, app q, *J* = 6.8 Hz, CH-C10), 4.00 (1H, dd, *J* = 7.7, 6.1 Hz, CH_2-C11), 3.63 (1H, d, *J* = 18.1 Hz, CH-C12), 3.49 (1H, appt, *J* = 7.9 Hz, CH_2-C11), 3.44 (1H, d, *J* = 18.1 Hz, CH_2-C12), 2.94 (1H, dd, *J* = 17.5, 5.3 Hz, CH_2-C17), 2.78 (1H, dd, *J* = 17.5, 3.9 Hz, CH_2-C17), 2.46 (1H,

app q, *J* = 7.1 Hz, CH-C6), 1.48 (2H, app q, *J* = 7.9 Hz , CH_2-C7), 1.35 (3H, s, CH_3-CMe_2), 1.35—1.24 (1H, m, CH_2-C8), 1.30 (3H, s, CH_3-CMe_2), 1.23—1.12 (1H, m, CH_2-C8), 1.03 (21H, s, 3×*i*Pr), 0.86 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0 (C-C13), 169.7 (C-C15), 140.8 (CH-C2), 140.6 (CH-C5), 125.2 (C-C3 or C-C4), 119.8 (C-C3 or C-C4), 118.6 (CH-C14), 109.2 (C-CMe_2), 99.8 (C-C18 or C-C19), 85.4 (C-C18 or C-C19), 80.6 (CH-C16), 79.7 (CH-C10), 68.2 (CH_2-C11), 38.4 (CH-C6), 34.6 (CH_2-C7), 26.7 (CH_3-CMe_2), 25.6 (CH_3-CMe_2), 23.7 (CH_2-C17), 23.4 (CH_2-C12), 20.6 (CH_2-C8), 18.7 (6×CH_3-*i*Pr), 14.3 (CH_3-C9), 11.3 (3×CH-*i*Pr);

LRMS (CI, Me_3CH): *m/z* (*int*) 515 (56), 457 (14), 369 (10), 293 (100). HRMS (CI, Me_3CH) calculated for $C_{30}H_{47}O_5Si$ $[M+H]^+$: 515.3193, found 515.3218, Δ +2.1 ppm.

4-{4-[(1*S*)-1-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)butyl]furan-3-yl}methyl-5-(prop-2-yn-1-yl)-2,5-dihydrofuran-2-one (368)



To a solution of alkyne **(+)-365** (37.8 mg, 0.0734 mmol) in THF (1.2 mL) at 0 °C was added dropwise TBAF (110 µL of a 1 M solution in THF, 110 µmol, 1.51 equiv). The mixture was stirred for 30 min at 0 °C and the reaction was quenched by the addition of water (5 mL). The mixture was diluted in Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL) and the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 6:4) affording terminal alkynes **368** in an inseparable mixture (1:1) of two diastereoisomers (16.5 mg, 63%). **(+)-368** and ***epi*-368** could be differenciated thanks to the synthesis of enantiopure **(+)-368** detailed further down (page 188).

$C_{21}H_{26}O_5$ **Molecular weight: 358.43 g·mol^{-1}**

R_f = 0.31 (PE—Et_2O, 4:6);

IR ν_{max} 3284, 2984, 2957, 2933, 2873, 1753, 1643, 1540, 1458 cm^{-1};

(+)-368

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, d, *J* = 1.4 Hz, CH-C2), 7.28 (1H, br s, CH-C5), 5.83 (1H, d, *J* = 1.1 Hz, CH-C14), 5.02 (1H, ddd, *J* = 5.5, 4.2, 1.1 Hz, CH-C16), 4.09 (1H, ddd, *J* = 7.7, 6.7, 6.1 Hz, CH-C10), 4.00 (1H, dd, *J* = 7.8, 6.1 Hz, CH_2-C11), 3.59 (1H, d, *J* = 18.2 Hz, CH_2-C12), 3.50 (1H, dd, *J* = 7.8, 7.7 Hz, CH_2-C11), 3.46 (1H, d, *J* = 18.2 Hz,

CH_2-C12), 2.85 (1H, ddd, *J* = 17.3, 5.5, 2.7 Hz, CH_2-C17), 2.71 (1H, ddd, *J* = 17.5, 4.2, 2.7 Hz, CH_2-C17), 2.50 (1H, ddd, *J* = 9.1, 6.7, 5.3 Hz, CH-C6), 2.07 (1H, t, *J* = 2.7 Hz, CH-C19), 1.52—1.45 (2H, m, CH_2-C7), 1.36 (3H, s, CH_3-CMe_2), 1.31 (3H, s, CH_3-CMe_2), 1.29—1.11 (2H, m, CH_2-C8), 0.86 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9 (C-C13), 169.6 (C-C15), 140.8 (CH-C2 or CH-C5), 140.7 (CH-C2 or CH-C5), 125.3 (C-C3 or C-C4), 119.8 (C-C3 or C-C4), 118.7 (CH-C14), 109.2 (C-CMe_2), 80.3 (CH-C16), 79.6 (CH-C10), 76.7 (C-C18), 72.6 (CH-C19), 68.2 (CH_2-C11), 38.3 (CH-C6), 34.9 (CH_2-C7), 26.7 (CH_3-CMe_2), 25.6 (CH_3-CMe_2), 23.3 (CH_2-C12), 22.6 (CH_2-C17), 20.6 (CH_2-C8), 14.3 (CH_3-C9);

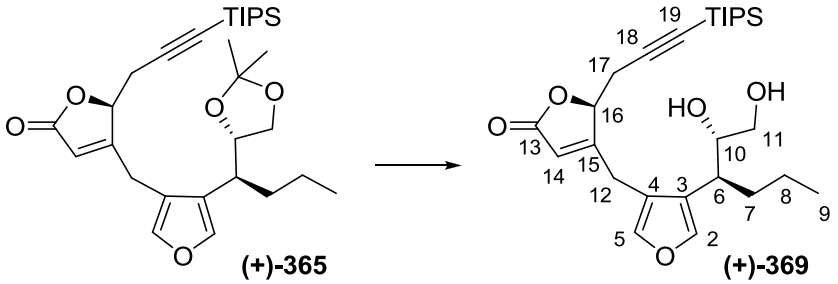
***epi*-368**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (1H, d, *J* = 1.4 Hz, CH-C2'), 7.28 (1H, s, CH-C5'), 5.82 (1H, d, *J* = 1.2 Hz, CH-C14'), 5.00 (1H, ddd, *J* = 5.3, 4.2, 1.2 Hz, CH-C16'), 4.12—3.97 (2H, m, CH-C10', CH_2-C11'), 3.66 (1H, d, *J* = 18.2 Hz, CH_2-C12'), 3.50 (1H, app t, *J* = 7.8 Hz, CH_2-C11'), 3.44 (1H, d, *J* = 18.2 Hz, CH_2-C12'), 2.88 (1H, ddd, *J* = 17.2, 5.3, 2.7 Hz, CH_2-C17'), 2.72 (1H, ddd, *J* = 17.2, 4.2, 2.7 Hz, CH_2-C17'), 2.59—2.45 (1H, m, CH-C6'), 2.06 (1H, t, *J* = 2.7 Hz, CH-C19'), 1.53—1.44 (2H, m, CH_2-C7'), 1.35 (3H, s, CH_3-CMe_2), 1.30 (3H, s, CH_3-CMe_2), 1.27—1.09 (2H, m, CH_2-C8'), 0.86 (3H, t, *J* = 7.3 Hz, CH_3-C9');

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8 (C-C13'), 169.6 (C-C15'), 140.9 (CH-C2' or CH-C5'), 140.7 (CH-C2' or CH-C5'), 125.3 (C-C3' or C-C4'), 119.9 (C-C3' or C-C4'), 118.8 (CH-C14'), 109.2 (C-CMe_2), 80.4 (CH-C16'), 80.0 (CH-C10'), 76.8 (C-C18'), 72.5 (CH-C19'), 68.3 (CH_2-C11'), 38.3 (CH-C6'), 34.4 (CH_2-C7'), 26.7 (CH_3-CMe_2), 25.7 (CH_3-CMe_2), 23.4 (CH_2-C12'), 22.7 (CH_2-C17'), 20.7 (CH_2-C8'), 14.2 (CH_3-C9');

LRMS (EI+): *m/z* (*int*) 358 (5), 343 (30), 258 (55), 220 (22), 205 (65), 149 (28), 101 (100), 83 (96), 43 (40). HRMS (EI+) calculated for $C_{21}H_{26}O_5$ $[M]^+$: 358.1780, found 358.1777, Δ −0.8 ppm.

(5*S*)-4-[4-((2*S*,3*S*)-1,2-Dihydroxyhexan-3-yl)furan-3-yl]methyl-5-{3-[*tris*(propan-2-yl)silyl]prop-2-yn-1-yl}-2,5-dihydrofuran-2-one ((+)-369)



To a solution of alkyne **(+)-365** (32.1 mg, 0.0624 mmol) in MeCN (0.5 mL) was added HF (5% in MeCN, 1.5 mL) at 0 °C. The mixture was warmed to rt and stirred for 3 days at rt. After cooling the solution to 0 °C, the reaction was very carefully quenched with

$NaHCO_3$ (10 mL) and the mixture was diluted with CH_2Cl_2 (20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (PE—EtOAc, 5:5) affording diol **(+)-369** (19.9 mg, 67%) as a colourless oil.

$C_{27}H_{42}O_5Si$ **Molecular weight: 474.70 g·mol^{-1}**

R_f = 0.34 (PE—EtOAc, 5:5);

$[\alpha]_D^{24}$ +59.6 (c = 1.10, $CHCl_3$);

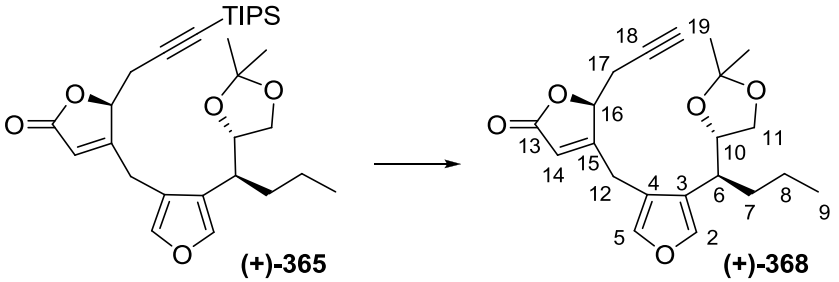
IR ν_{max} 3427, 2957, 2943, 2865, 2177, 1745, 1642, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, d, *J* = 1.5 Hz, CH-C2), 7.28 (1H, s, CH-C5), 5.75 (1H, d, *J* = 1.3 Hz, CH-C14), 5.02 (1H, ddd, *J* = 5.3, 3.8, 1.3 Hz, CH-C16), 3.71 (1H, ddd, *J* = 7.4, 5.5, 3.4 Hz, CH-C10), 3.61 (1H, d, *J* = 18.6 Hz, CH_2-C12), 3.93 (1H, dd, *J* = 10.9, 3.4 Hz, CH_2-C11), 3.48—3.37 (1H, m, CH_2-C11), 3.40 (1H, d, *J* = 18.6 Hz, CH_2-C12), 2.94 (1H, dd, *J* = 17.5, 5.3 Hz, CH_2-C17), 2.80 (1H, dd, *J* = 17.5, 3.8 Hz, CH_2-C17), 2.52 (1H, ddd, *J* = 10.3, 5.5, 5.3 Hz, CH-C6), 2.35 (2H, br s, 2×OH), 1.66—1.56 (1H, m, CH_2-C7), 1.55—1.44 (1H, m, CH_2-C7), 1.31—1.14 (2H, m, CH_2-C8), 1.02 (21H, s, 3×*i*Pr), 0.85 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1 (C-C13), 170.0 (C-C15), 141.3 (CH-C2), 140.0 (CH-C5), 124.6 (C-C3 or C-C4), 120.1 (C-C3 or C-C4), 118.5 (CH-C14), 100.0 (C-C18), 85.6 (C-C19), 80.8 (CH-C16), 74.6 (CH-C10), 65.0 (CH_2-C11), 37.7 (CH-C6), 35.0 (CH_2-C7), 23.8 (CH_2-C17), 23.3 (CH_2-C10), 20.8 (CH_2-C8), 18.7 (6×CH_3-*i*Pr), 14.1 (CH_3-C9), 11.4 (3×CH-*i*Pr);

HRMS (ESI) calculated for $C_{27}H_{42}NaO_5Si$ $[M+Na]^+$: 497.2694, found 497.2677, Δ +3.3 ppm.

(5*S*)-4-{4-[(1*S*)-1-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)butyl]furan-3-ylmethyl-5-prop-2-yn-1-yl-2,5-dihydrofuran-2-one (+)-368



TIPS-protected alkyne **(+)-365** (44.8 mg, 0.0870 mmol) was dissolved in MeCN (1 mL). At rt, AgF (21.2 mg, 0.167 mmol, 1.92 equiv) was added and the mixture was stirred for 3 h excluded from light. The reaction was quenched by the addition of aqueous HCl (1 M, 0.1 mL) at 0 °C. The dark solution was stirred for 10 min and diluted with water (5 mL) and Et_2O (10 mL). The phases were separated and the aqueous phase was

extracted with Et_2O (2 × 10 mL). Brine (10 mL) was added to the aqueous phase for a better separation. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography (PE—Et_2O, 5:5) to afford the terminal alkyne **(+)-368** (9.0 mg, 29%) as a colourless oil. NMR data are previously described on page 186. Additional data are described below.

$C_{21}H_{26}O_5$ **Molecular weight: 358.43 g·mol^{-1}**

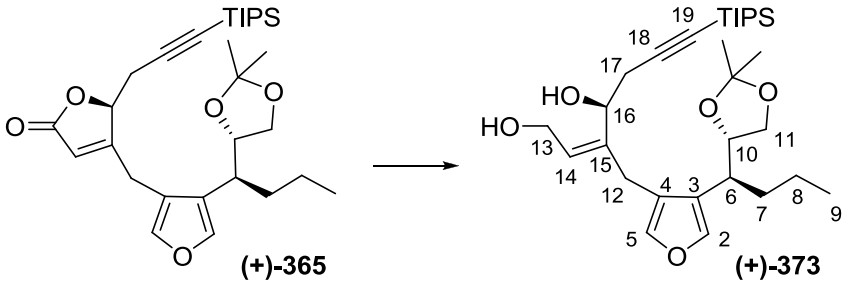
R_f = 0.31 (PE—Et_2O, 4:6);

$[\alpha]_D^{19}$ +58.6 (c = 0.40, $CHCl_3$);

IR ν_{max} 3282, 2958, 2933, 2874, 2364, 1759, 1643, 1541, 1456 cm^{-1};

LRMS (CI, Me_3CH): *m/z* (*int*) 359 (100), 301 (64), 113 (22), 73 (56). HRMS (CI, Me_3CH) calculated for $C_{21}H_{27}O_5$ $[M+H]^+$: 359.1858, found 359.1868, Δ +2.6 ppm.

(2*Z*,4*S*)-3-[4-(1*S*)-1-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)butylfuran-3-yl]methyl-7-*tris*(propan-2-yl)silyl-hept-2-en-6-yne-1,4-diol ((+)-373)



To a suspension of $LiAlH_4$ (40.7 mg, 1.07 mmol, 2.75 equiv) in Et_2O (1 mL) at 0 °C was added TMEDA (590 µL, 3.94 mmol, 10.1 equiv) dropwise. The suspension was stirred for 10 min at 0 °C and cooled to −78 °C. A solution of the unsaturated lactone **(+)-365** (200 mg, 0.389 mmol) in Et_2O (4 mL) was added dropwise and the mixture was stirred at −78 °C for 1 h before being slowly warmed to 0 °C over 1 h. The mixture was stirred 30 min at 0 °C and the reaction was quenched by the addition of saturated aqueous Rochelle salt (10 mL). Et_2O (20 mL) was added and the mixture was warmed to rt and stirred for 1 h. The phases were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The organic extracts were combined and dried over $MgSO_4$. After filtration and concentration *in vacuo*, the residue was purified by flash column chromatography (PE—Et_2O, 5:5) to afford the diol **(+)-373** (106 mg, 53%) as a colourless oil and as an inseparable mixture (6:1) with reduced diol **375**. Purification using silica impregnated with 10% $AgNO_3$ was possible on small scale (less than 10 mg) but was inefficient on larger scale. Another by-product, the conjugated reduction product **(+)-374**, was also detected from the reaction and characterised.

Diol **(+)-373**

$C_{30}H_{50}O_5Si$ **Molecular weight: 518.80 g·mol^{-1}**

R_f = 0.20 (PE—Et_2O, 4:6);

$[\alpha]_D^{25}$ +20.8 (c = 1.00, $CHCl_3$);

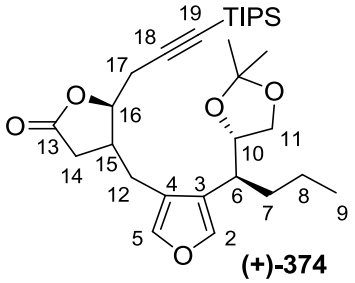
IR ν_{max} 3778, 2940, 2891, 2864, 2174, 1539, 1464, 1381, 1369 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, d, *J* = 1.5 Hz, CH-C2), 7.20 (1H, d, *J* = 1.5 Hz, CH-C5), 5.52 (1H, dd, *J* = 7.4, 7.0 Hz, CH-C14), 4.67 (1H, dd, *J* = 7.6, 6.5 Hz, CH-C16), 4.26 (1H, dd, *J* = 12.9, 7.4 Hz, CH_2-C13), 4.22—4.15 (1H, m, CH-C10), 4.17 (1H, dd, *J* = 12.9, 7.0 Hz, CH_2-C13), 3.94 (1H, dd, *J* = 7.9, 6.2 Hz, CH_2-C11), 3.55 (1H, t, *J* = 7.9 Hz, CH_2-C11), 3.26 (1H, d, *J* = 16.7 Hz, CH_2-C12), 3.18 (1H, d, *J* = 16.7 Hz, CH_2-C12), 2.78 (1H, br s, OH), 2.66 (1H, dd, *J* = 16.7, 7.6 Hz, CH_2-C17), 2.68—2.60 (1H, m, CH-C6), 2.55 (1H, dd, *J* = 16.7, 6.5 Hz, CH_2-C17), 2.03 (1H, br s, OH), 1.60—1.45 (2H, m, CH_2-C7), 1.38 (3H, s, CH_3-CMe_2), 1.32 (3H, s, CH_3-CMe_2), 1.34—1.18 (2H, m, CH_2-C8), 1.06 (21H, s, 3×*i*Pr), 0.87 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.8 (C-C15), 140.9 (CH-C5), 140.5 (CH-C2), 128.5 (CH-C14), 125.2 (C-C3 or C-C4), 122.6 (C-C3 or C-C4), 109.1 (C-CMe_2), 104.5 (C-C18), 83.9 (C-C19), 79.1 (CH-C10), 69.2 (CH-C16), 67.5 (CH_2-C11), 58.4 (CH_2-C13), 37.2 (CH-C6), 34.7 (CH_2-C7), 27.8 (CH_2-C17), 26.7 (CH_3-CMe_2), 26.3 (CH_2-C12), 25.6 (CH_3-CMe_2), 20.7 (CH_2-C8), 18.7 (6×CH_3-*i*Pr), 14.3 (CH_3-C9), 11.4 (3×CH-*i*Pr);

HRMS (ESI) calculated for $C_{30}H_{50}NaO_5Si$ $[M+Na]^+$: 541.3299, found 541.3320, Δ +3.9 ppm.

(5*S*)-4-{4-[(1*S*)-1-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)butyl]furan-3-yl}methyl-5-{3-[*tris*(propan-2-yl)silyl]prop-2-yn-1-yl}oxolan-2-one ((+)-374)



(+)-374

$C_{30}H_{48}O_5Si$ **Molecular weight: 516.78 g·mol^{-1}**

R_f = 0.58 (PE—Et_2O, 4:6);

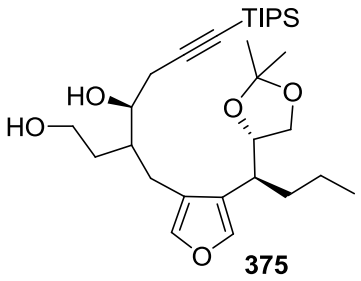
$[\alpha]_D^{25}$ +7.0 (c = 0.99, $CHCl_3$);

IR ν_{max} 2943, 2820, 2367, 2174, 1782, 1541, 1464 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (1H, d, *J* = 1.5 Hz, CH-C2), 7.20 (1H, d, *J* = 1.5 Hz, CH-C5), 4.36 (1H, dt, *J* = 5.9, 4.1 Hz, CH-C16), 4.11 (1H, dt, *J* = 7.9, 6.2 Hz, CH-C10), 3.99 (1H, dd, *J* = 7.9, 6.2 Hz, CH_2-C11), 3.51 (1H, t, *J* = 7.9 Hz, CH_2-C11), 2.86 (1H, dd, *J* = 17.8, 9.1 Hz, CH_2-C14), 2.78—2.49 (6H, m, CH-C6, CH-C15, CH_2-C12, CH_2-C17), 2.28 (1H, dd, *J* = 17.8, 5.3 Hz, CH_2-C14), 1.58—1.48 (2H, m, CH_2-C7), 1.35 (3H, s, CH_3-CMe_2), 1.31 (3H, s, CH_3-CMe_2), 1.33—1.16 (2H, m, CH_2-C8), 1.05 (21H, br s, 3×*i*Pr), 0.87 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9 (C-C13), 140.5 (CH-C2), 139.5 (CH-C5), 125.0 (C-C3 or C-C4), 122.1 (C-C3 or C-C4), 109.2 (C-CMe_2), 102.0 (C-C18), 84.8 (C-C19), 82.3 (CH-C16), 79.5 (CH-C10), 67.9 (CH_2-C11), 38.8 (CH-C15), 38.0 (CH-C6), 35.0 (CH_2-C14), 34.7 (CH_2-C7), 28.4 (CH_2-C17), 26.6 (CH_3-CMe_2), 26.3 (CH_2-C12), 25.6 (CH_3-CMe_2), 20.7 (CH_2-C8), 18.7 (6×CH_3-*i*Pr), 14.3 (CH_3-C9), 11.4 (3×CH-*i*Pr);
HRMS (ESI) calculated for $C_{30}H_{48}NaO_5Si$ $[M+Na]^+$: 539.3163, found 539.3146, Δ +3.3 ppm.

(4*S*)-3-{4-[(1*S*)-1-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)butyl]furan-3-yl}methyl-7-[*tris*(propan-2-yl)silyl]hept-6-yne-1,4-diol (375)

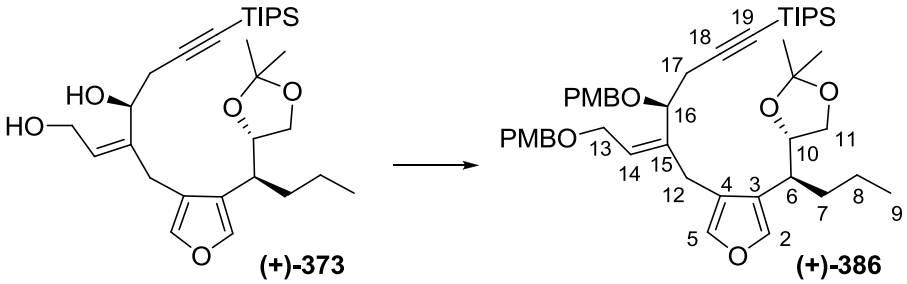


375

$C_{30}H_{52}O_5Si$ **Molecular weight: 520.82 g·mol^{-1}**

R_f = 0.20 (PE—Et_2O, 4:6);
HRMS (ESI) calculated for $C_{30}H_{52}NaO_5Si$ $[M+Na]^+$: 543.3476, found 543.3452, Δ +4.4 ppm.

((4*S*,5*Z*)-5-{4-[(1*S*)-1-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)butyl]furan-3-yl}methyl-4,7-*bis*(4-methoxyphenylmethoxy)hept-5-en-1-yn-1-yl)*tris*(propan-2-yl)silane ((+)-386)



To a solution of diol **(+)-373** (157 mg, 0.303 mmol) in DMF (3.0 mL) at 0 °C were added successively NaH (36.6 mg of a 60% dispersion in mineral oil, 1.53 mmol, 5.04 equiv), TBAI (11 mg, 0.030 mmol, 0.10 equiv) and PMBCl (180 µL, 1.24 mmol, 4.09 equiv). The mixture was allowed to slowly warm to rt and was stirred for 24 h. The reaction was quenched by careful addition of water (1 mL) and the mixture was diluted with EtOAc (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 9:1) to afford *bis*-PMB ether **(+)-386** (126 mg, 55%) as a colourless oil.

$C_{46}H_{66}O_7Si$ **Molecular weight: 759.10 g·mol^{-1}**

R_f = 0.56 (PE—Et_2O, 6:4);

$[\alpha]_D^{22}$ +0.1 (c = 1.00, $CHCl_3$);

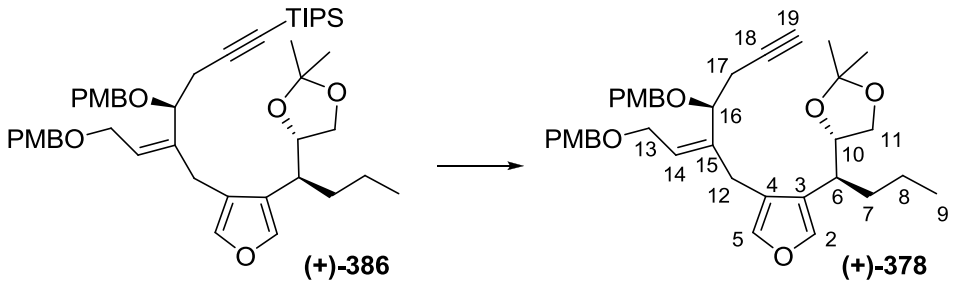
IR ν_{max} 2938, 2864, 2174, 1728, 1613, 1586, 1512, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, d, *J* = 1.5 Hz, CH-C2), 7.25—7.20 (1H, m, CH-C5), 7.23 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 7.22 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 6.85 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 6.84 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 5.53 (1H, dd, *J* = 7.0, 5.2 Hz, CH-C14), 4.46 (1H, d, *J* = 11.5 Hz, CH_2-PMB), 4.43—4.42 (1H, m, CH-C16), 4.40 (1H, d, *J* = 11.5 Hz, CH_2-PMB), 4.37 (1H, d, *J* = 11.5 Hz, CH_2-PMB), 4.26 (1H, d, *J* = 11.5 Hz, CH_2-PMB), 4.17 (1H, dd, *J* = 12.4, 7.0 Hz, CH_2-C13), 4.14 (1H, ddd, *J* = 7.9, 6.3, 5.2 Hz, CH-C10), 3.93 (1H, dd, *J* = 12.4, 5.2 Hz, CH_2-C13), 3.89 (1H, dd, *J* = 7.9, 6.3 Hz, CH_2-C11), 3.81 (3H, s, CH_3-PMB), 3.79 (3H, s, CH_3-PMB), 3.52 (1H, t, *J* = 7.9 Hz, CH_2-C11), 3.21 (1H, d, *J* = 17.7 Hz, CH_2-C12), 3.16 (1H, d, *J* = 17.7 Hz, CH_2-C12), 2.68 (1H, dd, *J* = 16.8, 6.5 Hz, CH_2-C17), 2.63—2.53 (1H, m, CH-C6), 2.53 (1H, dd, *J* = 16.8, 7.9 Hz, CH_2-C17), 1.61—1.45 (2H, m, CH_2-C7), 1.37 (3H, s, CH_3-CMe_2), 1.31 (3H, s, CH_3-CMe_2), 1.36—1.15 (2H, m, CH_2-C8), 1.04 (21H, s, 3×*i*Pr), 0.84 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3 (2×C-PMB), 141.0 (CH-C5), 140.3 (CH-C2), 139.4 (C-C15), 130.5 (C-PMB), 130.4 (C-PMB), 129.4 (2×CH-PMB), 129.3 (2×CH-PMB), 128.1 (CH-C14), 125.1 (C-C3 or C-C4), 122.4 (C-C3 or C-C4), 114.0 (2×CH-PMB), 113.9 (2×CH-PMB), 108.9 (C-CMe_2), 104.8 (C-C18), 82.2 (C-C19), 78.9 (CH-C10), 75.3 (CH-C16), 72.4 (CH_2-PMB), 70.5 (CH_2-PMB), 67.4 (CH_2-C11), 65.8 (CH_2-C13), 55.4 (CH_3-PMB), 55.4 (CH_3-PMB), 37.1 (CH-C6), 34.7 (CH_2-C7), 26.7 (CH_3-CMe_2), 25.8 (CH_2-C17), 25.6 (CH_3-CMe_2), 24.3 (CH_2-C12), 20.8 (CH_2-C8), 18.7 (6×CH_3-*i*Pr), 14.4 (CH_3-C9), 11.4 (3×CH-*i*Pr);

HRMS (ESI) calculated for $C_{46}H_{66}NaO_7Si$ $[M+Na]^+$: 781.4440, found 781.4470, Δ +3.9 ppm.

(4*S*)-4-((1*S*)-1-{4-[(2*Z*,3*S*)-3-(4-Methoxyphenylmethoxy)-2-[2-(4-methoxyphenylmethoxy)ethylidene]hex-5-yn-1-yl]furan-3-yl}butyl)-2,2-dimethyl-1,3-dioxolane ((+)-378)



To a solution of TIPS-protected alkyne **(+)-386** (126 mg, 0.166 mmol) in THF (2 mL) at 0 °C was added TBAF (330 μL of a 1 M solution in THF, 0.330 mmol, 1.99 equiv) dropwise. After 30 min the mixture was allowed to warm to rt and stirred for a further

3 h. The solution was concentrated *in vacuo* and the residue purified by flash column chromatography (PE—Et_2O, 8:2) to afford terminal alkyne **(+)-378** (95.7 mg, 96%) as a colourless oil.

$C_{37}H_{46}O_7$ **Molecular weight: 602.76 g·mol^{-1}**

R_f = 0.43 (PE—Et_2O, 6:4);

$[\alpha]_D^{25}$ +2.7 (c = 1.02, $CHCl_3$);

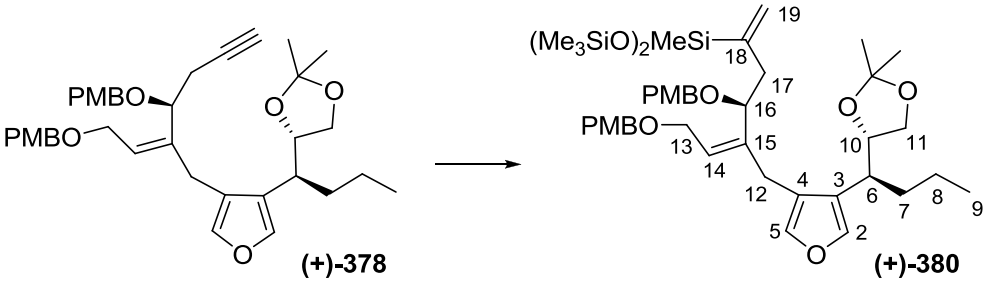
IR ν_{max} 3284, 2956, 2935, 2870, 2368, 1612, 1585, 1514, 1465 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (1H, d, *J* = 1.4 Hz, CH-C2), 7.25—7.21 (1H, m, CH-C5), 7.24 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 7.23 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 6.86 (4H, d, *J* = 8.6 Hz, 4×CH-PMB), 5.52 (1H, dd, *J* = 7.4, 5.2 Hz, CH-C14), 4.49 (1H, d, *J* = 11.6 Hz, CH_2-PMB), 4.41 (1H, d, *J* = 11.5 Hz, CH_2-PMB), 4.43—4.36 (1H, m, CH-C16), 4.37 (1H, d, *J* = 11.5 Hz, CH_2-PMB), 4.25 (1H, d, *J* = 11.6 Hz, CH_2-PMB), 4.16—4.09 (2H, m, CH-C10 and CH_2-C13), 3.95 (1H, dd, *J* = 12.4, 5.2 Hz, CH_2-C13), 3.91 (1H, dd, *J* = 7.8, 6.2 Hz, CH_2-C11), 3.81 (3H, s, CH_3-PMB), 3.80 (3H, s, CH_3-PMB), 3.51 (1H, t, *J* = 7.8 Hz, CH_2-C11), 3.18 (2H, s, CH_2-C12), 2.64—2.59 (1H, m, CH-C6), 2.59 (1H, ddd, *J* = 16.7, 6.4, 2.7 Hz, CH_2-C17), 2.47 (1H, ddd, *J* = 16.7, 8.0, 2.7 Hz, CH_2-C17), 1.95 (1H, t, *J* = 2.7 Hz, CH-C19), 1.55—1.48 (2H, m, CH_2-C7), 1.37 (3H, s, CH_3-CMe_2), 1.31 (3H, s, CH_3-CMe_2), 1.34—1.15 (2H, m, CH_2-C8), 0.83 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (C-PMB), 159.3 (C-PMB), 141.0 (CH-C5), 140.3 (CH-C2), 139.0 (C-C15), 130.4 (C-PMB), 130.1 (C-PMB), 129.5 (2×CH-PMB), 129.4 (2×CH-PMB), 128.4 (CH-C14), 125.2 (C-C3 or C-C4), 122.2 (C-C3 or C-C4), 113.9 (4×CH-PMB), 108.9 (C-CMe_2), 80.8 (C-C18), 79.2 (CH-C10), 74.5 (CH-C16), 72.4 (CH_2-PMB), 70.3 (2C, CH_2-PMB and CH-C19), 67.6 (CH_2-C11), 65.8 (CH_2-C13), 55.4 (CH_3-PMB), 55.4 (CH_3-PMB), 37.1 (CH-C6), 34.7 (CH_2-C7), 26.7 (CH_3-CMe_2), 25.6 (CH_3-CMe_2), 24.3 and 24.3 (2C, CH_2-C12 and CH_2-C17), 20.7 (CH_2-C8), 14.5 (CH_3-C9);

LRMS (EI+): *m/z* (*int*) 602 (10), 483 (11), 345 (25), 328 (30), 287 (17), 227 (31), 171 (18), 121 (100), 101 (100), 77 (29). HRMS (EI+) calculated for $C_{37}H_{46}O_7$ $[M]^+$: 602.3244, found 602.3246, Δ +0.4 ppm.

4-((4*S*,5*Z*)-5-{4-[(1*S*)-1-((4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)butyl]furan-3-yl}methyl-4,7-*bis*(4-methoxyphenylmethoxy)hepta-1,5-dien-2-yl)-2,2,4,6,6-pentamethyl-3,5-dioxa-2,4,6-trisilaheptane ((+)-380)



To a solution of terminal alkyne **(+)-378** (18.4 mg, 30.5 μmol) in CH_2Cl_2 (500 μL) was added 1,1,1,3,5,5,5-heptamethyltrisiloxane (12 μL, 44 μmol, 1.4 equiv) and $[Cp^*Ru(MeCN)_3]PF_6$ (1.2 mg, 2.4 μmol, 0.078 equiv). The mixture was stirred at rt for 1 h and then concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 9:1 to 85:15) to afford product **(+)-380** (19.9 mg, 79%) as a colourless oil.

$C_{44}H_{68}O_9Si_3$ **Molecular weight: 825.26 g·mol^{-1}**

R_f = 0.56 (PE—Et_2O, 6:4);

$[\alpha]_D^{24}$ +9.95 (c = 0.87, $CHCl_3$);

IR ν_{max} 2957, 2933, 2866, 2362, 1612, 1514 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (1H, d, *J* = 1.5 Hz, CH-C2), 7.21 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 7.20 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 7.17 (1H, d, *J* = 1.5 Hz, CH-C5), 6.85 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 6.84 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 5.61 (1H, d, *J* = 3.0 Hz, CH_2-C19), 5.52 (1H, d, *J* = 3.0 Hz, CH_2-C19), 5.42 (1H, dd, *J* = 7.3, 5.6 Hz, CH-C14), 4.40 (2H, 2×d, *J* = 11.3 Hz, 2×CH_2-PMB), 4.38 (1H, d, *J* = 11.3 Hz, CH_2-PMB), 4.34 (1H, dd, *J* = 8.4, 5.0 Hz, CH-C16), 4.22 (1H, d, *J* = 11.3 Hz, CH_2-PMB), 4.20—4.11 (2H, m, CH-C10, CH_2-C13), 3.97 (1H, dd, *J* = 12.2, 5.6 Hz, CH_2-C13), 3.87 (1H, dd, *J* = 7.8, 6.2 Hz, CH_2-C11), 3.80 (3H, s, CH_3-PMB), 3.79 (3H, s, CH_3-PMB), 3.51 (1H, t, *J* = 7.8 Hz, CH_2-C11), 3.21 (1H, d, *J* = 17.4 Hz, CH_2-C12), 3.13 (1H, d, *J* = 17.4 Hz, CH_2-C12), 2.61 (1H, dt, *J* = 9.7, 4.8 Hz, CH-C6), 2.57 (1H, dd, *J* = 14.5, 8.4 Hz, CH_2-C17), 2.27 (1H, dd, *J* = 14.5, 5.0 Hz, CH_2-C17), 1.65—1.56 (1H, m, CH_2-C7), 1.56—1.49 (1H, m, CH_2-C7), 1.36 (3H, s, CH_3-CMe_2), 1.30 (3H, s, CH_3-CMe_2), 1.35—1.18 (2H, m, CH_2-C8), 0.84 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.11 (9H, s, 3×CH_3-$SiMe_3$), 0.11 (9H, s, 3×CH_3-$SiMe_3$), 0.08 (3H, s, CH_3-SiMe);

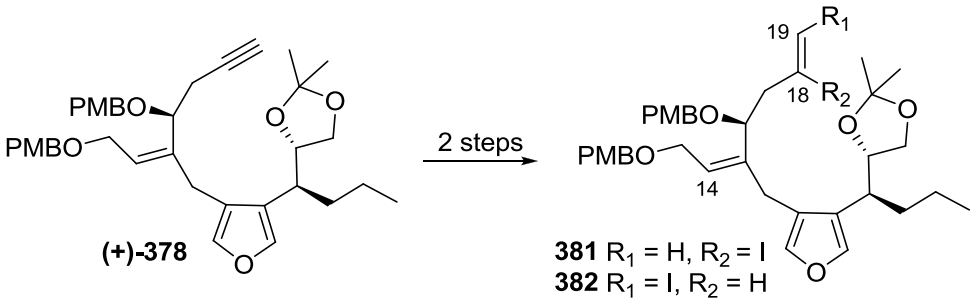
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5 (C-PMB), 159.4 (C-PMB), 146.5 (C-C18), 141.0 (CH-C5), 140.9 (C-C15), 140.4 (CH-C2), 139.4 (C-C15), 131.1 (C-PMB), 130.8 (C-PMB), 129.4 (2×CH-PMB), 129.3 (2×CH-PMB), 128.2 (CH_2-C19), 126.7 (CH-C14), 125.3 (C-C3 or C-C4), 122.5 (C-C3 or C-C4), 114.1 (2×CH-PMB), 113.9 (2×CH-PMB), 109.0 (C-CMe_2), 78.8 (CH-C10), 76.7 (CH-C16), 72.4 (CH_2-PMB), 70.4 (CH_2-PMB), 67.4 (CH_2-C11), 66.2 (CH_2-C13), 55.5 (CH_3-PMB), 55.4 (CH_3-PMB), 39.3 (CH_2-C17), 37.1 (CH-C6), 34.7 (CH_2-C7), 26.7 (CH_3-CMe_2), 25.7 (CH_3-CMe_2), 25.1 (CH_2-C12), 20.9 (CH_2-C8), 2.0 (6×CH_3-$SiMe_3$), −0.2 (CH_3-SiMe);

LRMS (EI+): *m/z* (*int*) 824 (10), 550 (47), 450 (15), 325 (16), 221 (87), 205 (23), 121 (100), 101 (55), 73 (30). HRMS (EI+) calculated for $C_{44}H_{68}O_9Si_3$ $[M]^+$: 824.4171, found 824.4175, Δ +0.5 ppm.

(4*S*)-4-[(1*S*)-1-(4-{(2*Z*,3*S*,5*Z*)-5-Iodo-3-(4-methoxyphenylmethoxy)-2-[2-(4-methoxyphenylmethoxy)ethylidene]hex-5-en-1-yl}furan-3-yl)butyl]-2,2-dimethyl-1,3-dioxolane (381)

and

(4*S*)-4-[(1*S*)-1-(4-{(2*Z*,3*S*,5*E*)-6-Iodo-3-(4-methoxyphenylmethoxy)-2-[2-(4-methoxyphenylmethoxy)ethylidene]hex-5-en-1-yl}furan-3-yl)butyl]-2,2-dimethyl-1,3-dioxolane (382)



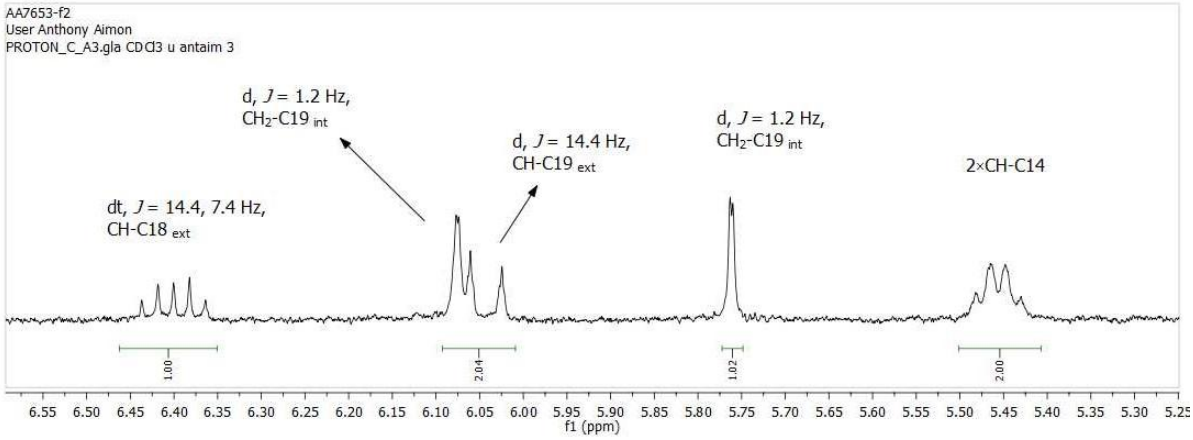
To a solution of terminal alkyne **(+)-378** (11.6 mg, 0.0192 mmol) in THF (1 mL) at rt was added $Pd(PPh_3)_4$ (1.2 mg, 1.0 µmol, 0.054 equiv) and Bu_3SnH (10 µL, 0.038 mmol, 2.0 equiv) dropwise. The mixture was stirred at rt for 30 min and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was diluted with Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL) and the organic extracts were combined, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE—Et_2O, 95:5 to 9:1) to give an inseparable mixture (13.0 mg) that was directly used in the next step without further characterisation.

To a solution of the mixture (13.0 mg) in CH_2Cl_2 (1 mL) at 0 °C was added I_2 (10.2 mg, 0.0402 mmol, 2.09 equiv). The mixture was stirred for 20 min and the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (5 mL). The mixture was then diluted with CH_2Cl_2 (10 mL) and stirred 10 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 55:45) to give the corresponding vinylic iodides **381** and **382** (1.3 mg, 9%) as an inseparable mixture (1:1).

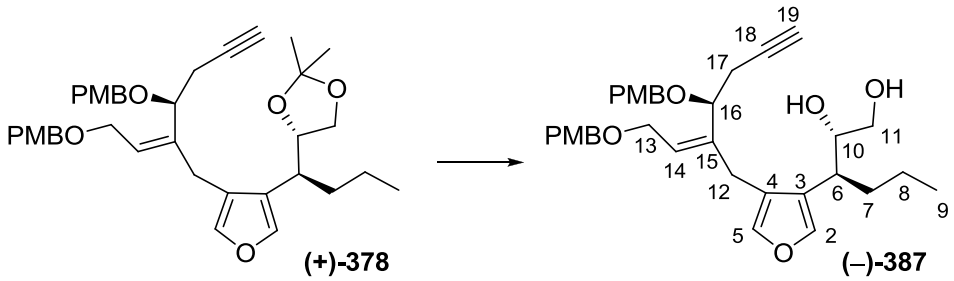
$C_{37}H_{47}IO_7$ **Molecular weight: 730.67 g·mol^{-1}**

R_f = 0.36 (PE—Et_2O, 7:3);

^{1}H NMR of the crude product showing the alkenyl regions for the internal—external ratio determination.



(2*S*,3*S*)-3-(4-{(2*Z*,3*S*)-3-(4-Methoxyphenylmethoxy)-2-[2-(4-methoxyphenylmethoxy)ethylidene]hex-5-yn-1-yl}furan-3-yl)hexane-1,2-diol ((−)-387)



To a solution of terminal alkyne **(+)-378** (95.7 mg, 0.159 mmol) in MeOH (1.6 mL) was added *p*-TSA (2.8 mg, 15 µmol, 0.093 equiv) at rt and the mixture was stirred for 15 h. Further *p*-TSA (10 mg, 52 µmol) was added and the mixture was stirred for 8 h at rt. After addition of K_2CO_3 (20 mg, 0.14 mmol), the mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (PE—Et_2O, 4:6 to 3:7) to afford the diol **(−)-387** (85.0 mg, 95%) as a colourless oil.

$C_{34}H_{42}O_7$ **Molecular weight: 562.69 g·mol^{-1}**

R_f = 0.26 (PE—Et_2O, 2:8);

$[\alpha]_D^{26}$ −11.5 (c = 1.00, $CHCl_3$);

IR ν_{max} 3442, 3292, 2998, 2955, 2870, 2358, 1513, 1464 cm^{-1};

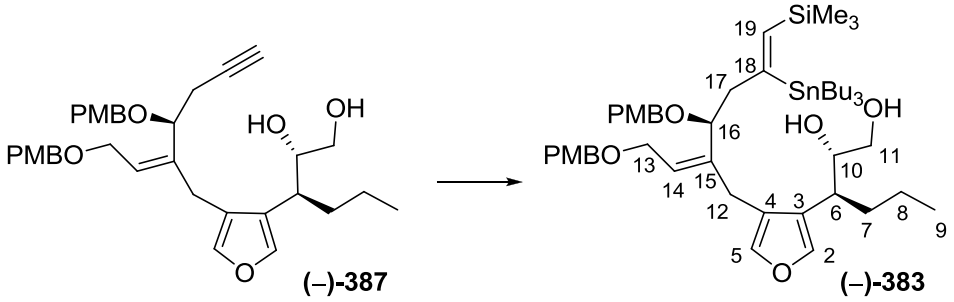
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (1H, d, *J* = 1.4 Hz, CH-C2), 7.26—7.21 (5H, m, *J* = 8.8 Hz, CH-C5, 4×CH-PMB), 6.87 (2H, d, *J* = 8.7 Hz, CH-PMB), 6.86 (2H, d, *J* = 8.8 Hz, CH-PMB), 5.50 (1H, dd, *J* = 8.2, 5.2 Hz, CH-C14), 4.49 (1H, d, *J* = 11.6 Hz, CH_2-PMB), 4.41 (1H, d, *J* = 11.4 Hz, CH_2-PMB), 4.38 (1H, d, *J* = 11.4 Hz, CH_2-PMB), 4.36 (1H, dd, *J* = 8.1, 6.5 Hz, CH-C16), 4.27 (1H, d, *J* = 11.6 Hz, CH_2-PMB), 4.12 (1H, dd, *J* = 11.8, 8.2 Hz, CH_2-C13), 3.92 (1H, dd, *J* = 11.8, 5.2 Hz, CH_2-C13), 3.80 (3H, s, CH_3-PMB), 3.79 (3H, s, CH_3-PMB), 3.77-3.73 (1H, m, CH-C10), 3.57—3.50 (1H, m, CH_2-C11), 3.41—3.33 (1H, m, CH_2-C11), 3.20 (1H, d, *J* = 17.4 Hz, CH_2-C12), 3.15 (1H, d, *J* = 17.4 Hz, CH_2-C12), 2.65

(1H, dt, *J* = 10.1, 5.1 Hz, CH-C6), 2.60 (1H, ddd, *J* = 16.7, 6.5, 2.6 Hz, CH_2-C17), 2.47 (1H, ddd, *J* = 16.7, 8.1, 2.6 Hz, CH_2-C17), 2.31 (1H, t, *J* = 8.6 Hz, OH), 2.24 (1H, d, *J* = 4.5 Hz, OH), 1.96 (1H, t, *J* = 2.6 Hz, CH-C19), 1.63—1.54 (1H, m, CH_2-C7), 1.49—1.41 (1H, m, CH_2-C7), 1.28—1.17 (2H, m, CH_2-C8), 0.83 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4 (C-PMB), 159.4 (C-PMB), 141.4 (CH-C5), 140.6 (CH-C2), 139.5 (C-C15), 130.1 (C-PMB), 130.0 (C-PMB), 129.6 (2×CH-PMB), 129.5 (2×CH-PMB), 127.8 (CH-C14), 125.1 (C-C3 or C-C4), 122.1 (C-C3 or C-C4), 114.0 (2×CH-PMB), 113.9 (2×CH-PMB), 77.4 (C-C18), 74.5 (CH-C16), 74.4 (CH-C10), 72.6 (CH_2-PMB), 70.4 (CH_2-PMB), 70.3 (CH-C19), 65.7 (CH_2-C13), 64.7 (CH_2-C11), 55.4 (CH_3-PMB), 55.4 (CH_3-PMB), 37.5 (CH-C6), 35.2 (CH_2-C7), 24.4 (CH_2-C12), 24.2 (CH_2-C17), 20.8 (CH_2-C8), 14.4 (CH_3-C9);

HRMS (ESI) calculated for $C_{34}H_{42}NaO_7$ $[M+Na]^+$: 585.2823, found 585.2808, Δ +2.5 ppm.

(2*S*,3*S*)-3-(4-{(2*Z*,3*S*,5*Z*)-3-(4-Methoxyphenylmethoxy)-2-[2-(4-methoxyphenylmethoxy)ethylidene]-5-tributylstannyl-6-trimethylsilyl-hex-5-en-1-yl}furan-3-yl)hexane-1,2-diol ((−)-383)



To a solution of alkyne **(−)-387** (89.3 mg, 0.159 mmol) in THF (0.5 mL) were added $Pd(PPh_3)_4$ (18 mg, 0.016 mmol, 0.10 equiv) and previously prepared silyl-stannane **272** (80 µL, 0.23 mmol, 1.4 equiv). The mixture was heated to reflux and stirred for 1 h. Further $Pd(PPh_3)_4$ (9.4 mg, 8.1 µmol, 0.051 equiv) and stannane **272** (20 µL, 0.056 mmol, 0.35 equiv) were added to the mixture. The mixture was stirred for 1.5 h, cooled to rt and the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The mixture was diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 10 mL) and the organic extracts were combined, washed with brine (20 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 5:5 to 4:6) affording the corresponding stannane **(−)-383** (97.3 mg, 66%) as a pale yellow oil.

$C_{49}H_{78}O_7SiSn$ **Molecular weight: 925.93 g·mol^{-1}**

R_f = 0.38 (PE—Et_2O, 3:7);

$[\alpha]_D^{26}$ −18.0 (c = 1.00, $CHCl_3$);

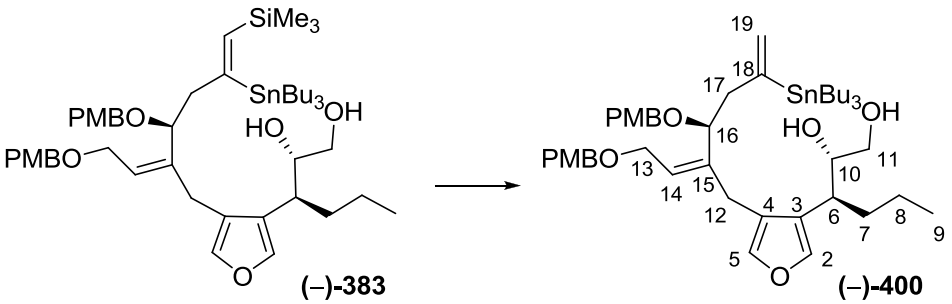
IR ν_{max} 3439, 2955, 2929, 2924, 2869, 2854, 2361, 2329, 1612, 1513, 1464 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (1H, d, *J* = 1.4 Hz, CH-C2), 7.24—7.18 (1H, m, CH-C5), 7.23 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 7.20 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 6.86 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 6.84 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 6.38 (1H, s, CH-C19), 5.36 (1H, dd, *J* = 8.8, 4.7 Hz, CH-C14), 4.43 (1H, d, *J* = 11.5 Hz, CH_2-PMB), 4.41 (1H, d, *J* = 11.3 Hz, CH_2-PMB), 4.38 (1H, d, *J* = 11.3 Hz, CH_2-PMB), 4.16 (1H, d, *J* = 11.5 Hz, CH_2-PMB), 4.14 (1H, dd, *J* = 7.6, 4.9 Hz, CH-C16), 4.08 (1H, dd, *J* = 11.2, 8.8 Hz, CH_2-C13), 3.83 (1H, dd, *J* = 11.2, 4.7 Hz, CH_2-C13), 3.80 (3H, s, CH_3-PMB), 3.79 (3H, s, CH_3-PMB), 3.79—3.72 (1H, m, CH-C10), 3.55 (1H, ddd, *J* = 10.6, 6.1, 4.4, CH_2-C11), 3.37 (1H, ddd, *J* = 10.6, 6.6, 4.9, CH_2-C11), 3.21 (1H, d, *J* = 17.5 Hz, CH_2-C12), 3.15 (1H, d, *J* = 17.5 Hz, CH_2-C12), 2.74 (1H, dd, *J* = 13.1, 7.6 Hz, CH_2-C17), 2.63 (1H, dt, *J* = 10.1, 5.1 Hz, CH-C6), 2.38 (1H, dd, *J* = 13.1, 4.9 Hz, CH_2-C17), 2.27 (1H, dd, *J* = 6.6, 4.4 Hz, OH), 2.17 (1H, d, *J* = 5.1 Hz, OH), 1.64—1.54 (1H, m, CH_2-C7), 1.51—1.38 (7H, m, CH_2-C7, 3×CH_2-$SnBu_3$), 1.29 (6H, qt, *J* = 7.3, 7.3 Hz, 3×CH_2-$SnBu_3$), 1.34—1.16 (2H, m, CH_2-C8), 0.93—0.84 (6H, m, 3×CH_2-$SnBu_3$), 0.88 (9H, t, *J* = 7.3 Hz, 3×CH_3-$SnBu_3$), 0.82 (3H, t, *J* = 7.3 Hz, CH_3-C9), 0.09 (9H, s, 3×CH_3-$SiMe_3$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9 (C-C18), 159.5 (C-PMB), 159.2 (C-PMB), 147.7 (CH-C19), 141.2 (CH-C5), 140.9 (C-C15), 140.5 (CH-C2), 130.6 (C-PMB), 129.9 (C-PMB), 129.6 (2×CH-PMB), 129.4 (2×CH-PMB), 126.0 (CH-C14), 125.3 (C-C3 or C-C4), 122.3 (C-C3 or C-C4), 114.0 (2×CH-PMB), 113.8 (2×CH-PMB), 76.7 (CH-C16), 74.5 (CH-C10), 72.8 (CH_2-PMB), 70.2 (CH_2-PMB), 66.1 (CH_2-C13), 64.6 (CH_2-C11), 55.4 (2×CH_3-PMB), 50.3 (CH_2-C17), 37.6 (CH-C6), 35.6 (CH_2-C7), 29.3 (3×CH_2-$SnBu_3$), 27.7 (3×CH_2-$SnBu_3$), 24.9 (CH_2-C12), 20.9 (CH_2-C8), 14.4 (CH_3-C9), 13.8 (3×CH_3-$SnBu_3$), 11.6 (3×CH_2-$SnBu_3$), 0.3 (3×CH_3-$SiMe_3$);

HRMS (ESI) calculated for $C_{49}H_{78}NaO_7Si^{120}Sn$ $[M+Na]^+$: 949.4395, found 949.4431, Δ +3.8 ppm.

(2*S*,3*S*)-3-(4-{(2*Z*,3*S*)-3-(4-Methoxyphenylmethoxy)-2-[2-(4-methoxyphenylmethoxy)ethylidene]-5-tributylstannylhex-5-en-1-yl}furan-3-yl)hexane-1,2-diol ((−)-400)



Diol **(−)-383** (42.8 mg, 0.0462 mmol) was diluted in DMSO (0.93 mL). TBAF (165 µL of a 1 M solution in THF, 165 µmol, 3.59 equiv) was added and the mixture was heated to reflux and stirred for 80 min at this temperature. The orange brown solution was cooled to rt and diluted with water (5 mL) and Et_2O (10 ml). The phases were separated, the aqueous phase was extracted with Et_2O (4 × 10 mL). The organic extracts were combined and dried over $MgSO_4$. After filtration and concentration *in vacuo*, the crude product was purified by flash column chromatography (PE—Et_2O, 5:5) affording stannane **(−)-400** (30.4 mg, 77%) as a pale yellow oil.

$C_{46}H_{70}O_7Sn$ **Molecular weight: 853.75 g·mol^{-1}**

R_f = 0.42 (PE—Et_2O, 1:9);

$[\alpha]_D^{23}$ −13.0 (c = 0.99, $CHCl_3$);

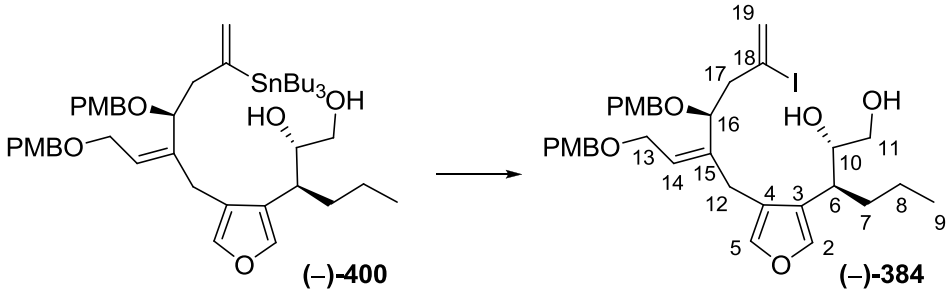
IR ν_{max} 3423, 2955, 2926, 2870, 2854, 1612, 1587, 1514, 1464 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (1H, d, *J* = 1.3 Hz, CH-C2), 7.23 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 7.24—7.20 (1H, m, CH-C5), 7.21 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 6.86 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 6.84 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 5.70 (1H, d, *J* = 2.5 Hz, CH-C19), 5.37 (1H, dd, *J* = 8.5, 5.0 Hz, CH-C14), 5.21 (1H, d, *J* = 2.5 Hz, CH-C19), 4.43 (1H, d, *J* = 11.6 Hz, CH_2-PMB), 4.41 (1H, d, *J* = 11.6 Hz, CH_2-PMB), 4.39 (1H, d, *J* = 11.6 Hz, CH_2-PMB), 4.22—4.16 (1H, m, CH-C16), 4.18 (1H, d, *J* = 11.6 Hz, CH_2-PMB), 4.12 (1H, dd, *J* = 11.3, 8.5 Hz, CH_2-C13), 3.87 (1H, dd, *J* = 11.3, 5.0 Hz, CH_2-C13), 3.80 (3H, s, CH_3-PMB), 3.79 (3H, s, CH_3-PMB), 3.75 (1H, dq, *J* = 6.3, 5.2 Hz, CH-C10), 3.53 (1H, ddd, *J* = 10.7, 5.2, 5.2, CH_2-C11), 3.36 (1H, ddd, *J* = 10.7, 6.3, 4.1, CH_2-C11), 3.19 (1H, d, *J* = 17.7 Hz, CH_2-C12), 3.14 (1H, d, *J* = 17.7 Hz, CH_2-C12), 2.68 (1H, dd, *J* = 14.0, 8.3 Hz, CH_2-C17), 2.61 (1H, dt, *J* = 10.3, 5.2 Hz, CH-C6), 2.36 (1H, dd, *J* = 14.0, 4.6 Hz, CH_2-C17), 2.24 (1H, dd, *J* = 5.2, 4.1 Hz, OH), 2.15 (1H, d, *J* = 5.2 Hz, OH), 1.62—1.52 (1H, m, CH_2-C7), 1.51—1.37 (7H, m, CH_2-C7, 3×CH_2-$SnBu_3$), 1.28 (6H, qt, *J* = 7.2, 7.2 Hz, 3×CH_2-$SnBu_3$), 1.24—1.13 (2H, m, CH_2-C8), 0.87 (9H, t, *J* = 7.3 Hz, 3×CH_3-$SnBu_3$), 0.85—0.79 (9H, m, 3×CH_2-$SnBu_3$, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5 (C-PMB), 159.2 (C-PMB), 151.1 (C-C18), 141.4 (C-C15), 141.2 (CH-C5), 140.5 (CH-C2), 130.6 (C-PMB), 129.9 (C-PMB), 129.6 (2×CH-PMB), 129.3 (2×CH-PMB), 128.2 (CH_2-C19), 125.9 (CH-C14), 125.3 (C-C3 or C-C4), 122.2 (C-C3 or C-C4), 114.0 (2×CH-PMB), 113.8 (2×CH-PMB), 76.7 (CH-C16), 74.5 (CH-C10), 72.8 (CH_2-PMB), 70.2 (CH_2-PMB), 65.9 (CH_2-C13), 64.7 (CH_2-C11), 55.4 (CH_3-PMB), 55.4 (CH_3-PMB), 45.5 (CH_2-C17), 37.6 (CH-C6), 35.5 (CH_2-C7), 29.2 (3×CH_2-$SnBu_3$), 27.6 (3×CH_2-$SnBu_3$), 25.0 (CH_2-C12), 20.8 (CH_2-C8), 14.4 (CH_3-C9), 13.9 (3×CH_3-$SnBu_3$), 9.8 (3×CH_2-$SnBu_3$);

HRMS (ESI) calculated for $C_{46}H_{70}NaO_7{}^{116}Sn$ $[M+Na]^+$: 873.4031, found 873.3991, Δ +4.6 ppm.

(2*S*,3*S*)-3-(4-{(2*Z*,3*S*)-5-Iodo-3-(4-methoxyphenylmethoxy)-2-[2-(4-methoxyphenylmethoxy)ethylidene]hex-5-en-1-yl}furan-3-yl)hexane-1,2-diol ((−)-384)



Stannane **(−)-400** (19.1 mg, 0.0224 mmol) was diluted in CH_2Cl_2 (1 mL). The solution was cooled to −78 °C before the addition of NIS (9.2 mg, 0.036 mmol, 1.8 equiv). The mixture was stirred for 40 min and the reaction was quenched with aqueous saturated $Na_2S_2O_3$ (3 mL). The mixture was diluted with CH_2Cl_2 (5 mL) and warmed to rt. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 5:5) affording 16.6 mg of vinylic iodide **(−)-384** (14.9 mg, 96% based on ^{1}H NMR) as an inseparable mixture with succinimide formed during the reaction.

$C_{34}H_{43}IO_7$ **Molecular weight: 690.61 g·mol^{-1}**

R_f = 0.37 (PE—Et_2O, 1:9);

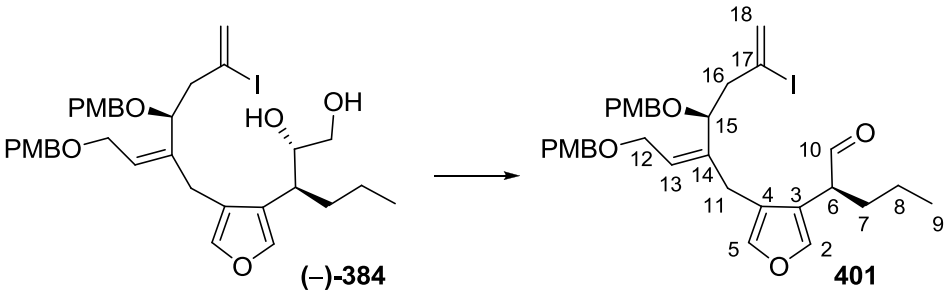
$[\alpha]_D^{20}$ −9.6 (c = 0.75, $CHCl_3$);

IR ν_{max} 3450, 2953, 2933, 2864, 2359, 1776, 1710, 1612, 1585, 1514, 1464 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (1H, d, *J* = 1.2 Hz, CH-C2), 7.25 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 7.23—7.21 (1H, m, CH-C5), 7.22 (2H, d, *J* = 8.6 Hz, 2×CH-PMB), 6.86 (4H, d, *J* = 8.6 Hz, 4×CH-PMB), 6.08 (1H, s, CH-C19), 5.76 (1H, s, CH-C19), 5.46 (1H, dd, *J* = 8.3, 5.5 Hz, CH-C14), 4.47 (1H, dd, *J* = 8.5, 4.5 Hz, CH-C16), 4.46 (1H, d, *J* = 11.4 Hz,

CH_2-PMB), 4.46—4.39 (2H, m, CH_2-PMB), 4.27 (1H, d, *J* = 11.4 Hz, CH_2-PMB), 4.16 (1H, dd, *J* = 11.4, 8.3 Hz, CH_2-C13), 3.95 (1H, dd, *J* = 11.4, 5.5 Hz, CH_2-C13), 3.81 (3H, s, CH_3-PMB), 3.79 (3H, s, CH_3-PMB), 3.73 (1H, app dq, *J* = 6.2, 5.2 Hz, CH-C10), 3.51 (1H, ddd, *J* = 11.0, 6.2, 4.5, CH_2-C11), 3.37 (1H, ddd, *J* = 11.0, 6.4, 5.2, CH_2-C11), 3.20 (1H, d, *J* = 17.3 Hz, CH_2-C12), 3.10 (1H, d, *J* = 17.3 Hz, CH_2-C12), 2.77 (1H, dd, *J* = 14.5, 8.5 Hz, CH_2-C17), 2.62 (1H, dt, *J* = 10.1, 5.2 Hz, CH-C6), 2.47 (1H, dd, *J* = 14.5, 4.5 Hz, CH_2-C17), 2.29—2.26 (1H, m, OH), 2.22 (1H, d, *J* = 5.2 Hz, OH), 1.61—1.53 (1H, m, CH_2-C7), 1.45—1.37 (1H, m, CH_2-C7), 1.27—1.15 (2H, m, CH_2-C8), 0.82 (3H, t, *J* = 7.3 Hz, CH_3-C9);
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5 (C-PMB), 159.4 (C-PMB), 141.3 (CH-C5), 140.6 (CH-C2), 140.6 (C-C15),130.2 (C-PMB), 129.9 (C-PMB), 129.8 (2×CH-PMB), 129.6 (2×CH-PMB), 128.4 (CH_2-C19), 126.8 (CH-C14), 125.2 (C-C3 or C-C4), 122.2 (C-C3 or C-C4), 114.0 (2×CH-PMB), 113.9 (2×CH-PMB), 107.2 (C-C18), 75.1 (CH-C16), 74.5 (CH-C10), 72.9 (CH_2-PMB), 70.8 (CH_2-PMB), 65.7 (CH_2-C13), 64.5 (CH_2-C11), 55.4 (CH_3-PMB), 55.4 (CH_3-PMB), 50.1 (CH_2-C17), 37.5 (CH-C6), 35.4 (CH_2-C7), 25.3 (CH_2-C12), 20.9 (CH_2-C8), 14.4 (CH_3-C9);
HRMS (ESI) calculated for $C_{34}H_{43}INaO_7$ $[M+Na]^+$: 713.1946, found 713.1936, Δ +1.4 ppm.

(2*S*)-2-(4-{(2*Z*,3*S*)-5-Iodo-3-(4-methoxyphenylmethoxy)-2-[2-(4-methoxyphenylmethoxy)ethylidene]hex-5-en-1-yl}furan-3-yl)pentanal (401)



To a solution of diol **(−)-384** (14.9 mg, 0.0216 mmol) in MeOH (1 mL) and water (0.5 mL) at 0 °C was added $NaIO_4$ (51.2 mg, 0.239 mmol, 11.1 equiv). The mixture was warmed to rt and stirred for 50 min. The reaction was quenched with water (2 mL) and the mixture was diluted with Et_2O (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic extracts were combined, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 70:30) affording aldehyde **401** (10.4 mg, 73%) as a colourless oil.

$C_{33}H_{39}IO_6$ **Molecular weight: 658.56 g·mol^{-1}**

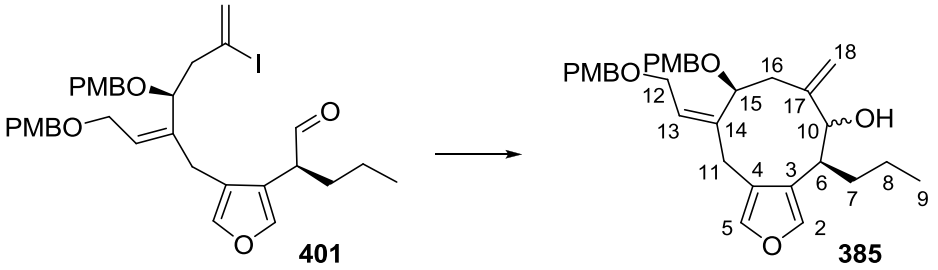
R_f = 0.57 (PE—Et_2O, 6:4);

IR ν_{max} 2957, 2926, 2856, 1724, 1612, 1514, 1464 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (1H, d, *J* = 2.9 Hz, HCO-C10), 7.30 (1H, d, *J* = 1.2 Hz, CH-C2), 7.24 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 7.26—7.21 (1H, m, CH-C5), 7.23 (2H, d, *J* = 8.7 Hz, 2×CH-PMB), 6.86 (4H, d, *J* = 8.7 Hz, 4×CH-PMB), 6.11 (1H, d, *J* = 1.2 Hz, CH-C18), 5.77 (1H, d, *J* = 1.2 Hz, CH-C18), 5.40 (1H, dd, *J* = 7.3, 5.7 Hz, CH-C13), 4.46 (1H, dd, *J* = 8.1, 4.7 Hz, CH-C15), 4.44 (1H, d, *J* = 11.4 Hz, CH_2-PMB), 4.43—4.39 (2H, br s, CH_2-PMB), 4.26 (1H, d, *J* = 11.4 Hz, CH_2-PMB), 4.13 (1H, dd, *J* = 12.2, 7.3 Hz, CH_2-C12), 4.01 (1H, dd, *J* = 12.2, 5.7 Hz, CH_2-C12), 3.80 (3H, s, CH_3-PMB), 3.79 (3H, s, CH_3-PMB), 3.25 (1H, app td, *J* = 7.3, 2.9 Hz, CH-C6), 3.18 (1H, d, *J* = 17.3 Hz, CH_2-C11), 3.07 (1H, d, *J* = 17.3 Hz, CH_2-C11), 2.76 (1H, dd, *J* = 14.7, 8.1 Hz, CH_2-C16), 2.48 (1H, dd, *J* = 14.7, 4.7 Hz, CH_2-C16), 1.92—1.81 (1H, m, CH_2-C7), 1.68—1.57 (1H, m, CH_2-C7), 1.35—1.25 (2H, m, CH_2-C8), 0.88 (3H, t, *J* = 7.3 Hz, CH_3-C9);

HRMS (ESI) calculated for $C_{33}H_{39}INaO_6$ $[M+Na]^+$: 681.1684, found 681.1670, Δ +2.0 ppm.

(4*S*,8*S*,9*Z*)-8-(4-Methoxyphenylmethoxy)-9-[2-(4-methoxyphenylmethoxy)ethylidene]-6-methylidene-4-propyl-4*H*,5*H*,6*H*,7*H*,8*H*,9*H*,10*H*-cyclonona[c]furan-5-ol (385)



To a solution of $CrCl_2$ (23.2 mg, 0.190 mmol, 12.0 equiv) and $NiCl_2$ (0.6 mg, 0.05 μmol, 0.3 equiv) in degassed DMSO (three freeze-thaw cycles, 0.7 mL) was added a solution of aldehyde **401** (10.4 mg, 15.8 μmol) in degassed DMSO (three freeze-thaw cycles, 1.5 mL) at rt. The dark green mixture was stirred at 25 °C for 3 days. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and the mixture was diluted with EtOAc (10 mL). The biphasic mixture was stirred for 30 min, the phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (PE—Et_2O, 8:2 to 6:4) affording bicycle **385** in an inseparable 3:1 ratio of diastereoisomers along with an uncharacterised by-product (4.2 mg in total). From this mixture, **385** (2.0 mg, 24%) was isolated after several purifications by flash column chromatography, with the same diastereoisomeric ratio.

$C_{33}H_{40}O_6$ **Molecular weight: 532.67 g·mol^{-1}**

R_f = 0.29 (PE—Et_2O, 5:5);

IR ν_{max} 3419, 2957, 2932, 2868, 2732, 2333, 1764, 1724, 1612, 1585, 1514, 1464 cm^{-1};

Major diastereoisomer

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27—7.21 (6H, m, CH-C2, CH-C5, 4×CH-PMB), 6.91—6.85 (4H, m, *J* = 8.8 Hz, 4×CH-PMB), 5.86 (1H, dd, *J* = 7.8, 4.6 Hz, CH-C13), 5.02 (1H, s, CH_2-C18), 4.75 (1H, s, CH_2-C18), 4.48 (1H, d, *J* = 11.7 Hz, CH_2-PMB), 4.44 (1H, d, *J* = 11.3 Hz, CH_2-PMB), 4.40 (1H, d, *J* = 11.3 Hz, CH_2-PMB), 4.35 (1H, dd, *J* = 10.6, 6.7 Hz, CH-C15), 4.21 (1H, d, *J* = 11.7 Hz, CH_2-PMB), 4.06 (1H, dd, *J* = 12.6, 7.8 Hz, CH_2-C12), 3.98 (1H, d, *J* = 9.5 Hz, CH-C10), 3.83 (1H, ddd, *J* = 12.6, 4.6, 1.3 Hz, CH_2-C12), 3.81 (6H, s, 2×CH_3-PMB), 3.75 (1H, d, *J* = 15.5 Hz, CH_2-C11), 3.11 (1H, d, *J* = 15.5 Hz, CH_2-C11), 3.05 (1H, dd, *J* = 9.1, 6.6 Hz, CH-C6), 2.26 (1H, dd, *J* = 13.5, 6.7 Hz, CH_2-C16), 2.00 (1H, dd, *J* = 13.5, 10.6 Hz, CH_2-C16), 1.75 (1H, d, *J* = 9.5 Hz, OH), 1.72—1.65 (1H, m, CH_2-C7), 1.63 (1H, dddd, *J* = 13.7, 7.5, 7.5, 6.6 Hz, CH_2-C7), 1.31 (2H, tq, *J* = 7.5, 7.3 Hz, CH_2-C8), 0.86 (3H, t, *J* = 7.3 Hz, CH_3-C9);

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4 (C-PMB), 159.3 (C-PMB), 146.8 (C-C14 or C-C17), 140.9 (CH-C2 or CH-C5), 140.3 (CH-C2 or CH-C5), 130.6 (CH-C13), 130.3 (C-PMB), 129.6 (C-PMB), 129.5 (2×CH-PMB), 129.2 (2×CH-PMB), 116.6 (CH_2-C18), 114.0 (2×CH-PMB), 113.9 (2×CH-PMB), 77.7 (CH-C10), 72.5 (CH_2-PMB), 69.8 (CH_2-PMB), 66.3 (CH_2-C12), 55.4 (2×CH_3-PMB), 38.7 (CH-C6), 36.6 (CH_2-C7), 20.8 (CH_2-C8),14.0 (CH_3-C9);

Carbon peaks missing:

- From HSQC: CH-C15 (under $CDCl_3$ peaks), CH_2-C16 (*ca* 33.5), CH_2-C11 (*ca* 29.5);
- C-C4, C-C3, C-C14 or C-C17;

HRMS (ESI) calculated for $C_{33}H_{40}NaO_6$ $[M+Na]^+$: 555.2717, found 555.2691, Δ +4.7 ppm.

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Appendices

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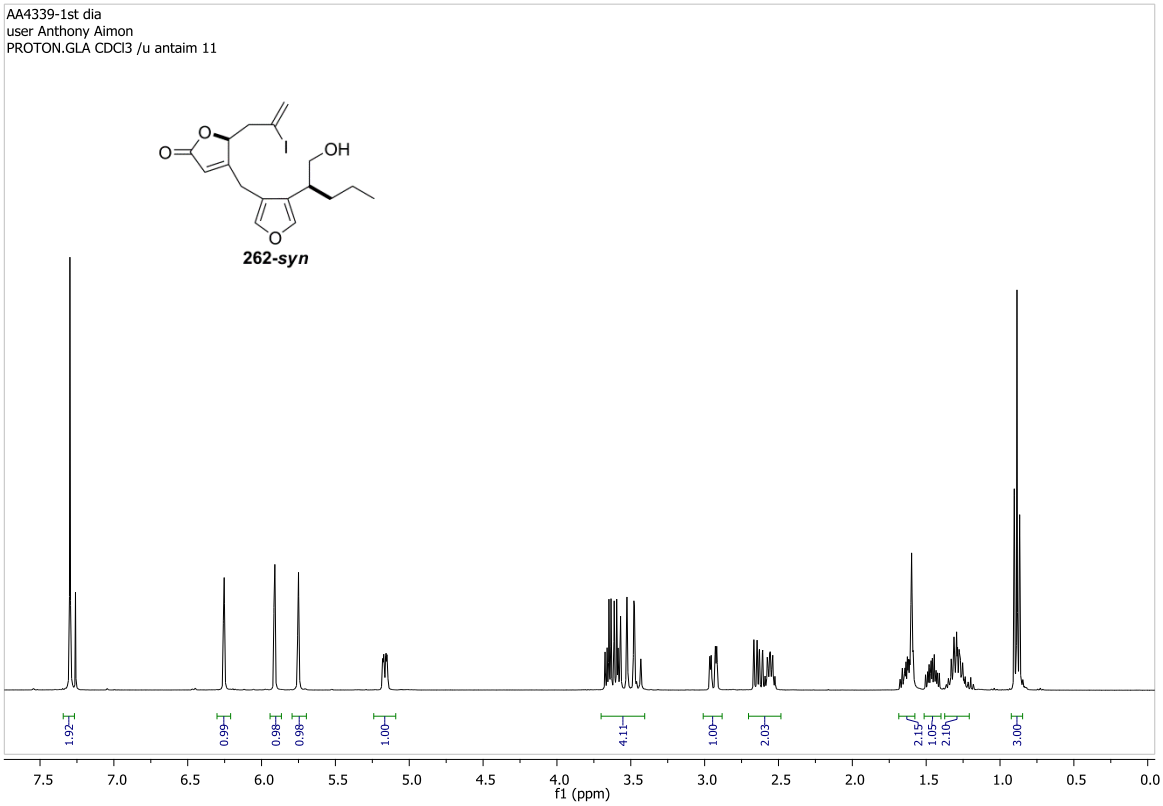
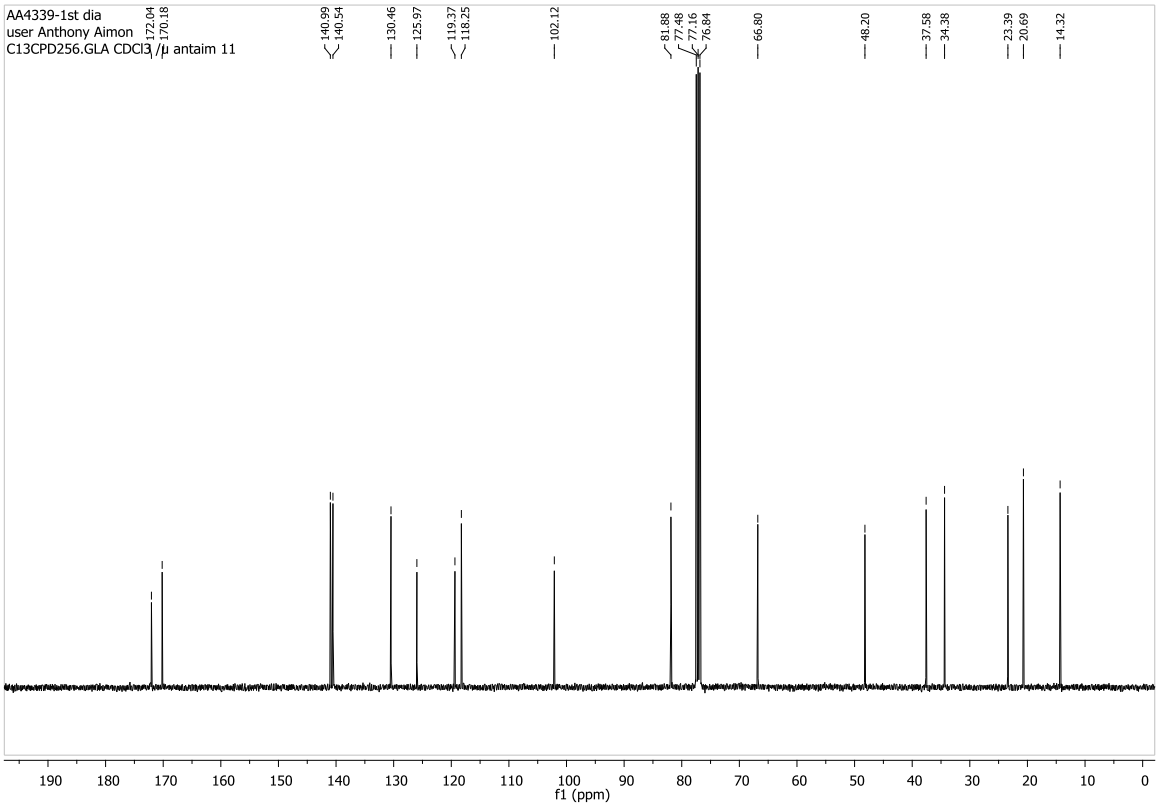
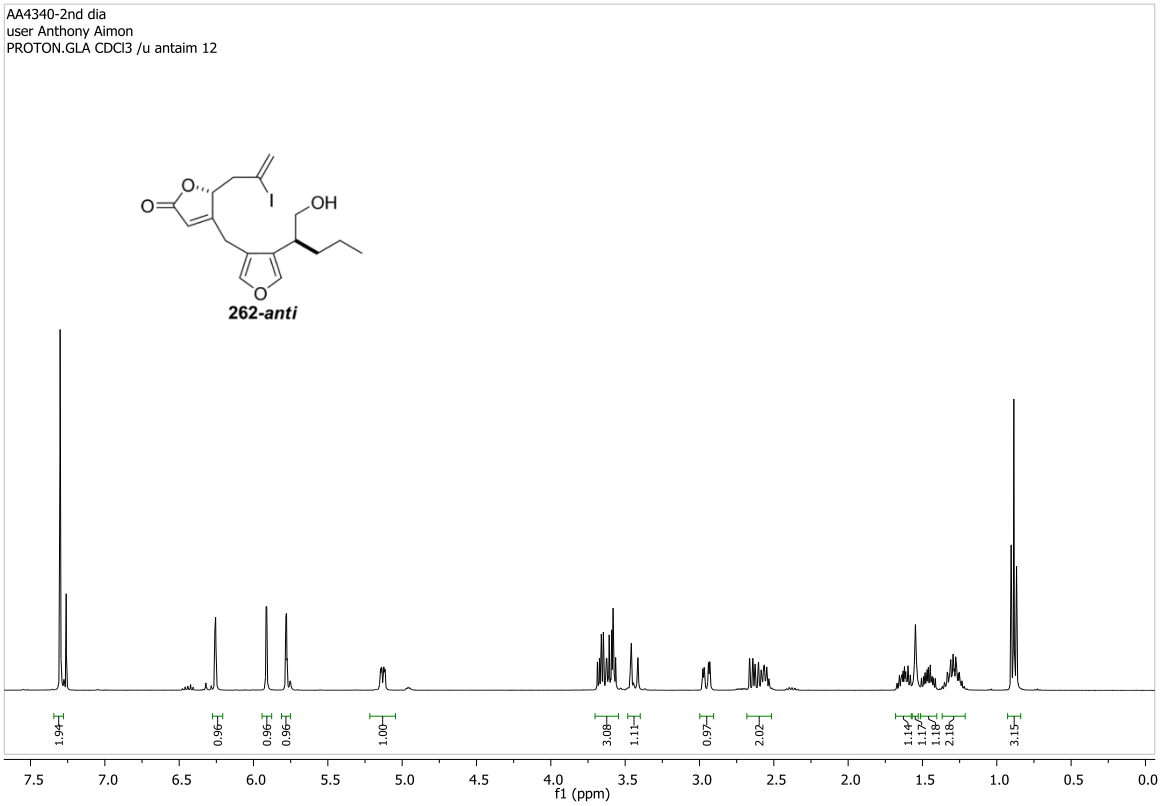
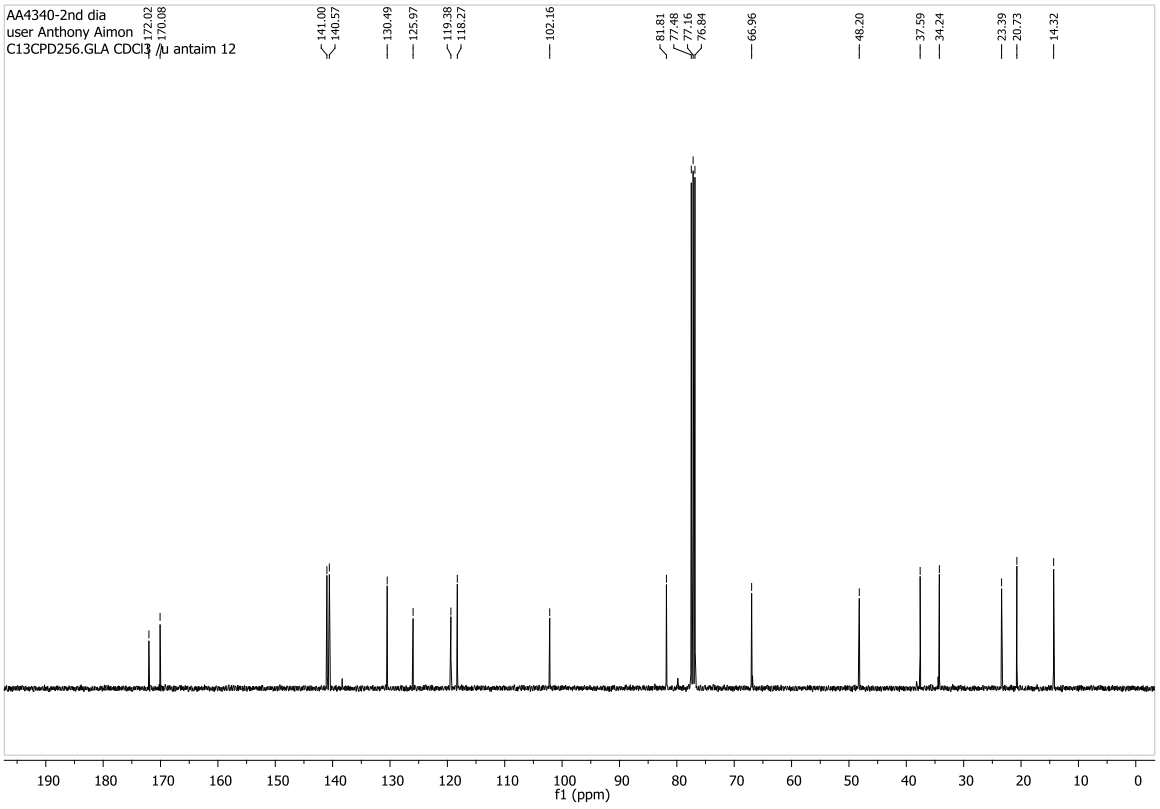
Appendix 1: ^{1}H and ^{13}C NMR of compound 262-syn



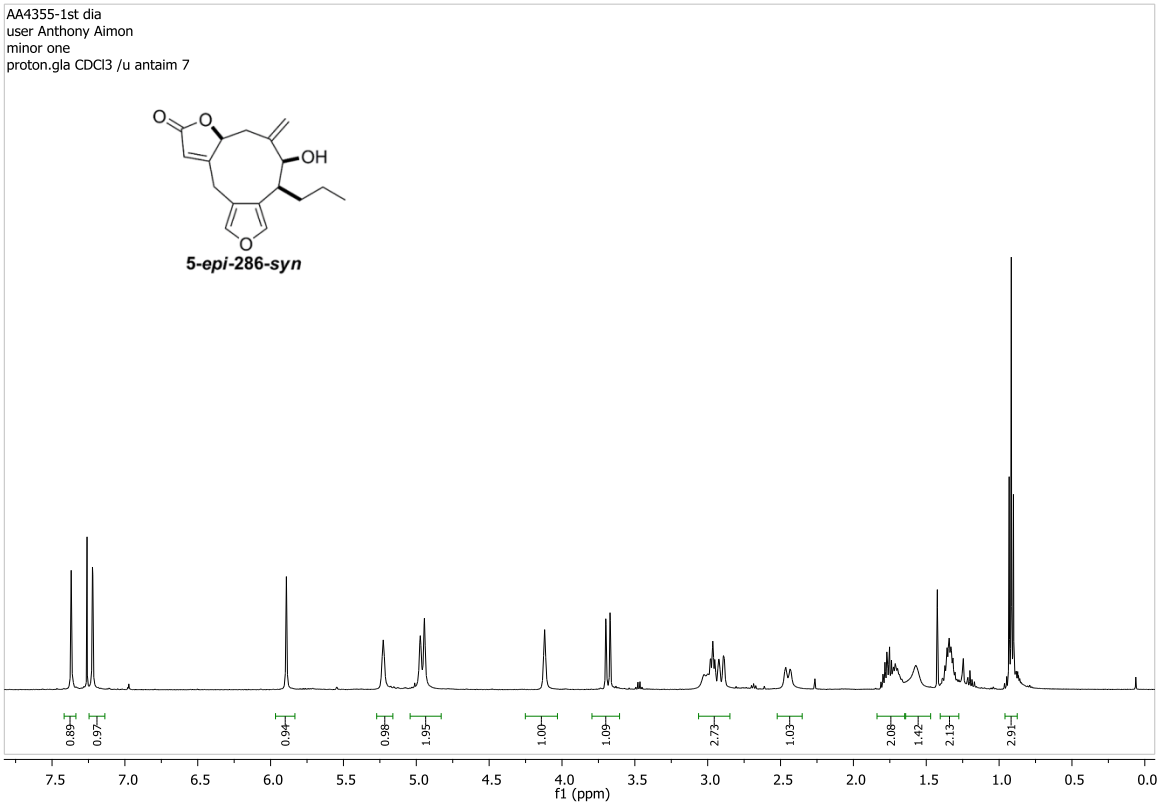


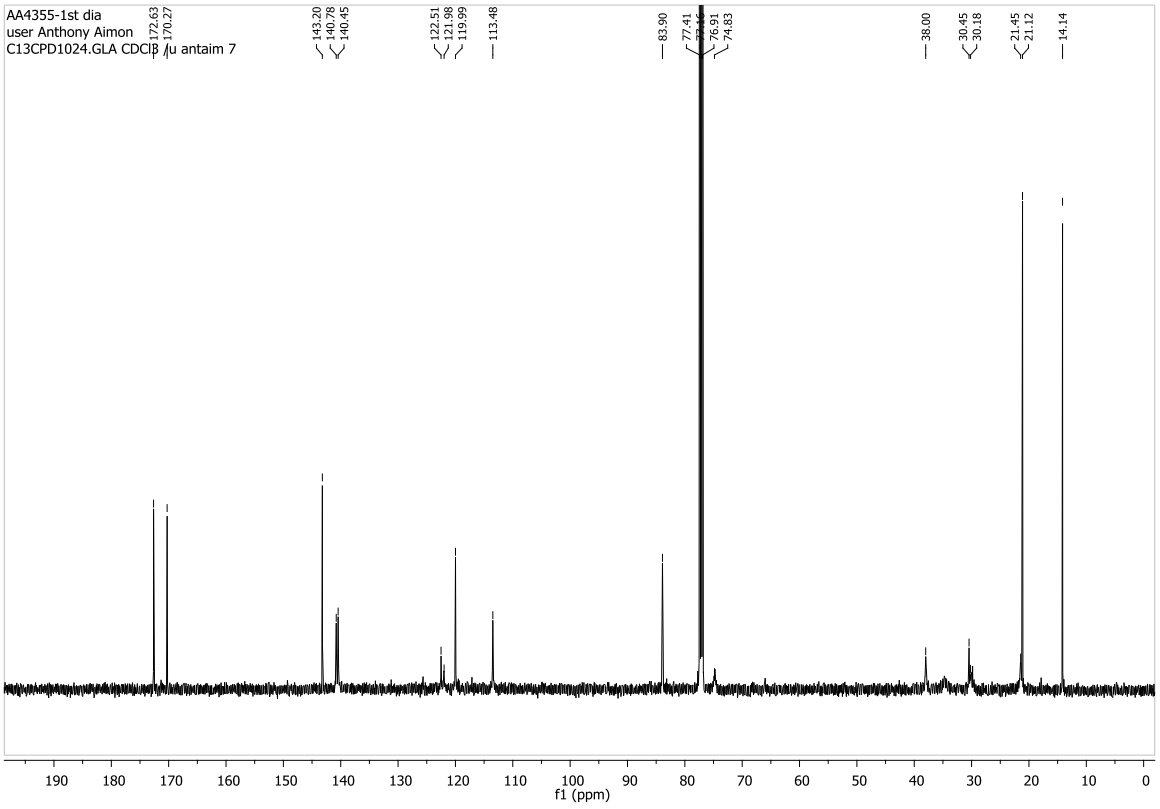
Appendix 2: ^{1}H and ^{13}C NMR of compound 262-anti



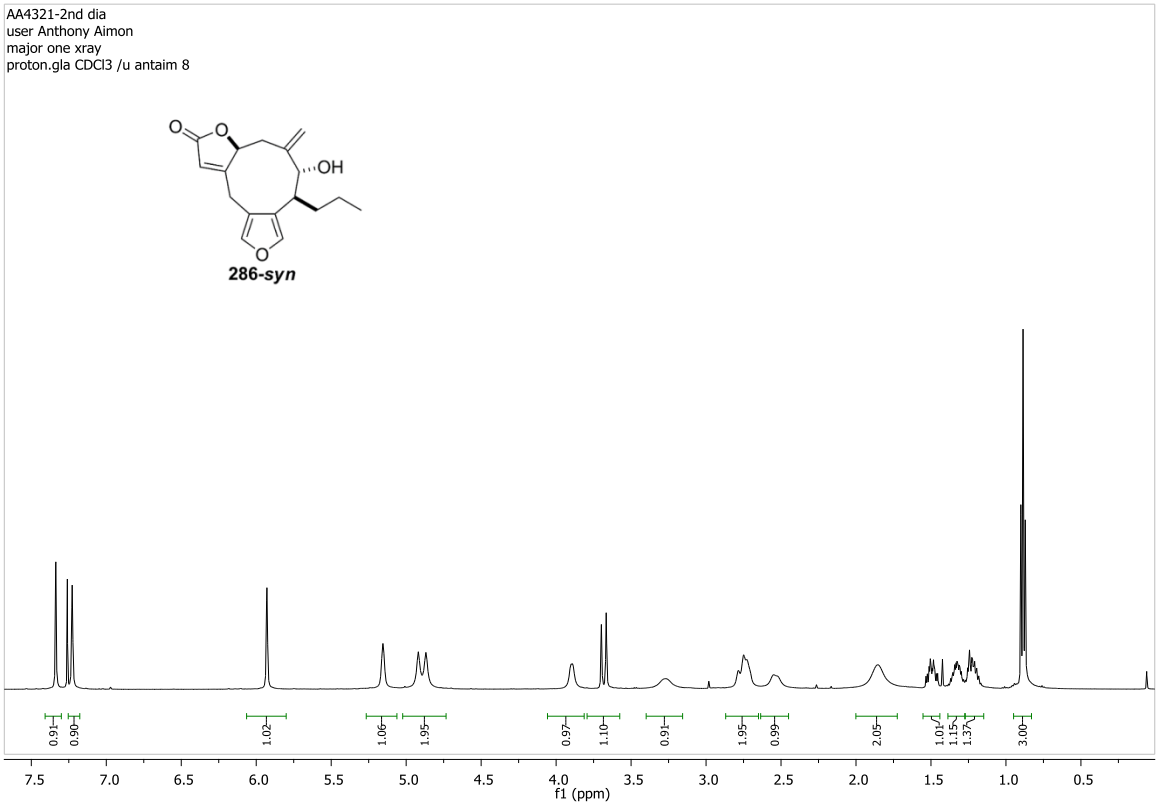


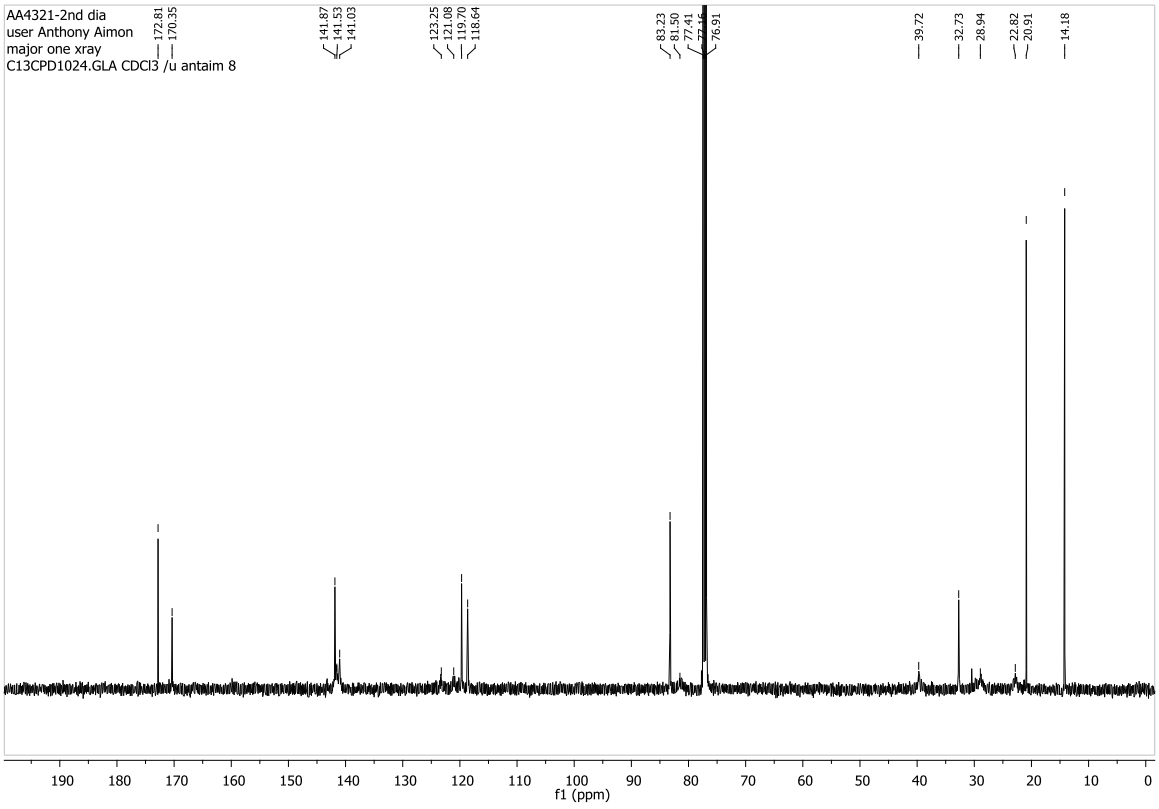
Appendix 3: ^{1}H and ^{13}C NMR of compound 5-epi-286-syn



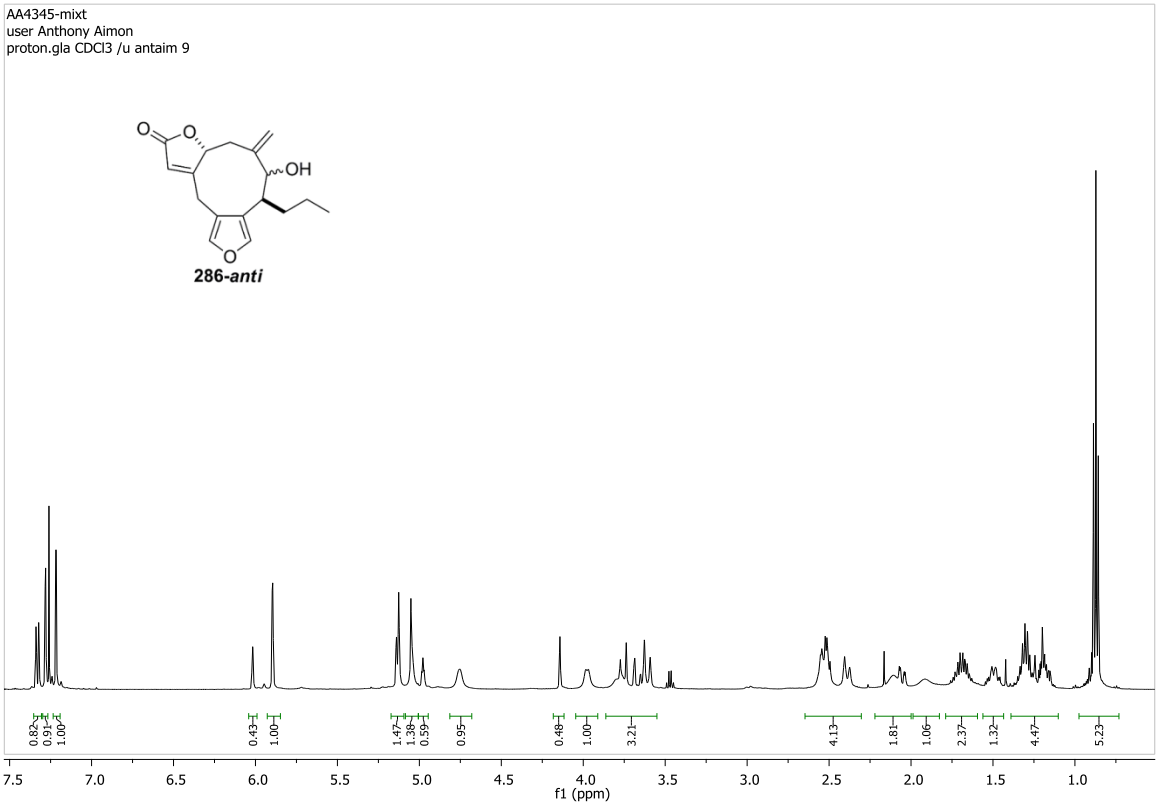


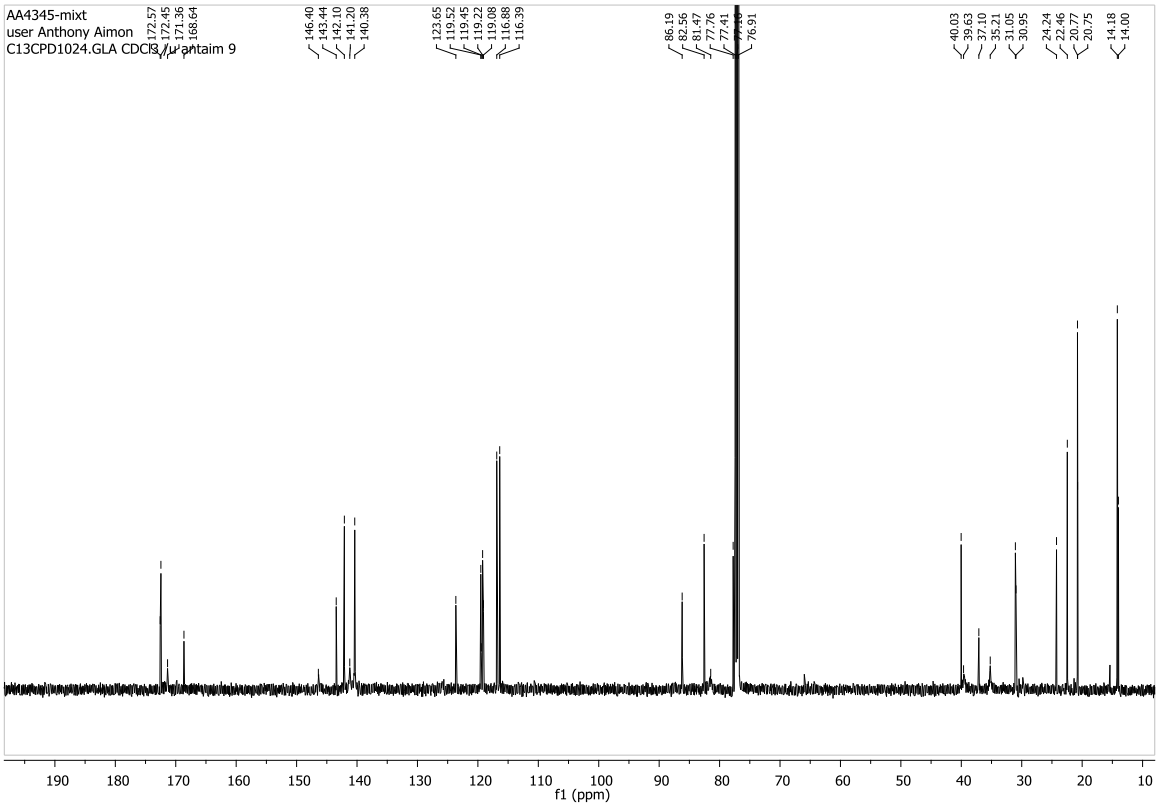
Appendix 4: ^{1}H and ^{13}C NMR of compound 286-syn



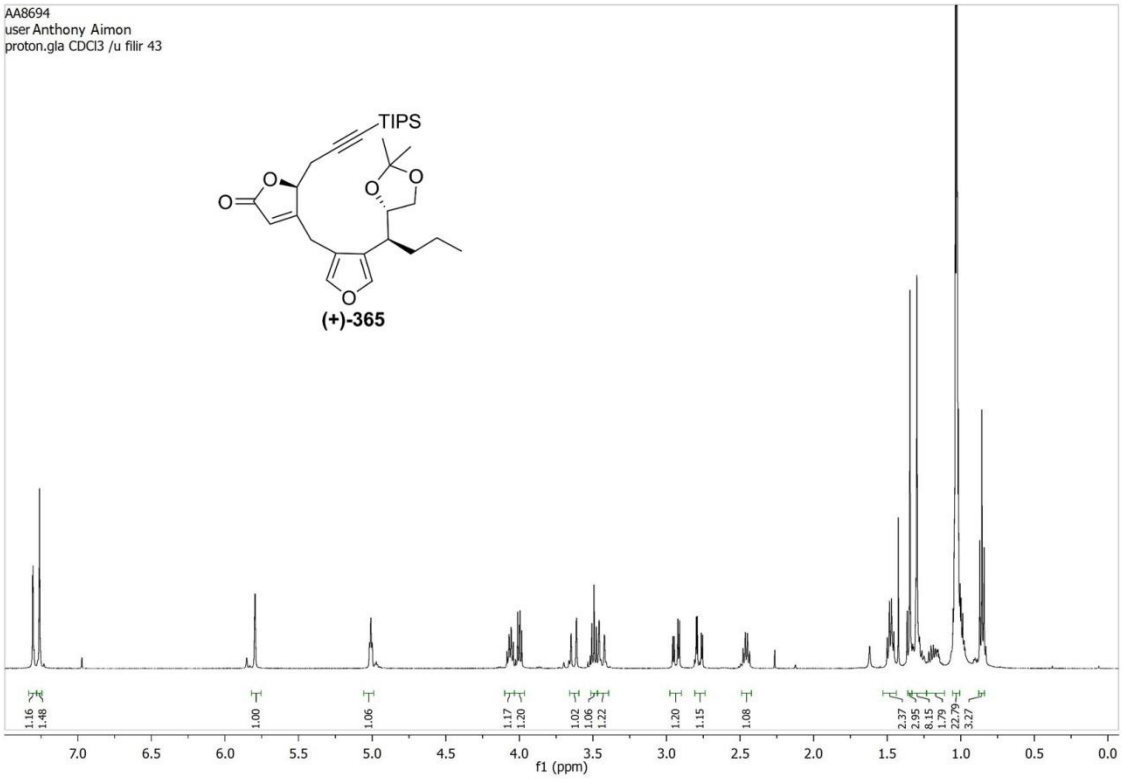


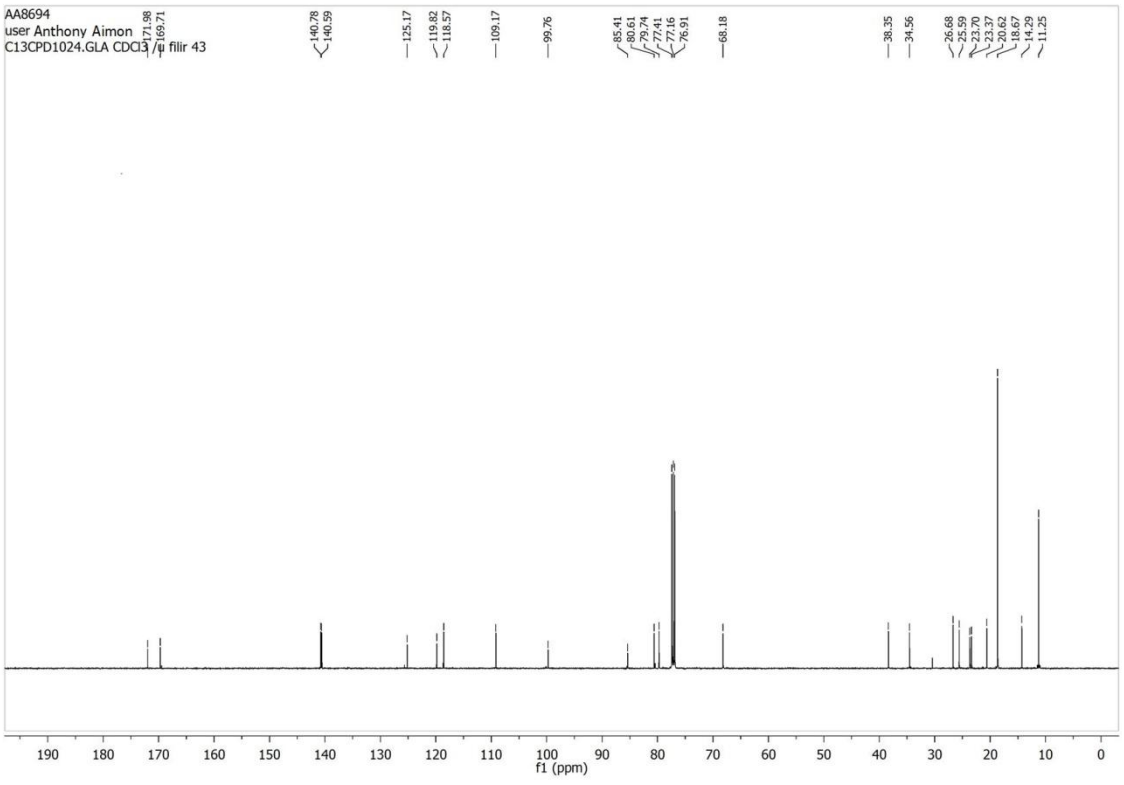
Appendix 5: ^{1}H and ^{13}C NMR of compound 286-anti



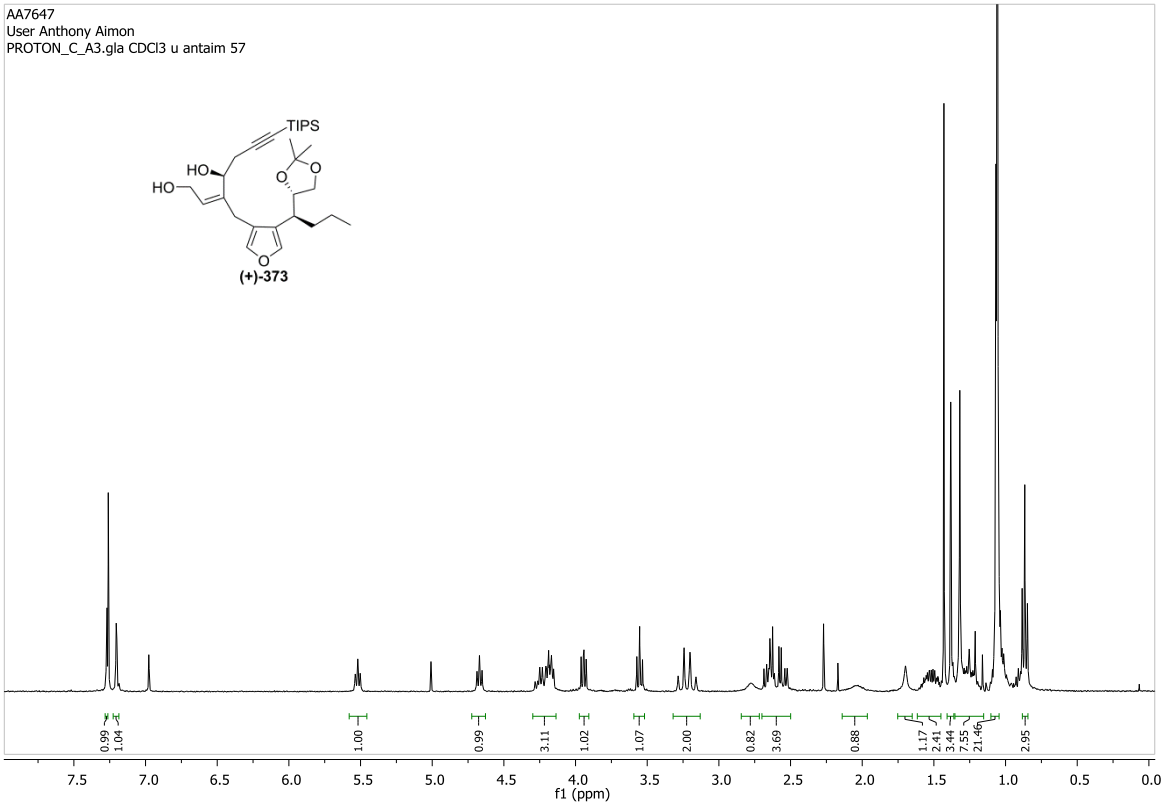


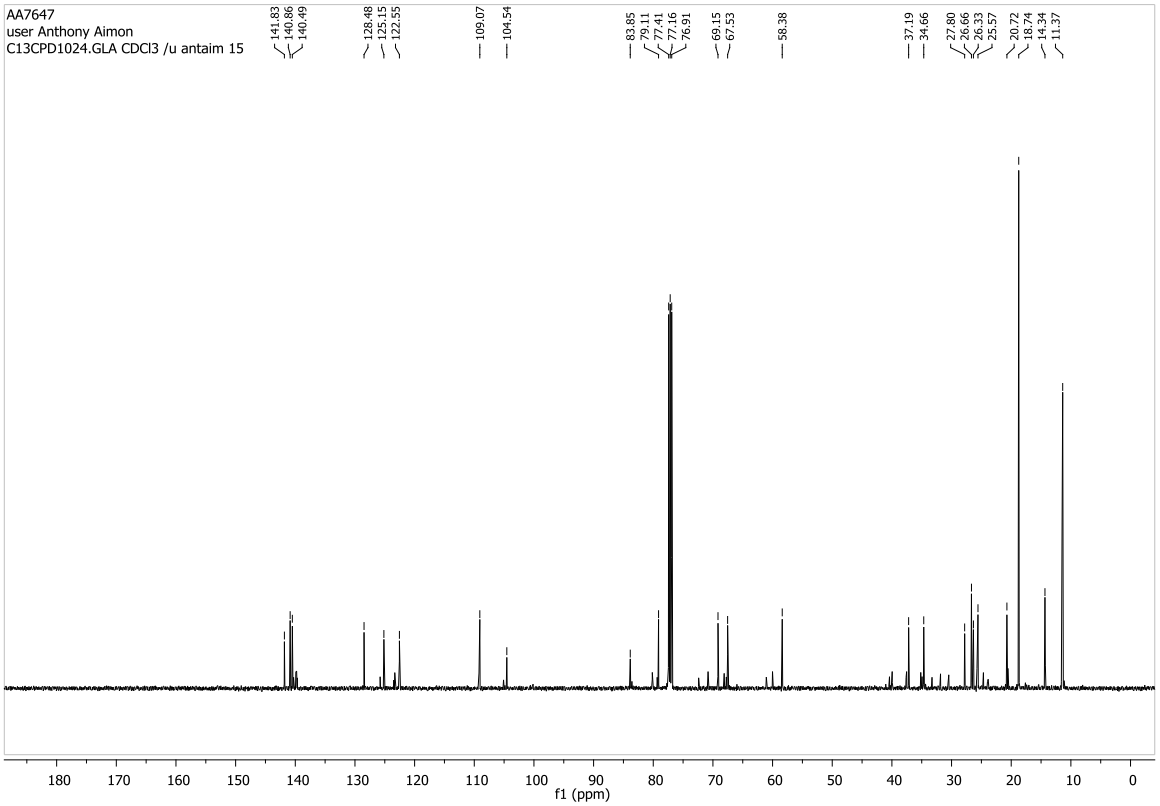
Appendix 6: ^{1}H and ^{13}C NMR of compound (+)-365



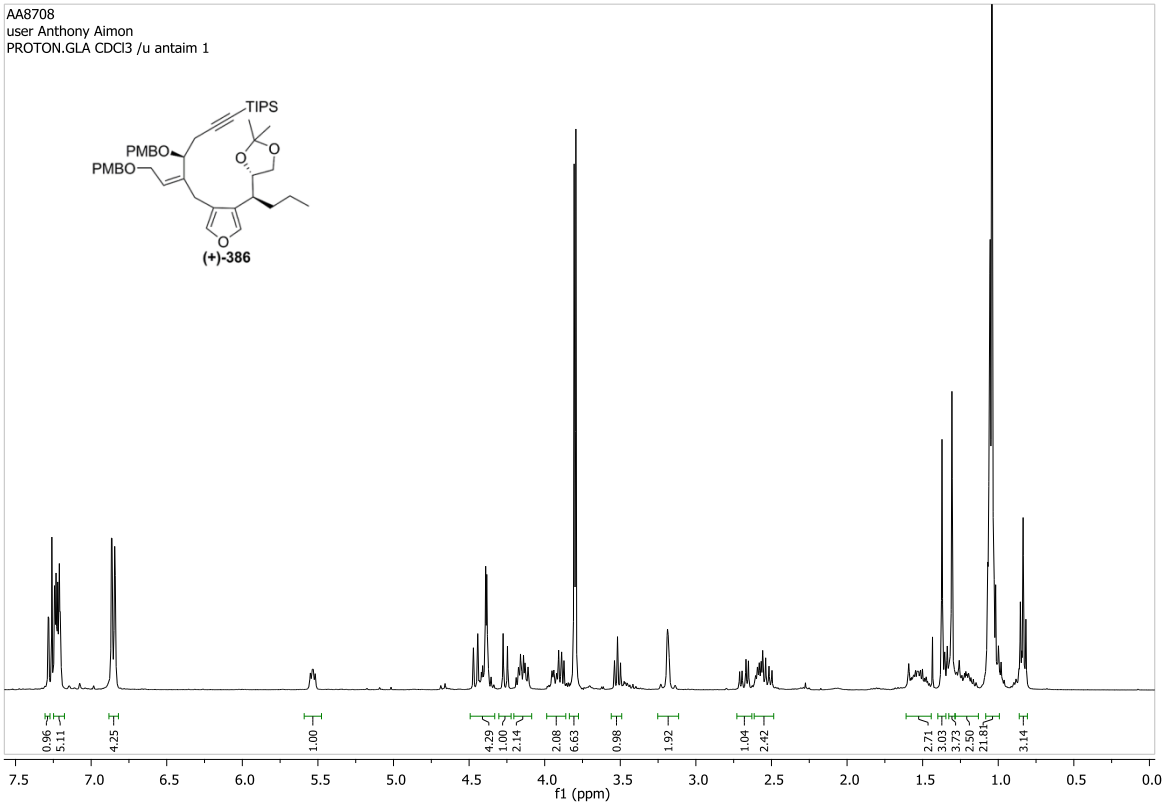


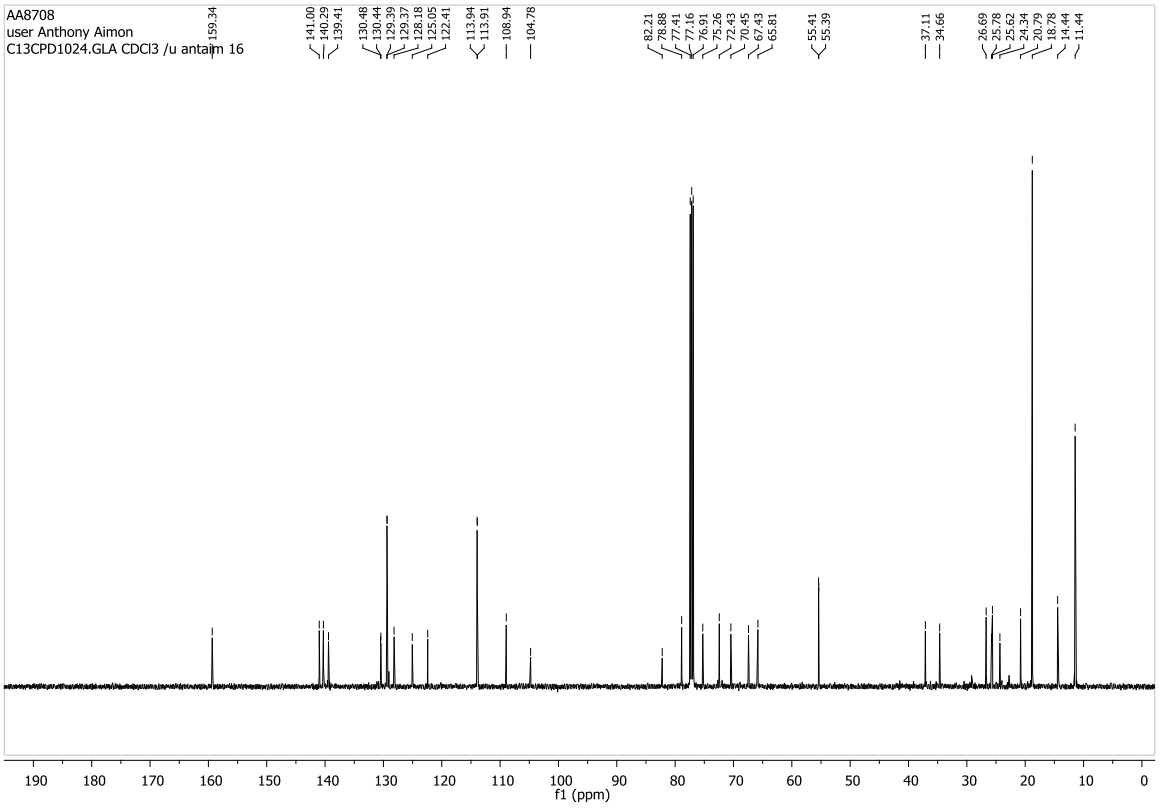
Appendix 7: ^{1}H and ^{13}C NMR of compound (+)-373



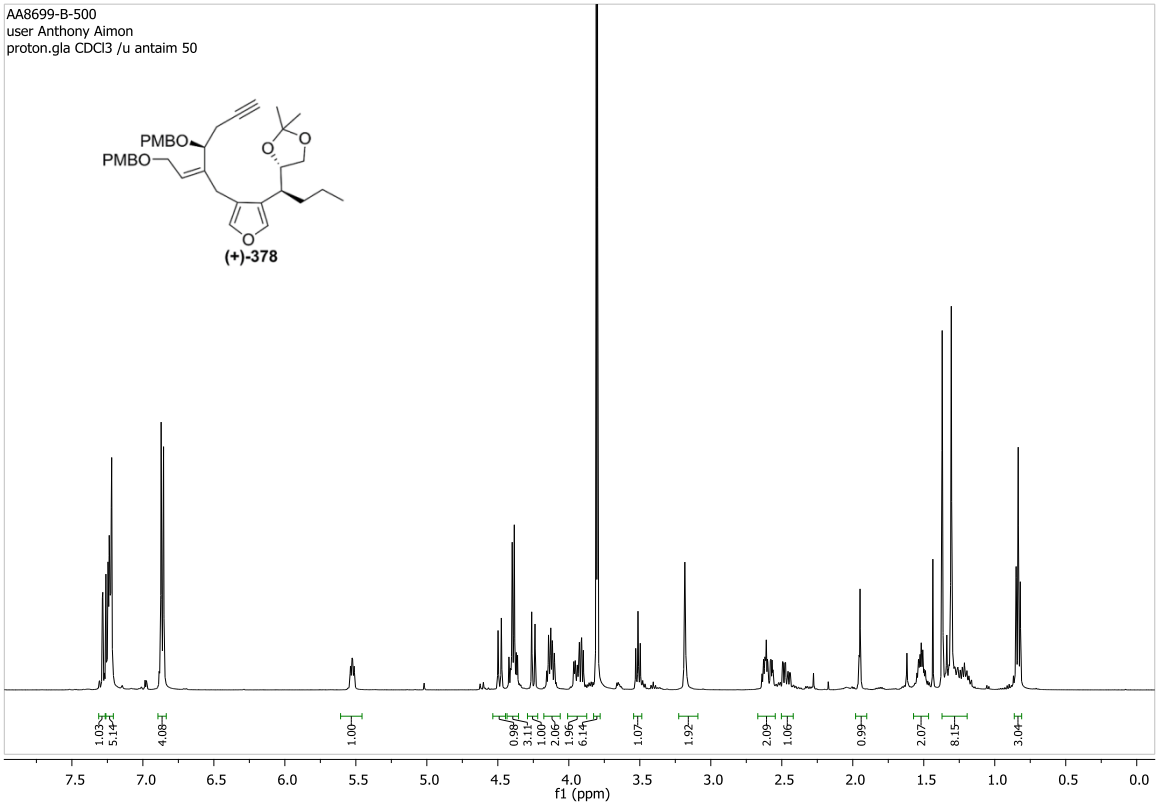


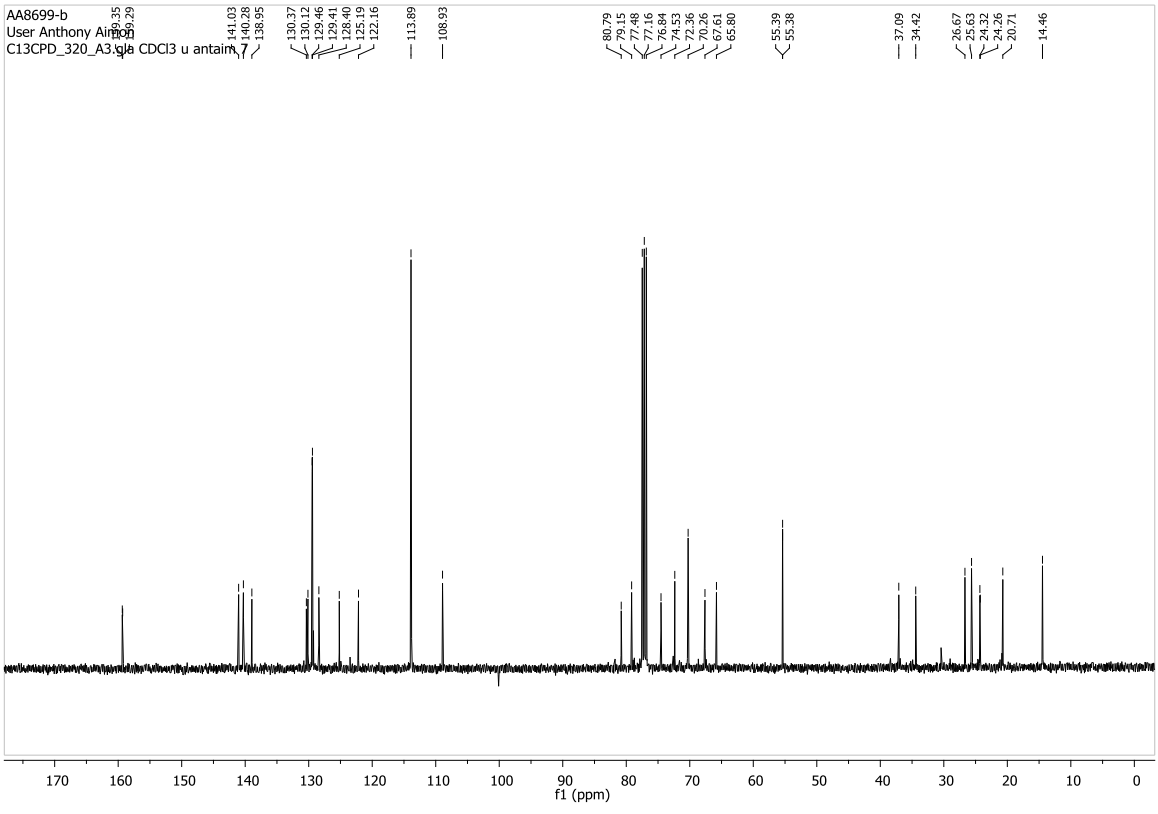
Appendix 8: ^{1}H and ^{13}C NMR of compound (+)-386



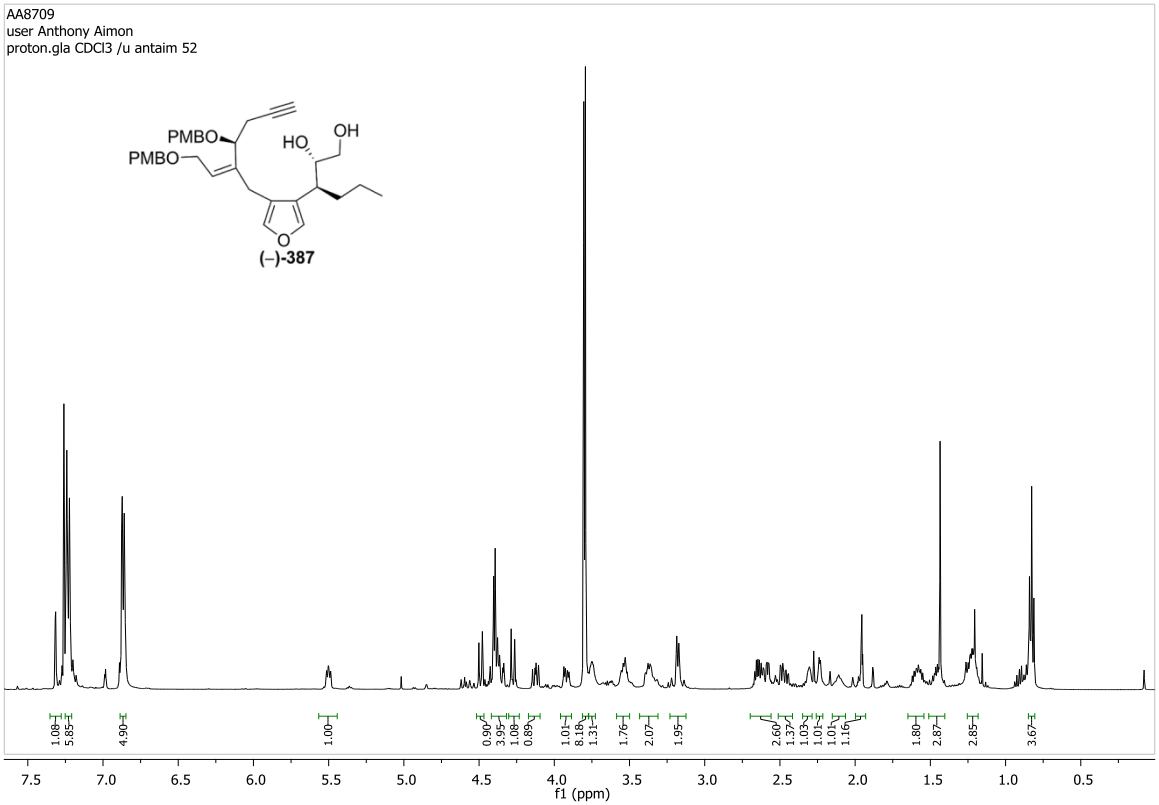


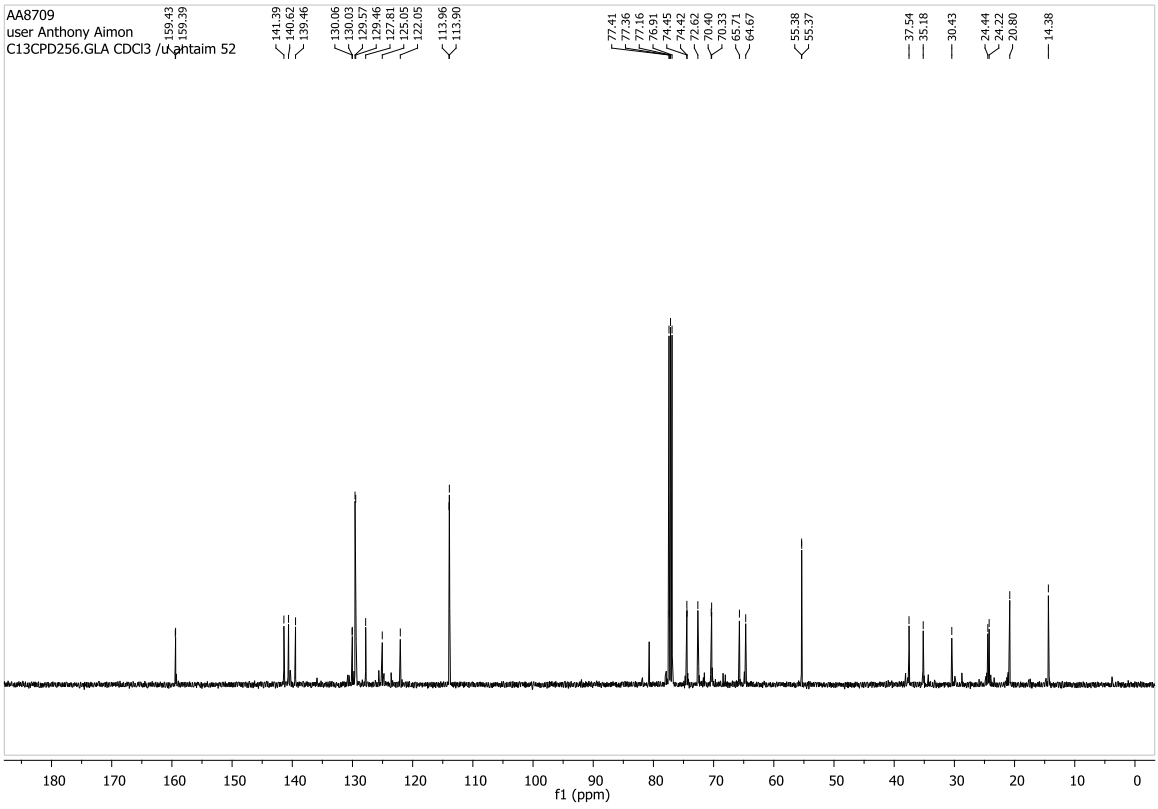
Appendix 9: ^{1}H and ^{13}C NMR of compound (+)-378



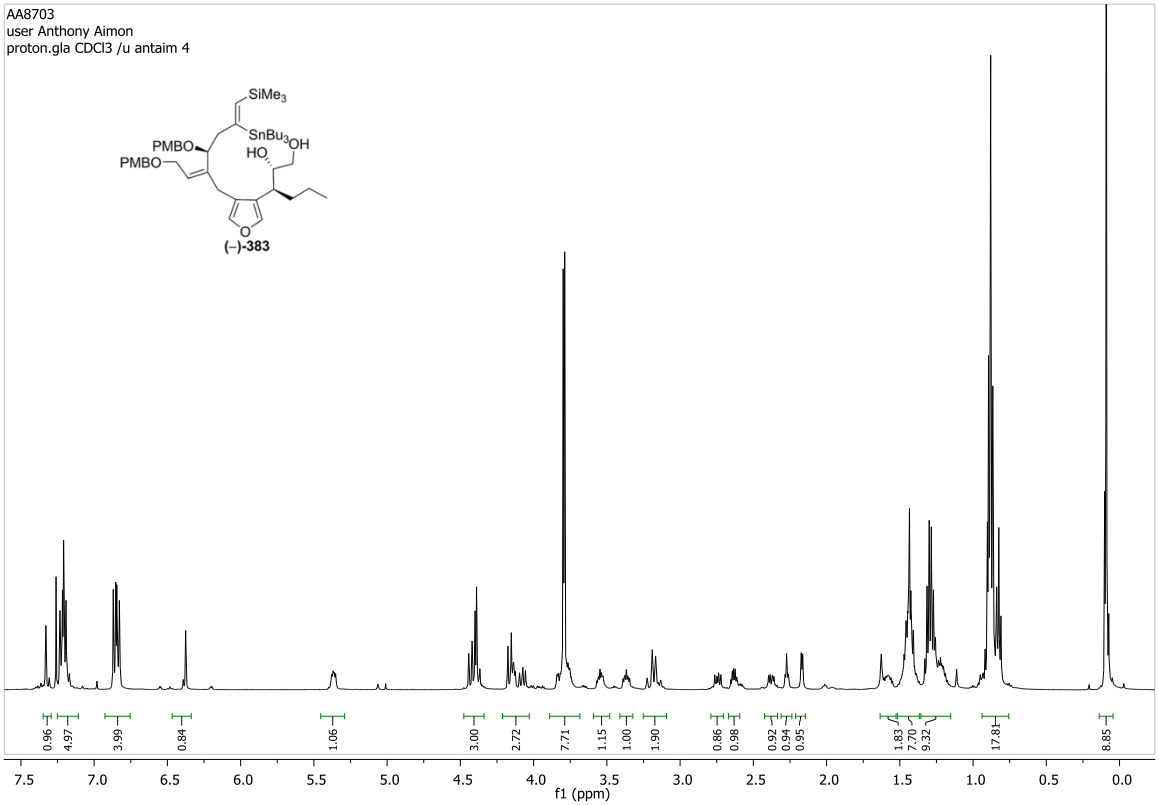


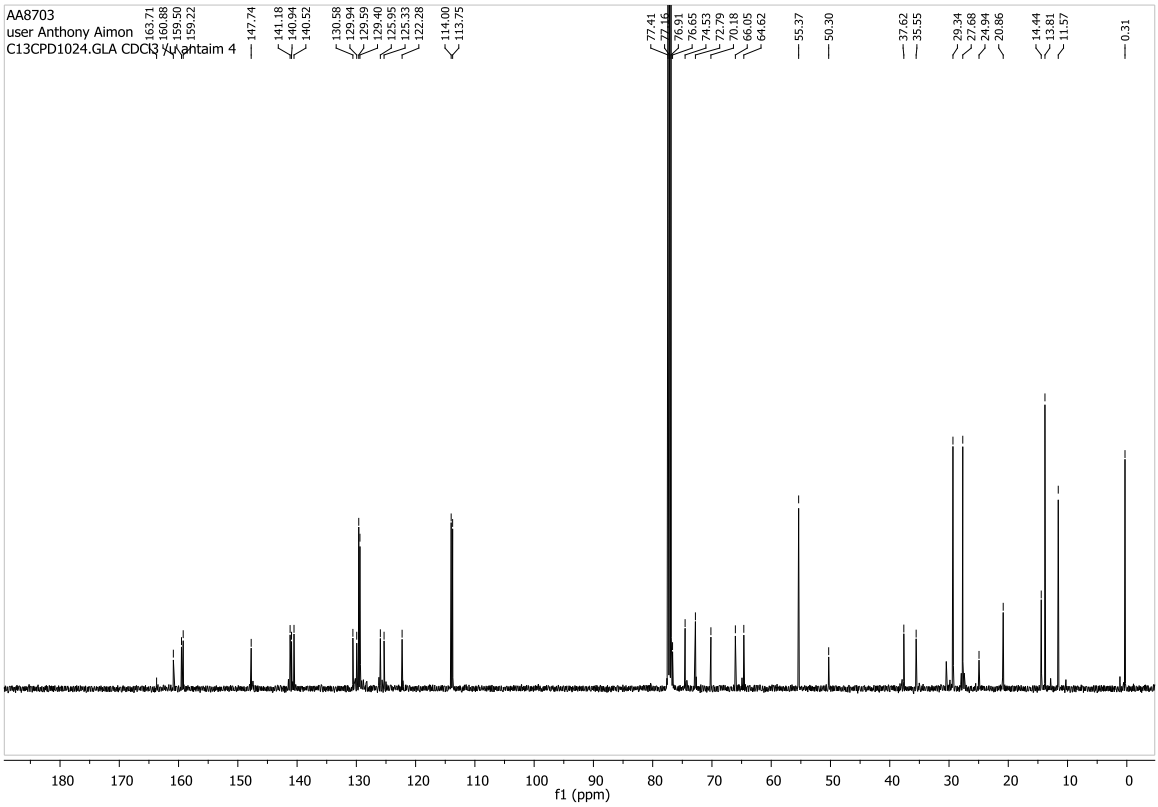
Appendix 10: ^{1}H and ^{13}C NMR of compound (−)-387



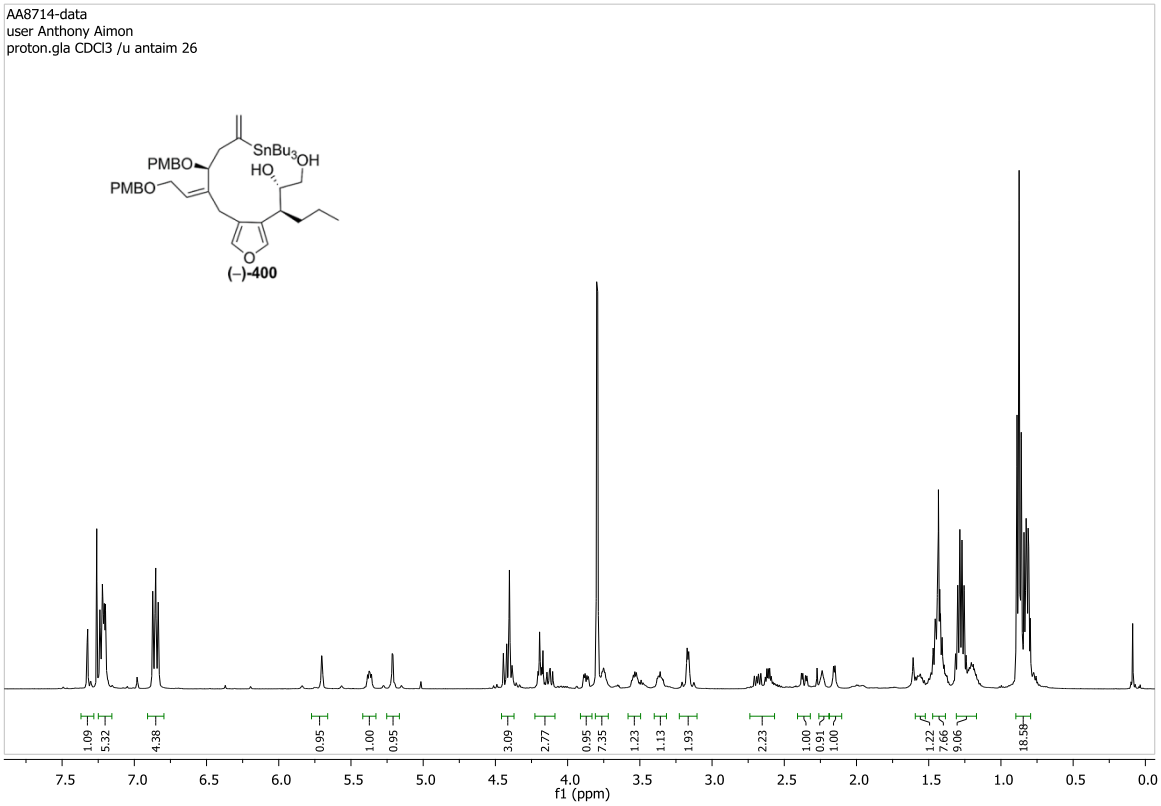


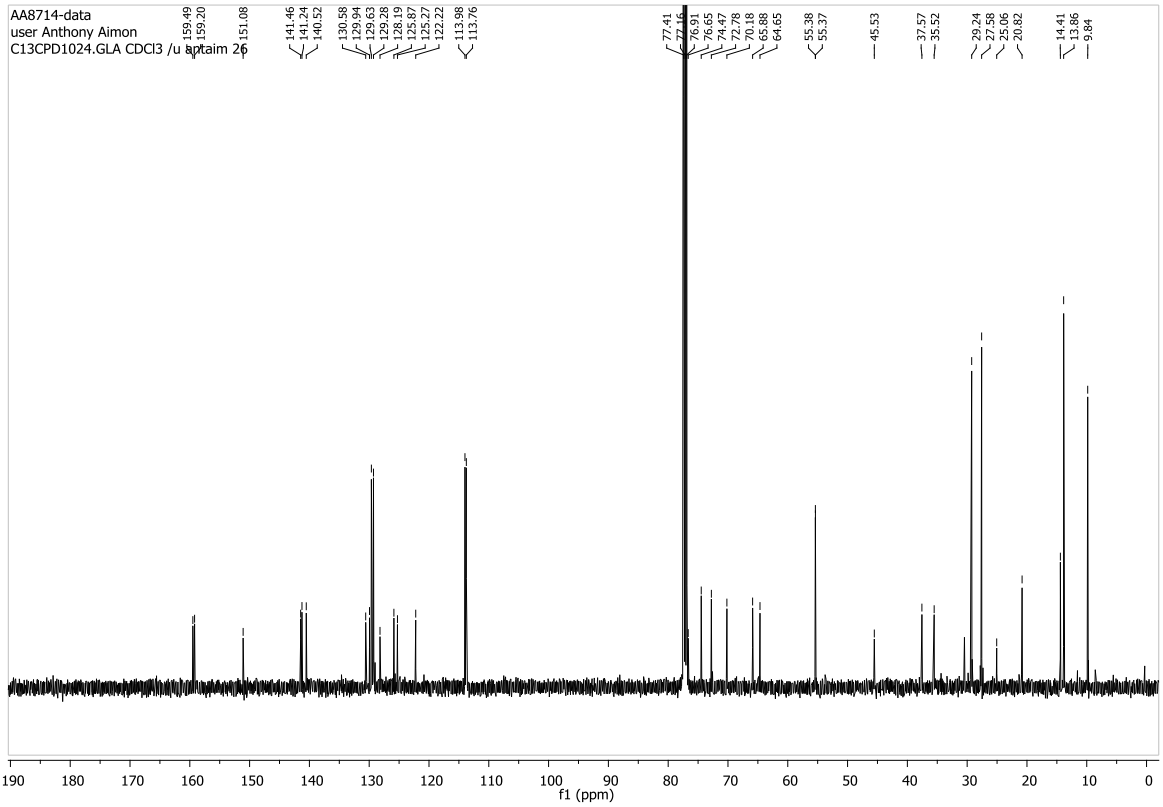
Appendix 11: ^{1}H and ^{13}C NMR of compound (−)-383



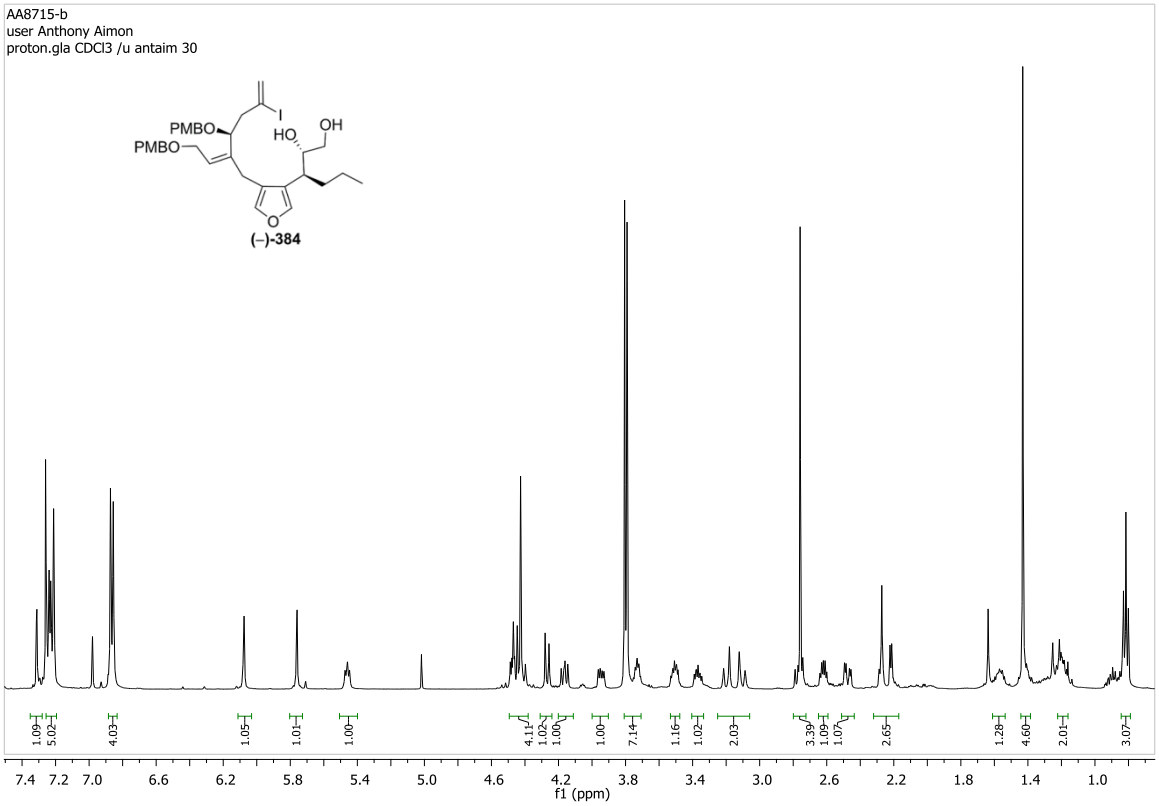


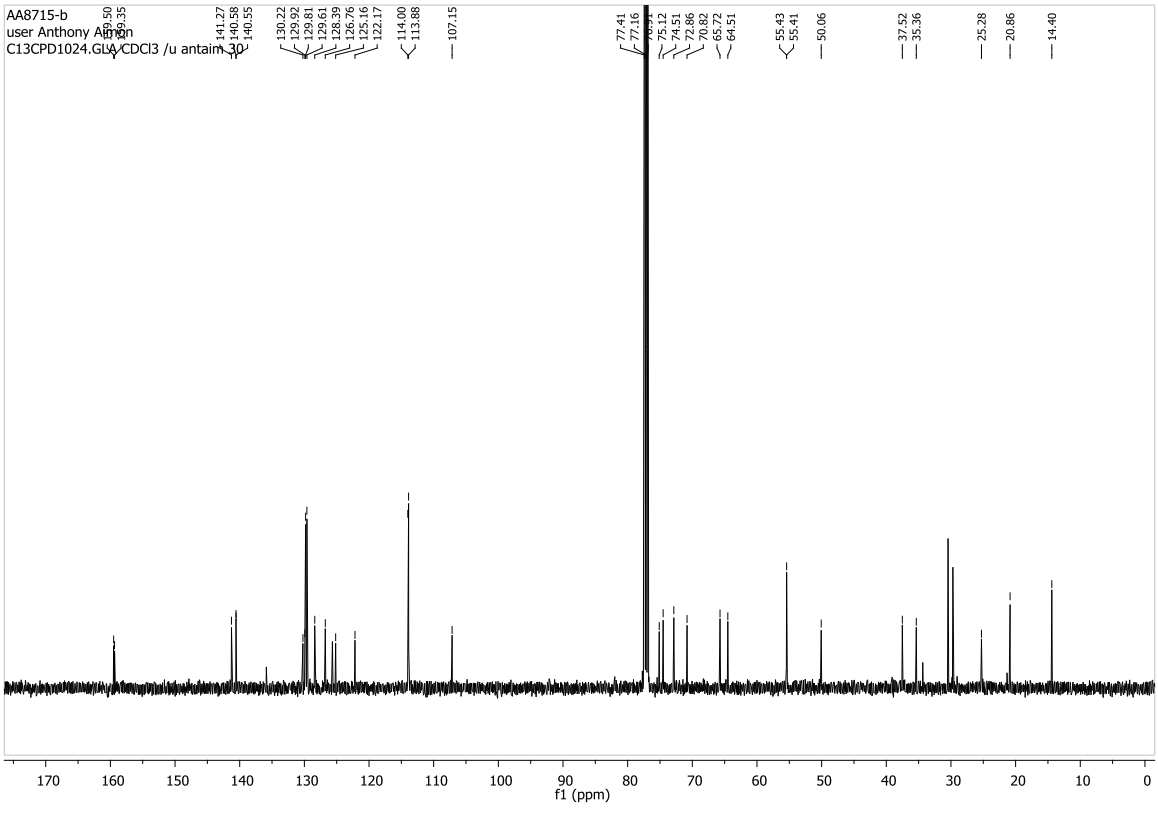
Appendix 12: ^{1}H and ^{13}C NMR of compound (−)-400



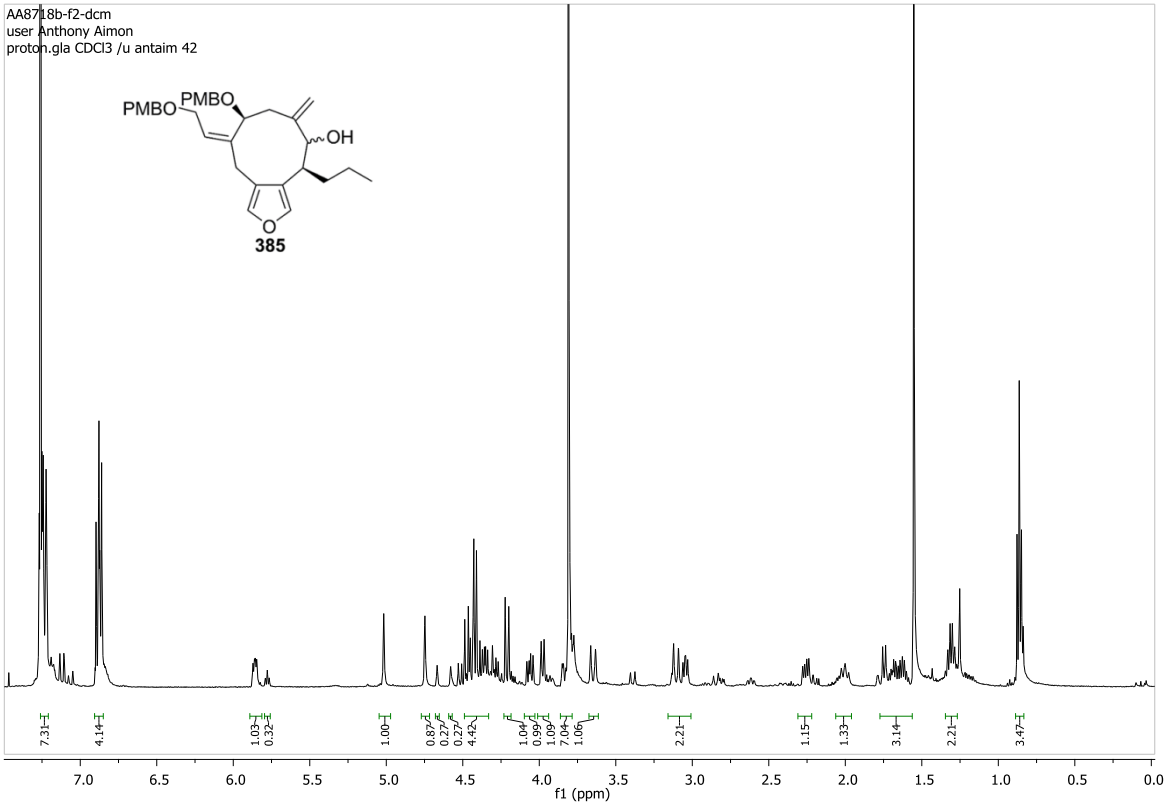


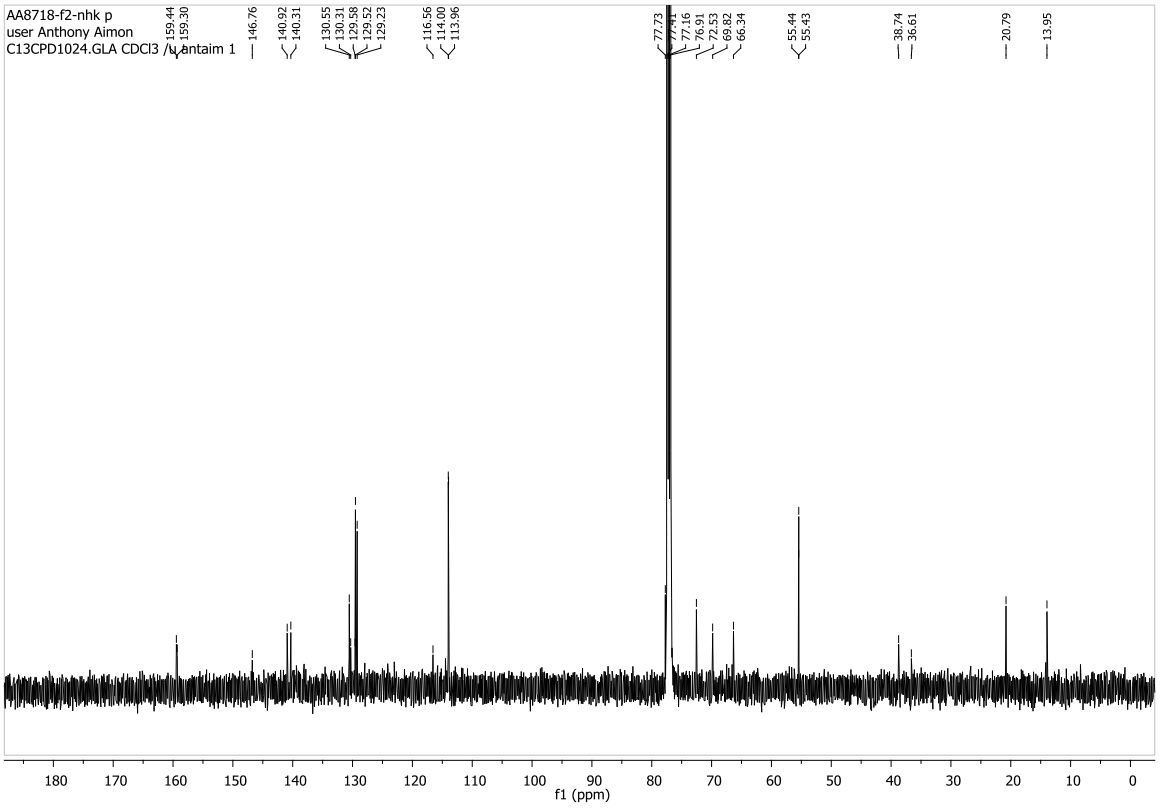
Appendix 13: ^{1}H and ^{13}C NMR of compound (−)-384





Appendix 14: ^{1}H and ^{13}C NMR of compound 385





Appendix 15: X-ray crystallography of compound 286-syn

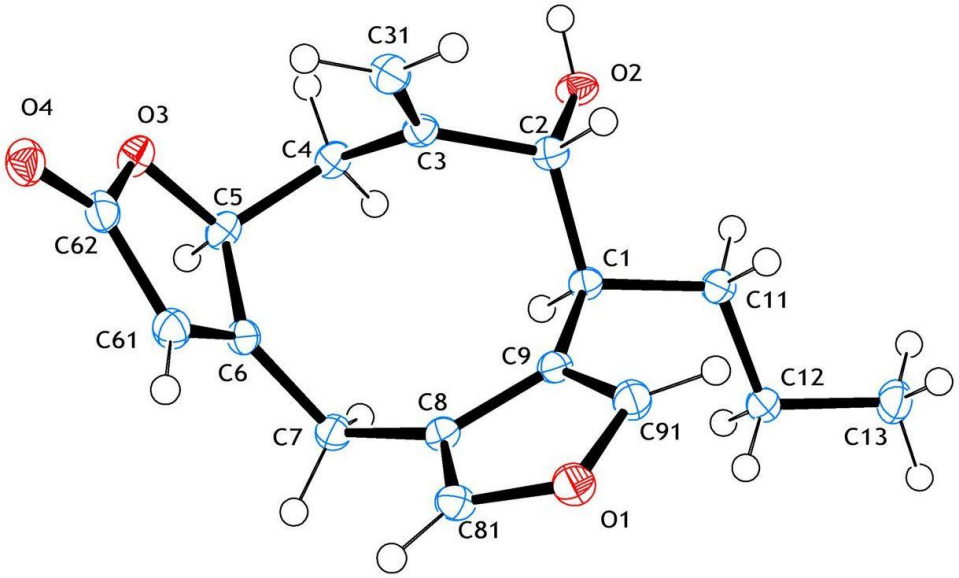


Table 1: Crystal data and structure refinement for 286-*syn*

Empirical formula	$C_{17}H_{20}O_4$	
Formula weight	288.33	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.2695(5) Å	α = 90°
	b = 11.8269(10) Å	β = 90°
	c = 17.3278(12) Å	γ = 90°
Volume	1489.77(19) $Å^3$	
Z	4	
Density (calculated)	1.286 g/cm^3	
Absorption coefficient	0.091 mm^{-1}	
Crystal size	0.5 × 0.2 × 0.2 mm^3	
F(000), F(000)'	616, 616.33	
Theta range for data collection	3.08 to 30.78°	
Index ranges	−10 ≤ h ≤ 10	
	−16 ≤ k ≤ 17	
	−24 ≤ l ≤ 24	
Reflections collected	2650	
Independent reflections	2468	
Data completness	1.00 / 0.57	
Theta (max)	30.780	
Absorption correction method	multi-scan	
Min. and max. transmission	0.902 and 0.982	
Refinement method	on F^2 against all reflections	
Data / restraints / parameters	2650 / 0 / 192	
Goodness-of-fit on F_2	1.041	
Final R indices [I>2sigma(I)]	R1 = 0.0386, wR2 = 0.0924	
R indices (all data)	R1 = 0.0347, wR2 = 0.0904	
Largest diff. peak and hole	0.283 and −0.248 e.$Å^{-3}$	

Table 2: Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for 286-*syn*. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	10184(19)	5274 (12)	4070 (7)	148(2)
C2	8927(19)	6144(12)	3660(8)	155(3)
C3	7407(19)	5673(12)	3156(8)	151(2)
C4	8010(19)	4996(12)	2451(7)	172(3)
C5	7012(19)	3871(13)	2324(8)	171(3)
C6	6766(2)	3154(12)	3032(7)	161(3)
C7	8350(2)	2816(12)	3541(8)	174(3)
C8	8243(2)	3392(12)	4318(7)	155(2)
C9	9050(19)	4463(12)	4545(8)	149(2)
C11	11586(19)	5922(12)	4574(8)	169(3)
C12	13040(2)	5185(13)	4971(8)	185(3)
C13	14253(2)	5885(15)	5510(9)	239(3)
C31	5661(2)	5948(13)	3301(9)	193(3)
C61	4971(2)	2936(13)	3129(8)	190(3)
C62	3937(2)	3504(12)	2517(8)	184(3)
C81	7354(2)	2988(12)	4947(8)	182(3)
C91	8592(2)	4597(13)	5302(8)	190(3)
O1	7539(15)	3710(9)	5562(6)	206(2)
O2	10109(14)	6841(9)	3191(6)	194(2)
O3	5139(14)	4054(10)	2045(6)	194(2)
O4	2284(15)	3553(10)	2406(7)	224(2)

Table 3: Bond lengths (Å) and angles (°) for 286-*syn*.

C1—C9	1.5096(19)	C9—C91	1.3628(19)
C1—C11	1.5460(19)	C11—C12	1.533(2)
C1—C2	1.5482(19)	C11—H11A	0.99
C1—H1	1	C11—H11B	0.99
C2—O2	1.4420(17)	C12—C13	1.527(2)
C2—C3	1.5151(19)	C12—H12A	0.99
C2—H2	1	C12—H12B	0.99
C3—C31	1.335(2)	C13—H13A	0.98
C3—C4	1.5253(19)	C13—H13B	0.98
C4—C5	1.531(2)	C13—H13C	0.98
C4—H4A	0.99	C31—H31A	0.95
C4—H4B	0.99	C31—H31B	0.95
C5—O3	1.4611(17)	C61—C62	1.464(2)
C5—C6	1.502(2)	C61—H61	0.95
C5—H5	1	C62—O4	1.2181(18)
C6—C61	1.341(2)	C62—O3	1.3623(18)
C6—C7	1.505(2)	C81—O1	1.3719(17)
C7—C8	1.5108(19)	C81—H81	0.95
C7—H7A	0.99	C91—O1	1.3741(18)
C7—H7B	0.99	C91—H91	0.95
C8—C81	1.3545(19)	O2—H2A	0.84
C8—C9	1.4494(19)		
C9—C1—C11	111.52(11)	C2—C3—C4	116.49(12)
C9—C1—C2	110.51(11)	C3—C4—C5	115.80(11)
C11—C1—C2	108.57(11)	C3—C4—H4A	108.3
C9—C1—H1	108.7	C5—C4—H4A	108.3
C11—C1—H1	108.7	C3—C4—H4B	108.3
C2—C1—H1	108.7	C5—C4—H4B	108.3
O2—C2—C3	108.63(11)	H4A—C4—H4B	107.4
O2—C2—C1	106.67(11)	O3—C5—C6	104.06(11)
C3—C2—C1	116.74(11)	O3—C5—C4	111.10(12)
O2—C2—H2	108.2	C6—C5—C4	115.44(11)
C3—C2—H2	108.2	O3—C5—H5	108.7
C1—C2—H2	108.2	C6—C5—H5	108.7
C31—C3—C2	119.69(13)	C4—C5—H5	108.7
C31—C3—C4	123.51(13)	C61—C6—C5	109.14(13)

C61—C6—C7	128.25(13)	H12A—C12—H12B	108
C5—C6—C7	122.56(13)	C12—C13—H13A	109.5
C6—C7—C8	111.30(12)	C12—C13—H13B	109.5
C6—C7—H7A	109.4	H13A—C13—H13B	109.5
C8—C7—H7A	109.4	C12—C13—H13C	109.5
C6—C7—H7B	109.4	H13A—C13—H13C	109.5
C8—C7—H7B	109.4	H13B—C13—H13C	109.5
H7A—C7—H7B	108	C3—C31—H31A	120
C81—C8—C9	106.46(12)	C3—C31—H31B	120
C81—C8—C7	125.60(13)	H31A—C31—H31B	120
C9—C8—C7	127.94(12)	C6—C61—C62	108.64(13)
C91—C9—C8	105.29(13)	C6—C61—H61	125.7
C91—C9—C1	125.77(13)	C62—C61—H61	125.7
C8—C9—C1	128.94(12)	O4—C62—O3	121.01(14)
C12—C11—C1	115.27(12)	O4—C62—C61	129.97(15)
C12—C11—H11A	108.5	O3—C62—C61	108.99(12)
C1—C11—H11A	108.5	C8—C81—O1	110.98(12)
C12—C11—H11B	108.5	C8—C81—H81	124.5
C1—C11—H11B	108.5	O1—C81—H81	124.5
H11A—C11—H11B	107.5	C9—C91—O1	111.27(13)
C13—C12—C11	111.39(12)	C9—C91—H91	124.4
C13—C12—H12A	109.4	O1—C91—H91	124.4
C11—C12—H12A	109.4	C81—O1—C91	105.99(11)
C13—C12—H12B	109.4	C2—O2—H2A	109.5
C11—C12—H12B	109.4	C62—O3—C5	109.16(11)

Symmetry transformations used to generate equivalent atoms:

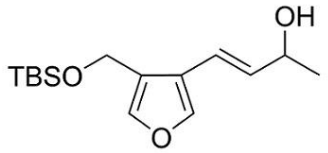
Table 4: Anisotropic displacement parameters ($Å^2 \times 10^3$) for 286-*syn*. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	14(6)	15(6)	15(5)	0(4)	0(5)	0(5)
C2	13(6)	15(6)	16(6)	2(5)	1(5)	0(5)
C3	15(6)	15(6)	14(5)	3(4)	0(5)	0(5)
C4	15(6)	21(6)	14(5)	2(5)	0(5)	−1(5)
C5	14(6)	21(7)	15(5)	0(5)	0(5)	1(5)
C6	19(6)	15(6)	14(5)	−1(5)	−1(5)	0(5)
C7	17(6)	16(6)	17(6)	−1(5)	−1(5)	2(5)
C8	15(6)	15(6)	15(5)	0(5)	−1(5)	1(5)
C9	14(6)	14(6)	15(5)	1(5)	−1(5)	0(5)
C11	15(6)	16(6)	18(6)	0(5)	−2(5)	0(5)
C12	18(6)	16(6)	20(6)	0(5)	−3(5)	0(5)
C13	21(7)	26(8)	24(7)	−4(6)	−6(6)	0(6)
C31	15(6)	18(6)	23(6)	0(5)	0(5)	0(5)
C61	19(6)	18(6)	18(6)	0(5)	0(5)	2(6)
C62	18(6)	17(6)	19(6)	−4(5)	−1(5)	−1(5)
C81	19(6)	15(6)	19(6)	2(5)	0(5)	0(5)
C91	21(7)	18(7)	16(6)	0(5)	0(5)	−2(5)
O1	25(5)	20(5)	15(4)	1(4)	2(4)	−2(4)
O2	16(5)	19(5)	22(5)	7(4)	0(4)	−1(4)
O3	15(5)	24(5)	17(4)	0(4)	−2(4)	0(4)
O4	16(5)	22(5)	27(5)	−4(4)	−2(4)	−0(4)

Table 5: Hydrogen coordinates (× 10^4) and equivalent isotropic displacement parameters ($Å^2$ × 10^3) for 286-*syn*.

	x	y	z	U(eq)
H1	1087	4836	3669	18
H2	8353	6635	4064	19
H4A	9344	4841	2497	21
H4B	7831	5472	1987	21
H5	7703	3424	1929	21
H7A	9522	3021	3287	21
H7B	8335	1986	3616	21
H11A	12224	6484	4246	20
H11B	10903	6344	4976	20
H12A	12422	4583	5272	22
H12B	13819	4819	4575	22
H13A	14914	6458	5210	36
H13B	15140	5388	5768	36
H13C	13483	6258	5899	36
H31A	5375	6437	3720	23
H31B	4703	5655	2987	23
H61	4455	2488	3530	23
H81	6691	2297	4962	22
H91	8952	5224	5611	23
H2A	9476	7333	2964	29

Appendix 16: HPLC analysis for compound (±)-325



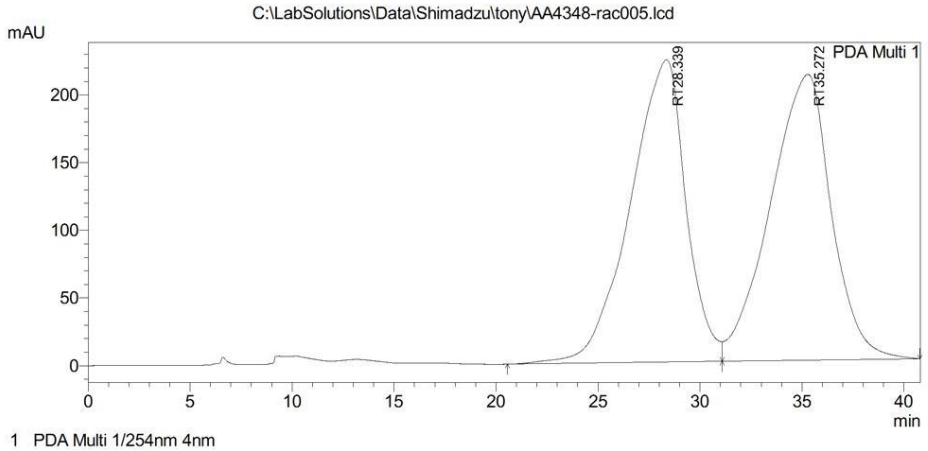
(±)-325

HPLC Report

Sample Name	: AA4348-rac; 4;	Injection Volume	: 20 uL
Data File Name	: AA4348-rac005.lcd		
Method File Name	: 95-5.lcm		
Acquired	: 25/11/2011 16:25:41;	Data Processed	: 25/11/2011 17:06:31

0.25% ipa odh 1ml/min

<Chromatogram>



1 PDA Multi 1/254nm 4nm

<Results>

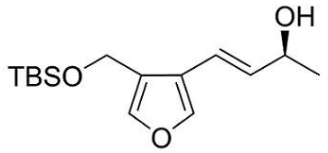
PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	28.339	42461316	223469	49.050	51.400
2	35.272	44106929	211294	50.950	48.600
Total		86568245	434763	100.000	100.000

C:\LabSolutions\Data\Shimadzu\tony\AA4348-rac005.lcd

Appendix 17: HPLC analysis for compound (−)-325



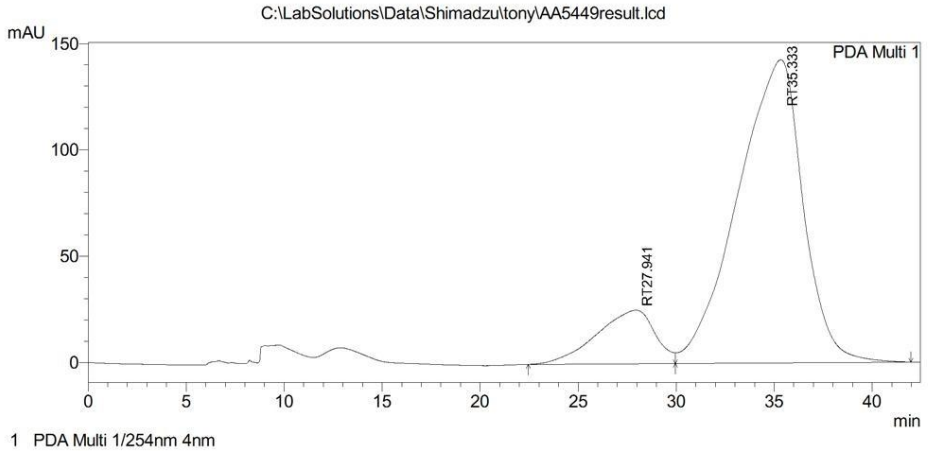
(−)-325

HPLC Report

Sample Name	: AA5448; 4;	Injection Volume	: 20 uL
Data File Name	: AA5449result.lcd		
Method File Name	: 95-5.lcm		
Acquired	: 25/11/2011 17:13:09;	Data Processed	: 25/11/2011 18:08:23

0.25% ipa odh 1ml/min

<Chromatogram>



1 PDA Multi 1/254nm 4nm

<Results>

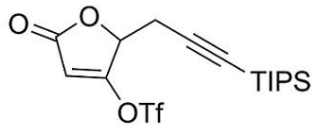
PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.941	5197201	25203	13.569	15.022
2	35.333	33105563	142563	86.431	84.978
Total		38302764	167766	100.000	100.000

C:\LabSolutions\Data\Shimadzu\tony\AA5449result.lcd

Appendix 18: HPLC analysis for compound (±)-254



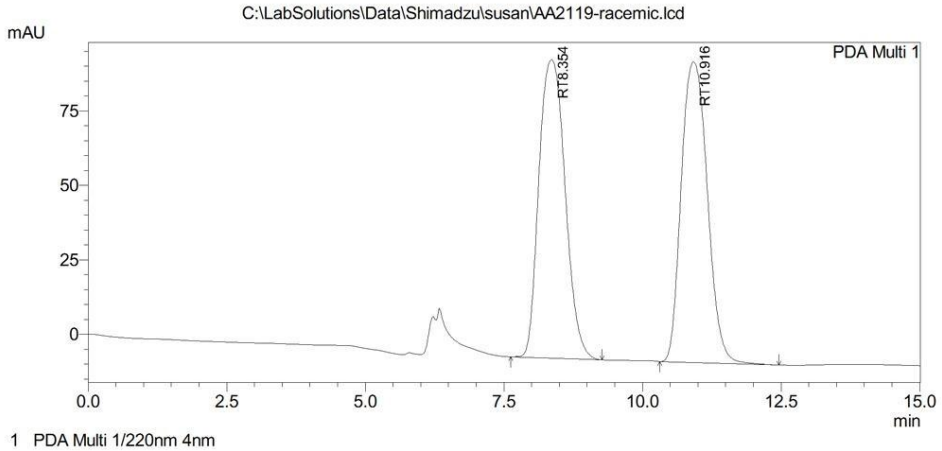
(±)-254

HPLC Report

Sample Name	: AA2119; 1;	Injection Volume	: 20 uL
Data File Name	: AA2119-racemic.lcd		
Method File Name	: 98pc-0.5mlmin.lcm		
Acquired	: 13/04/2012 10:47:52;	Data Processed	: 13/04/2012 11:25:27

2% ipa adh 0.5ml/min

<Chromatogram>



1 PDA Multi 1/220nm 4nm

<Results>

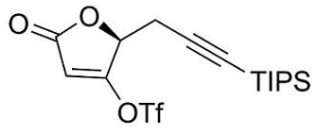
PeakTable

PDA Ch1 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.354	3304107	100160	49.934	49.816
2	10.916	3312776	100900	50.066	50.184
Total		6616883	201060	100.000	100.000

C:\LabSolutions\Data\Shimadzu\susan\AA2119-racemic.lcd

Appendix 19: HPLC analysis for compound (+)-254



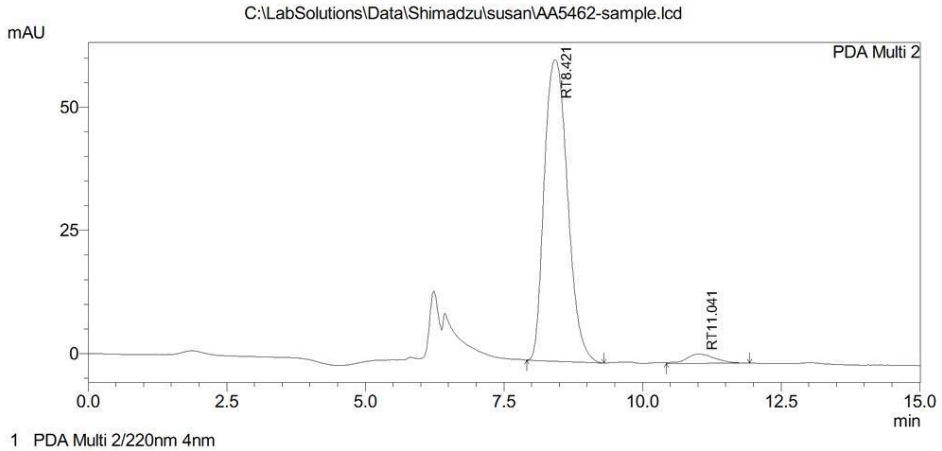
(+)-254

HPLC Report

Sample Name	: AA5462; 1;	Injection Volume	: 20 uL
Data File Name	: AA5462-sample.lcd		
Method File Name	: 98pc-0.5mlmin.lcm		
Acquired	: 13/04/2012 11:05:49;	Data Processed	: 02/03/2013 15:37:37

2% ipa adh 0.5ml/min

<Chromatogram>



1 PDA Multi 2/220nm 4nm

<Results>

PeakTable

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	8.421	1791323	61226	96.343	97.017
2	11.041	67995	1882	3.657	2.983
Total		1859318	63108	100.000	100.000

C:\LabSolutions\Data\Shimadzu\susan\AA5462-sample.lcd