Synthetic Studies towards Aruncin B: Total Synthesis, Structural Revision and Synthesis of Analogues for Biological Evaluation

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Abstract

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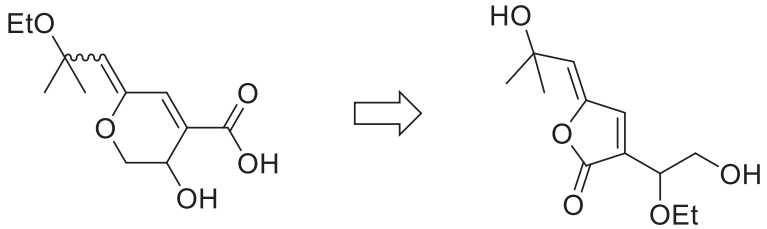
This thesis describes synthetic studies towards the recently isolated and previously unsynthesised cytotoxin aruncin B, a small molecule inhibitor of the Bcl-2 family anti-apoptotic proteins.

An initial approach relying on an Achmatowicz reaction is first presented. This method was unsuccessful. An alternative approach relying on a RCM / ethoxyselenation–selenoxide elimination was then envisaged. This method successfully delivered the Na salts of the *Z*- and *E*- isomer of the originally proposed structure of aruncin B, along with a third closely related isomeric Na salt. The free acids could not be obtained from these salts, suggesting structural misassignment of aruncin B. An alternative γ-alkylidenebutenolide structure is proposed, and its synthesis using a related RCM / hydroxyselenation–selenoxide sequence is presented. This sequence confirmed the true structure of aruncin B, but suffered from reproducibility issues. An alternative sequence based on β-iodo MBH followed by Sonogashira cross-coupling–5-*exo*-*dig*-lactonisation was successfully applied to the synthesis of the true structure of aruncin B, as well as 15 analogues for biological evaluation.



Originally proposed structure of aruncin B

Revised structure

Acknowledgements

First of all, I would like to thank my supervisor Prof David Hodgson for welcoming me in his research group. I am grateful for his patience, support and enthusiasm during my DPhil. I will not forget our long meetings thoroughly discussing the various aspects of my research project.

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Statement of Authorship

The work described in this thesis is entirely my own, with the following exceptions:

- X-Ray crystallographic analysis of selenide **172** (performed and provided by Amber L. Thompson).
- Biological assays (performed and provided by Frances Willenbrock, Christopher Tower and Laia Culleré).
- Where reference is given to a published source.

Abbreviations

Ac: acetyl

acac: acetylacetonate

t-Bu: *tert*-butyl

cat.: catalyst

CIP: Cahn-Ingold-Prelog rules

CM: Cross Metathesis

COSY: Correlated Spectroscopy

m-CPBA: *meta*-chloroperbenzoic acid

DIBAL-H: diisobutylaluminium hydride

DMAP: *N,N*-dimethylaminopyridine

DMF: *N,N*-dimethylformamide

DMP : Dess-Martin periodinane

Et: ethyl

ESI: electrospray ionisition

FGI: Functional Group Interconversion

GI: Grubbs' first generation catalyst

GII: Grubbs' second generation catalyst

HGII: Hoveyda- Grubbs' second generation catalyst

HMBC: Heteronuclear Multiple Bond Correlation

HSQC: Heteronuclear Single Quantum Coherence

IBX: 2-iodobenzoic acid

IR: infrared

LAH: lithium aluminium hydride

LDA: lithium diisopropylamide

LG: Leaving Group

MB: Methylene Blue

MBH: Morita-Baylis-Hillman reaction

Me: methyl

Ms: methanesulfonyl

MS: Mass Spectrometry

NBS: *N*-bromosuccinimide

NHK: Nozaki-Hiyama-Kishi reaction

NMR: Nuclear Magnetic Resonnance

nOe: nuclear Overhauser effect

Nu: nucleophile

[Ox]: oxidation

i-Pr: *iso*-propyl

py: pyridine

R, R^1, R^2, etc: generic group

RB: rose Bengal

RCM: Ring-Closing Metathesis

Red: reductant

SAR: Structure Activity Relationship

TBS: *tert*-butyldimethylsilyl

Tf: trifluoromethanesulfonyl

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TMEDA: *N,N,N′,N′*-tetramethylethylenediamine

TMS: trimethylsilyl

TPP: tetraphenylporphine

Ts: *para*-toluenesulfonyl

UV: ultraviolet

Table of content

1. **Introduction**……....1

1.1. Foreword…….…..1

1.2. Aruncin B: origin and biological activity…….....2

1.3. Original retrosynthesis ……..4

1.4. The Achmatowicz reaction and some of its applications in complex target synthesis..5

2. **Results and discussion:** Early synthetic studies: Achmatowicz reaction……9

2.1. Hydroxyl directed oxidation approach ……9

2.2. Investigations on the photooxygenation of furanols……...19

3. **Results and discussion:** The RCM / ethoxyselenation–selenoxide elimination approach to the dihydropyran derivatives……..24

3.1. New retrosynthesis…….24

3.2. Oxyselenation–selenoxide elimination chemistry and some of its application……..26

3.3. Use of RCM strategies for synthesis of dihydropyran-3(6*H*)-ones……..…...35

3.4. Model study: the α-unsubstituted dihydropyranone……..…….38

3.5. Synthesis of *Z*-aruncin B Na salt…….45

3.6. Synthesis of *E*-aruncin B Na salt…….58

3.7. Synthesis of regioisomeric ether structure of aruncin B…….59

4. **Results and discussion:** Structural revision and synthesis of newly postulated structure of aruncin B…….62

4.1. The *Z*-γ–ethylidenebutenolide hypothesis……...…...62

4.2. Some examples of γ–alkylidenebutenolide synthesis…….66

4.3. RCM / ethoxyselenation–selenoxide elimination approach: model study: the α-unsubstituted butenolide……..……71

4.4. RCM / ethoxyselenation–selenoxide elimination approach to newly postulated structure of aruncin B…….....74

4.5. The β-iodo MBH / Sonogashira cross coupling–lactonisation route to aruncin B…..80

4.6. Postulation on the origin of aruncin B…….84

4.7. Studies towards the asymmetric synthesis of aruncin B…….….86

5. **Results and discussion:** Synthesis of analogues for biological evaluation……93

5.1. Synthesis of α,β-saturated lactone analogues…….93

5.2. Synthesis of γ–alkylidenebutenolide analogues of aruncin B…….96

5.3. Preliminary biological results……....100

6. **Conclusion and outlook**……..104

7. **Experimental Section**…….…106

7.1. General information……..106

7.2. Synthesis of novel compounds……..108

7.3. Viability assays……..198

8. **References**……..….199

9. **Appendices**……..211

9.1. Ru alkene metathesis catalysts……...….211

9.2. Published work……...…212

9.3. Crystal data and structure refinement for **172**……...…242

1. Introduction

1.1 Foreword

Since the disclosure of the synthesis of urea from ammonium cyanate by Wöhler in 1828,[1] which is often regarded as the first total synthesis; organic chemists have been interested in synthesising complex molecular structures possessing interesting biological functions. A high state of the art was reached in 1972, when Robert B. Woodward (Harvard) and Albert Eschenmoser (ETH Zurich) reported their syntheses of vitamin B12.[2,3] This "tour de force" in the field of organic chemistry was the result of more than a decade of collaborative work involving more than a hundred researchers.

Total synthesis can provide material for biological studies of low abundance natural products, help establish the true structure of recently isolated compounds, demonstrate the efficiency of synthetic methods developed in laboratories or even be used as a source of inspiration for the design of new reactions.[4,5]

In this thesis, I will present the work I have conducted towards the total synthesis of the cytotoxin aruncin B.[6,7] The original strategy which was used to attempt the synthesis of the postulated structure of aruncin B, the revised synthetic route towards the latter as well as the structural reassignment will all be discussed. The application of the sequence designed for the synthesis of the true structure of aruncin B will also be shown to prepare analogues for biological evaluation. Where appropriate, previous work on specific synthetic methods will be briefly reviewed and placed in the context of the current synthetic work.

1.2 Aruncin B: origin and biological activity

The wild leafy edible vegetable *Aruncin diocus* var. *Kamtschaticus* (Rosaceae) found on the Korean island Ulleungdo had been known for its antioxidant, antidiabetic and anti-AIDS properties,[8] although the isolation of the compounds responsible for this activity had not been reported.

In 2011, Woo and co-workers reported the activity-directed isolation from the EtOH extracts of Rosaceae aerial parts (6.9 kg) enabled the discovery of 5 previously unknown secondary metabolite compounds.[6] Among these compounds, aruncin B (**1**, Figure 1, 29.2 mg isolated) stood out due to a combination of its cytotoxic activity against Jurkat T malignant cells with an IC_{50} of 17.15 μg/mL, together with its intriguing chemical structure. Spectroscopic methods (NMR, IR and MS) led to the assignment of aruncin B (**1**) as dihydropyran-3-ol-containing monoterpenoid, with an unusual cross-conjugating exocyclic enol ether, with its exact geometry undetermined. Another striking feature of aruncin B (**1**) as originally described, is the coexistence of a potentially acid labile tertiary allylic ether and carboxylic acid functionality. Polarimetric analysis gave a positive specific rotation ($[\alpha]_D^{20}$ + 27 (*c* 0.1 in MeOH)) suggesting enantiopure or enantioenriched material, but the use of Mosher's ester method led to decomposition and the absolute configuration could not be determined.

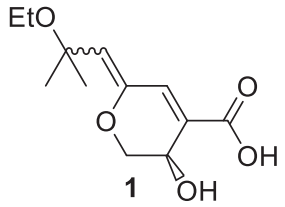


Figure 1. Originally reported structure of aruncin B (**1**).

A subsequent report suggested that the cytotoxic activity of aruncin B (**1**) against Jurkat cells was due to inhibitive properties of the Bcl-2 family anti-apoptotic proteins, although the exact mode of action was not established.[7]

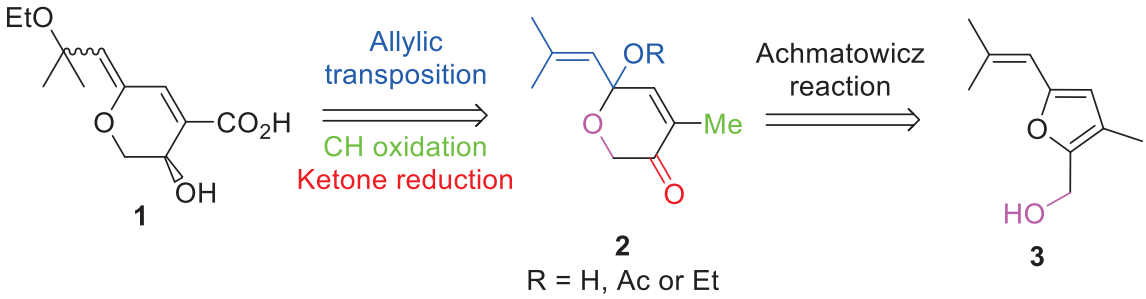
Bcl-2 family anti-apoptotic proteins are often overexpressed in malignant cell and could be responsible for drug resistance. Small molecule inhibitors of these proteins are seen as promising lead compounds for the development of new cancer therapies, either alone or in combination with other conventional treatments.[9]

The interesting structural features together with the potentially interesting biological activity made aruncin B (**1**) an attractive target.

The aims of this project were to synthesise aruncin B to confirm the proposed structure of aruncin B (**1**), establish the exocyclic enol ether geometry and absolute configuration as well as to provide sufficient amounts for more detailed biological studies. The synthetic route should also provide the opportunity for an asymmetric version once the absolute configuration has been established, and be flexible enough to enable the synthesis of analogues for SAR profiling.

1.3. Original retrosynthesis

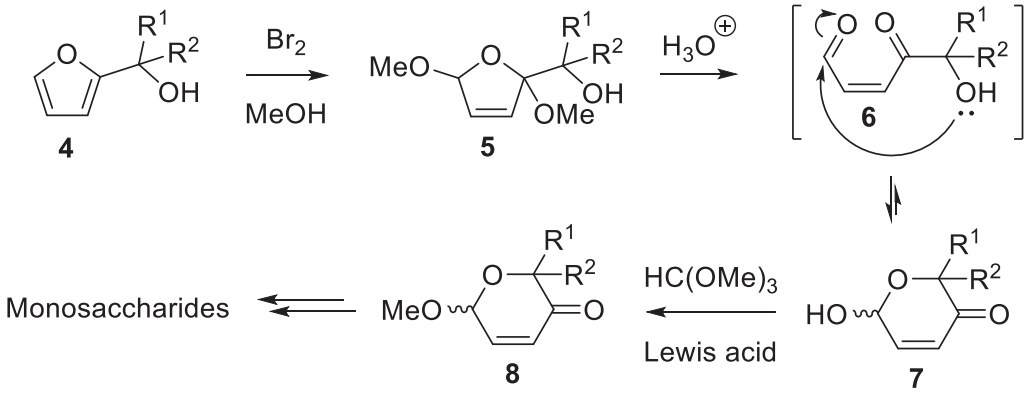
Retrosynthetically, the synthesis of aruncin B was originally envisaged by late-stage FGI of a 6-alkoxy, acetoxy or hydroxy-dihydropyranone **2** (Scheme 1): allylic transposition, (asymmetric) ketone reduction and CH_3 oxidation (possibly biocatalysed) to the carboxylic acid (Scheme 1). The 6-oxy-dihydropyranone **2** was anticipated to be prepared by Achmatowicz reaction of the corresponding 2-furanol **3**.[10,11]



Scheme 1. Original retrosynthesis of aruncin B (**1**).

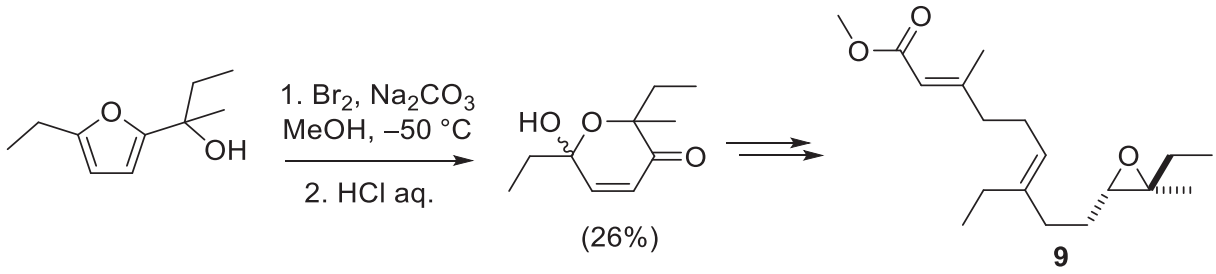
1.4. The Achmatowicz reaction and some of its applications in complex target synthesis

In 1971, Achmatowicz and co-workers reported the synthesis of 6-methoxy-dihydropyran-3-ones **8** from 2-furfurylcarbinols **4** (Scheme 2).[10] Oxidation of the latter using bromine in methanol delivered 2,5-dimethoxy-2,5-dihydrofurans **5**, which upon acidic hydrolysis formed 1,4-dicarbonyl compounds **6**; these intermediates rapidly cyclised to give the hydroxypyranones **7**. Ketal formation using trimethylorthoformate in the presence of a Lewis acid delivered 6-methoxy-dihydropyran-3-ones **8**. The latter could be further elaborated to monosaccharides.



Scheme 2. Achmatowicz synthesis of 6-methoxy-dihydropyran-3-ones **5**.

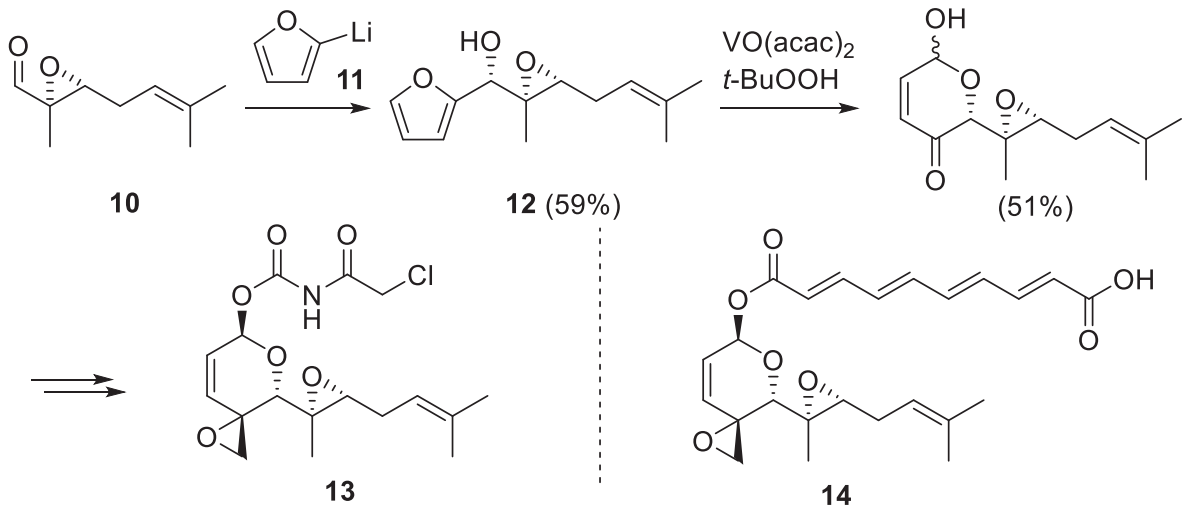
Although this oxidative ring expansion of furans is now referred to as the Achmatowicz reaction,[11] the first report of this transformation was given in 1969 by Cavill and co-workers,[12] in the course of a total synthesis of juvenile hormone **9** (Scheme 3), the latter being isolated from the giant silkworm; this transformation was not studied in detail at that point.



Scheme 3. Cavill's synthesis of the juvenile hormone **9** by furan ring expansion.

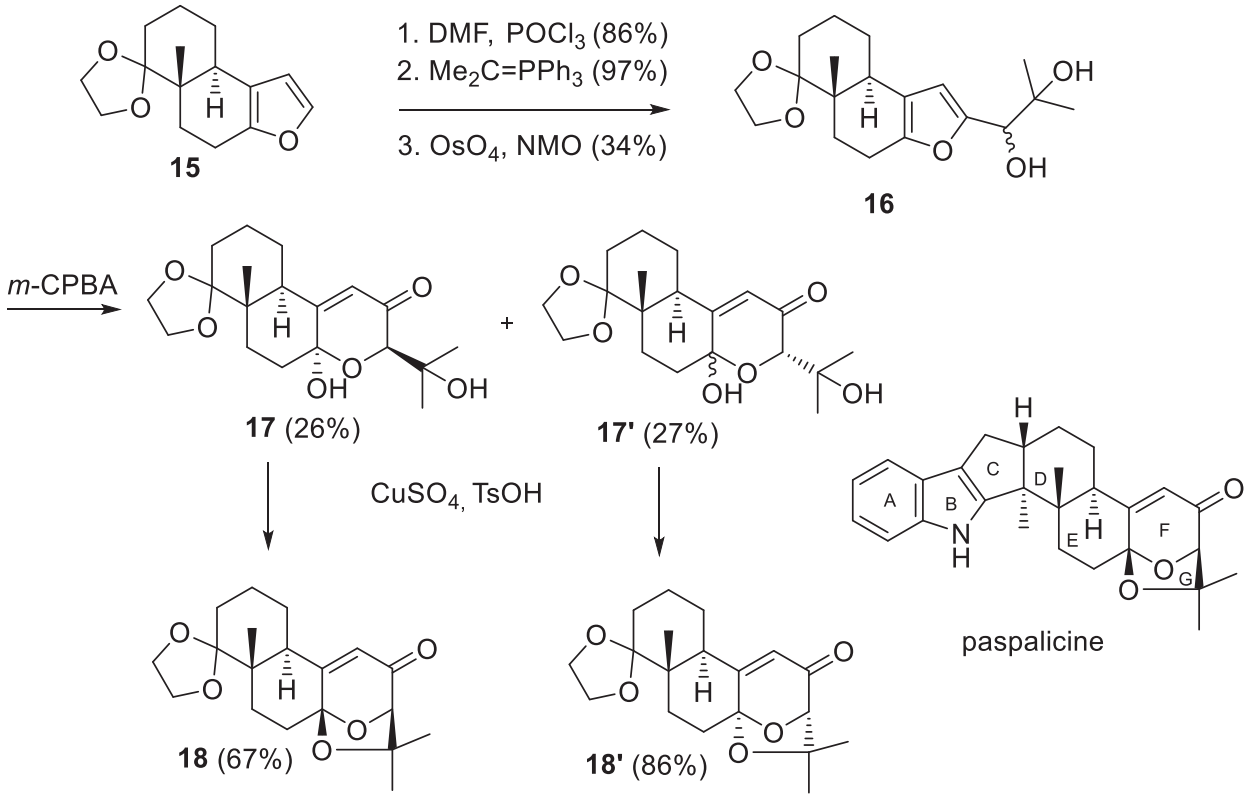
Subsequently, alternative milder oxidants than bromine have been used, such as NBS,[13] dioxirane,[14] titanium silicalite/H_2O_2[15] and $MeReO_3/CO(NH_2)_2$-H_2O_2.[16] Hydroxyl-directed epoxidations of the furan ring using *m*-CPBA or *t*-BuOOH/$VO(acac)_2$ are also commonly used. In addition to traditional chemical oxidations, reactions using photooxygenation,[17] anodic oxidation[18] and enzymatic catalysis[19] have also been reported.

The Achmatowicz reaction has proved to be a valuable transformation, having been used in various total, formal and fragment syntheses of complex natural products and analogues. The furanol precursor **12** for an Achmatowicz reaction could easily be obtained by addition of 2-lithiofuran (**11**) to a epoxyaldehyde **10** (Scheme 4); this strategy was used in Baldwin's synthesis of TNP-470 (**13**) an analogue of the anti-cancer agent fumagillin (**14**).[20]



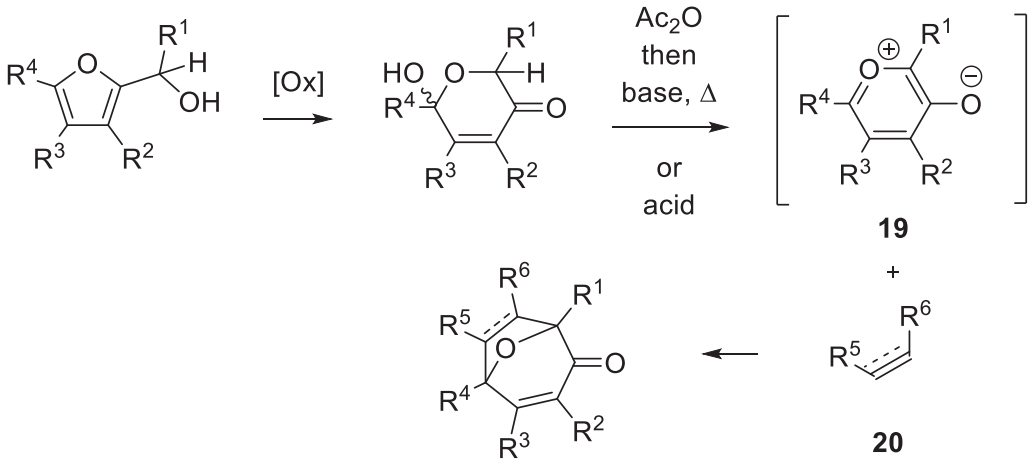
Scheme 4. Baldwin's synthesis of TNP-470 (**13**).

In the synthesis of the D-G rings of paspalicine (Scheme 5), Ali and co-workers[21] presented another interesting way of introducing the 2-furanol motif for an Achmatowicz reaction. Starting from furan **15**, a Vilsmeier-Haack reaction gave the corresponding 2-furfural. After sequential Wittig olefination and dihydroxylation, diol **16** was then subjected to Achmatowicz reaction conditions, using *m*-CPBA. Taking advantage of the resulting hemiketal functionality in **17** / **17'**, TsOH allowed direct conversion to the bridged alkoxy-dihydropyranones **18** / **18'** containing the D-G ring motif of paspalicine.



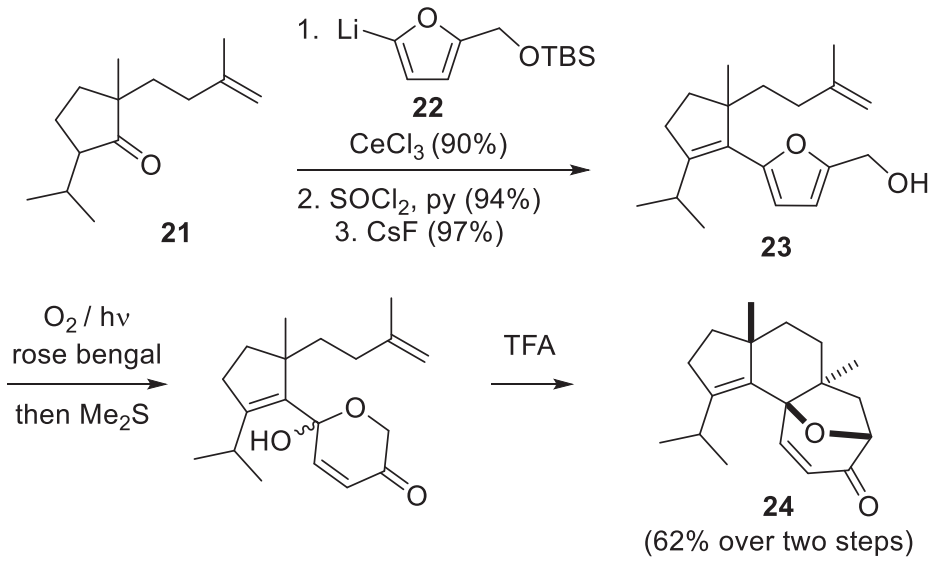
Scheme 5. Ali's synthesis of the paspalicine D-G ring system **18** / **18'**.

Another synthetic utility of the Achmatowicz reaction resides in the ability of the resulting 6-hydroxy-dihydropyranones to generate oxidopyryliums **19** (Scheme 6, usually using Ac_2O in the presence of a base such as pyridine or Et_3N, or under acidic conditions), which are reactive intermediates for [5+2] cycloadditions with dipolarophiles **20**.[11]



Scheme 6. Generation of oxidopyryliums **19** followed by [5+2] cycloaddition.

The above strategy has been used in an intramolecular fashion by Magnus and co-workers in the synthesis of the cyathin diterpene skeleton **24** (Scheme 7).[22] Addition of lithitated furan **22** (the 2-hydroxymethyl moiety being already present on the furan) to cyclopentanone **21**, followed by dehydration and desilylation provided 2-furanol **23**. Photooxygenation, followed by acid-catalysed generation of the oxidopyrylium delivered the desired intramolecular [5+2] cycloadduct **24**.

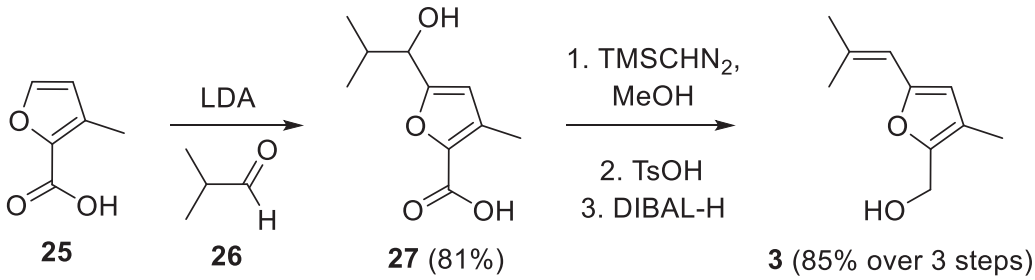


Scheme 7. Magnus' synthesis of the cyathin skeleton **24**.

2. Results and discussion: Early synthetic studies: Achmatowicz reaction

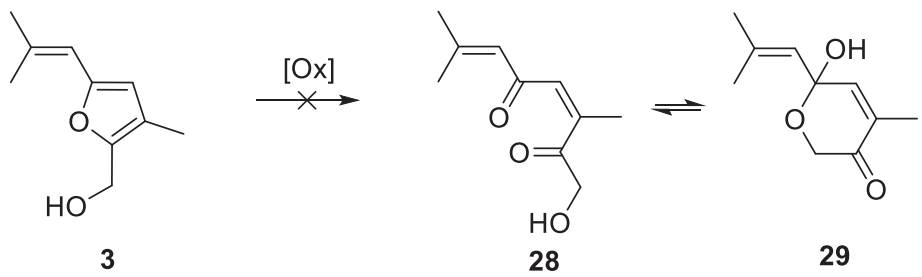
2.1. Hydroxyl-directed oxidation approach

The synthesis of the key furanol intermediate **3** (Schemes 1 and 8) was viewed as arising from addition of a lithiated furan to isobutyraldehyde, followed by elimination. Thus, the dianion derived from 3-methyl-2-furoic acid (**25**)[23] was added to isobutyraldehyde (**26**). Attempted elimination under various conditions ($MsCl/Et_3N$, PPh_3/CBr_4 followed by addition of base, TsOH) did not proceed on the resulting free acid **27**, which was therefore esterified using $TMSCHN_2$. Acid-induced elimination then proceeded smoothly. DIBAL-H reduction of the ester then gave 2-furanol **3**, our substrate for the key Achmatowicz reaction.



Scheme 8. Synthesis of 2-furanol **3**.

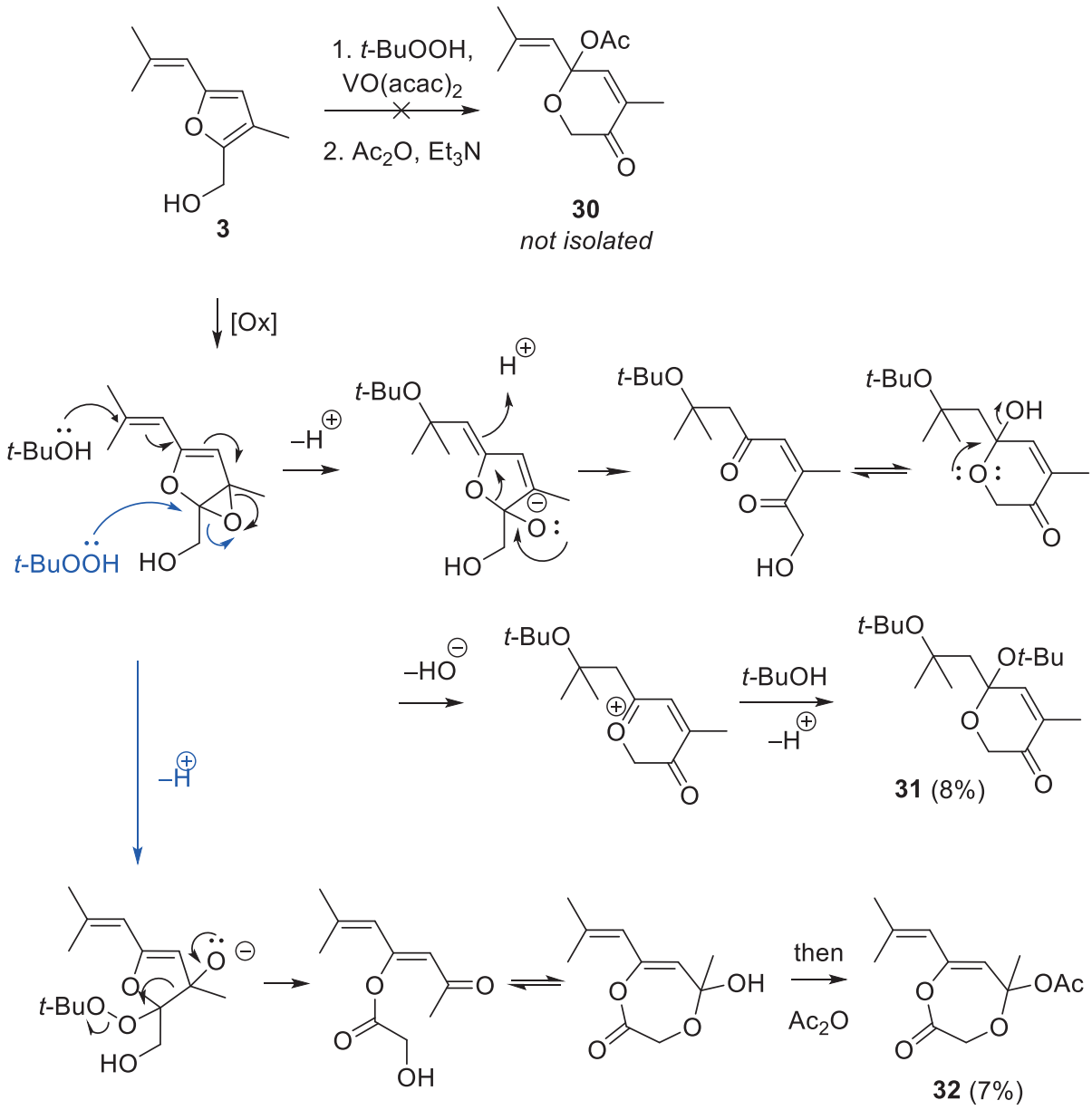
Unfortunately, oxidation of 2-furanol **3** (Scheme 9) using various conditions, such as *t*-BuOOH/$VO(acac)_2$ or *m*-CPBA in the presence or absence of AcONa buffer, failed to deliver the desired 6-hydroxy-dihydropyranone **29**; none of the free hydroxy-dienedione **28**, the initial product of oxidative ring opening, was isolated either.



Scheme 9. Initial Achmatowicz reaction attempt.

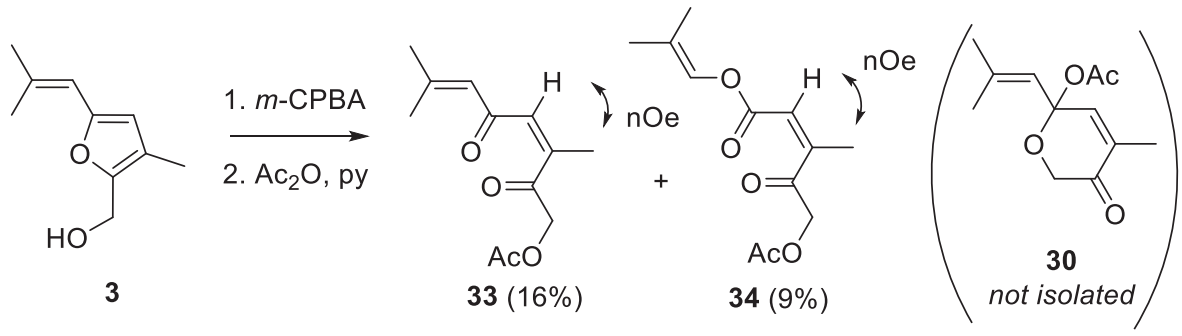
The above failure to deliver the desired 6-membered ring system could be attributed to the likely instability of the hydroxy-dienedione **28**. The instability of hydroxy-dienedione intermediates has already been observed by Trauner and co-workers.[24] and could potentially be overcome by acetylation of the free hydroxy group of the cyclic 6-hydroxy-dihydropyranone form **29**.[24,25]

Oxidation of 2-furanol **3** using *t*-BuOOH/$VO(acac)_2$ followed by acetylation failed to deliver the desired product **30**, but gave a separable mixture of two unexpected products, both in low yield (Scheme 10). The structures of these two compounds could not be established with certainty due to limited quantities of product and inconclusive mass spectrometric analysis. Nonetheless, NMR and IR data are supportive for the structures as described and the formation of these products could be rationalised by initial epoxidation of the furan ring, followed by attack at the side-chain by *t*-BuOH to form **31**, or by oxidative cleavage of the ring to give **32**.



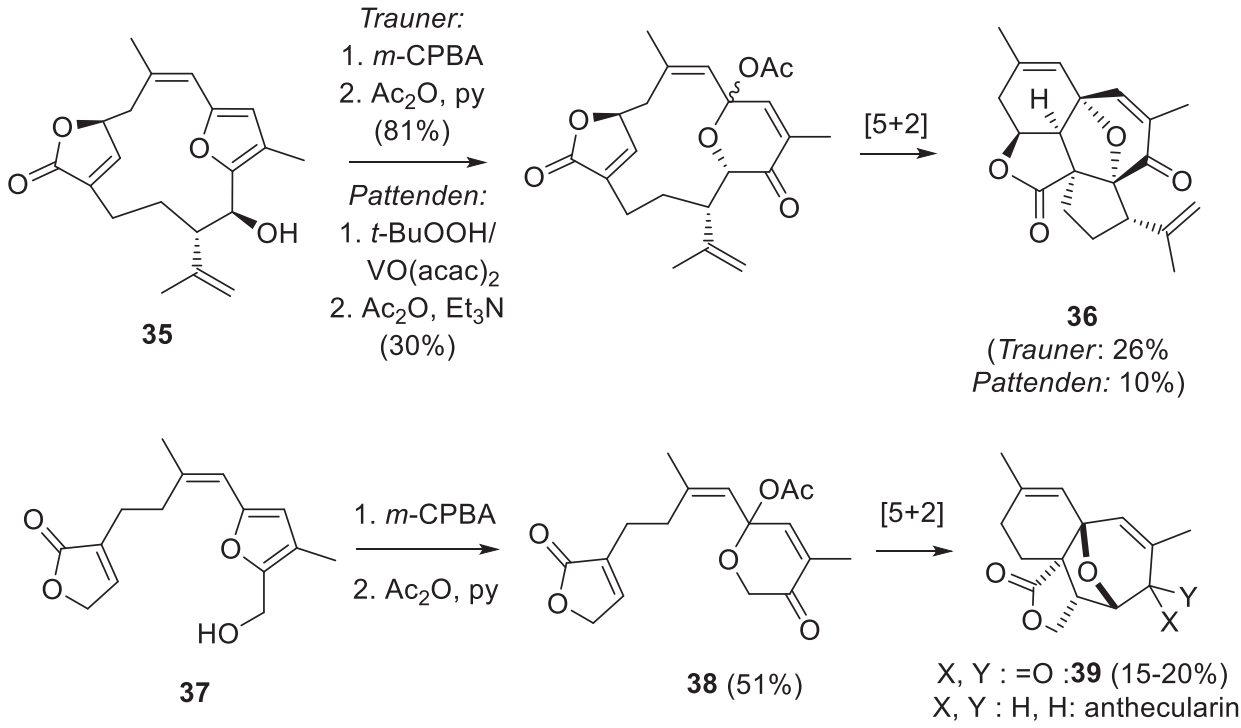
Scheme 10. Achmatowicz attempt and rationalisation of by-product formation.

The presence of nucleophilic species such as *t*-BuOOH and *t*-BuOH in the oxidation appeared to be problematic and we therefore decided to use an electrophilic oxidant instead. However oxidation of **3** using *m*-CPBA (Scheme 11), followed by acetylation also did not deliver the desired pyranone **30**, but rather a separable mixture of dienedione **33**, corresponding to the acetylated derivative of the hydroxy-dienedione **28** (Scheme 9) and ester **34**, formed by Baeyer-Villiger oxidation of hydroxy-dienedione **28** followed by acetylation.



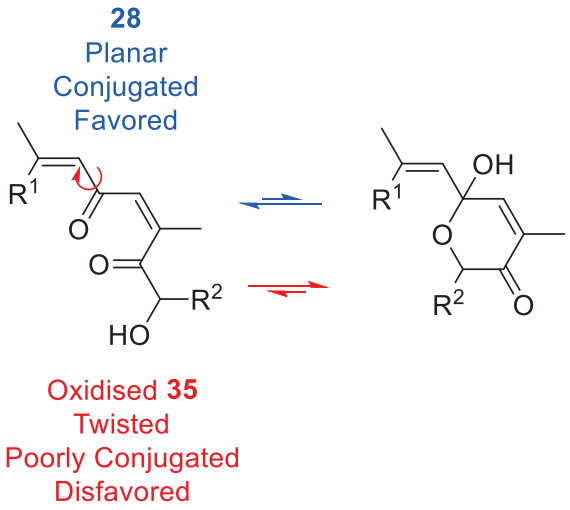
Scheme 11. Attempted synthesis of acetylated hydroxypyranol **30**.

The inability to obtain acetylated hydroxypyranol **30** was surprising, since the use of a conjugated 5-alkenyl-2-furanol precursor has been previously described. In 2006, Trauner[24] and Pattenden[25] independently reported the biomimetic synthesis of intricarene (**36**) from bipinnatin J (**35**, Scheme 12) using an Achmatowicz rearrangement followed by a [5+2] cycloaddition. In 2009, Pattenden[26] also reported the synthesis of anthecularin, from reduction of **39** (Scheme 12) obtained using the same sequence starting from a closely related 5-alkenyl-2-furanol **37**.



Scheme 12. Trauner's[24] and Pattenden's[25] synthesis of intricarene (**36**), Pattenden's[26] synthesis of anthecularin.

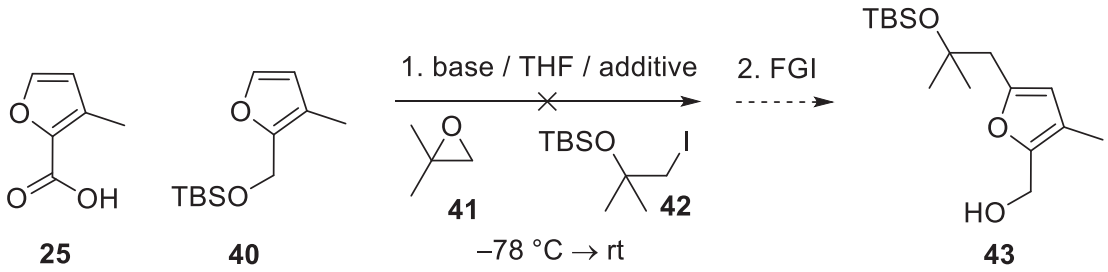
We hypothesised that in our system, the loss of conjugation in tautomerisation to the cyclic 6-hydroxy-dihydropyranone **29** could account for the apparent thermodynamic preference for the linear dienedione **28**. Due to the macrocyclic nature of bipinnatin J (**35**) and its corresponding dienedione oxidation product, the corresponding olefin is potentially slightly twisted out of the plane of the ring, or of the ene-1,4-dione motif (Scheme 13). This would account for a poorer conjugation of the system, the relative enthalpy loss on the cyclic form would be lower, therefore favouring it.



Scheme 13. Possible explanation of differences in equilibrium of hydroxy-dienediones.

The transformation of furanol **37** to 6-acetoxy-dihydropyranone **38** (Scheme 12) also differs from our system, possibly due to a remote inductive effect of the butenolide, lowering the conjugation of the dienedione system.

The above results suggested that the presence of this unsaturation was problematic due to its reactivity (attack by *t*-BuOH / *t*-BuOOH) and its electronic effect (shifting the equilibrium towards **28** (Scheme 9, p. 9). We therefore decided to synthesise furanol analogues bearing a protected alcohol on the side-chain. However, attempts to obtain tertiary alcohol **43** (Scheme 14), by nucleophilic attack of the lithiated furans from **25** or **40**[27], to epoxide **41** or silylated iodohydrin **42**[28] failed, probably due to the steric hindrance of the electrophiles.



Furan	Base	Electrophile	Additive
25	LDA	**41**	no
"	"	"	$BF_3{\cdot}Et_2O$
"	"	**42**	no
"	"	"	TMEDA
40	*n*-BuLi	**41**	no
"	"	"	TMEDA
"	"	**42**	no
"	"	"	TMEDA

Scheme 14. Attempted synthesis of tertiary alcohol **43**.

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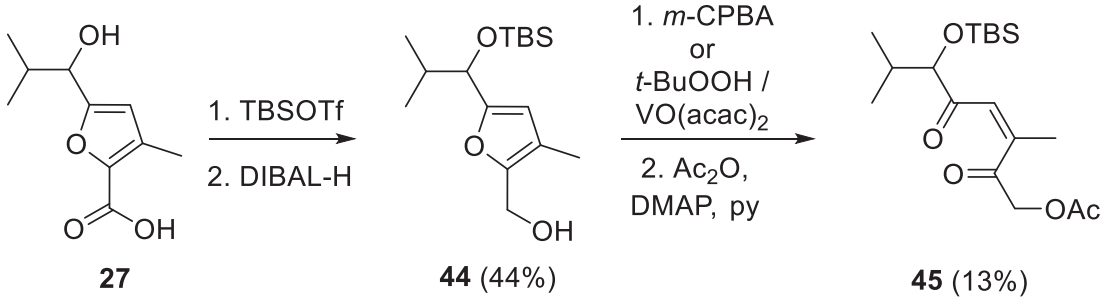
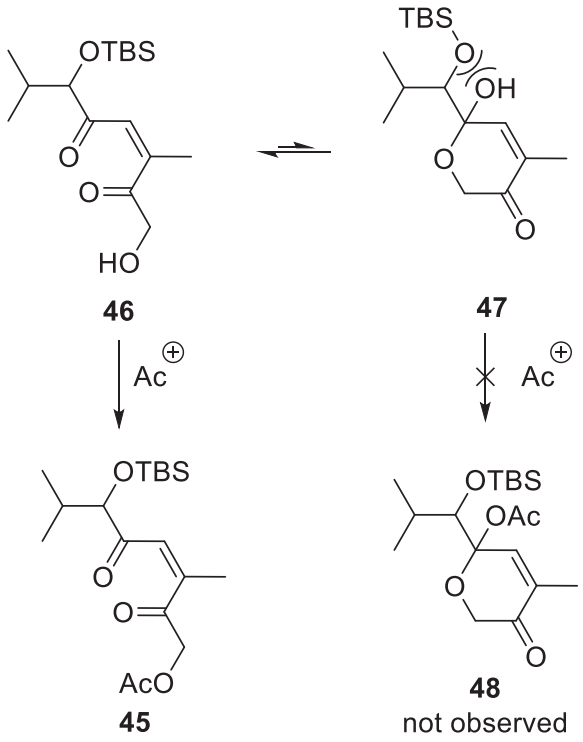
Reaction of furanol **27** (Scheme 15) with excess TBSOTf, followed by reduction using DIBAL-H afforded the protected secondary alcohol **44**. Unfortunately, oxidation followed by acetylation again delivered (in low yield) a linear ene-1,4-dione **45** oxidation product.



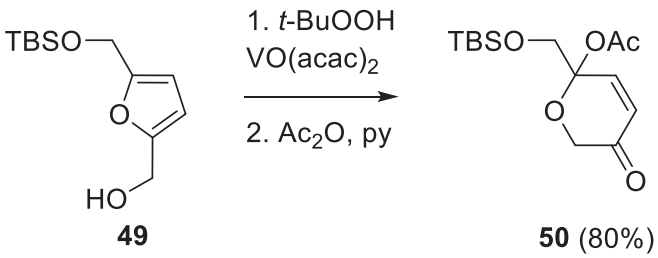
Scheme 15. Synthesis and oxidation of protected secondary alcohol **44**.

In this case, the preference for the linear ene-1,4-dione **45** could not be attributed to the loss of conjugation, but could be rationalised as due to the sterically demanding environment around the hemiketal centre in the cyclic 6-hydroxy-dihydropyranone form (**47**, Scheme 16), shifting the equilibrium towards the former.



Scheme 16. Steric hindrance on the hemiketal centre.

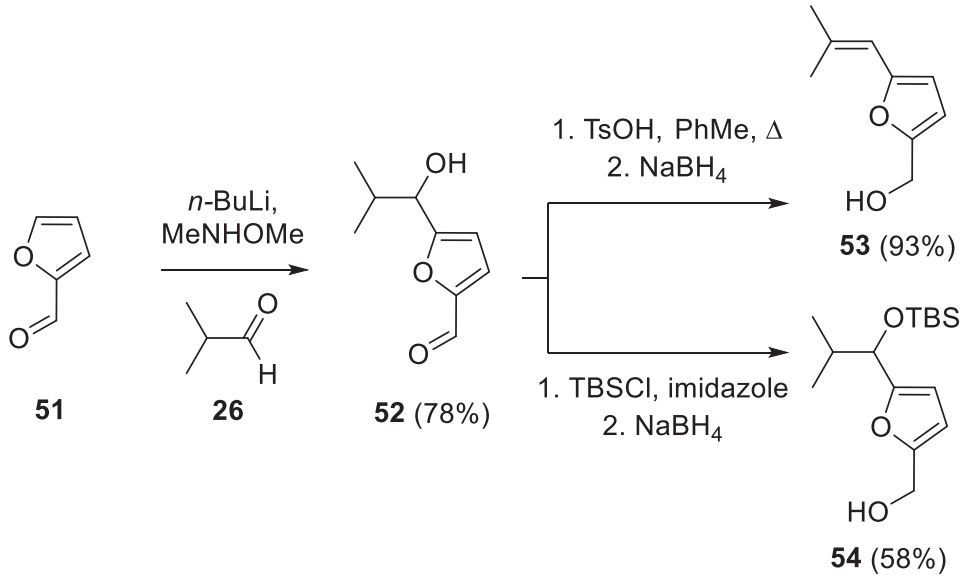
Following the above analysis, use of a less sterically hindered furanol should enable formation of the cyclic system. Oxidation of furanol **49**[29] followed by acetylation indeed provided 6-acetoxy-dihydropyranone **50** (Scheme 17).



Scheme 17. A less sterically hindered furanol provided the desired 6-membered ring system.

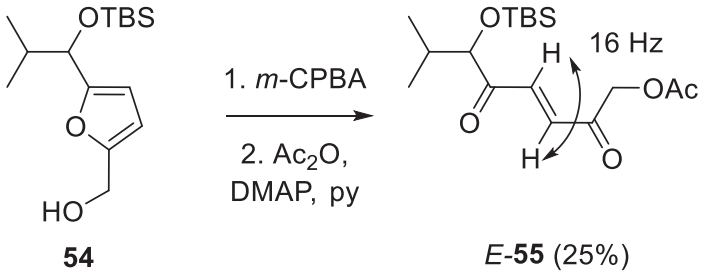
The 3-methyl analogue of this product could, in principle, be further elaborated to the desired 6-acetoxy-dihydropyranone **30** (Scheme 10, p.11), by subsequent desilylation, oxidation to the aldehyde and Wittig olefination. However, this synthetic route was not explored due to its overall length.

The above studies indicated that, despite some literature precedent of Achmatowicz reaction on related furanols, the synthesis of **30** from **3** (Scheme 10, p.11) was not straightforward. It appeared necessary to have access to a greater amount of furanols for the studies and we decided to synthesise 2-furanols **53** and **54** lacking a 3-methyl group (Scheme 18), which could be accessed in three steps from inexpensive furfural (**51**). *In situ* protection / lithiation[30] of furfural (**52**) followed by addition to isobutyraldehyde (**26**) gave furanal **52** in good yield. Subsequent acid-catalysed elimination followed by reduction gave furanol **53**. It is noteworthy that, while scaling up (>500 mg), the elimination did not proceed but instead, gave decomposition; this step was not further optimised at this point and the problem was overcome by splitting the reaction into ~ 250 mg batches. TBS-protection of **52** followed by reduction provided furanol **54**.



Scheme 18. Synthesis of furanols **53** and **54**.

Oxidation of the latter compounds were then carried out using conditions described above (Schemes 10, 11). Unfortunately, starting from olefin containing furanol **53**, complete decomposition was observed, whereas oxidation of furanol **54** (Scheme 19), followed by acetylation, surprisingly led to the *E*-isomer of the oxidation product dienedione **55** (assigned on the basis of 16 Hz ^3J olefinic coupling). This isomerisation could be explained by reversible conjugate addition of DMAP to the initial *Z*-2-ene-1,4-dione. *Z*→*E* isomerisation was not observed in our previous systems (**3**→**33**, Scheme 11, p. 12, **44**→**45**, Scheme 15, p.15), probably due to the additional methyl group retarding nucleophilic attack.



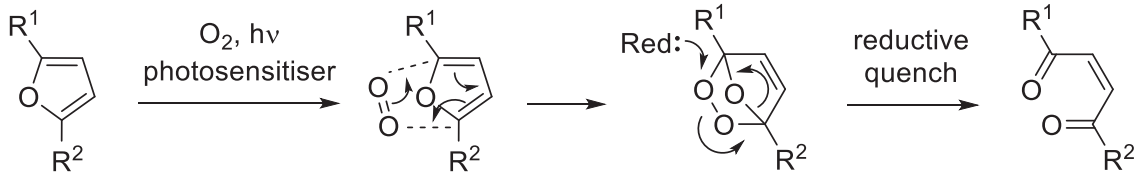
54 *E*-**55** (25%)

Scheme 19. Oxidation of furanol **54**.

It appeared that replacing the olefin in the side-chain by a protected alcohol (**44** and **54,** Schemes 15 and 19) was not a viable alternative, probably due to steric hindrance preventing formation of the cyclic 6-acetoxy-dihydropyranones. Therefore, we decided to refocus our effort on a system featuring the olefinic side chain (**53**).

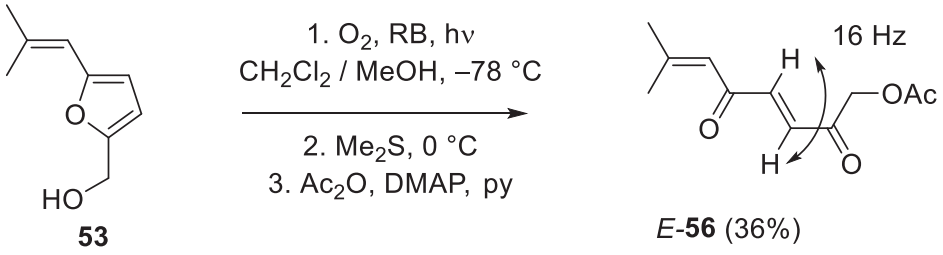
2.2. Investigations on the photooxygenation of furanols

Our earlier studies (Schemes 10 and 11, p. 11-12) showed that using traditional chemical oxidation the presence of a conjugated olefin such as that contained in furanol **53** was problematic (facile nucleophilic attack, or Baeyer-Villiger type chemistry). With this in mind, we studied the photooxygenation of **53** (Scheme 20, [4+2] cycloaddition of singlet oxygen with the furan),[17] as this was anticipated to proceed with better chemoselectivity: this transformation could be conducted in the presence of electron rich olefins as exemplified by Magnus et al. in the photooxygenation of conjugated 5-alkenyl-2-furanol **27** (Scheme 7, p. 8).[22]



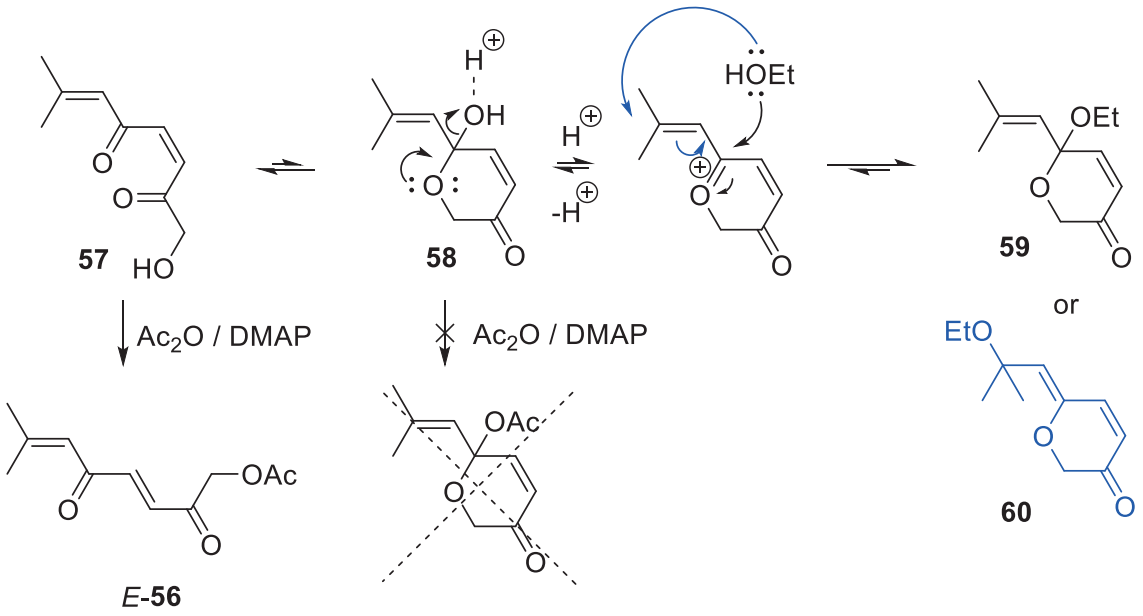
Scheme 20. General principle of furan photooxygenation.

Photooxygenation of furanol **53** (Scheme 21) using rose Bengal (RB) as photosensitiser in a mixture of CH_2Cl_2 / MeOH at low temperature, followed by dimethyl sulfide reductive quench and acetylation, resulted in the acetylated *E*-isomer of the open chain ene-1,4-dione **56**. It was hypothesised that this isomerisation occurred *via* the same mechanistic pathway as suspected in **54**→**55** (Scheme 19).



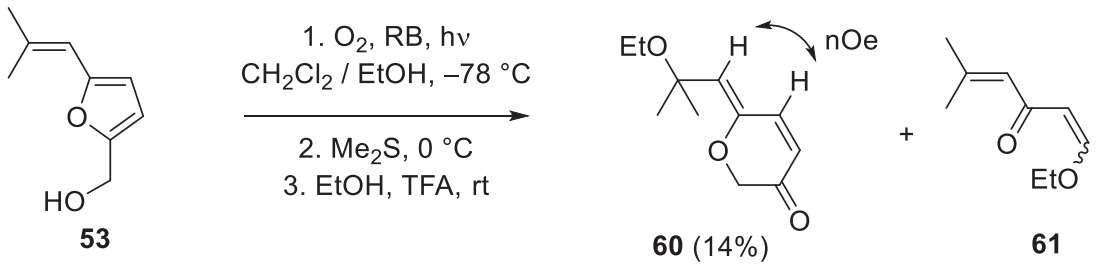
Scheme 21. Photooxygenation–acetylation of furanol **53**.

In the case of oxidation of olefin-containing furanol **53**, the desired 6-acetoxy-pyranone **58** (Scheme 22) seemed to be thermodynamically disfavoured, possibly due to the loss of conjugation as previously discussed (p.13). Acid-catalysed ethoxylation of this species, rather than an electrophilic trapping (i.e. acetylation), could provide a driving force for the generation of the cyclic dihydropyranones **59** and **60** (Scheme 22); furthermore, these conditions would avoid the use of nucleophilic base / catalyst such as Et_3N or DMAP typically used in acetylation and suspected to cause *Z*→*E* isomerisation of the ene-1,4-dione motif found in diene-1,4-diones **57** and **56**.



Scheme 22. Anticipated outcome of acid-catalysed ethoxylation *vs* electrophilic trapping.

Photooxygenation of **53** followed by acid-catalysed ethoxylation, using conditions described by Magnus,[22] indeed resulted in the formation of dihydropyranone **60** (Scheme 23). Despite the low yield (14%), this result was encouraging, because for the first time a 6-membered ring product was generated *via* the Achmatowicz strategy.



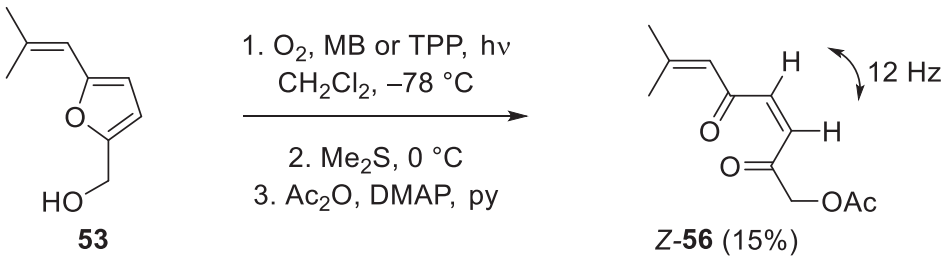
Scheme 23. Photooxygenation furanol **53**.

Unfortunately, on repeat runs, only traces amounts (<5%) of desired dihydropyranone *Z*-**60** were isolated. Complex mixtures were obtained, with the tentative formation of **61**[†] being the only other detectable product, and being presumably obtained *via* Baeyer-Villiger chemistry.[31]

The presence of this latter by-product led us to study the photooxygenation in more depth. So as to simplify the study, we decided to take a step back and isolate the oxidation products as their acetylated forms. The trapping of the oxidised species would be studied, once the oxidation conditions were optimised.

Earlier, we hypothesised that the isomerisation process was occurring during the acetylation step due to the presence of nucleophilic species such as DMAP. Photooxygenation of furanol **53** (Scheme 24), using methylene blue (MB) or tetraphenylporphine (TPP) in CH_2Cl_2 (no alcoholic solvent present), followed by the same reductive quench and acetylation was therefore expected to give enedione *E*-**56**, but instead resulted in the formation of enedione *Z*-**56**.

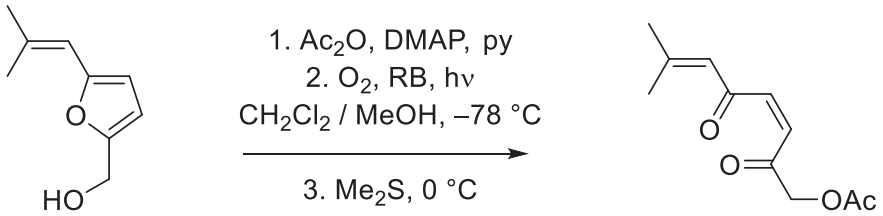
[†] Only small amounts were obtained (<5 mg from 50 mg of furanol **47**) as impure fractions but characteristic olefinic peaks seen by NMR spectrometry were: ^{1}H NMR ($CDCl_3$): 2 d (*J* 12.5) at 7.56 and 5.63 ppm for CH=C<u>H</u>OEt and C<u>H</u>=CHOEt, respectively. ^{13}C NMR ($CDCl_3$): 161.2 ppm <u>C</u>H=CHOEt and 107.8 ppm CH=<u>C</u>HOEt.



53 *Z*-**56** (15%)

Scheme 24. Photooxygenation of furanol **53** using alcohol free solvent mixture.

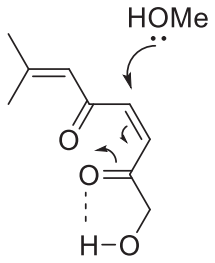
Interestingly, photooxygenation of furanol **53** after acetylation, under the conditions described above (CH_2Cl_2 / MeOH, Scheme 21), also resulted in the formation of *Z*-**56** (Scheme 25).



53 *Z*-**56** (11%)

Scheme 25. Acetylation–photooxygenation of furanol **53**.

As negative controls: the transformation described earlier **53**→*E*-**56** (Scheme 21), was repeated using a flask shielded from light during the acetylation step, enedione *E*-**56** was once again obtained; in a separate test enedione *Z*-**56** was stirred overnight in EtOH; but no isomerisation was observed. These results suggested that, contrary to what was postulated earlier, in the transformations **53**→*Z*-**56** (Scheme 21, p. 19), the isomerisation does not occur during the acetylation step: either by reversible conjugate addition of a nucleophile to the ene-1,4-dione **57** or **56** (Scheme 22, p. 20), or by a light-induced pathway. The isomerisation is most likely to happen on the free hydroxy-dienedione **57** during the reductive quench *via* a reversible oxy-Michael addition, in the presence of alcoholic solvent. This isomerisation was observed only on the free hydroxy system, possibly due to the existence of intramolecular hydrogen bonding, enhancing the reactivity of the dienedione **57** (Figure 2).



57

Figure 2. Intramolecular hydrogen bonding promoting oxy-Michael addition.

The furan oxidation processes proved low yielding and poorly selective, leading to the formation of 1,4-enediones instead of the desired 6-hydroxy-dihydropyranones. Moreover, some of these 1,4-enediones showed high configurational liability. Therefore, despite the encouraging but non-reproducible transformation of furanol **53** to dihydropyranone *Z*-**60** (Scheme 23); the use of Achmatowicz reaction for the synthesis of the postulated structure of aruncin B was abandoned. Instead a synthetic route relying on a potentially more reliable ring formation using ring-closing alkene metathesis (RCM) was next examined (Section 3).

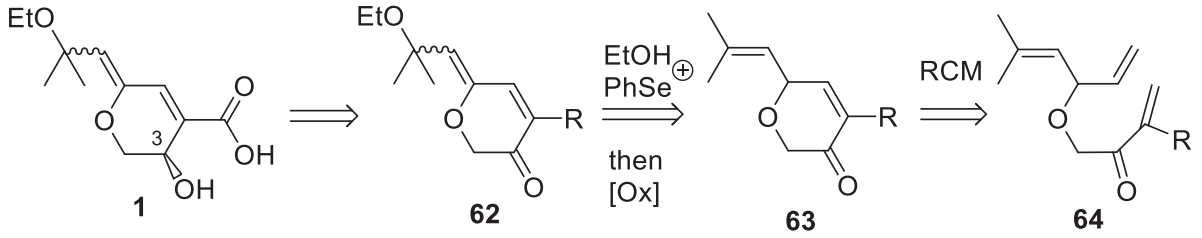
3. Results and discussion: The RCM / ethoxyselenation–selenoxide elimination approach to the dihydropyran derivatives

3.1. New retrosynthesis

The inability to obtain the 6-membered ring system by oxidation of furanol derivatives (Section 2, p. 9-23) highlighted the need for a strategy relying on an efficient and reliable way of generating a dihydropyran intermediate. A sequence based on a Ring-Closing Alkene Metathesis (RCM) approach (Scheme 1) seemed to fulfil these requirements perfectly, as many cases of the use of RCM strategies to construct 6-membered oxa-cyclic natural products or natural product-like compounds have been disclosed.[32-34]

Another challenging aspect of the synthesis was the installation of the key, (acid) sensitive, enol ether motif. The generation of this functional group was envisaged through an ethoxyselenation–selenoxide elimination sequence. This method was chosen for its chemoselectivity as well as its mildness: the ethoxyselenation occurs on the most electron rich olefin and in the oxidative elimination step the selenium atom could be selectivily oxidised in the presence of other functional groups. Moreover, elimination of the *in situ* generated selenoxide does not require high temperature or the use of strong base.[35]

Retrosynthetically, the synthesis of aruncin B was envisaged *via* late stage FGI of γ-alkylidenedihydropyranone **62** (Scheme 1). The key enol ether motif would be obtained by an ethoxyselenation–selenoxide elimination sequence (**63→62**), and the dihydropyranone ring **63** would be formed by RCM of an appropriate triene precursor **64**. The exact order of the late stage FGI and the nature of the side chain (R) would be determined through experimentation.



Scheme 26. Revised retrosynthesis of originally postulated structure of aruncin B (**1**).

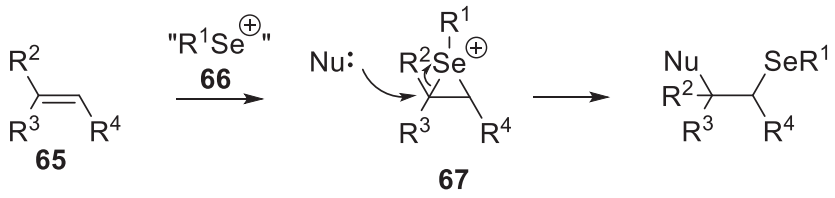
The presence of a ketone at C(3) would present several advantages: avoiding dealing with diastereoisomers prior to installation of the enol ether, differentiating the electron density of the endo and exocyclic olefins and would provide the opportunity for a late-stage asymmetric reduction (such as a Noyori or Itsuno reduction).[36,37]

As this new strategy mainly focused on two different synthetic methods: addition of electrophilic selenium species to olefin followed by oxidative elimination and RCM, these chemistries will be briefly discussed and placed in the context of target oriented synthesis.

3.2. Oxyselenation–selenoxide elimination chemistry and some of its applications

Although the use of selenium reagents is often disregarded by the synthetic community due to their malodour, toxicity and the generation of significant amounts of waste; they show some useful applications for the synthesis of complex molecules.[35]

Reaction of an electrophilic selenium species **66** with olefins **65** forms the three-membered ring intermediate seleniranium cation **67** (Scheme 27). In the case of a reaction with a polyunsaturated substrate, this occurs preferentially at the most electron rich olefin. This cationic intermediate **67** can then be opened by a nucleophile; the latter attacking at the more substituted position from the opposite face of the seleniranium bridge.

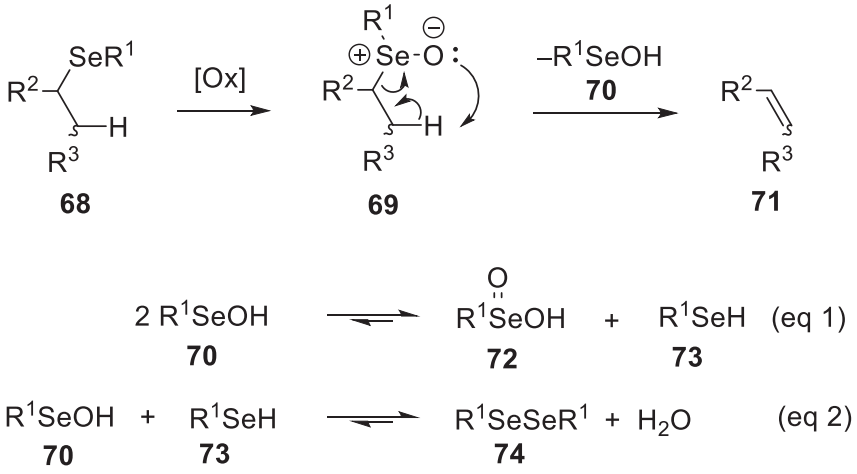


Scheme 27. General reaction scheme for selenation of olefins.

While using water or an alcohol as nucleophile, this sequence enables the synthesis of β-hydroxy or alkoxy selenides. Usually R^1 = Ph, but examples using R^1 = Me, 2-Pyridyl,or *p*- or *o*-$NO_2C_6H_4$ have also been reported. Selenyl chloride or bromide are the most commonly used sources of electrophilic selenium, but the cationic species **66** could be obtained by oxidation of the corresponding diaryl (or dialkyl)diselenide (R^1SeSeR^1).[35]

Selenides **68** can be easily oxidised to the corresponding selenoxides **69** (Scheme 28). Compared with sulfoxides, Se–O bonds are more polarised than the corresponding S–O due to the lower electronegativity of the Se atom, making the selenoxides more basic than sulfoxides. Moreover, Se–O and Se–C bonds are longer than the corresponding S ones. As a result, in the presence of β-protons, selenoxides easily undergo a *syn*-elimination reaction, generating

selenenic acid **70** and the corresponding olefin **71** (Scheme 28). This fragmentation generally occurs at rt or lower, whereas temperatures typically higher than 60 °C are required for the *syn*-elimination of sulfoxides (>200 °C for the corresponding aminoxides). In the case of a selenoxide **69** having only one β-proton which could be involved in the *syn*-elimination, the geometry of the resulting olefin is dictated by the stereochemical relationship between the α and β carbon centres. The resulting selenenic acid **70** is unstable and disproportionates to seleninic acid **72** and selenol **73** (eq 1). The selenol **73** can further react with the selenenic acid **70** present to loose water and give diselenide **74** (eq 2).



Scheme 28. Selenoxide elimination and selenenic acid disproportionation.

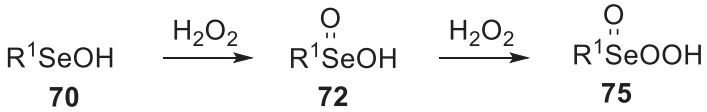
Many oxidative conditions have been reported in the literature but the most commonly used are:

- Ozonolysis: which could be carried out in the presence of olefins, the selenium atom reacting approximately 50 times faster than an olefin.[38] Ozonolyses are generally carried out at low temperature (–78 °C) in aprotic solvent, after appearance of the blue colour the reaction is warmed to allow the *syn*-elimination.

-*m*-CPBA: likewise, this method could be carried out at low temperatures. This usually requires the use of a mild base, to neutralise the carboxylic acid generated from reduction of the peracid.[39]

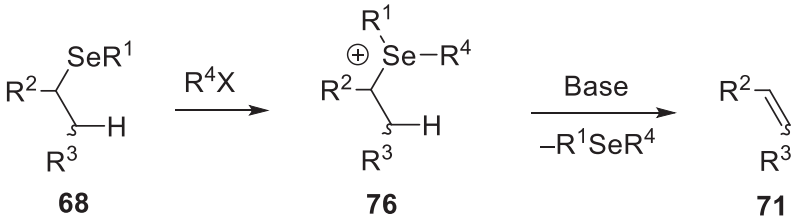
-$NaIO_4$: this method is very mild and is often chosen for oxidation of aldehyde-containing selenides. They are usually run in aqueous alcohol at 0 °C or rt.[40]

-Peroxides: H_2O_2 is cheap, commonly used and the oxidation occurs rapidly.[41] It also further oxidises the generated selenenic acid into perseleninic acid **75** (Scheme 29), responsible for Baeyer-Villiger chemistry on carbonyl-containing selenides. The use of *t*-BuOOH instead of H_2O_2 prevents the formation of perseleninic acid.[42]



Scheme 29. Perseleninic acid **75** formation.

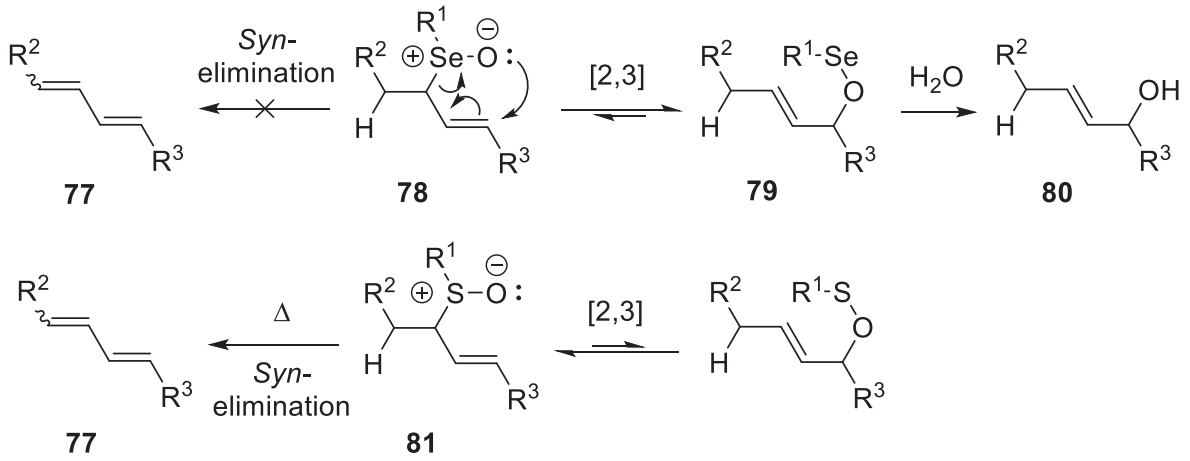
Although the following method is less well-known and examples are rather elusive, selenides **68** could be alkylated (typically using MeI or Magic Methyl) and the resulting selenonium **76** eliminated in the presence of a base (*t*-BuOK or KOH) (Scheme 30). To the best of my knowledge, the mechanism of the elimination has not been determined.[43]



Scheme 30. Selenide alkylation and selenonium elimination.

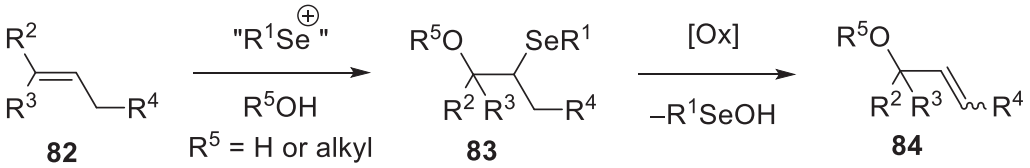
It is worth noting that the oxidation of an allylic selenide **78** (Scheme 31), generally does not result in the formation of a diene **77**, but rather an allylic alcohol **80**, due to the tendency of

allylic selenoxides to undergo [2,3] sigmatropic rearrangement. The rearrangement product **79** is readily hydrolysed to form the alcohol **80**. This is in contrast with the reactivity of the corresponding sulfoxide **81**, in which case the [2,3] sigmatropic rearrangement is disfavoured and the diene **77** can be obtained upon heating by *syn*-elimination.[44]



Scheme 31. Comparison between the reactivity of allylic selenoxides **78** and sulfoxides **81**.

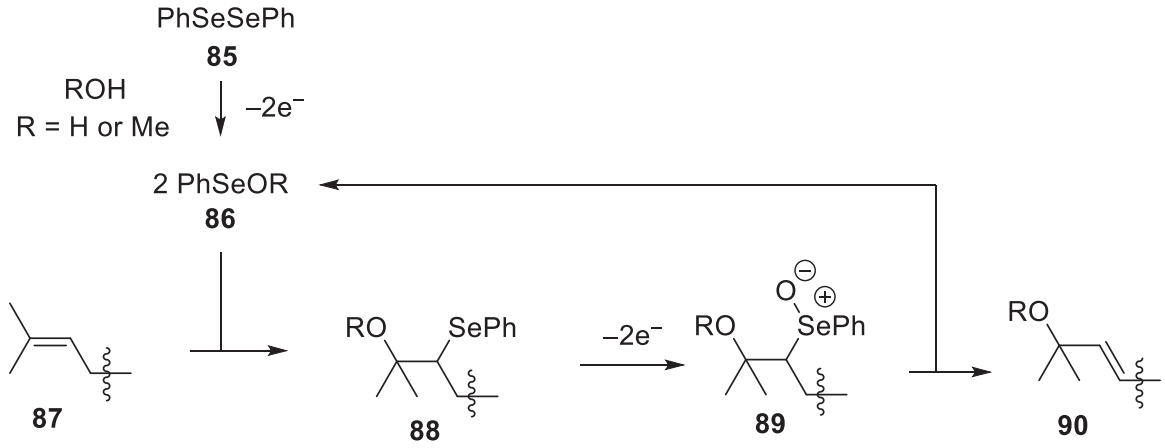
Carrying out the addition of the electrophilic selenium species to an olefin **82** in the presence of water or an alcohol (Scheme 32), followed by oxidation of the resulting β-hydroxy or alkoxyselenide **83** and *syn*-elimination of the resulting selenoxide, represents an efficient method for the synthesis of allylic alcohols or ethers **84** from olefins.



Scheme 32. Synthesis of allylic alcohols or ethers from olefins.

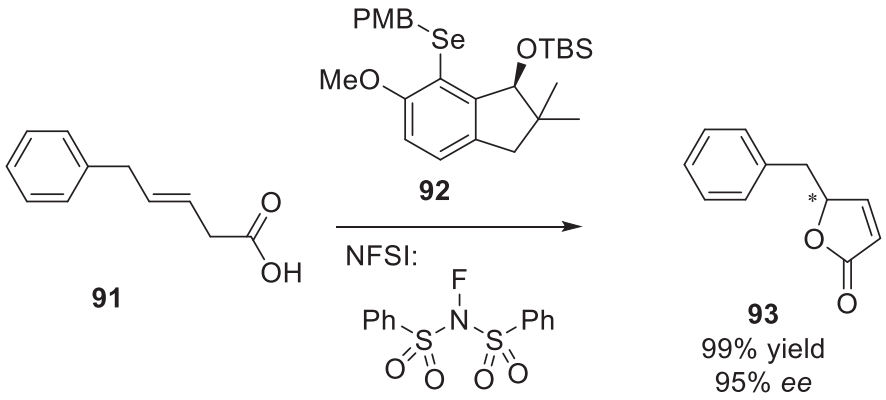
In 1980, Torii reported the synthesis of allylic alcohol (or methyl ether) **89** from olefin **86** (Scheme 33), with substoichiometric amount of selenium reagent under electrochemical conditions.[45] The diphenyl diselenide (**85**) precatalyst (10 mol%) was oxidised to the corresponding phenylselenenic acid (or the corresponding methyl ester) (**86**), which was then

added to the olefin **87**. Oxidation of the resulting selenide **88** followed by *syn*-elimination of the selenoxide **89** delivered the desired allylic alcohol (or methyl ether) **90**. The phenylselenenic acid could then re-enter in the catalytic cycle and add to another olefin.



Scheme 33. Torii's electrochemical method for synthesis of allylic alcohol and ether.

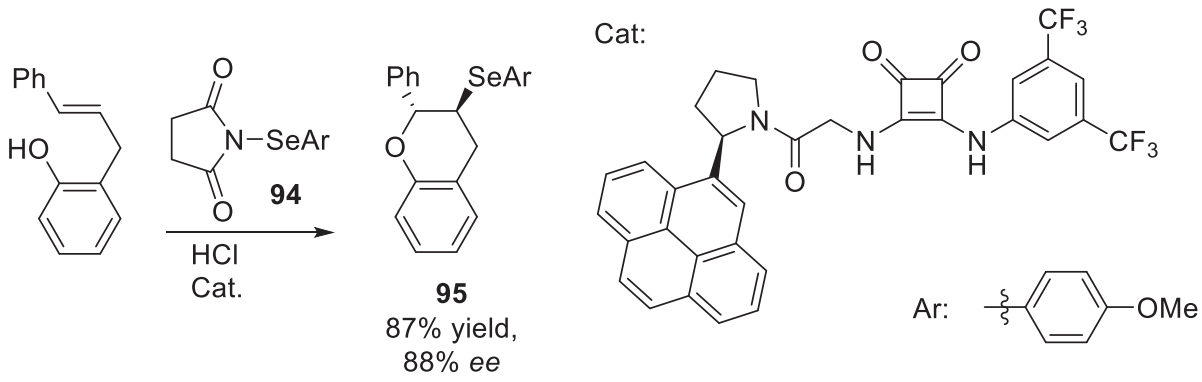
A more advanced use of this concept had been recently reported by Maruoka et al., for the enantioselective synthesis of α,β-unsaturated γ-lactone **93** from β,γ-unsaturated acid **91**, using a chiral selenium precatalyst **92** with NFSI as the stochiometric oxidant (Scheme 34).[46]



Scheme 34. Maruoka's enantioselective synthesis of α,β-unsaturated γ-lactone **93**.

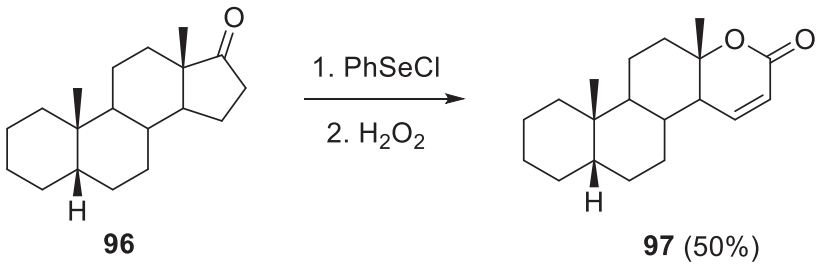
Jacobsen et al. recently reported another method for the enantioselective synthesis of alkoxyselenide **95**, using this time an achiral (and stochiometric) source of electrophilic

selenium **94** (Scheme 35).[47] The enantioselectivity originates from a dynamic kinetic resolution of the selenarium intermediate.



Scheme 35. Enantioselective intramolecular alkoxyselenation by dynamic kinetic resolution of selenarinium intermediate.

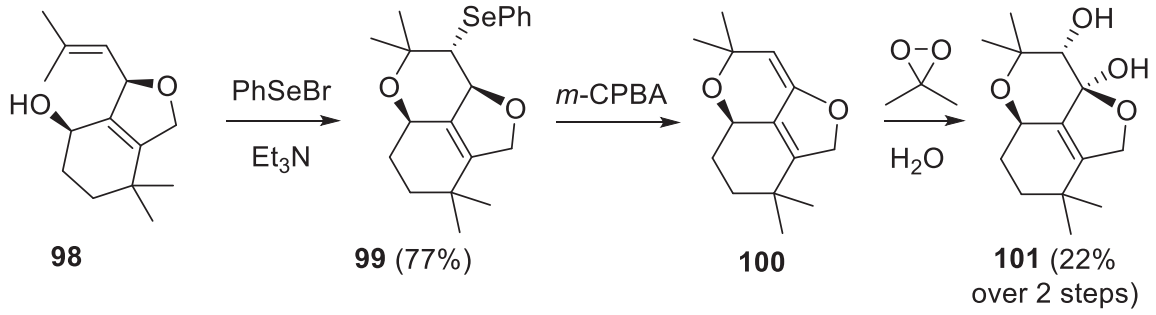
In 1977, Fetizon showed an interesting way of taking advantage of the selenium by-products generated in the *syn*-elimination, to synthesise the steroidal α,β-unsaturated δ-lactone **97** from the corresponding cyclopentanone **96** (Scheme 36).[48] α-selenylation of the ketone followed by oxidation delivered the unsaturated ketone which underwent Baeyer-Villiger oxidation in the presence of the phenylperseleninic acid formed by action of the excess H_2O_2 on the phenylselenenic acid.



Scheme 36. Fetizon's synthesis of α,β-unsaturated δ-lactone from cyclopentanone.

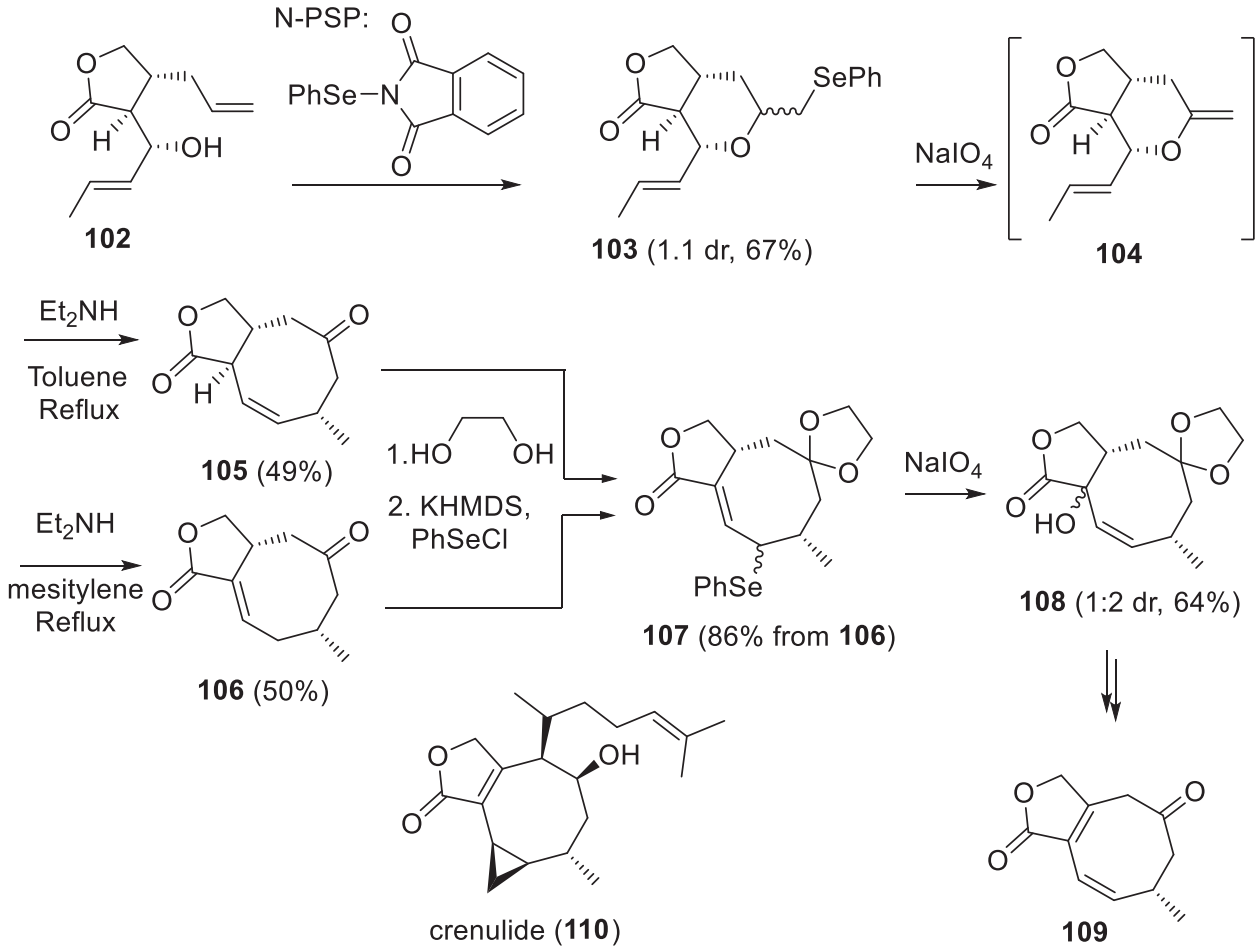
In 1996, in synthetic studies towards phomactin A, Pattenden et al. described an interesting intramolecular alkoxyselenation of the bicycle **98** to form the tricyclic alkoxyselenide **99**,

which after oxidation formed the enol ether **100** (Scheme 37).[49] The latter was then dihydroxylated using aqueous dimethyl dioxirane to give the desired α-hydroxyl hemiketal **101**.



Scheme 37. Pattenden's synthesis of Phomactin tricyclic core.

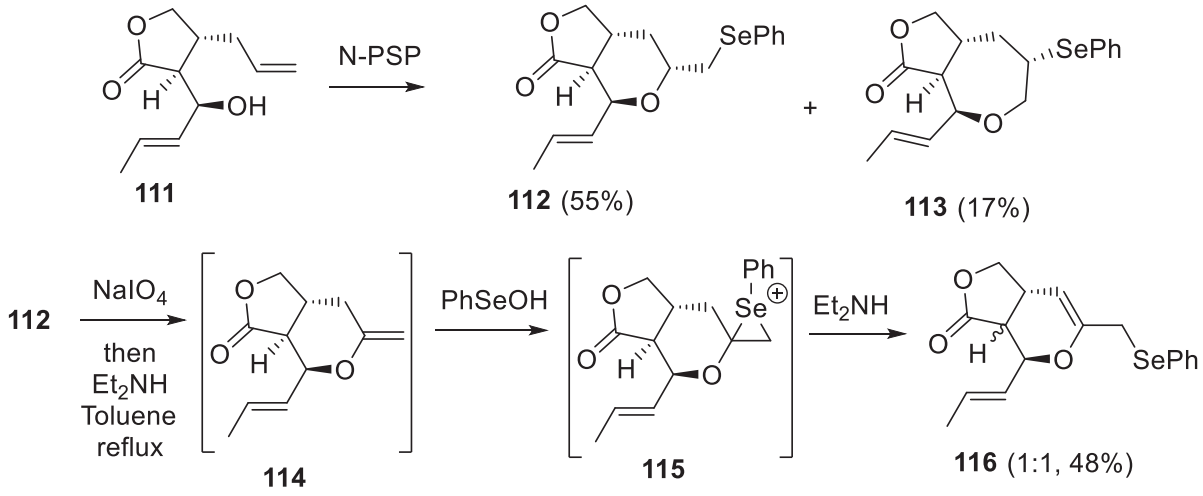
In his synthetic studies towards the core structure **109** of the diterpene crenulide (**110**, Scheme 38), Paquette demonstrated the value of the use of selenium reagents in several instances.[50] The starting allylic alcohol **102** was prepared *via* oxidation-selenoxide elimination of an α-hydroxy selenide, resulting from aldol condensation between a lactone and the corresponding α–seleno aldehyde (not illustrated). Intramolecular alkoxyselenation of allylic alcohol **102** gave the desired selenide **103** as a 1:1 mixture of diastereoisomers. Oxidation-elimination delivered the desired enol ether **104**, which in solution in refluxing toluene in the presence diethylamine underwent Claisen rearrangement to give the 8-membered ring intermediate **105**. The use of refluxing mesitylene resulted in further isomerisation to give the conjugated product **106**. Starting from either of these isomers, ketone protection followed by selenylation using PhSeCl of the extended lactone enolate generated by action of KHMDS gave allylic selenide **107**. Oxidation of the later resulted in the formation of the allylic alcohol **108** *via* [2,3] sigmatropic rearrangement–hydrolysis, the poor diastereoselectivity of the latter sequence was inconsequential since the alcohol was eliminated later.



Scheme 38. Paquette's synthetic studies towards crenulide (**110**) bicyclic core **109**.

It is worth noting that starting from allylic alcohol **111** (Scheme 39), an epimer of **102**, the outcome of the intramolecular alkoxyselenation–selenoxide elimination sequence was different. Using the same conditions as described above the selenide **112** resulting from the intramolecular alkoxyselenation of allylic alcohol **111** was, this time, isolated as a single diastereoisomer, but was accompanied by a 7 membered-ring by-product **113**, corresponding to a 8-*endo*-*tet*-opening of the seleniranium intermediate. Oxidation of alkoxyselenide **112** followed by treatment with diethylamine in refluxing toluene did not result in the desired Claisen rearrangement product but in allylic selenide **116**. The product was suspected to be formed by further reaction of the enol ether **114** (the desired product of the selenoxide elimination) with the resulting phenylselenenic acid to give seleniranium **115**, which was then

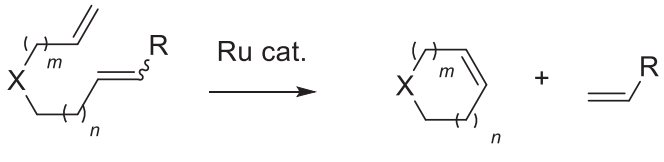
opened under basic treatment. The α-ester stereogenic centre was also epimerised under these conditions.



Scheme 39. Unexpected allylic selenide **116** formation.

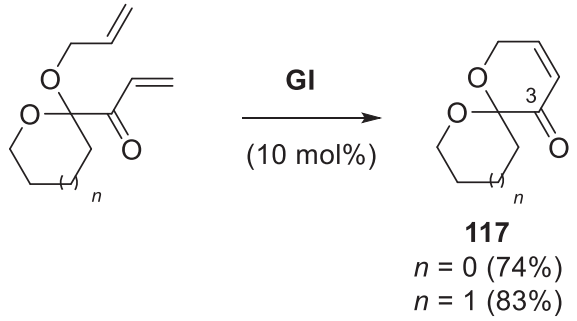
3.3. Use of RCM strategies for synthesis of dihydropyran-3(6*H*)-ones

Due to the development of bench-stable Ru catalysts[†] for alkene metathesis in the early 1990s, RCM strategies (Scheme 40) have been employed in many instances for the synthesis of complex heterocycle containing natural products, fragments and biologically active molecules.[51,32-34] Many syntheses take advantage of the functional group tolerance of the catalysts, the ease of preparation of the di(poly)ene precursor and the opportunities to further functionalised the newly formed olefin.



Scheme 40. RCM for heterocycles synthesis.

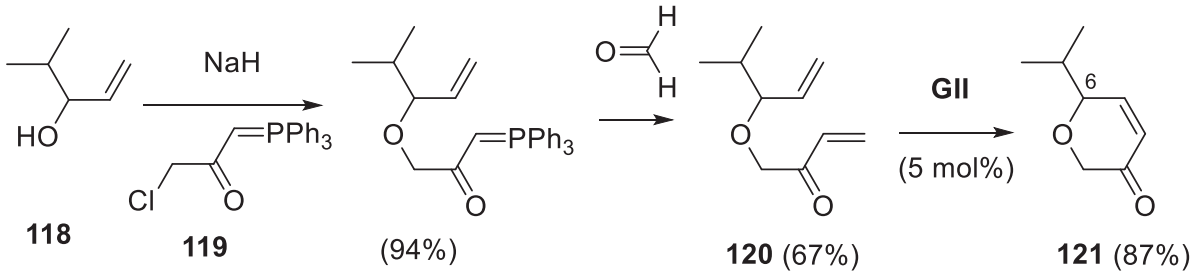
Unsurprisingly, this method has found some applications for the synthesis of dihydropyran-3(6*H*)-ones. In 2004, Hsung et al. reported the synthesis of spiroketal containing dihydropyran-3(6*H*)-ones **117** using RCM (Scheme 41). This method has been used to form different ring sizes (6- to 8- membered cycloalkenes) with different oxidation levels at C3.[52]



Scheme 41. Hsung approach to spiroketal-containing dihydropyranones **117**.

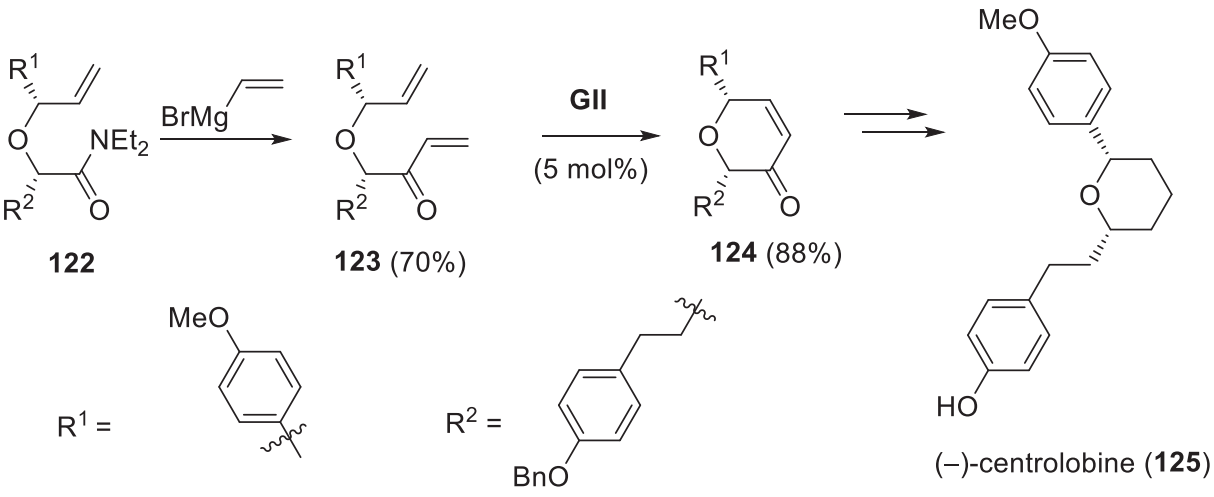
[†] The Ru catalysts mentioned in this chapter are depicted in appendix 1 (p. 211)

Cossy et al. described the synthesis of dihydropyranone **121** starting from allylic alcohol **118** (Scheme 42). *O*-alkylation of the latter using the ketophosphorane derivative **119**, followed by Wittig olefination gave diene precursor **120**, which upon exposure to Grubb's second generation catalyst (**GII**) delivered **121**.[53] This strategy has been applied to the synthesis of 6- to 8- membered 3-oxooxa- and 3-oxoazacycloalk-4-enes with various substituents at C(6) [C(7) and C(8) for 7- and 8- membered heterocycles, respectively].



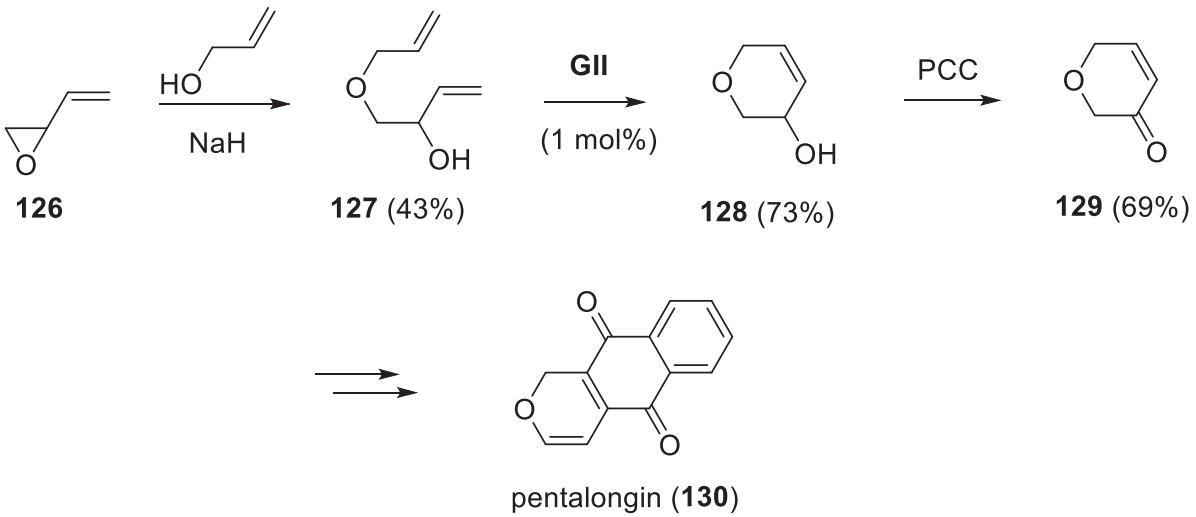
Scheme 42. Cossy synthesis of dihydropyranone **2.53**.

In Kim's synthesis of (–)-centrolobine (**125**), the precursor diene **123** (Scheme 43) was obtained by addition of vinylmagnesium bromide to the diethylamide derivative **122**.[54] RCM using **GII** smoothly delivered the desired dihydropyranone **124** which was reduced to (–)-centrolobine.



Scheme 43. Kim's synthesis of (–)-centrolobine (**125**).

Dihydropyranones can also be obtained by oxidation of the corresponding dihydropyranols. In De Kimpe's synthesis of pentalongin (**130**, Scheme 44), the precursor diene **127** was obtained by alcoholate attack on the epoxide **126**. Exposure of the diene **127** to **GII** delivered the dihydropyranole **128**, which was oxidised to the desired dihydropyranone **129** by PCC oxidation.[55] Hoveyda also reported the synthesis of dihydropyranone **129**, by Ley oxidation of the dihydropyranol **128**, also obtain by RCM of diene **127**.[56]

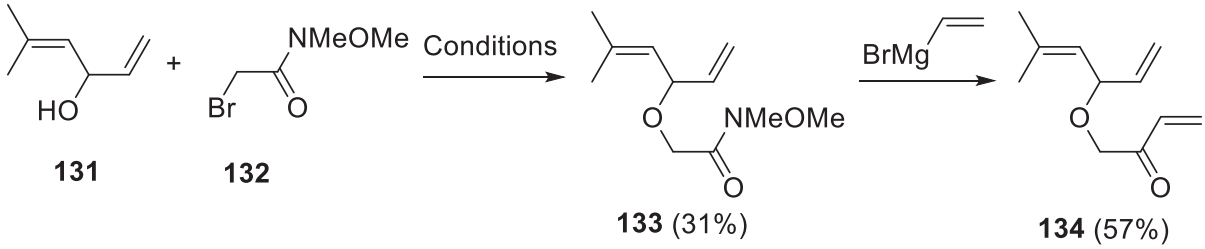


Scheme 44. De Kimpe's synthesis of pentalongin.

3.4. Model study: the α-unsubstituted dihydropyranone

In order to determine the viability of the RCM / ethoxyselenation–selenoxide elimination sequence we decided to first study a simplified system lacking the α-side chain (R = H, Scheme 26, p. 25). The final product using this system would be the same as that obtained from the photooxygenation of furanol **53** (Section 2., Scheme 23, p. 21).

The synthesis started with the reaction of the *bis*-allylic alcohol **131** (Scheme 45, prepared from addition of vinylmagnesium bromide to prenal)[57] and the α-bromo Wenreib amine derivative **132** (prepared from bromoacetyl bromide and *N,O*-dimethylhydroxylamine hydrochloride).[58] To the best of our knowledge, nucleophilic substitution on this bromide has not been reported using a secondary allylic alcohol. This reaction proved challenging; various conditions were tried (Table 1), however the substitution proceeded only with modest yield at best (Table 1, entry 3), while using 15-crown-5 ether to generate a naked alcoholate.[59] Addition of vinylmagnesium bromide to ether **133** delivered the acid sensitive triene **134** (Scheme 45), precursor for the RCM.[60]



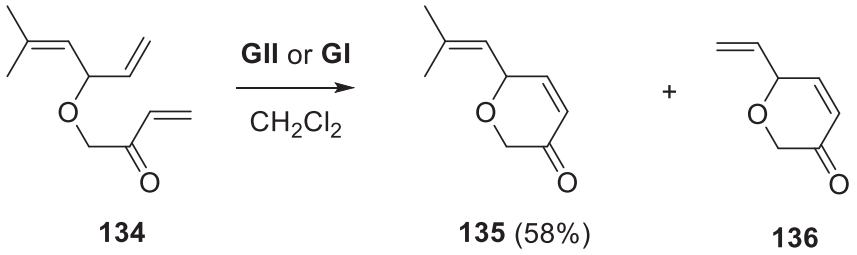
Scheme 45. Synthesis of triene **134**.

Entry	Base	Solvent	Other reagent(s)	Conidtions	Outcome
1	NaH	THF	NaI	rt (overnight)	No reaction
2	KHMDS	THF	-	-78°C (3h), rt (24h) then reflux (24h)	No reaction
3	NaH	THF	15-crown-5, TBAI	rt (overnight)	31%
4	NaH	THF	15-crown-5, TBAI	Reflux (overnight)	13% (320 mg scale)
5	NaOH	Benzene/water	TBAB (cat)	rt (overnight)	No reaction
6	KF	ACN	Al_2O_3	rt (overnight)	No reaction
7	KOH	THF	-	rt (overnight)	No reaction
8	LiH	THF	TMEDA, TBAI	rt (overnight)	No reaction
9	NaH	DMF	-	rt (overnight)	7%

Table 1. Reaction conditions for synthesis of **133**, 50 mg scale (except where stated otherwise).

Reaction of triene **134** with **GII** gave an inseparable 3:1 mixture of the desired dihydropyranone **135** and the terminal olefin containing **136** (Scheme 46).[53] The presence of this by-product could be explained by some initiation on the more hindered but more electron rich *gem*-dimethyl olefin. A screen of conditions (Table 2), showed that bubbling argon through

the solution, to remove ethylene generated during the reaction, slightly reduced the amount of dihydropyranone **136** (entries 1 *vs* 2) and subsequent reaction with 2-methyl-2-butene does not totally suppress dihydropyranone **136** (entry 3).[61] We found that the use of the less reactive **GI** (entries 4-6) prevents metathetical involvement of the electron rich *gem*-dimethyl olefin and provided the dihydropyranone **135** as the only product and the argon stream was not necessary.



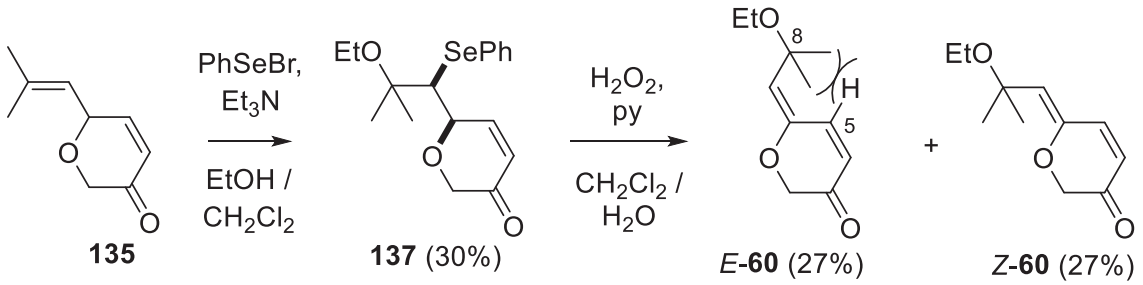
Scheme 46. RCM of triene **135**.

Entry	Catalyst	Time	Temperature	Concentration	Argon stream through solution	Ratio 135:136
1	**GII**	10 h	40 °C	0.005 M	No	3:1
2	**GII**	1 h	40 °C	0.005 M	Yes	8:1
3	**GII**	As above, then 30 equiv. of 2-methyl-2-butene, 10 h, 35 °C				13:1
4	**GI**	10 h	40 °C	0.005 M	Yes	**135** only
5	**GI**	10 h	40 °C	0.05 M	Yes	**135** only
6	**GI**	10 h	rt	0.05 M	No	**135** only

Table 2. Reaction conditions for RCM: 30-60 mg scale, 55-60% yield.

With dihydropyranone **135** in hand we were able to investigate the ethoxyselenation–selenoxide elimination sequence. The use of different sources of electrophilic selenium derivatives under various conditions such as PhSeCl,[62] PhSeCl / Et_3N,[63]

PhSeSePh / $(NH_4)_2S_2O_8$,[64] PhSeSePh / DDQ,[65] PhSeBr / AgOTf[66] led to decomposition of the material, however, we found that using PhSeBr in the presence of Et_3N,[49] in a mixture of EtOH and CH_2Cl_2 (to help solubilise the reaction mixture), dihydropyranone **135** was smoothly converted to the desired ethoxyselenide **137** (Scheme 47) as a single diastereoisomer (by ^1H NMR analysis of the crude reaction mixture). This complete diastereoselectivity was also observed in the ethoxyselenation of all dihydropyran intermediates **143**, **168** and **165mj** used during these synthetic studies (Schemes 53, 60 and 61, p. 48, 54 and 55), with the same sense of induction: the typical $^3J_{OCH\rightarrow SeCH}$: ~ 1.5 Hz was found in every product. The relative stereochemistry was later supported by X-Ray crystallography of an ethoxyselenide derivative **172** (Figure 3, p. 56).

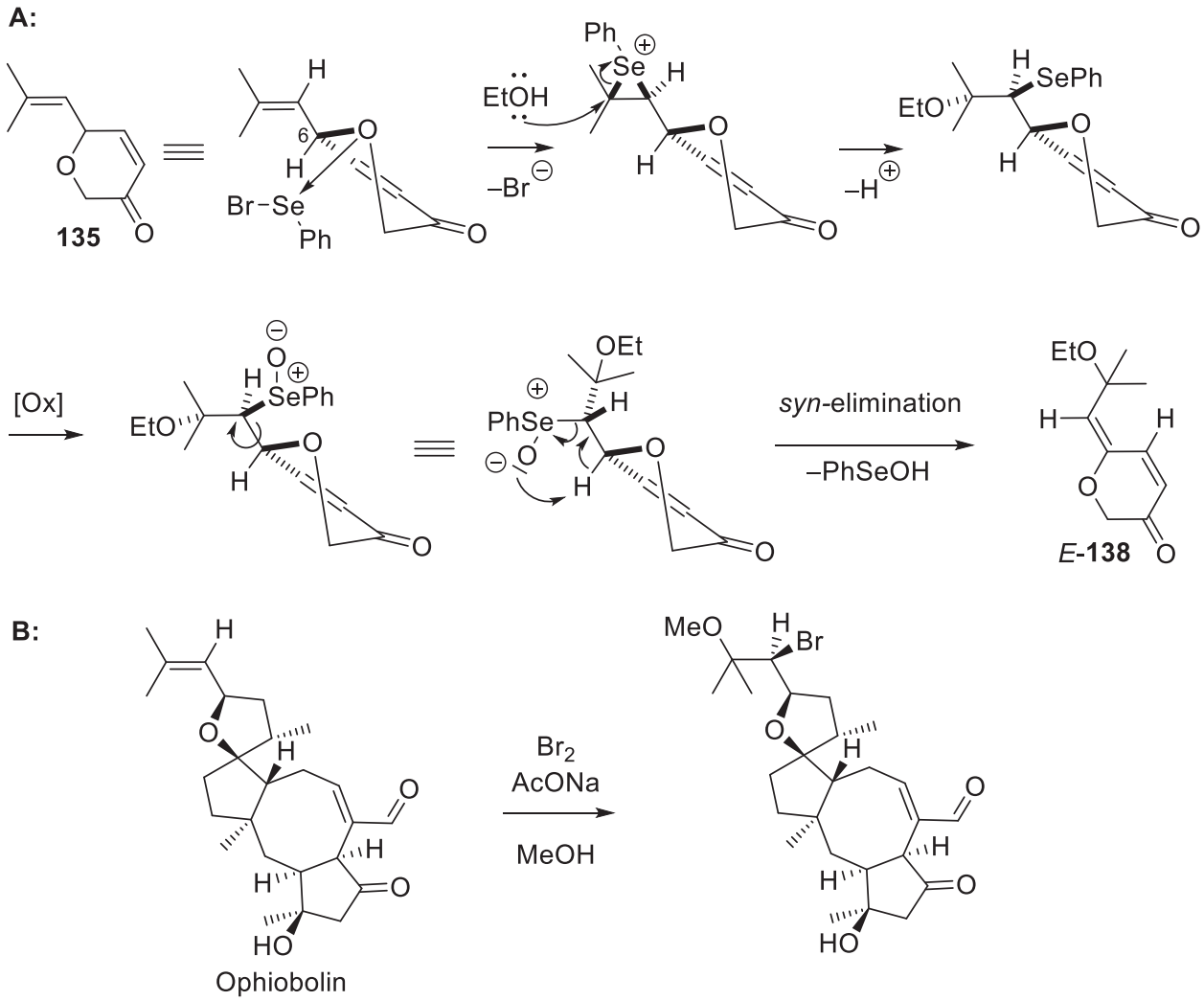


Scheme 47. Ethoxyselenation–selenoxide elimination sequence.

The ethoxyselenation is expected to occur on the lowest energy conformer of the dihydropyranone **135** (Scheme 48A): placing the isobutenyl group pseudo-equatorial and its plane orthogonal to the plane of the ring with the ring OC(6)H then eclipsing one of the methyl substituent of the olefin to minimise allylic strain.[67] The approach of the electrophilic selenium centre is then directed by initial coordination with the cyclic ether oxygen.[68] Moreover, electrophiles preferentially add to the double bond from the opposite side of the most electron donating allylic substituent.[67] The C(5)-C(6) bond having a greater σ electron donating effect than the C(5)-O favours the attack opposite to it. These two effects are complementary and could account for the complete diastereoselectivy of this transformation. The same

stereochemical outcome has been observed in the methoxyhalogenation of α-isobutenyl-substituted 5-[68] and 6-[69] membered cyclic ethers (with the stereochemistry unambiguously assigned by X-Ray crystallography, Scheme 48B).[68]

Oxidation of the ethoxyselenide **137** using hydrogen peroxide (Scheme 47),[70] followed by the elimination of the *in situ* generated selenoxide resulted in a separable mixture of enol ethers a *E*-**60** and *Z*-**60** (cf. Section 2., p. 21). This result was somewhat surprising since, by starting from a single diastereoisomer, in the *syn*-elimination of the selenoxide we expected to observe only a single geometric isomer of the enol ether being formed (namely the *E*-isomer, Scheme 48A). However, close TLC monitoring of the reaction revealed initial formation of the expected *E*- isomer which then isomerised under the reaction conditions. A reversible 1,6-addition to the dienone during the course of the reaction is suspected to be one of the possible modes of isomerisation. It is also worth noting that this isomerisation also occurs on standing: a $CDCl_3$ solution of *E*-**60** showed a 4:1 *E*/*Z* -mixture after standing 12 h at rt; neat samples stored in the freezer (–20 °C) showed the same level of isomerisation after several days. *Z*- to *E*-olefin isomerisation was not observed. A lower allylic strain on the *Z*-isomer (ring O *vs* C(5)H interactions with C(8)Me_2OEt, Scheme 3) is the likely origin for the thermodynamic preference for the latter. The same *E*- to *Z*- isomerisation was also observed in the oxidative elimination of the other ethoxyselenides studied **145** and **170** (Schemes 53 and 61, p. 48 and p. 55); the *E*- or *Z*-stereochemistry was assigned by comparison of the C(5)H chemical shift (>8.00 ppm or 7.50-7.00, respectively).

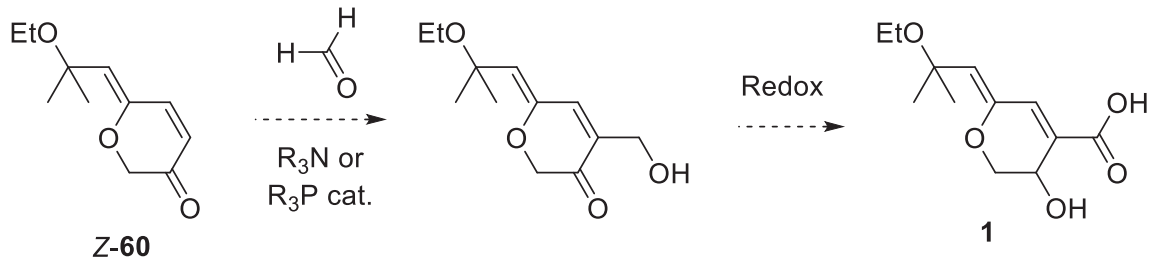


Scheme 48. A: Rationale for stereochemical outcome of the ethoxyselenation sequence

B: Methoxybromination of ophiobolin.[68]

These studies proved the value of the RCM / ethoxyselenation–selenoxide elimination sequence for the synthesis of a γ-alkylidenedihydropyranone. Moreover, the apparent thermodynamic preference for the *Z*-isomer as well as the C(5)H chemical shift observed indicated that aruncin B was most likely to correspond to the *Z*-isomer (reported[6] value for C(5)H: 7.47 ppm in CD_3OD).

Z-**60** could, in principle, be elaborated to the postulated structure of aruncin B *via* α-functionalisation of the enone, *via* a Morita-Baylis-Hillman (MBH) reaction using formaldehyde as an electrophile, followed by redox adjustment (Scheme 49).

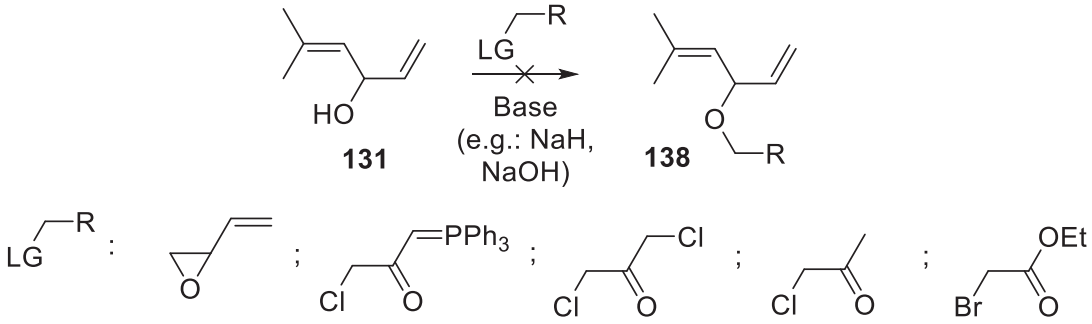


Scheme 49. Potential synthesis of aruncin B from *Z*-**60**.

However, the synthetic route to *Z*-**60** was mainly impaired by the low yielding transformation from **131** to **133** (Scheme 45, p. 39) and the low stability of triene **134**. We therefore decided not to study the route suggested in Scheme 49, and instead focussed our efforts on finding an electrophile featuring greater reactivity than the Wenreib amide derivative **132** (Scheme 45, p. 39) and developing a related new route to intermediates featuring the additional α-side-chain lacking in the previous system.

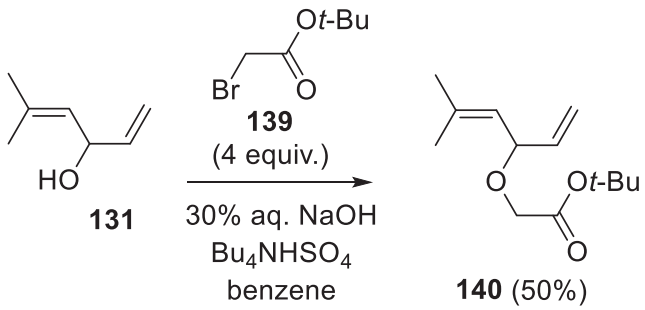
3.5. Synthesis of *Z*-aruncin B Na Salt

In our efforts to find a superior route to our key intermediate **64** (Scheme 26, p.25) we were looking for another reaction partner for the *O*-alkylation of *bis*-allylic alcohol **131** (Scheme 45, p. 39). The latter proved very unreactive towards many electrophiles under a variety of conditions and all reactions afforded, at best, a trace amount of the desired product **138** (Scheme 50).



Scheme 50. Examples of failed electrophiles examined in *O*-alkylation of alcohol **131**.

However, to our delight, use of *tert*-butyl bromoacetate (**139**) as the electrophile, under phase-transfer catalysis[71] delivered the desired ether **140** in reasonable yield (Scheme 51).



Scheme 51. Successful *O*-alkylation of alcohol **5**.

After optimisation, it was found that:

-a crude alcohol **131** / THF mixture (resulting from the addition of vinylmagnesium bromide to prenal)[57] could be used.

- benzene could be replaced by toluene.

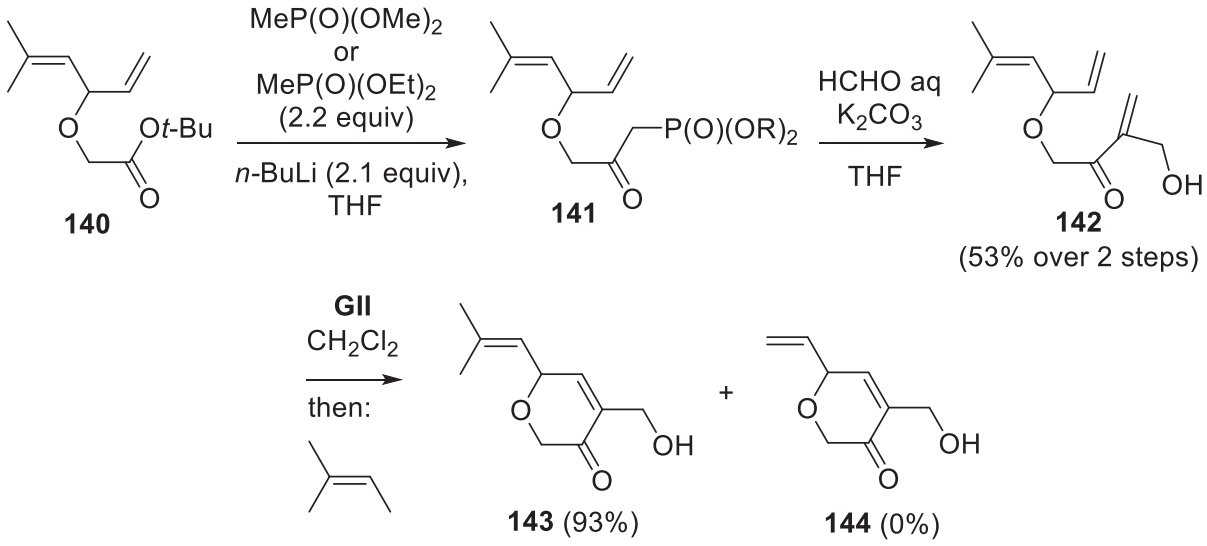
-the quantity of *tert*-butylbromoacetate could be reduced to 1.1 equiv.

-the reaction could be carried out on multigram scale using mechanical stirring, giving the desired ether **140** in excellent yields (93%, over the 2 steps) without the need of chromatographic purification. Up to 19 g (93 mmol) of ether **140** was synthesised in a single batch.

The ether **140** could be converted to the corresponding phosphonate using a Claisen-type condensation with a lithiated dialkyl methylphosphonate (Scheme 52).[72] Dimethyl and diethyl methylphosphonate could both be used for this transformation giving similar yields, however dimethyl methylphosphonate possesses a greater water solubility. This meant that its excess could be easily removed during an aqueous work-up, avoiding a chromatographic purification or distillation required when using diethyl methylphosphonate.

Using the Villiéras procedure,[73] a modified Horner-Wadsworth-Emmons reaction, enabled the conversion of phosphonate **141** to the α-hydroxymethyl enone **142**. In repeat runs, α-hydroxymethyl enone **142** was found to be occasionally contaminated by inseparable and unknown impurities. Many modifications of the reaction conditions were investigated to avoid the formation of these impurities, such as: different methods for purification of the phosphonate **141** (crude, distilled or chromatographically separated), reaction concentration, temperature, flow conditions were also used without giving any significant improvement. Nonetheless, it was found that the dimethyl phosponate **141** could be used crude; using a 2:1 H_2O / THF mixture[74] (instead of H_2O as originally described) and not exceeding 0.5 g scale gave more consistent results. Moreover, small amounts of these impurities do not seem to affect the following reactions and could be removed after the next step by chromatographic purification.

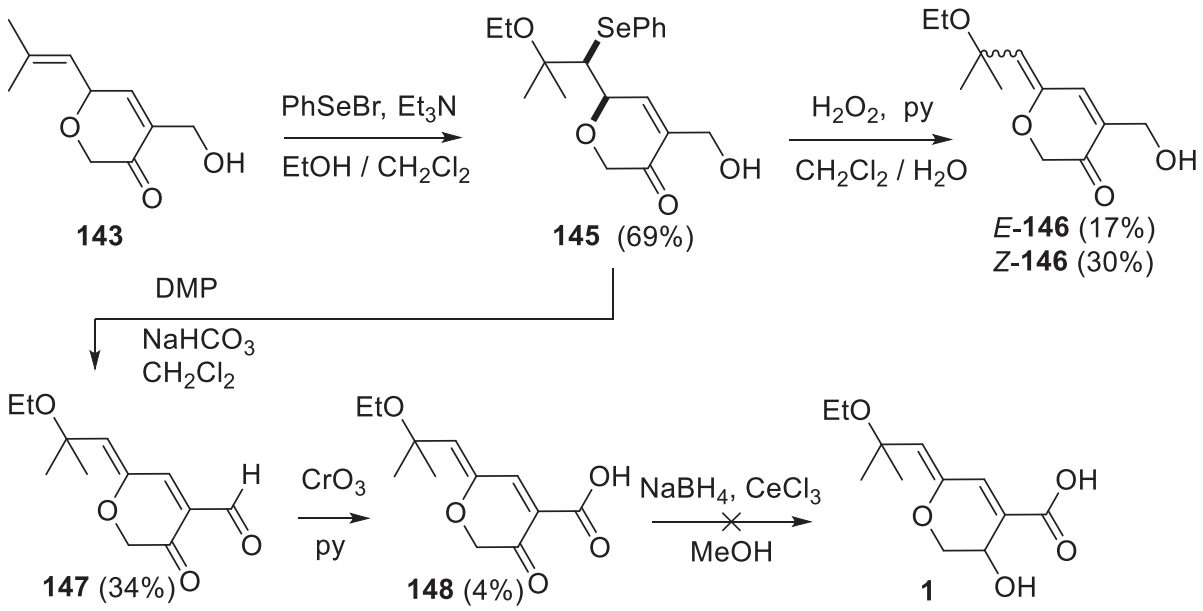
Triene **142** contains the extra α-carbon side chain missing in our above study (3.4. Model study: the α-unsubstituted dihydropyranone, p.38-44) and presents a greater stability towards acidic conditions than triene **134**. RCM of triene **142** using **GII** delivered an inseparable 9:1 mixture of desired dihydropyranone **143** and terminal olefin containing dihydropyranone **144**. Contrary to the α-unsubstituted system (**134**→**135**, Scheme 46, p. 40), the use of **GI** under the conditions previously described did not afford good yields (<25%), likely due to the more sterically demanding nature of the α–hydroxymethyl enone **142**. A rapid screen of Ru catalysts (**GI**, **GII**, **HGII** or Grela's cat. (see appendix 1 (p. 211) for cat. structures) under various conditions (varying temperature and solvent) did not give satisfactory results, affording either low conversions / yields or mixtures of dihydropyranones **143** / **144**. However, it was found that adding excess 2-methyl-2-butene at the end of the reaction converted the unwanted dihydropyranone **144** to the desired one **143**.[61]



Scheme 52. Synthesis of dihydropyranone **143**.

It is important to note that dihydropyranone **143** contains all the carbon atoms of the core structure originally proposed for aruncin B (**1**). Ethoxyselenation of **143** (Scheme 53), using previously described conditions showed a high level of diastereoselectively and subsequent

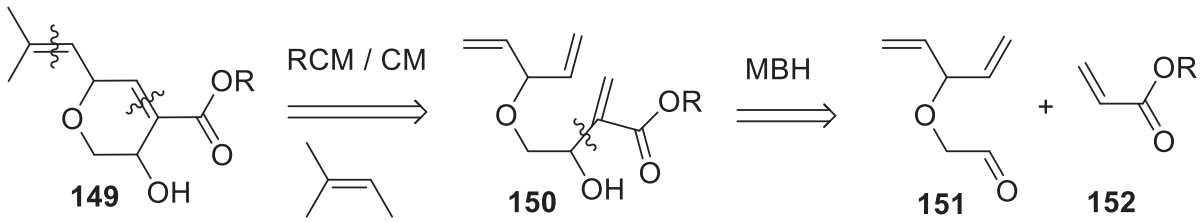
peroxide-induced oxidation of ethoxyselenide **145** followed by elimination resulted in a separable mixture of *Z*/*E*-enol ethers **146**. Unfortunately, this enol ether proved unstable and decomposed over a few days, even while stored at –20 °C, and thus could not be used in a subsequent alcohol-oxidation step. In 2013, White reported in the course of synthetic studies towards providencinthe, the inopportune simultaneous oxidations of a selenide to its corresponding selenoxide (followed by *syn*-elimination) and a primary alcohol to the corresponding aldehyde using Dess-Martin periodinane (DMP).[75] We considered we could take advantage of these concomitant oxidations to obtain the ketoaldehyde **147** without the isolation of intermediate enol ether **146**. Exposure of ethoxyselenide **145** to DMP delivered ketoaldehyde **147** in modest yields. This was followed by oxidation to the ketoacid **148**, which proceeded in our best attempt in 4% yield.[76] Attempts to reduce the small amount of ketoacid **148** generated (~ 2 mg) to the corresponding hydroxyacid (aruncin B (**1**)) using Luche conditions failed.[77]



Scheme 53. Attempted FGI end game.

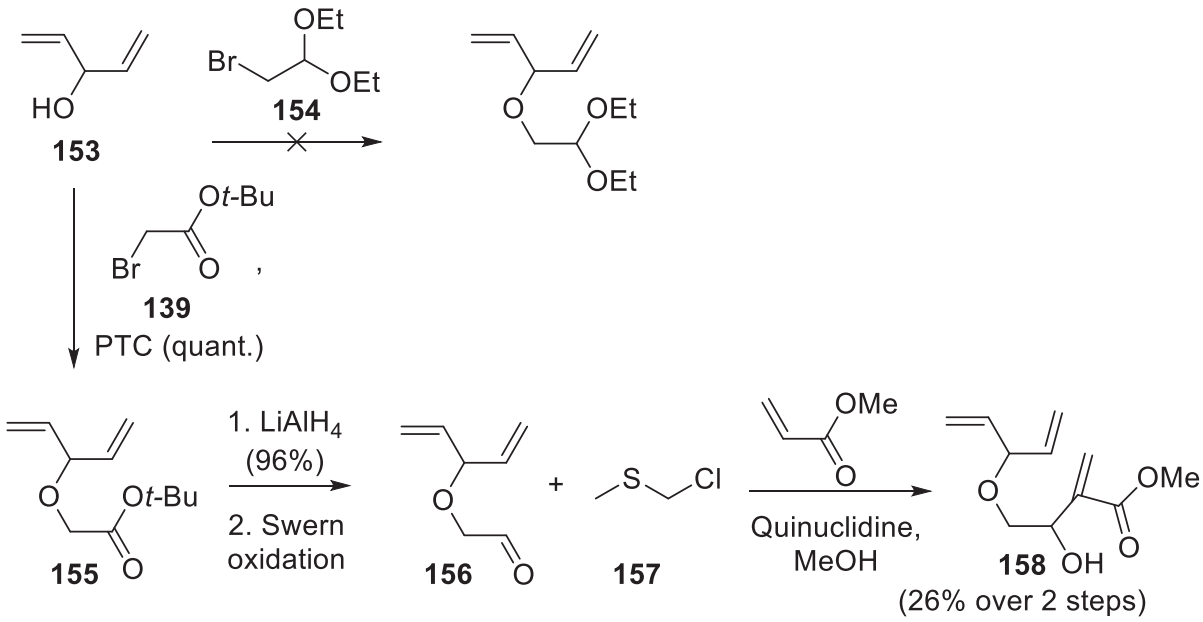
The failure of the above chemistry highlighted the necessity to have the correct oxidation level at C(3) and at the side-chain. A redesigned route to the key dihydropyranol **149** could proceed

by RCM / CM[61,78] of the triene **150**, which would be obtained from acrylate **152** and aldehyde **151** by Morita-Baylis-Hillman reaction (Scheme 54).



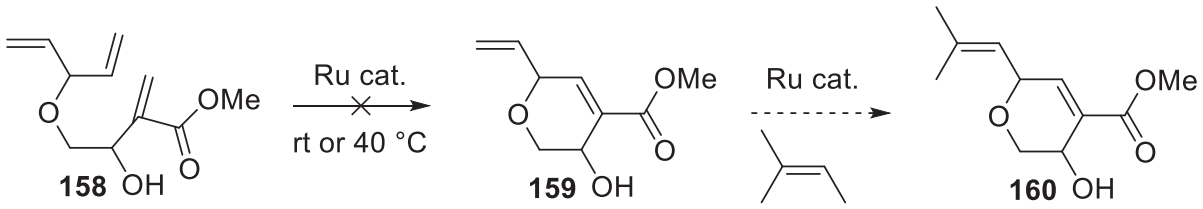
Scheme 54. Retrosynthesis for alternative strategy.

Attempted *O*-alkylation of commercially available 1,4-divinyl carbinol (**153**) with the α-bromoacetal derivative **154** using a variety of conditions proved unsuccessful (Scheme 55). Even forcing conditions, such as in the presence of KH / KI in diglyme at 200 °C (sealed tube) for 60 h led to no observable reaction. However, the use of the PTC conditions previously described using *tert*-butyl bromoacetate resulted in clean and quantitative *O*-alkylation of carbinol **153**. Reduction of the resulting ester **155** (as well as related pyrrolidine and morpholine amide derivatives) to the corresponding aldehyde **156** using various reductants (DIBAL-H, $Li(EtO)_3AlH$ or $Li(i\text{-}Bu)_2n\text{-}BuAlH$)[79] all failed to provide the desired aldehyde **156**. LAH reduction of the ester, followed by Swern oxidation of the resulting alcohol gave the unstable aldehyde **156**, contaminated by chloromethyl methylsulfide (**157,** ~ 25mol%) resulting from Pummerer rearrangement of dimethylchlorosulfonium. Various MBH reaction conditions were examined on the crude aldehyde **156** (DABCO, DBU, $n\text{-}Bu_3P$) and it was found that conditions described by Aggarwal and co-workers delivered the desired adduct **158**, albeit in modest yields.[80]



Scheme 55. Synthesis of MBH adduct **158**.

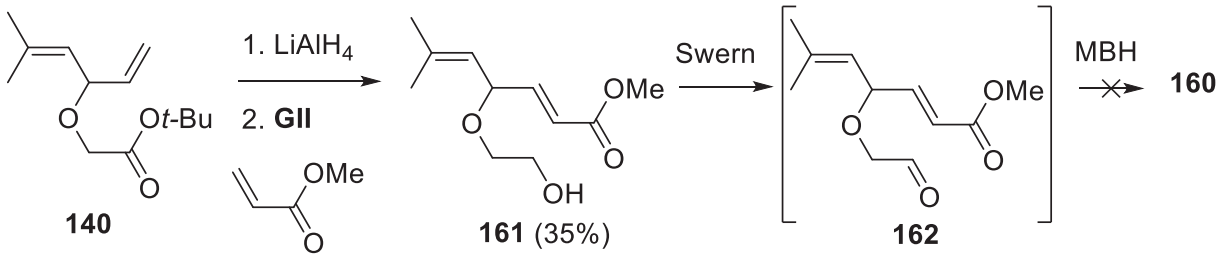
The use of MBH adducts to form 6-membered rings by RCM has been recently described by Krafft and co-workers.[81] Despite this precedent, RCM attempts using a variety of Ru catalyst such as **GI**, **GII**, **HGII**, *o*-tolyl **GII**, fast initiating Grubbs' and Grela's cat. (see appendix 1 (p. 211) for cat. structures); all failed to deliver the desired dihydropyranols **159** or **160** (Scheme 56).



Scheme 56. Attempted RCM / CM sequence.

Another alternative approach to directly obtain a dihydropyranol intermediate **149** (Scheme 54) featuring the correct level of oxidation on the side-chain, consisted of a CM with an acrylate followed by an intramolecular MBH reaction. LAH reduction of **140**, followed by CM using **GII** delivered the *E*-α-β-unsaturated ester **161** (Scheme 57). This transformation was low

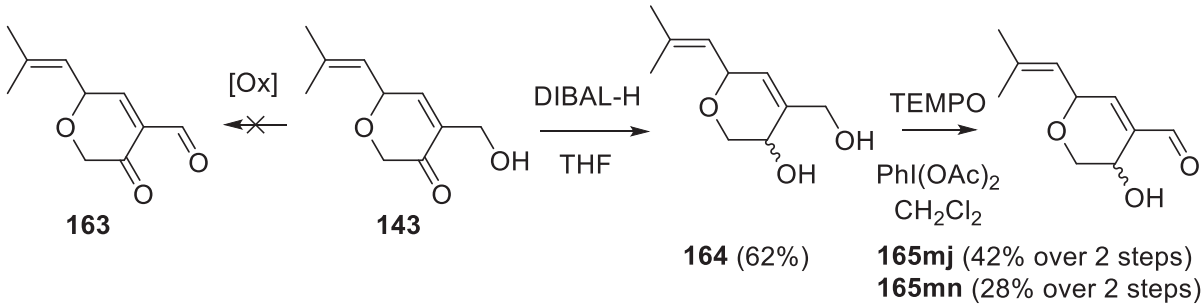
yielding but it was found that slow addition of **GII** over 12 h using a syringe pump gave better results. Swern oxidation delivered the aldehyde **162**, as a 1:1 mixture with the starting alcohol, which proved to be unstable to chromatography. Various conditions for intramolecular MBH reaction (quinuclidine in MeOH or dimethoxyethane, *n*-Bu_3P in $CHCl_3$)[82] were examined on the crude mixture of **161** / **162**, but all led to decomposition of the material.



Scheme 57. Attempted CM / intramolecular MBH sequence.

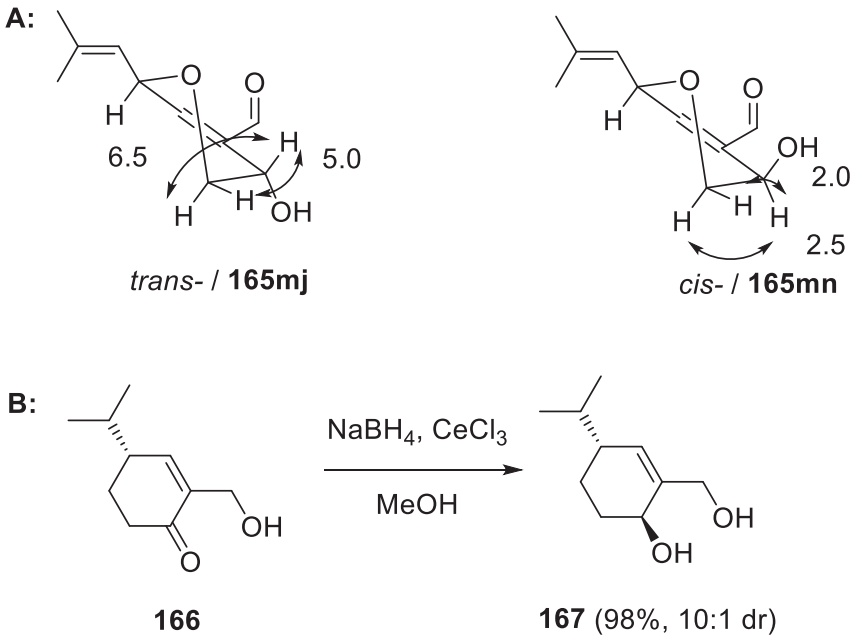
These failures highlighted the difficulties of attempting to directly access the dihydropyranol intermediate **149** (Scheme 54, p. 49) featuring the correct oxidation level on the side-chain. Obtention of **149** was therefore envisaged by a redox interchange sequence starting from the previously synthesised dihydropyranone **143** (Scheme 52, p. 47). Attempted oxidation of **143** to the ketoaldehyde **163** using MnO_2 (in CH_2Cl_2 at rt or 40 °C, or in benzene at 80 °C) did not show any conversion (Scheme 58); the use of other oxidation procedures, such as DMP, Swern or IBX led to decomposition of the material. This was initially surprising considering the ketoaldehyde **147** had been synthesised (Scheme 53, p. 48); the desired ketoaldehyde **163** was probably formed but rapidly decomposed under the reaction conditions. The doubly allylic ring-OCH, positioned next to the very electron deficient unsaturation, was likely to be prone to hydrogen abstraction or deprotonation, and could account, for the instability of ketoaldehyde **163**. DIBAL-H 1,2-reduction of the ketone delivered the diol **164** as an inseparable 3:1 mixture of diastereoisomers.[83] Selective primary alcohol oxidation to the aldehyde **165** was achieved through TEMPO catalysis,[84] with no ketone formation observed. The diol **164** did not show

great stability under chromatographic conditions, and it was found that the sequence gave slightly better overall yields when the oxidation was carried on the crude diol **164**. For analytical convenience, the diastereoisomers were separated at that point and the following sequences were carried out on the major aldehyde diastereoisomer **165mj**.



Scheme 58. Redox interchange of **143**.

The relative stereochemistry of the hydroxyaldehydes **165** was initially assigned by comparison of ring vicinal coupling constants observed on the likely dominant contributing half-chair conformer of each diastereoisomer (Scheme 59A). In the *trans*-diastereoisomer, the isobutenyl and hydroxyl substituent are expected to be pseudo-equatorial. For the dominant contributing conformer of the *cis*-diastereoisomer, the bulkier isobutenyl group is expected to be pseudo-equatorial. This places the hydroxyl group in a pseudo-axial conformation, favoured by its smaller size and a stereoelectronic $\pi-\sigma^*_{C\text{-}O}$ stabilisation.[85,86] The higher coupling constants (≥5 Hz) observed on the major diastereoisomer are characteristic of 3,6-disubstituted-3,6-dihydro-*2H*-pyrans featuring a pseudo-equatorial hydroxyl group, corresponding therefore to the *trans*-isomer. The lower coupling constants (<3 Hz) observed in the minor diastereoisomer are characteristic of a pseudo-axial hydroxyl group, equating to the *cis*-isomer. *Trans*-selective 1,2 reduction of a 4-substituted α-(hydroxymethyl)cyclohexanone has been previously described (**166→167**, Scheme 59B).[87]



Scheme 59. A: Half-chair conformers for *trans/cis* **165** with observed ring ^{3}J values (Hz);

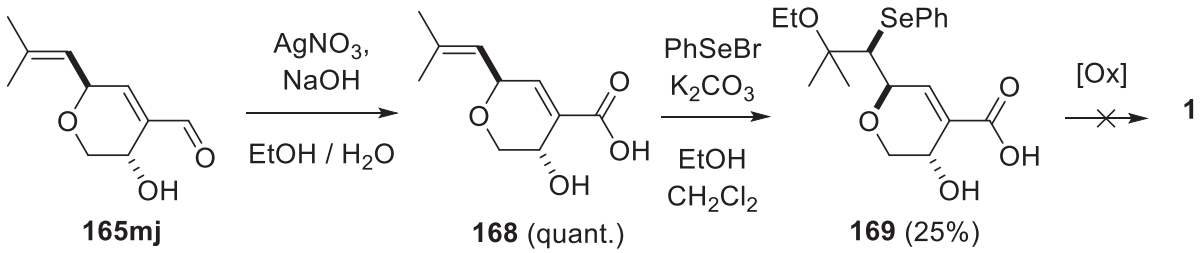
B: previously reported *trans*-selective reduction of **166**.[87]

With dihydropyranone **143** various reduction conditions and reagents were examined ($NaBH_4$ / $CeCl_3$,[87] Et_2BOMe / $NaBH_4$,[88] Li(*t*BuO)$_3$AlH,[89] $NaAcOBH_3$, Na(AcO)$_3$BH,[90] Meerwein-Ponndorf-Verley reduction, or Evans-Tischenko reaction) but none of them gave significant improvement in yield or diastereoselectivity, compared with the DIBAL-H method.

Selective oxidation of hydroxyaldehyde **165mj** to the hydroxyacid **168** was successfully achieved using *in situ* generated Ag_2O (Scheme 60).[91] Ethoxyselenation of hydroxyacid **168** under slightly modified conditions to those described previously, by using an inorganic base: K_2CO_3 instead of Et_3N resulted in low yielding formation of ethoxyselenide **169**; It is important to note that, unfortunately, on repeat runs the yield of this transformation proved inconsistent.

Nonetheless, the oxidative elimination of selenide **169** was studied, a variety of conditions were examined: H_2O_2, $NaIO_4$, $NaIO_4$ / $NaHCO_3$ or *m*-CPBA / *i*-Pr_2NH. Despite mass spectrometry monitoring of the reaction suggesting formation of both the corresponding selenoxide and the elimination product, no desired aruncin B was isolated from these attempts. It was hypothesised

that the desired product was formed during the course of the reaction but the electrophilic phenylselenenic acid (PhSeOH) or one of its disproportion by-products (cf discussion Scheme 28 p. 27, and also Scheme 39 p. 33-34) further reacted with the highly reactive formed enol ether.[35] One potential way to avoid this decomposition would be to generate the selenoxide at low temperature to prevent elimination to the enol ether *in situ* and the reaction mixture would then be warmed up in presence of a phenylselenenic scavenger. However, selenoxide formation from selenide **169** at –78 °C *via* ozonolysis, followed by addition of excess 2-methoxypropene (10 equiv) prior to elevation of the temperature also failed to deliver the desired enol ether.

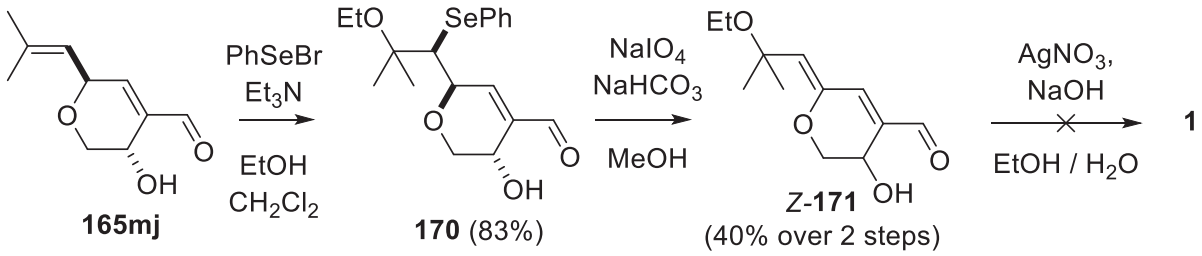


Scheme 60. Attempted synthesis of aruncin B (**1**) *via* late stage ethoxyselenation-selenoxide elimination.

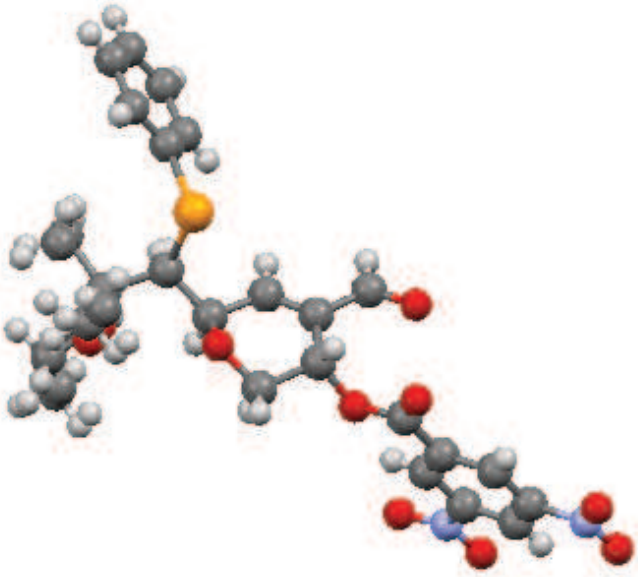
The presence of the free carboxylic acid may have been problematic for the success of the elimination step, and with the silver(I) oxidation of the hydroxyaldehyde proving a mild method to obtain the hydroxyacid motif we decided to carry out the ethoxyselenation-selenoxide elimination sequence on the hydroxyaldehyde **165mj**. This would leave oxidation to the hydroxyacid as the last step of the synthesis.

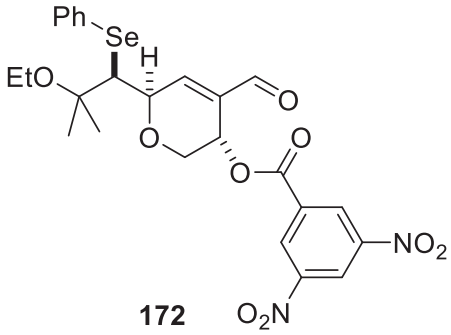
Ethoxyselenation of **165mj** proceeded under the original conditions (Scheme 61). During the reaction, small amounts of the corresponding diethyl acetal of **170** were formed, but these could be conveniently converted back to the desired ethoxyselenide **170** using an acidic workup. X-Ray crystallography of the 3,5-dinitrobenzoate **172** derived from ethoxyselenide **170** confirmed the strereochemical outcomes of the ethoxyselenation and the DIBAL-H 1,2-

reduction (Figure 3, see also appendix 3). Oxidation of the ethoxyselenide **170** was carried out using $NaIO_4$ instead of H_2O_2, to avoid potential Baeyer-Villiger chemistry at the aldehyde (cf discussion p. 28 and also Scheme 36, p. 31).[35,48] In that case, only a trace amount of *E*-**171** was found in the crude mixture (characteristic ^{1}H NMR olefinic shifts for *E*-isomer: 7.93 and 5.46 ppm) but not isolated. It is worth noting that, for analytical consideration, the ethoxyselenide **170** was first purified by column chromatography; it was later found that the oxidation could be directly carried out on the crude ethoxyselenide **170** to give **171** in similar overall yields (40% over 2 steps). The almost exclusive isolation of *Z*-**171** could be explained by the longer reaction time while using $NaIO_4$, compared with the peroxide-induced method (typically 12 h *vs* 1-3 h respectively), allowing full isomerisation by the time the reaction reached completion.



Scheme 61. Ethoxyselenation–selenoxide elimination sequence starting from hydroxyaldehyde **165mj**.





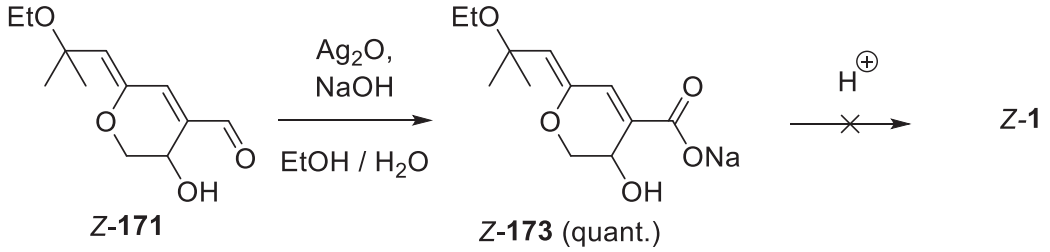
172

Figure 3. Structure of 3,5-dinitrobenzoate **172**.

Unfortunately, silver(I) oxidation of *Z*-**171** failed to deliver aruncin B, although mass spectrometric analysis suggested formation of the desired carboxylic acid. The presence of NO_3^- ions, from the $AgNO_3$ in the oxidation reaction resulting in the formation of nitric acid during the acidic workup of the reaction could account for the decomposition of the material.[92] Another attempt using freshly prepared Ag_2O rather than *in situ* generated Ag_2O, was carried out.[92] Again mass spectrometric analysis suggested formation of the desired carboxylic acid, so a variety of mildly acidic conditions for the workup were examined: dilute HCl, NH_4Cl, tartaric acid, acetic acid or $B(OH)_3$ solutions. However, none of these conditions enabled the isolation of the free acid **1**.

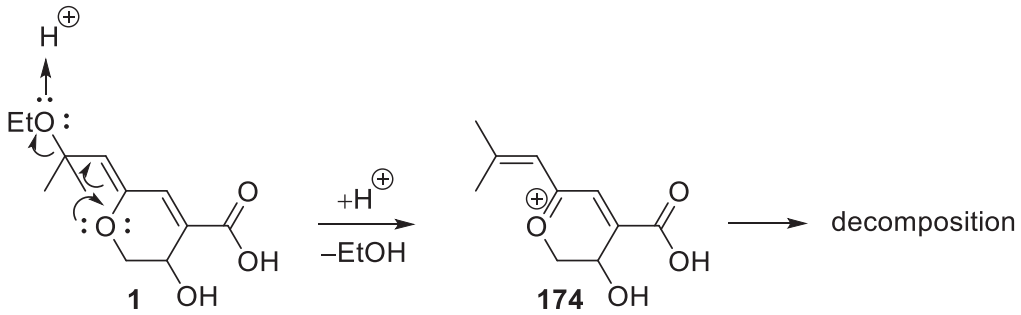
We therefore decided to attempt to isolate the product of the oxidation as the Na salt rather than as the free acid (Scheme 62). Oxidation using freshly prepared Ag_2O, followed by concentration of the reaction mixture, delivered *Z*-**173**, the Na salt of the postulated structure of aruncin B. However, mild acidification of *Z*-**173** using, for example pH 6 buffer solution,

addition of accurately measured 1 equiv of HCl in Et_2O at –78 °C or carboxylic acid-supported ion-exchange resin (amberlite® CG 50) all resulted in complete decomposition of the material.



Scheme 62. Synthesis of sodium salt *Z*-**173** and attempted acidification.

The decomposition was suspected to occur *via* initial protonation of the ether *O*-atom (Scheme 63), followed by elimination of EtOH assisted by the ring *O*-atom lone pair. The oxonium **174** generated was expected to be extremely unstable, leading to the observed decomposition.



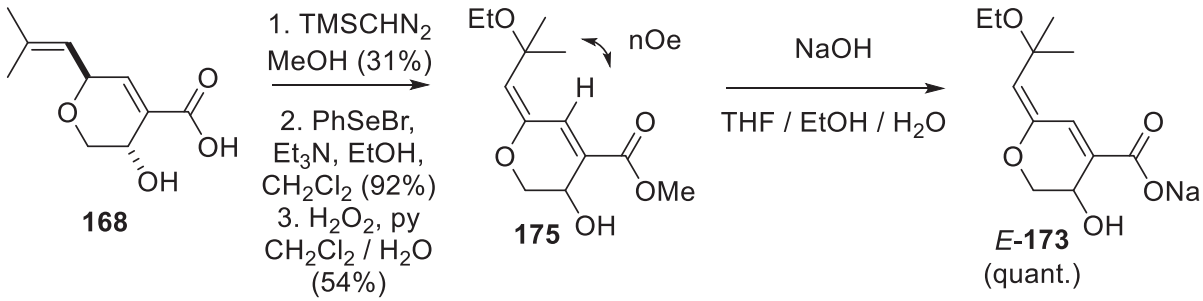
Scheme 63. Suspected decomposition pathway.

The inability to obtain **1** from **148**, **169** and *Z*-**173** (Schemes 53, 60 and 62, p. 48, 54 and 57) led us to the consideration that *Z*-**1** is not likely to correspond to aruncin B. Since in the isolation paper,[6] the exact configuration of the exocyclic olefin was not unambiguously assigned (no NOESY reported), we were curious to establish whether the *E*-olefin *E*-**1** would present a greater acid sensitivity and correspond to aruncin B.

3.6. Synthesis of *E*-aruncin B Na salt

As discussed earlier, *E*- to *Z*- isomerisation of dienones **60** (Scheme 47, p. 41), and **146** (Scheme 53, p. 48), dienal-one **147** (Scheme 53, p. 48) and dienal **171** (Scheme 61, p. 55) is suspected to occur predominantly *via* reversible addition to the δ-position of these conjugated dienes. We therefore postulated that the use of a slightly less electron deficient system, such as a dienoate, would lower the rate of isomerisation and thus potentially enable the isolation of the *E*- enol ether as the major product.

$TMSCHN_2$-induced esterification of hydroxyacid **168** (Scheme 64), followed by the previously described ethoxyselenation–selenoxide elimination sequence afforded the *E*-enol ether **175**, which presented a greater configurational stability, although isomerisation on standing (neat samples at –20 °C) could be observed after several days. Saponification gave the Na salt *E*-**173** which however possessed the same acid sensitivity as its *Z*-isomer.



Scheme 64. Synthesis of *E*-**173**.

3.7. Synthesis of regioisomeric ether structure of aruncin B

Comparison between the ^{13}C NMR data recorded on the Na salts *E*- and *Z*-**173** and those reported for aruncin B showed inconsistencies related to the ether connectivity (Figure 4).

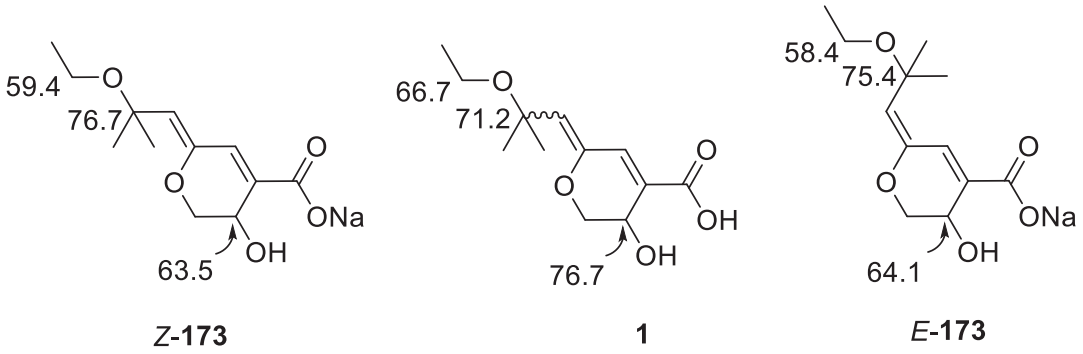


Figure 4. Selected ^{13}C NMR data (ppm, 125 MHz, CD_3OD) reported for aruncin B (**1**) and observed for *E*- and *Z*-**173**.

Comparison with other known tertiary allylic ethers **176**[93] and (*E*)-*O*-ethylsuberenol (**177**)[94] and alcohols **178**[93] and **179**[95] (Figure 5) indicated that the ^{13}C chemical shifts observed for synthetic *E*- and *Z*-**173** are not anomalous and the shift observed for the tertiary allylic position of aruncin B is closer to that expected for a free alcohol rather than an ether.

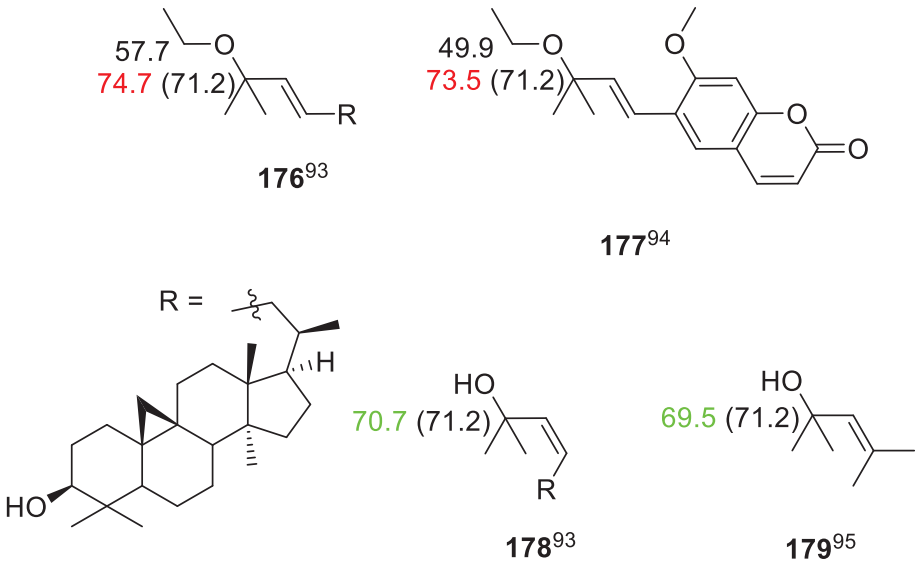
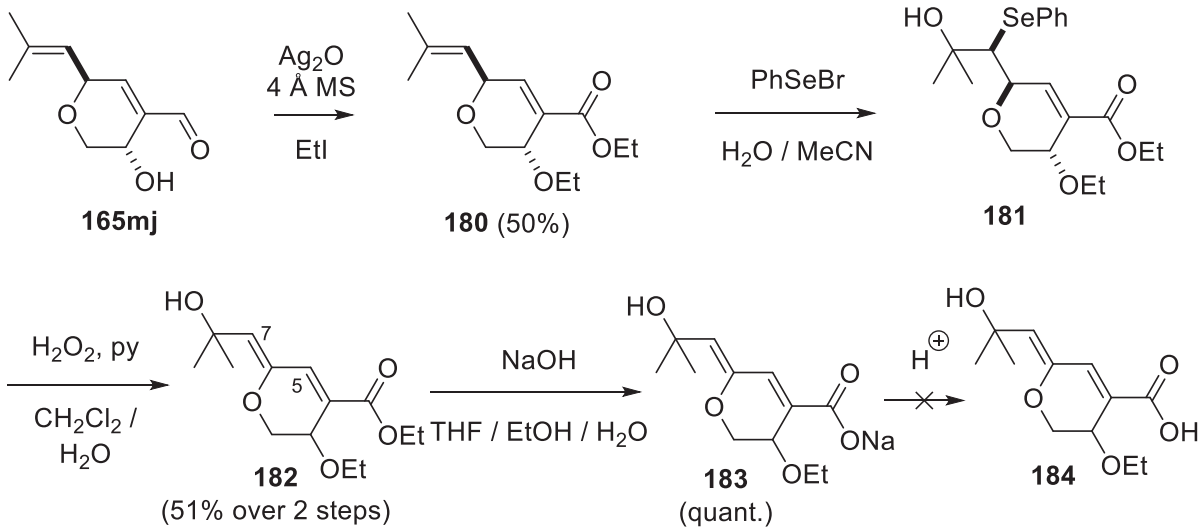


Figure 5. Characteristic ^{13}C NMR values (ppm) for previously reported tertiary allylic ethyl ethers and alcohols, value reported for aruncin B in parenthesis.

Taking into account the above analytical considerations, we therefore decided to synthesise a regioisomeric structure featuring a free alcohol at the tertiary allylic position, with the ethyl group being born by the C(3) secondary alcohol (**182** / **183**, Scheme 65). Moreover, the presence of a less basic group (-OH *vs* -OEt) at the tertiary allylic position might prevent the initial protonation of the oxygen atom, suspected to trigger the first step of the decomposition pathway by elimination of H_2O or EtOH (Scheme 63, p. 57).

Attempted *O*-alkylation of the hydroxyaldehyde **165mj**, using an alkylating agent (EtI, Meerwein salt) in presence of a base (such as NaH, KOH, Et_3N) led to decomposition of the starting material. Fortuitously, it was found that using EtI as a solvent in the presence of excess Ag_2O and a drying agent such as 4 Å MS, simultaneously effected the desired *O*-alkylation of the secondary alcohol, but also oxidised the aldehyde to the corresponding carboxylic acid and subsequently esterified it to give the diethyl ether ester **180** (Scheme 65). Similarly to the previously described ethoxyselenation, hydroxyselenation of ether ester **180** using PhSeBr in H_2O / MeCN gave the hydroxyselenide **181** as a single diastereoisomer.[65] Interestingly no base

was required for this transformation. Peroxide-induced elimination delivered the *Z*-enol ether **182**. The formation of the *Z*-enol ether contrasts with the results observed in the oxidative elimination resulting in the formation of enol ether **175** (featuring a methyl ester on the side chain, Scheme 64, p. 58). Careful inspection of the ^{1}H NMR spectrum of the crude mixture indicated traces of *E*- enol ether **182** were present, with characteristic values of 8.18 and 5.51 ppm ($CDCl_3$) for C(5)H and C(7)H, respectively. These values are slightly higher than those observed for *E*-**175** (8.03 and 5.35 ppm ($CDCl_3$) for C(5)H and C(7)H, respectively). These are indicative of a potentially more electron deficient conjugated system in *E*-enol ether **182**, which could account for a greater rate of isomerisation leading to the isolation of only the *Z*-enol ether **182**. Saponification gave the Na salt **183**, but subsequent acidification of the salt resulted once again, only in decomposition.



Scheme 65. Hydroxyselenation-selenoxide elimination sequence and attempted acidification of **183**.

The acid sensitivity of the γ-alkylidenedihydropyranol derivatives, together with inconsistencies observed in the analytical data led to the conclusion that aruncin B had been missassigned and did not correspond to this type of compound. A more profound structural revision was therefore necessary, and this is discussed in the following chapter.

4. Results and discussion: Structural revision and synthesis of a newly postulated structure of aruncin B

4.1. The *Z*-γ–ethylidenebutenolide hypothesis

Analysis of the UV data reported for aruncin B is consistent with a γ-alkoxy-α,β,γ,δ-unsaturated carboxyl motif (Woodward-Fieser rules, Figure 6).[96,97] As mentioned towards the end of the previous chapter (p. 58-59), ^{13}C NMR data suggested an alternative structure having a free hydroxy group on the tertiary allylic position (rather than an ether). Moreover, ^{1}H NMR values are consistent with a *Z*- geometry of the enol ether. These three considerations led to the conclusion that fragment **A** (Figure 6) was present in the true structure of aruncin B. Furthermore, the originally assigned ring C(3)HO is likely to correspond to the site of etherification rather than being a free alcohol, comparison with eupaglehnin D[98] (Figure 6) showed that the originally assigned ring $C(2)H_2$ gave a better match for a primary alcohol, rather than an enol ether; the dioxygenated portion would therefore correspond to fragment **B**. Finally, the acid sensitivity raised questions on the coexistence of the carboxylic acid with the oxygenated tertiary allylic motif; the carboxyl motif observed could be esterified instead. The above analysis led to the conclusion that *Z*-γ–ethylidenebutenolide **185** could be the true structure of aruncin B.

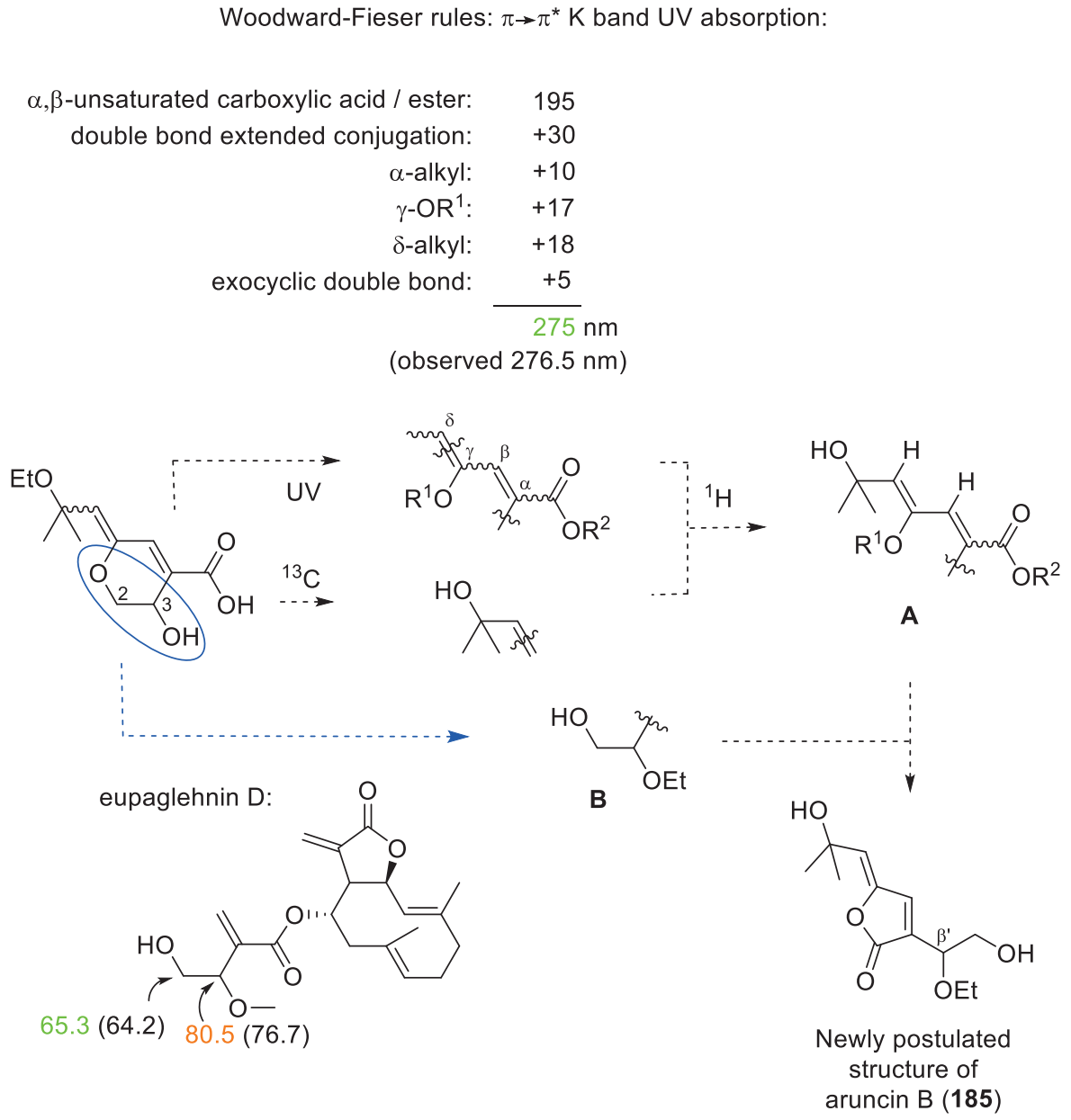


Figure 6. The *Z*-γ–ethylidenebutenolide hypothesis, characteristic ^{13}C NMR values (ppm) for eupaglehnin D,[98] with data for aruncin B in parenthesis.

Various γ-alkylidenebutenolide natural products (e.g., **186**-**193**, Figure 7)[99-104] have been isolated, including the complex oxidized tirucallane triterpenoid (**192**)[103] and novaxenicin D (**193**)[104] (Figure 7). ^{1}H NMR data observed for the dienoate **186** is indicative of the *Z*-geometry of the butenolide. Comparison of ^{13}C chemical shifts observed for the α-side-chain between tenuifolide B (**187**) and 4,5-didehydroacaterin (**188**) is indicative of the β' carbon bearing an

ether. Comparison of ^{13}C chemical shifts observed for the allylic position between **192** and **193**, strengthen the hypothesis of the presence of the tertiary allylic alcohol.

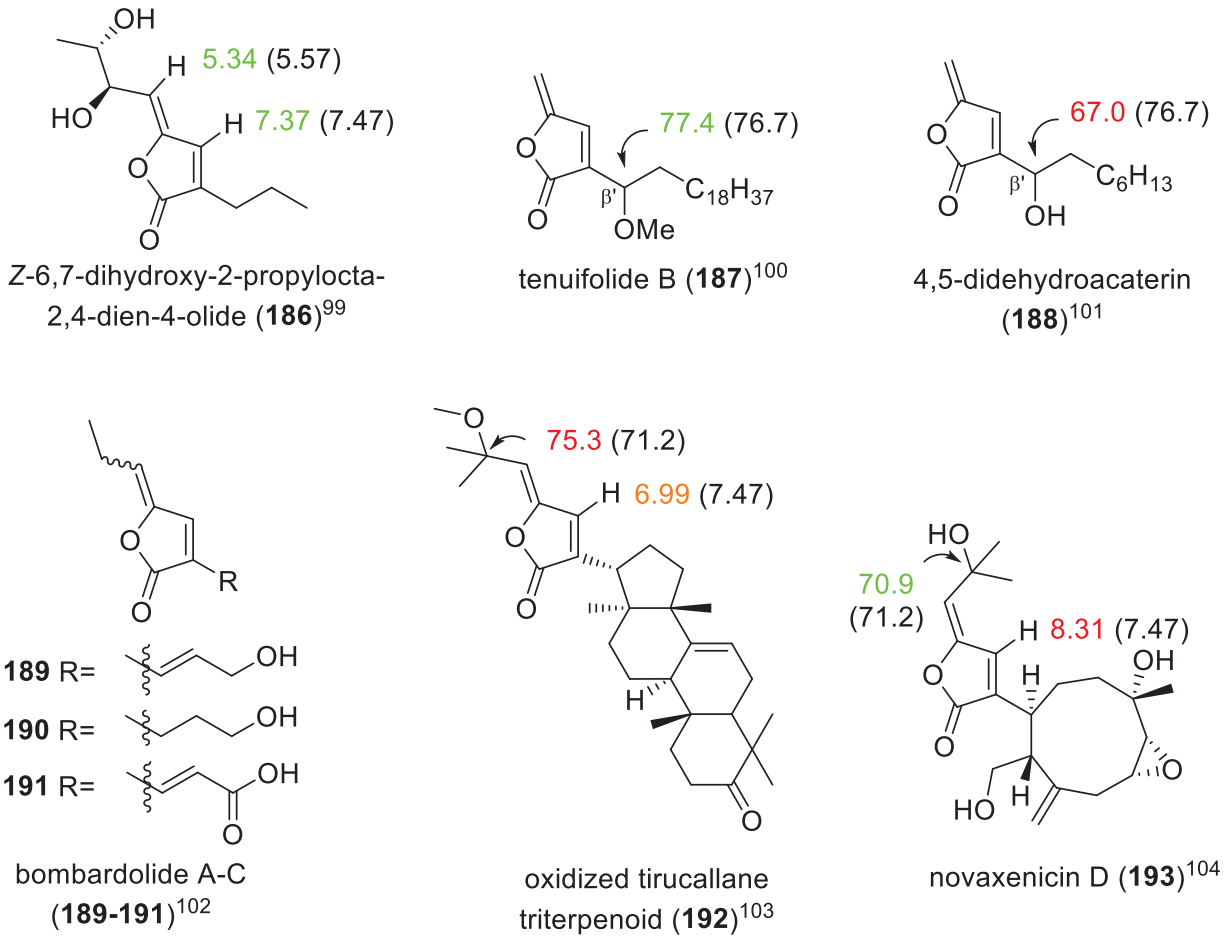


Figure 7. Naturally occurring γ-alkylidenebutenolides.

Although the above data analysis encouraged us to consider structure **185** (Figure 1), one significant piece of data was inconsistent. While a C=O IR stretch of 1724 cm^{-1} was reported for aruncin B, the anticipated stretch for the type of butenolide we were now considering should be around 1755 cm^{-1}.[104] We contacted the authors of the original publication asking to provide us with copies of all the data recorded on the natural isolate. They provided us with all the NMR and MS data they had (Figure 8); but stated the IR spectrum could not be found:

Dear Professor David M. Hodgson;

Please find the copies of all the spectra of Aruncin B (UV, 1H, 13C, HSQC, COSY, HMBC, MS). Now I can not find IR spectrum only.

Sincerely yours,

Mi Hee Woo, Professor
Catholic University of Daegu

Figure 8. Copy of the communication between Prof. Hodgson and Woo.

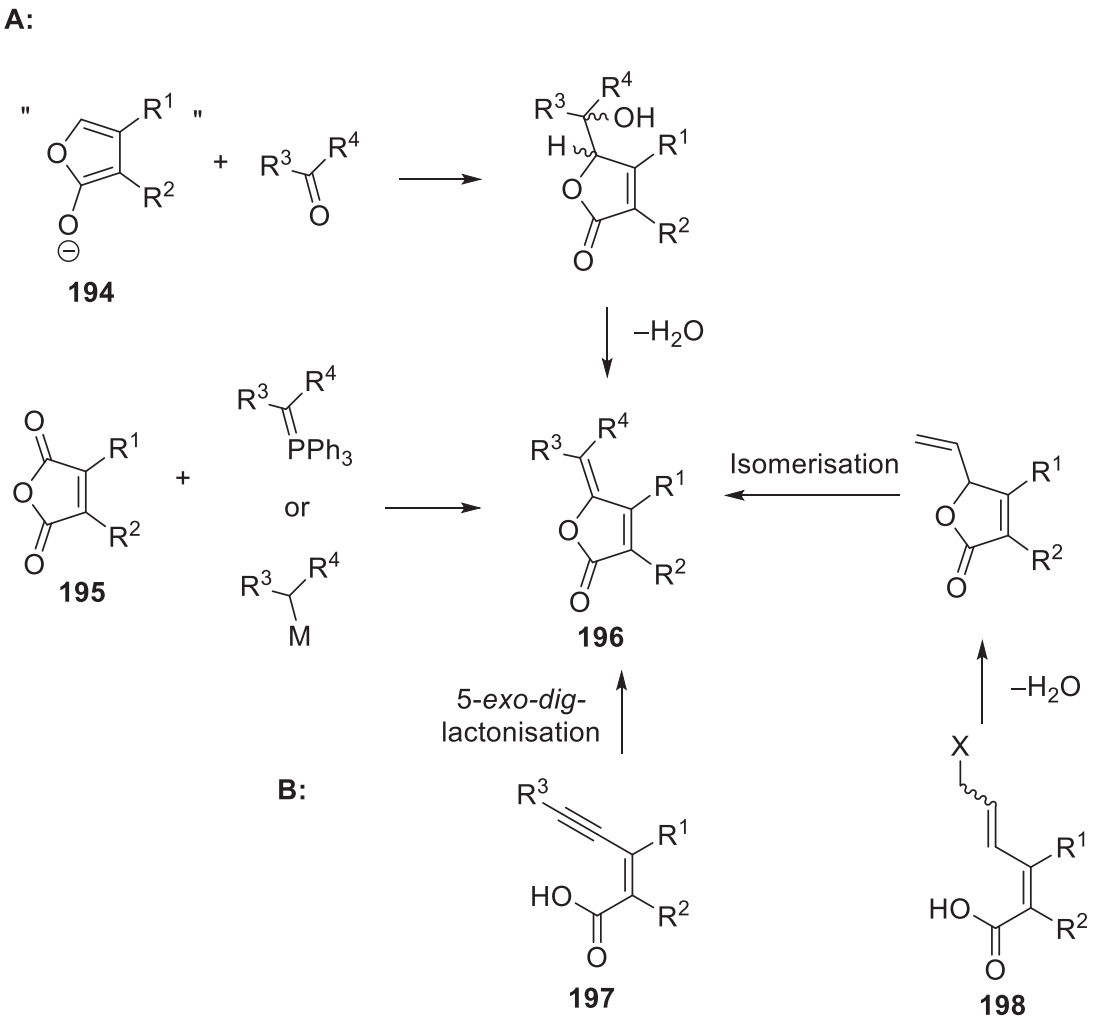
It is important to note that in the HMBC provided by Prof. Woo, no reciprocal correlation between the OCH_2 of the ethyl group and the carbon centre bearing the ether could be seen; the site of etherification could not be determined with more certainty than from comparison with other known compounds.

Since the only piece of original data which was not consistent with our γ-alkylidenebutenolide hypothesis "could not be located", we decided to synthesise *Z*-γ-ethylidenebutenolide **185**.

The commonly used methods for γ-alkylidenebutenolide synthesis will be briefly presented in the following section.

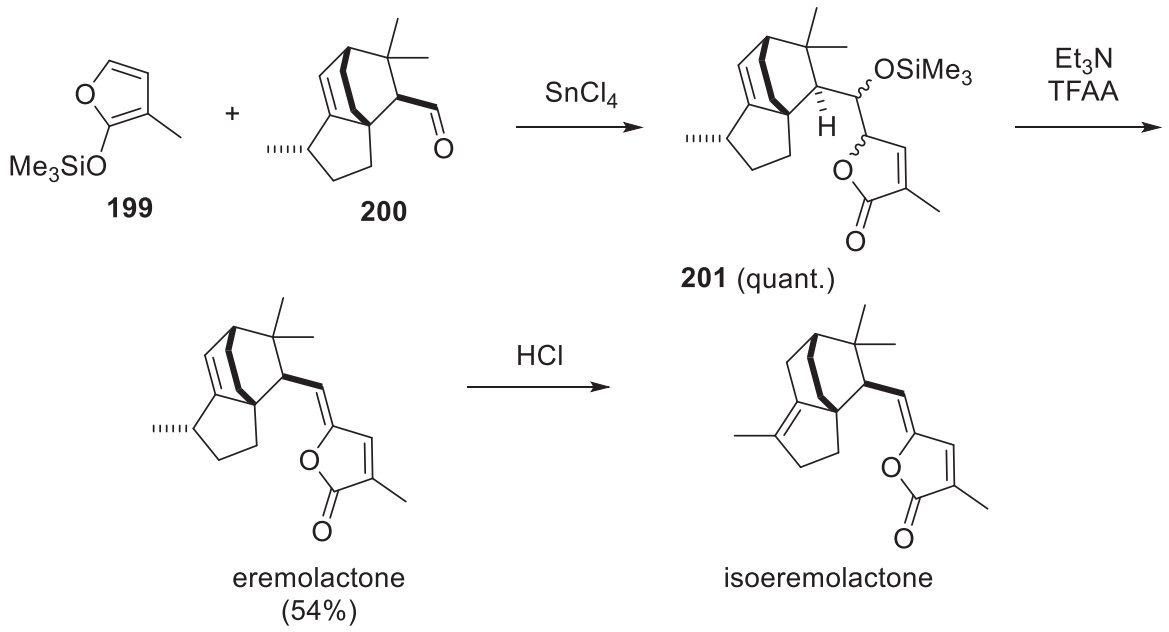
4.2. Some examples of γ–alkylidenebutenolide synthesis

Syntheses of γ–alkylidenebutenolides **196** have been well studied in the past and have been reviewed several times in the past two decades.[105] Methods for synthesis of this class of compounds can be divided into two broad types: A) functionalisation of 5-membered oxacycles, either by condensation of extended enolates **194** with a carbonyl compound or by olefination of a maleic anhydride derivatives **195** and B) lactonisation of unsaturated carboxylic acids, such as **197** and **198** (Scheme 66).



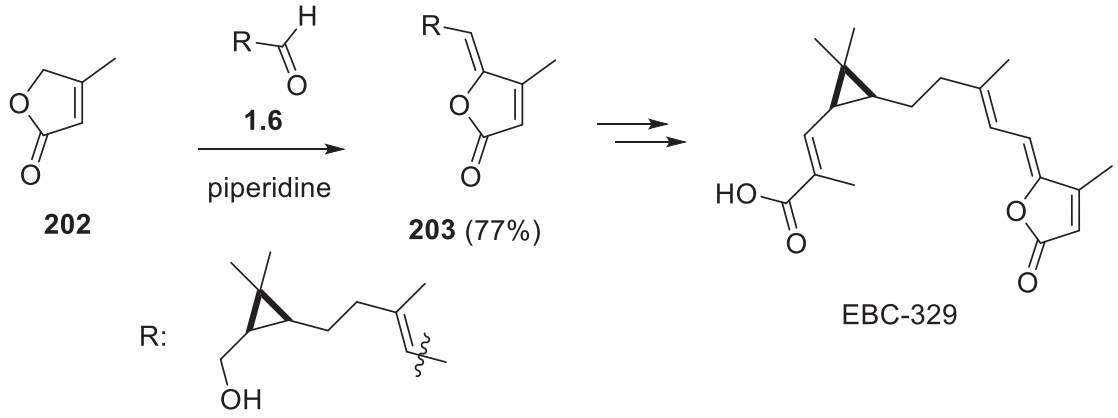
Scheme 66. Principal methods for γ–alkylidenebutenolide synthesis.

The extended enolate **194** (Scheme 66), could be generated by Lewis acid treatment of a silylated 2-oxyfuran. In 1983, Ramage and Takei, independently reported the synthesis of eremolactone and isoeremolactone (Scheme 67).[106,107] In the presence of $SnCl_4$, silyloxyfuran **199** smoothly added to the aldehyde **200** which, following elimination of silyl ether **201**, gave the desired eremolactone.



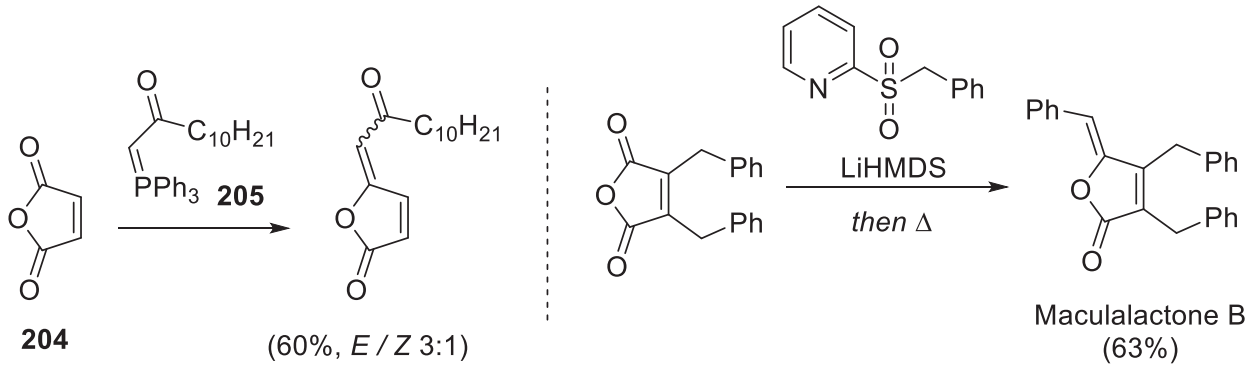
Scheme 67. Ramage and Takei syntheses of eremolactone / isoeremolactone.

The extended enolate **194** (Scheme 66) could also be synthesised by the action of a base on an α,β-unsaturated γ-lactone. Lactone **202** (Scheme 68) smoothly condensed with the aldehyde **203** in the presence of piperidine. The butenolide was further functionalised to give EBC-329, an anti-leukemic diterpene natural product.[108]



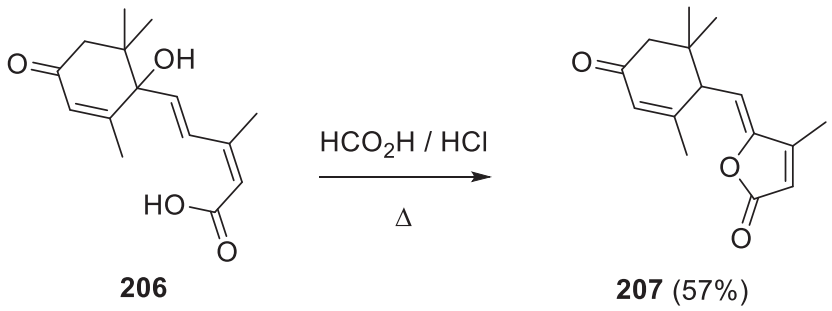
Scheme 68. Synthesis of EBC-329.

For the synthesis of ramariolide natural products, Sieber et al. described the synthesis of γ–alkylidenebutenolides using Wittig condensation between maleic acid (**204**) and ketophosphorane **205** (Scheme 69).[109] Gueyrard et al. recently reported a similar type of transformation using a modified Julia olefination, which was used for the synthesis of maculalactone B.[110]



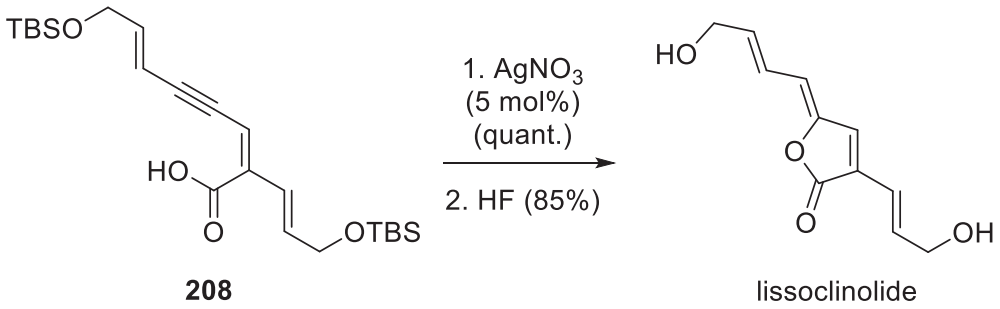
Scheme 69. Syntheses of γ–alkylidenebutenolides by olefination of maleic acid derivatives.

Ryback et al. showed that dehydration of abscisic acid (**206**), resulted in the formation of the butenolide **207** (Scheme 70).[111]



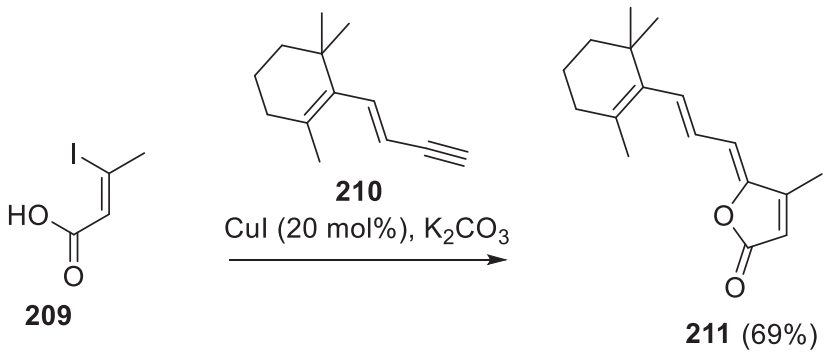
Scheme 70. Dehydration of abscisic acid (**206**).

As noted above (Scheme 66B, p. 66) γ–alkylidenebutenolides can be obtained by cyclisation of 4-alkynoic acids. As shown by Negishi et al., when exposed to catalytic Ag(I) polyunsaturated acid **208** smoothly cyclised, to give after desilylation the natural antibiotic lissoclinolide (Scheme 71).[112] These types of cyclisations have also been reported using Hg, Pd and Rh catalysts. These metal-catalysed methods usually delivered the *Z*-isomer of the desired butenolide; in some case formation of small amounts of pyran-2-one obtained from 6-*endo-dig*-cyclisation could also be observed.



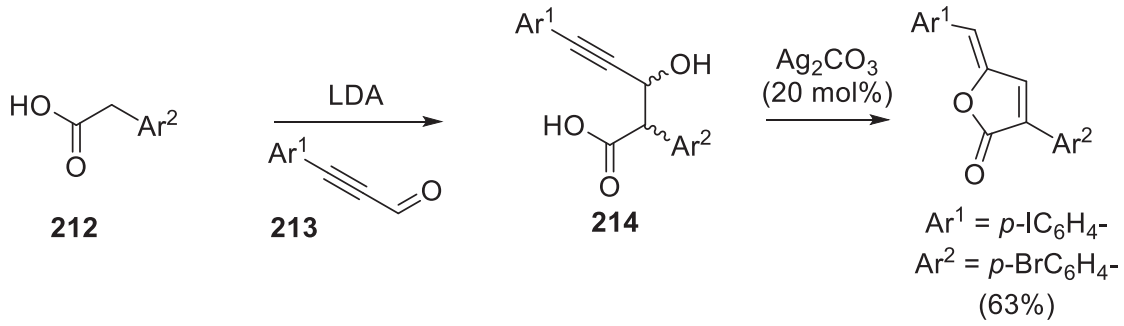
Scheme 71. Negishi synthesis of lissoclinolide.

In a more convergent manner, Sonogashira cross-coupling between an appropriate *Z*-iodoacrylic acid and an alkyne results in the formation of the desired 4-alkyn-2-enoic acid, which under the reaction condition can undergo lactonisation. Abarbri and Parrain provided nice examples of this transformation, under Pd free conditions, as exemplified by the coupling between iodoacrylic acid **209** and alkyne **210** to give butenolide **211** (Scheme 72).[113]



Scheme 72. Palladium-free Sonogashira cross-coupling followed by lactonisation.

More recently, Brückner showed an interesting approach, starting from addition of the dianion formed from an arylacetic acid **212** to an alkynyl aldehyde **213** (Scheme 73). The adduct **214** was then cyclised and dehydrated in the presence of Ag_2CO_3 catalyst.[114] This can be carried out in the presence of halide functionality on the aromatic substituent giving the opportunity for further functionalisation. 28 examples were synthesised using this sequence.

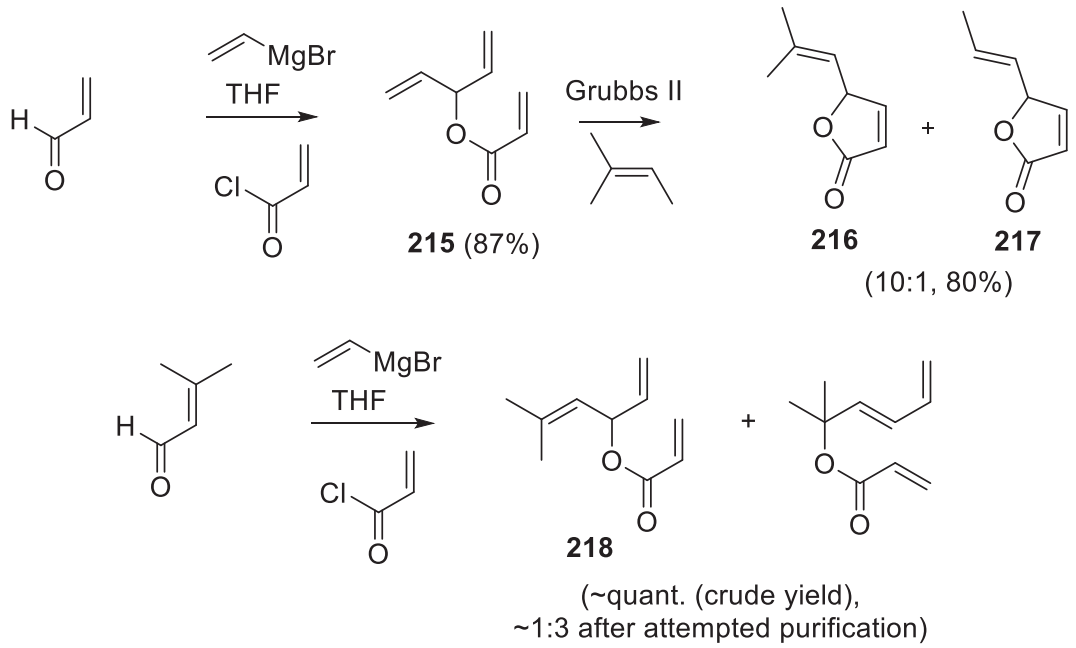


Scheme 73. Brückner's approach to butenolides.

4.3. RCM / ethoxyselenation–selenoxide elimination approach: model study: the α-unsubstituted butenolide

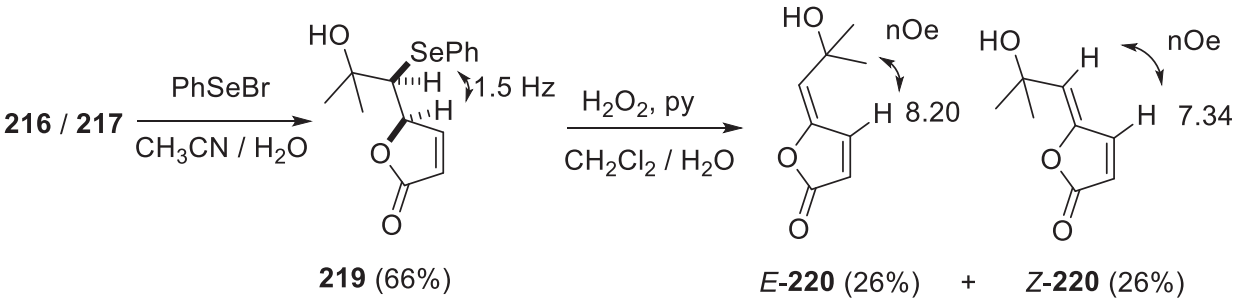
As discussed in the previous section (4.2. Some examples of γ–alkylidenebutenolide synthesis) there are many methods reported for the synthesis of γ-alkylidenebutenolides.[105] However, we were interested in establishing the viability of the RCM / hydroxyselenation-selenoxide elimination sequence, which proved effective for the synthesis of γ-alkylidenedihydropyrans, for the synthesis of γ-alkylidenebutenolides. Similarly to the 6-membered ring system, we were initially interested in synthesising the *Z*-γ–ethylidenebutenolide missing the α-side chain, so as to establish the viability of the sequence.

The synthesis starts with the addition of the *in situ* generated magnesium alcoholate resulting from the reaction between vinylmagnesium bromide and commercially available acrolein,[115] to acroloyl chloride which provided the triene **215**[116] precursor for the RCM / CM reaction (Scheme 74).[61,78] From a practical viewpoint, the triene **215** was difficult to handle due to its high volatility and low stability; it was therefore preferable to freshly prepare it prior to the RCM / CM reaction. The latter was carried out using **GII** in the presence of 2-methyl-2-butene,[61] giving the desired lactone **216** as a 10:1 inseparable mixture with mono-methyl olefin-containing lactone **217**.[117] In the first experiments, a red oil was isolated after chromatographic purification, in greater than quantitative yield. This was likely due to the presence of Ru catalyst residues, which could be easily eliminated by stirring the reaction in the presence of activated charcoal, for a further 24 h.[118] To avoid the formation of the undesired lactone **217** the use of triene **218** in a classical RCM was envisaged. The latter could be synthesised *via* the same sequence as described above, starting from prenal (instead of acrolein), but compound **218** showed even greater instability and had a strong tendency to undergo allylic rearrangement (during workup and chromatographic purification or distillation).



Scheme 74. Synthesis of butenolide **216** and attempted synthesis of triene **218**.

Hydroxyselenation was carried out on the **216** / **217** mixture (Scheme 75) using the conditions previously described (Scheme 65, p. 61). The presence of **217** did not interfere with the course of the reaction as the resulting by-products were easily removed by column chromatography. The hydroxyselenation proceeded again with complete diastereoselectivity, with the relative configuration being the same as seen earlier in the 6-membered ring system (**137**, Scheme 47, p. 41, on the basis of similar $^{3}J_{OCH \rightarrow SeCH}$ values: ~ 1.5 Hz). Oxidation of hydroxyselenide **219** followed by elimination delivered the desired butenolide **220** as a 1:1 *E*/*Z* mixture, the *E*-isomer being the initial product of the elimination, the *Z*-isomer resulting from isomerisation of the latter. ^{1}H NMR data observed for these butenolides (8.20 and 7.34 ppm ($CDCl_3$) for *E*- and *Z*-**220**, respectively; 7.47 (CD_3OD) for aruncin B (**1**)) as well as the apparent thermodynamic preference for the *Z*-isomer, reinforced our confidence in our assignement of the exocyclic olefin of aruncin B having the *Z*-geometry. This model study proved the viability of the RCM / hydroxyselenation-selenoxide elimination sequence for the synthesis of a γ–alkylidenebutenolide.



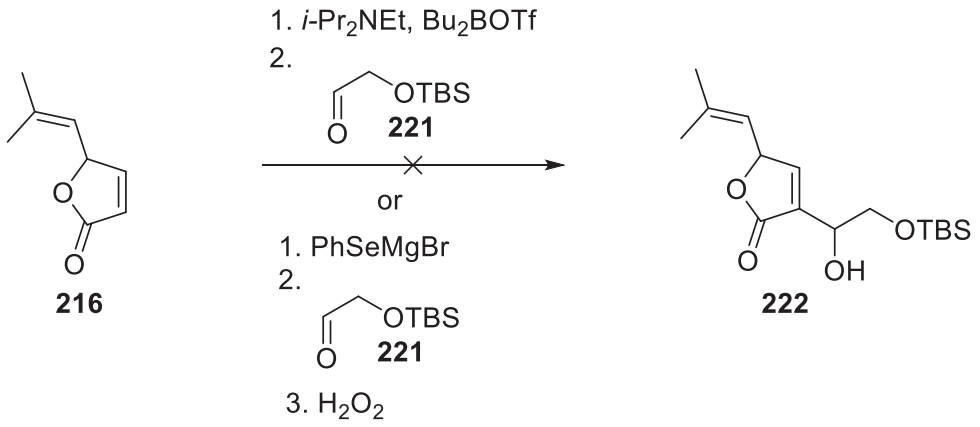
Scheme 75. Synthesis of butenolides *E*- and *Z*-**220**, with relevant ^{1}H NMR values (ppm) and ^{3}J values (Hz).

4.4. RCM / ethoxyselenation–selenoxide elimination approach to the newly postulated structure of aruncin B

With the viability of this sequence established, we decided to apply it to the synthesis of the newly postulated structure of aruncin B **185**. The side-chain would be installed by α-functionalisation of the lactone **216** with an appropriate aldehyde prior to the hydroxyselenation-selenoxide elimination sequence.

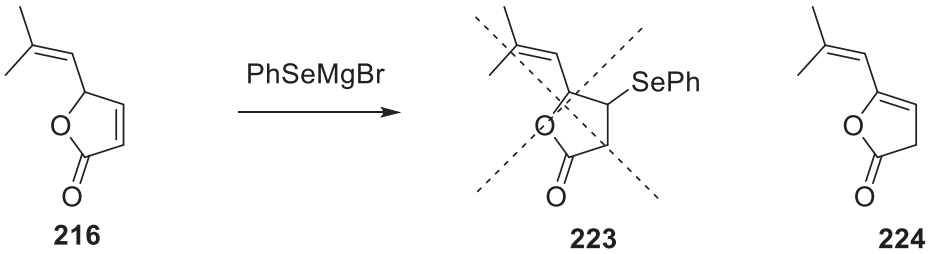
We were particularly attracted by a boron furanolate aldol condensation[119,120] and a metallic selenolate mediated Michael-aldol cascade[121] strategy, between lactone **216** and aldehyde **221** (Scheme 76, aldehyde **221** is commercially available or easily prepared in two steps from 1,4 butenediol, by protection followed by ozonolysis)[122]. However, addition of the corresponding conjugated boron enolate of **216** to the aldehyde **221**, resulted in a complex mixture with none of the desired α–functionalised α,β-unsaturated lactone **222** or recovered starting material **216** observed.

1,4-Addition of magnesium phenylselenolate (Scheme 76, prepared *in situ* from elemental selenium and phenylmagnesium bromide) to the lactone **216**, should result in formation of the β-selenoenolate, which could be engaged in an aldol addition with the aldehyde **221** and would then hopefully give after oxidative workup the desired adduct **222**. Unfortunately, this attempt also resulted in a complex mixture, and none of the desired α-functionalised butenolide **222** or recovered starting material **216** was observed.



Scheme 76. Attempted α-functionalisation of lactone **216**.

In a separate run, following the addition of magnesium phenylselenolate, the reaction was quenched (using standard aqueous workup, no oxidant). Instead of observing β–selenolactone **223** (Scheme 77), the β,γ-unsaturated lactone **224** was clearly seen in the crude mixture[†] as the only detectable product. This isomerisation is most likely to be induced due to the basicity of the magnesium phenylselenolate and favoured by aromaticity of the conjugate base and extended conjugation with the exocyclic olefin.

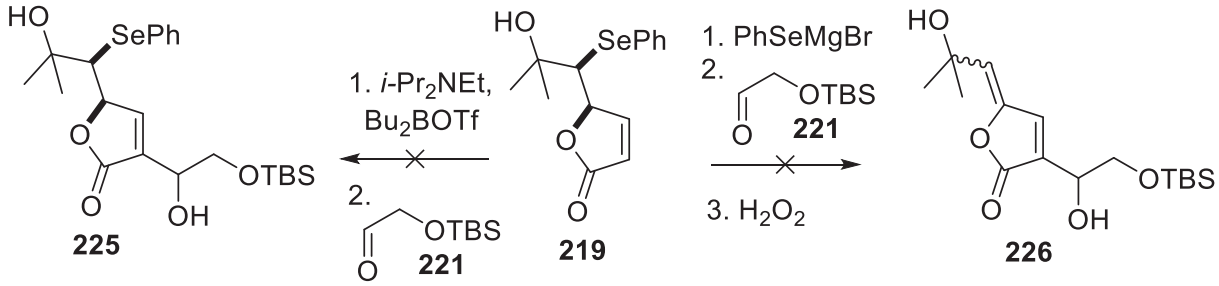


Scheme 77. Magnesium phenylselenolate induced isomerisation of **15**.

In order to overcome this isomerisation, we envisaged carrying out the α-functionalisation on the hydroxyselenide **219** (Scheme 78). With the magnesium phenylselenolate method, the oxidative workup should result in simultaneous α-functionalisation and enol ether formation.

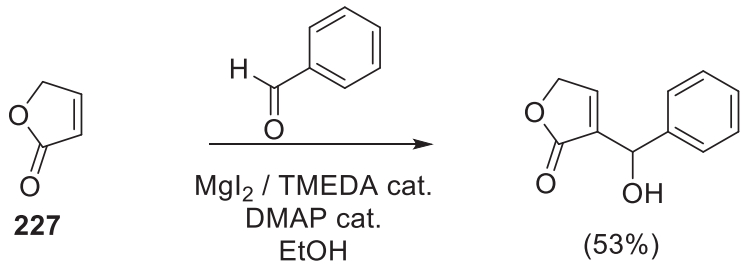
[†] Characteristic ^{1}H NMR data (400 MHz, $CDCl_3$): 5.69-5.67 (1H, m, C<u>H</u>=C$(CH_3)_2$), 5.19 (1H, t *J* 2.5, OC=CH)), 3.27-3.24 (2H, m, CH_2C(=O)-O)), 1.96 and 1.88 (2 x 3H, 2 x s, C$(CH_3)_2$).

The same conditions as described above were attempted on hydroxyselenide **219**, but again resulted in complex mixtures: no major by-products were isolated to help in rationalising the outcome of the reaction.



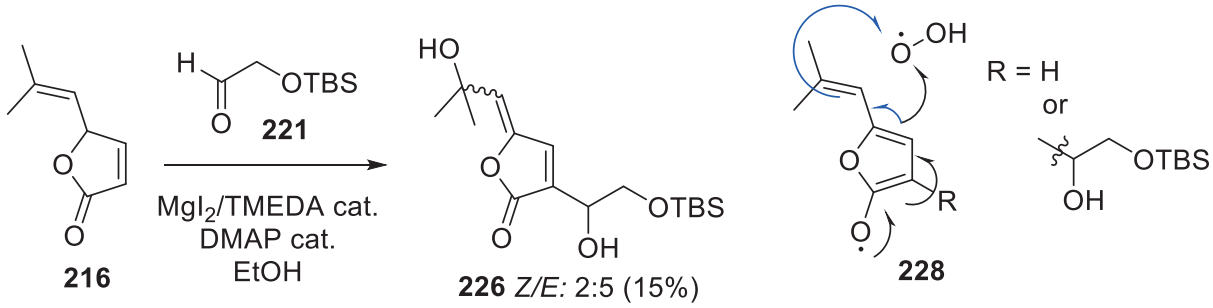
Scheme 78. Attempted α-functionalisation of hydroxyselenide **219**.

Connell et al.[123] recently reported the use of a MgI_2/TMEDA complex–DMAP catalytic system for MBH functionalisation of various activated alkenes, including the simple furan-2(5*H*)-one (**227**, Scheme 79).



Scheme 79. Connell's conditions for MBH functionnalisation of furan-2(5*H*)-one **227**.

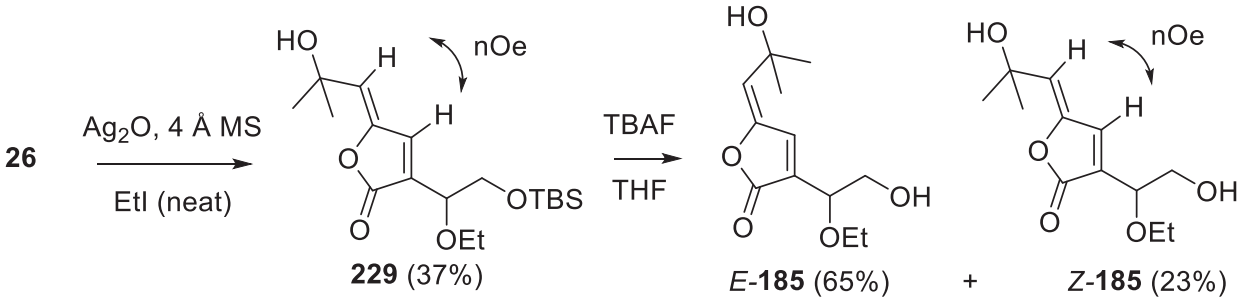
This method was applied to the synthesis of MBH adduct **222**. Surprisingly, reaction of butenolide **216** and aldehyde **221** did not result in formation of the desired MBH adduct **222**, but in an inseparable *E*/*Z* mixture of γ-ethylidenebutenolide **226** (Scheme 80). This fortuitous and unexpected allylic oxidation was suspected to occur *via* hydrogen atom abstraction of the *bis*-allylic OCH (on butenolides **216** and / or **222**). This aerobic oxidation was not observed in the 6-membered ring, and the difference in reactivity could be rationalised by the existence of aromaticity for the putative radical species **228**, favouring the hydrogen abstraction.



Scheme 80. Unexpected outcome of MBH reaction and postulated radical intermediate.

Unfortunately, on repeat runs, the above transformation did not prove reproducible, resulting at best in even smaller amounts of γ-ethylidenebutenolide **226**. In order to understand the cause of these failures, we decided to examine the transformation reported by Connell between furan-2(5*H*)-one and benzaldehyde (Scheme 79), but were not able to reproduce his results. We contacted the authors of the publication to ask for any helpful practical advice: different batches of MgI_2 were used, various EtOH drying procedures (straight from the bottle, 4 Å MS or distillation over $Mg(OEt)_2$ (from Mg turnings)) were examined but none of these attempts resulted in the formation of the desired product.

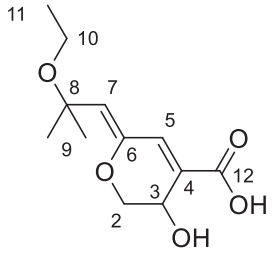
Nonetheless, around 30 mg of γ-ethylidenebutenolide **226** had been obtained in total, which was considered enough to try to establish whether *Z*-γ-ethylidenebutenolide **185** corresponded to the true structure of aruncin B. *O*-Ethylation was carried out using Ag_2O in neat EtI in the presence of 4 Å MS, giving ether **229** as a single geometric *Z*-isomer, albeit in modest yields (37%, Scheme 8). Desilylation using TBAF in THF delivered the desired primary alcohol **185**. Surprisingly, the deprotection was accompanied by partial isomerisation of the exocyclic olefin, giving preferentially the apparently thermodynamically disfavoured isomer (3:1).



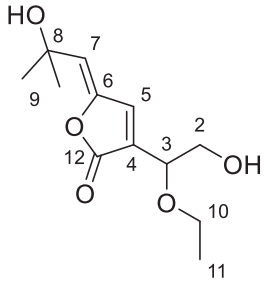
Scheme 81. Synthesis of **185**.

To our delight, analytical data recorded for the synthetic material *Z*-**185** corresponded to that described for the natural isolate (Table 3), excepting the IR data, which corresponded to what was anticipated for this type of butenolide (1755 cm^{-1} with KBr disc or thin film).

Even though this synthetic route successfully provided material to confirm the true structure of aruncin B, the low yielding, poorly reproducible transformation from butenolide **216** to **226** (Scheme 79) and the fluoride-induced isomerisation of primary alcohol **2** considerably impaired the synthetic value of this sequence. From this arose the need for an efficient and reliable synthesis of aruncin B (*Z*-**185**).



Aruncin B
originally proposed
structure (**1**)



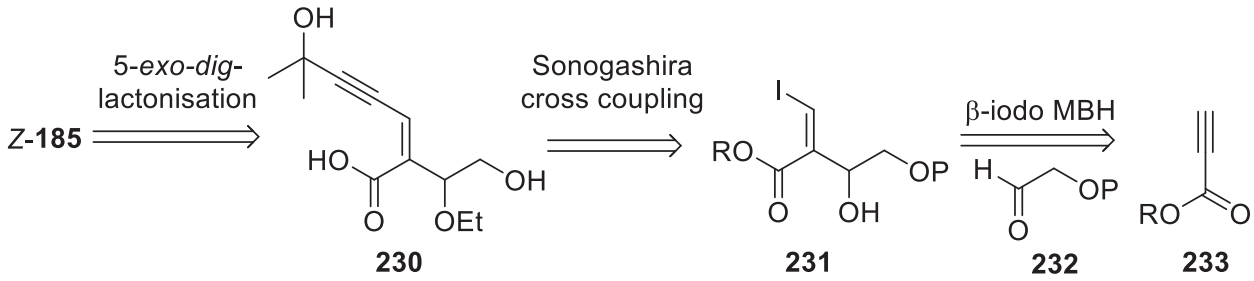
Aruncin B
revised
structure (*Z*-**185**)

Atom #	^{1}H NMR of natural isolate (500 MHz, CD_3OD)	^{1}H NMR of synthetic material (500 MHz, CD_3OD)	^{13}C NMR of natural isolate (125MHz, CD_3OD)	^{13}C NMR of synthetic material (125 MHz, CD_3OD)
2	3.76, dd *J* 12.0, 4.4 3.65, dd *J* 12.0, 5.6	3.76, dd *J* 11.5, 4.0 3.65, dd *J* 11.5, 6.0	64.2	64.3
3	4.29, dd *J* 5.6, 4.4	4.28-4.26, m	76.7	76.8
4	-		132.1	132.3
5	7.47, s	7.46-7.45, m	143.1	143.0
6	-		147.4	147.5
7	5.57, s	5.54 s	125.0	124.9
8	-		71.2	71.3
9	1.50, s	1.50, s	30.3	30.3
10	3.57, q *J* 7.2	3.59-3.55, m	66.7	66.8
11	1.22, t *J* 7.2	1.22, d *J* 7.0	15.8	15.8
12	-		170.8	170.8

Table 3. NMR comparison between natural isolate and synthetic material.

4.5. The β-iodo MBH / Sonogashira cross coupling–lactonisation route to aruncin B

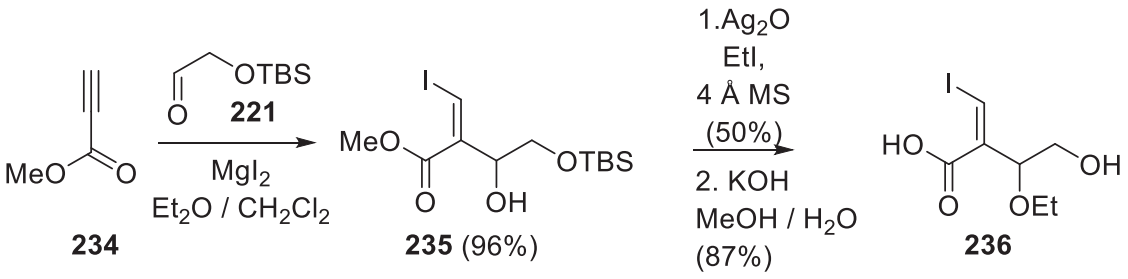
In order to overcome the above-mentioned issues, a synthetic route relying on a late stage 5-*exo-dig*-lactonisation was envisaged (Scheme 66B, p. 66, see also Schemes 71-72, p. 69-70).[105,112,113] The desired enyne **230** would be derived from the *Z*-iodide **231**, obtained by β-iodo MBH reaction between an aldehyde **232** and a propiolate **233** (Scheme 82).[124]



Scheme 82. New retrosynthesis.

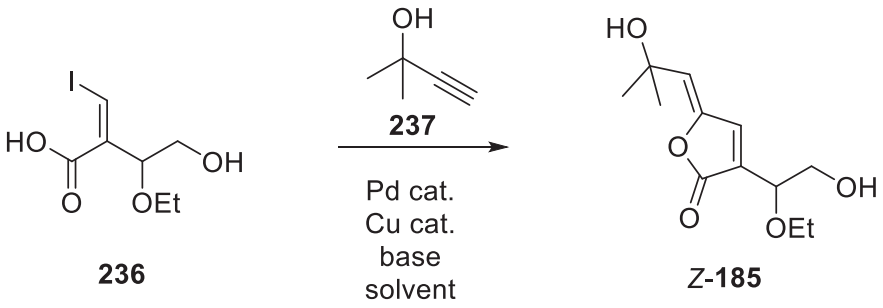
After several attempts using a variety of iodide sources (TMSI, MgI_2 (obtained commercially), $n$$Bu_4NI$) it was found that the use of *in situ* generated MgI_2 (from Mg turnings and I_2 in Et_2O) smoothly effected the β-iodo MBH reaction between methyl propiolate **234** and aldehyde **221** (Scheme 83).[125] This transformation is particularly valuable because it installed in one step the α-side-chain, which had proved difficult using other methods (4.4. RCM / ethoxyselenation–selenoxide elimination approach to the newly postulated structure of aruncin B), as well as the necessary *Z*-vinyl iodide requested for the late-stage Sonogashira cross-coupling. *O*-Alkylation of *Z*-iodo acrylic acid **235** proved very difficult and could not be carried out by the simple use of an alkylating agent (EtI) in the presence of a base (NaH, only inducing decomposition). However, the use Ag_2O in neat EtI in the presence of 4 Å MS did achieve the *O*-ethylation of *Z*-iodo acrylic acid **235**, to give the corresponding ethyl ether. This method preserved the geometrical integrity of the *Z*-vinyl iodide. Saponification under concentrated

reaction conditions (~ 1 M) was, helpfully, accompanied by desilylation, to give hydroxyacid **236**.



Scheme 83. Synthesis of hydroxyacid **35**.

Taking advantage of Sonogashira cross-coupling functional group tolerance and mildness, the coupling between hydroxyacid **236** and the commercially available alkyne **237** (Scheme 84), could be carried in the presence of the two free alcohols and one carboxylic acid. Furthermore, the desired 5-*exo*-*dig*-lactonisation occurred, in a *one pot* fashion under the reaction conditions. After a screen of conditions (Table 4), it was found that Pd free conditions (entry 1) did not result in the formation of the desired product.[112] The use of Pd on charcoal (entry 2) as a source of catalyst gave some of the desired butenolide *Z*-**185**, but with substantial contamination by residual catalyst.[126] The latter was therefore replaced by $Pd(PPh_3)_2Cl_2$, which proved to be an efficient catalyst for the reaction and did not require any heating (entries 3-4); optimal conditions for this transformation were found using acetonitrile as solvent (entries 4-6) in the presence of Et_3N as a base (entries 6-8).[127] This reaction could also be carried out in good yield with a low Pd catalyst loading (entry 9). This proved important, since higher catalyst loading resulted in slight contamination of the product by catalyst residues. Using the optimised conditions, up to 200 mg (~1 mmol scale) of aruncin B could be synthesised in one batch.



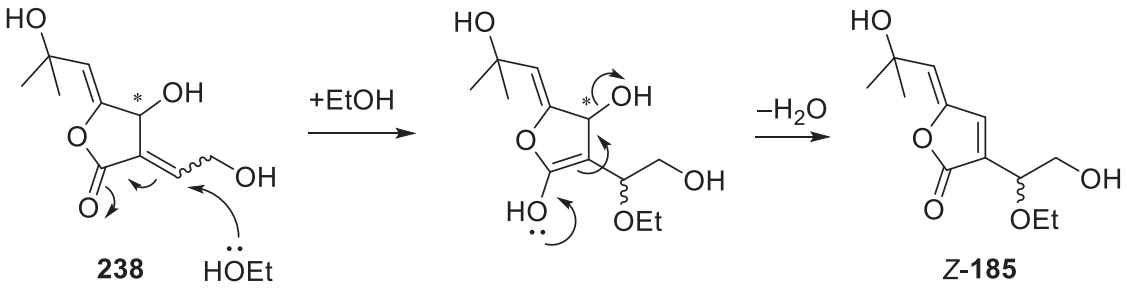
Scheme 84. Final *one-pot* Sonogashira cross coupling–5-*exo*-*dig*-lactonisation.

Entry	Pd (mol%)	CuI (mol%)	Base	Solvent	Temp. (°C)	Yield (%)
1[112]	-	200 mol%	K_2CO_3 (2 equiv)	DMF	55	0
2[126]	Pd / C (2,5) + PPh_3 (10)	5 mol%	Et_3N (3equiv)	1,4-dioxane	80	35
3	$Pd(PPh_3)_2Cl_2$ (5)	10 mol%	Et_3N (3 equiv)	1,4-dioxane	80	44
4	$Pd(PPh_3)_2Cl_2$ (5)	10 mol%	Et_3N (3 equiv)	1,4-dioxane	rt	42
5	$Pd(PPh_3)_2Cl_2$ (5)	10 mol%	Et_3N (3 equiv)	THF	rt	20
6[127]	$Pd(PPh_3)_2Cl_2$ (5)	10 mol%	Et_3N (3 equiv)	MeCN	rt	55
7	$Pd(PPh_3)_2Cl_2$ (5)	10 mol%	iPr_2NH (3 equiv)	MeCN	rt	40
8	$Pd(PPh_3)_2Cl_2$ (5)	10 mol%	K_2CO_3 (3 equiv)	MeCN	rt	30
9	$Pd(PPh_3)_2Cl_2$ (1)	2 mol%	Et_3N (3 equiv)	MeCN	rt	60

Table 4. Screen of conditions for final step synthesis of aruncin B (*Z*-**185**).

4.6. Postulation on the origin of aruncin B

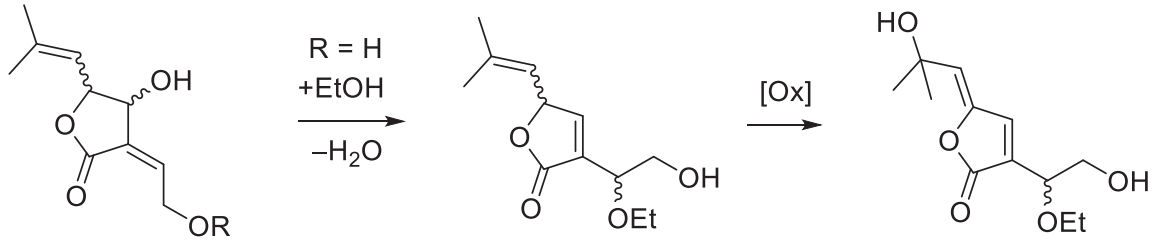
With plenty of synthetic *rac*-aruncin B in hand, we were able to separate the individual enantiomers using semiprep HPLC. Interestingly, the specific rotations recorded for the enantiopure samples showed significantly higher values than the one reported for the natural isolate ($[\alpha]_D^{25}$ +/– 90 (*c* 1.0 in MeOH), lit.[6] $[\alpha]_D^{20}$ + 27 (*c* 0.1 in MeOH), respectively). The lower literature specific rotation value suggested that aruncin B might not have been isolated enantiopure but rather as a slightly enantioenriched mixture. Moreover, the site of ethoxylation in the true structure of aruncin B seemed rather unusual. It is important to bear in mind that, aruncin B had been isolated by EtOH extraction of the aerial parts of the plant. The potentially low enantiomeric excess together with the unusual site of etherification led us to consider that aruncin B might not be an actual natural product, but rather an artefact of the isolation process by incorporation of ethanol to a natural product precursor. We therefore viewed aruncin B as possibly being derived from a α-(2-hydroxyethylidene)-γ-lactone **238**[128] (Scheme 85), by a modestly diastereoselective conjugate addition of EtOH, followed by elimination of water.



Scheme 85. Our suggested origin of aruncin B (*Z*-**185**).

Soon after our first report on the total synthesis and structural revision of aruncin B was published,[129] Zidorn and co-workers reported the isolation of monoterpenoids from extract of the shoots of *A. dioicus* var. *vulgaris* (closely related to the plant found in Ulleungdo).[130] They isolated several compounds which had been isolated at the same time as aruncin B. Based on our synthetic studies, they revised the structures of three of them. They also reported the

isolation of lactone **239** and its aglycone **240** (Scheme 86); which had been previously isolated from different plants.[128] In the light of this recent report, the aglycone **240** seems more likely than **238** to correspond to the natural product precursor of aruncin B (*Z*-**185**). Formation of aruncin B (*Z*-**185**) could then occur by conjugate addition of EtOH–elimination of water (as shown in Scheme 86), followed by a related aerobic oxidation as the one observed in the transformation from butenolides **216→226** also occurring in ethanol (Scheme 80, p.77).



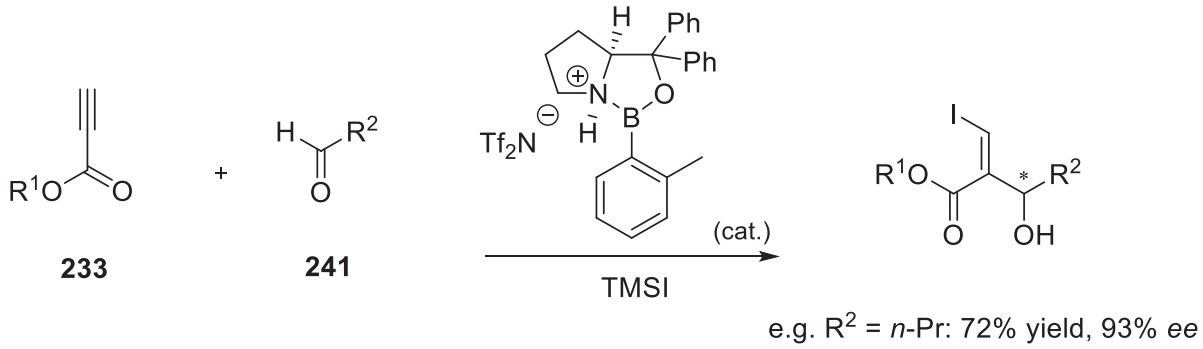
239: R = β-D-glucose
240: R = H

222 *Z*-**185**

Scheme 86. Pathway to aruncin B (*Z*-**185**) from aglycone **240**.

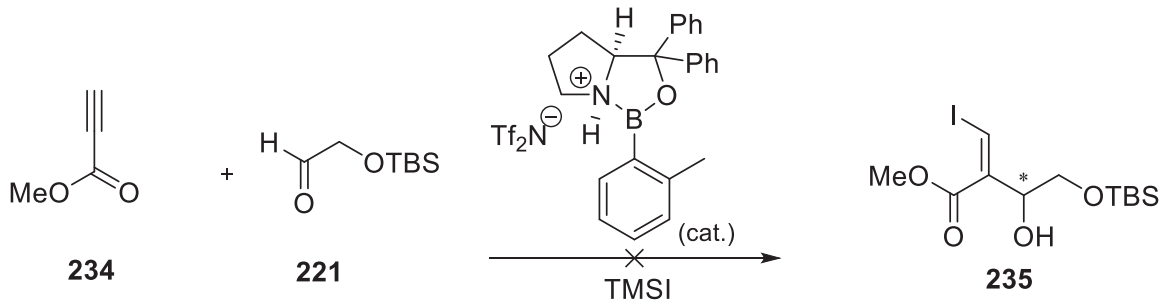
4.7. Studies towards the asymmetric synthesis of aruncin B

Despite the fact aruncin B was probably not isolated as a single enantiomer we were interested in developing an asymmetric synthesis of aruncin B *Z*-**185**. In our synthetic route leading to aruncin B, the one and only stereogenic centre present in aruncin B is constructed during the first step of the synthesis by β-iodo MBH reaction. An obvious way to render the synthesis asymmetric was to carry out this step enantioselectively. In 2009, Ryu reported the use of TMSI and a protonated oxazaborolidine catalyst for the asymmetric β-iodo MBH between methyl or ethyl propiolate **233** and an aliphatic or aromatic aldehyde **241** (Scheme 87).[131]



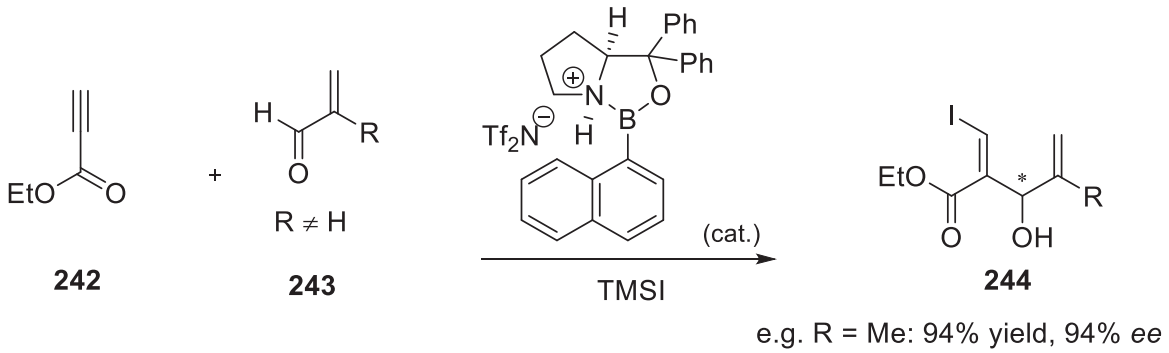
Scheme 87. Ryu's asymmetric β-iodo MBH reaction.

The above transformation seemed to perfectly fulfil our need, and we attempted to apply it to the aldehyde **221** (Scheme 88). Unfortunately, this transformation did not prove applicable to our substrate and only resulted in complete decomposition of the material. For validation of the experimental protocol, the reported reaction using *n*-butyraldehyde was repeated (with methyl and ethyl propiolate), resulting in the formation of the enantioenriched adduct in 40-50% yield (instead of the 72% reported in the original publication).



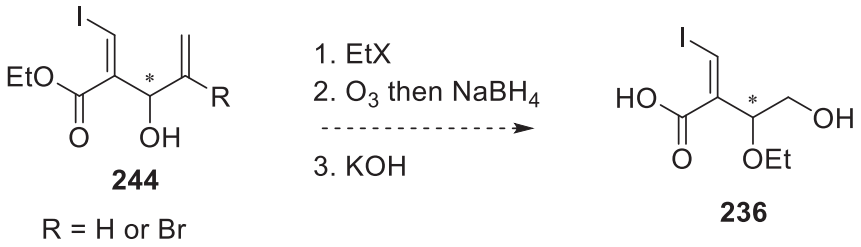
Scheme 88. Attempted enantioselective synthesis of **236** using Ryu's condition.

In 2013, Ryu et al. also described the synthesis of enantioenriched β-iodo MBH adducts from α–branched enals, using a similar catalytic system under slightly modified conditions (Scheme 89).[132]



Scheme 89. Ryu's asymmetric β-iodo MBH reaction with α–branched enal.

With R = H or Br, the β-iodo MBH adduct could potentially be elaborated to hydroxyacid **236**, by *O*-ethylation, ozonolysis followed by reduction and saponification (Scheme 90). However, attempts to apply this reaction between acrolein or α-bromo acrolein (R = H or Br) with methyl or ethyl propiolate all failed.



Scheme 90. Envisaged synthesis of **236** from **244**.

We decided to investigate this transformation in more detail using methacrolein (R = CH_3), the substrate which showed the best results in Ryu's report; but unfortunately we were not able to reproduce the results reported in this second publication. We contacted the authors asking for more experimental details, but none of their additional information provided proved helpful. We also tried different modification of the reaction conditions:

-methyl *vs* ethyl propiolate

-*o*-tolyl *vs* 1-naphtyl oxazaborolidine precatalyst

-nature of the counter anion: Tf_2N^- *vs* TfO^- (resulting from the addition of freshly sublimed Tf_2NH or distilled TfOH, respectively, to the oxazaborolidine precatalyst)

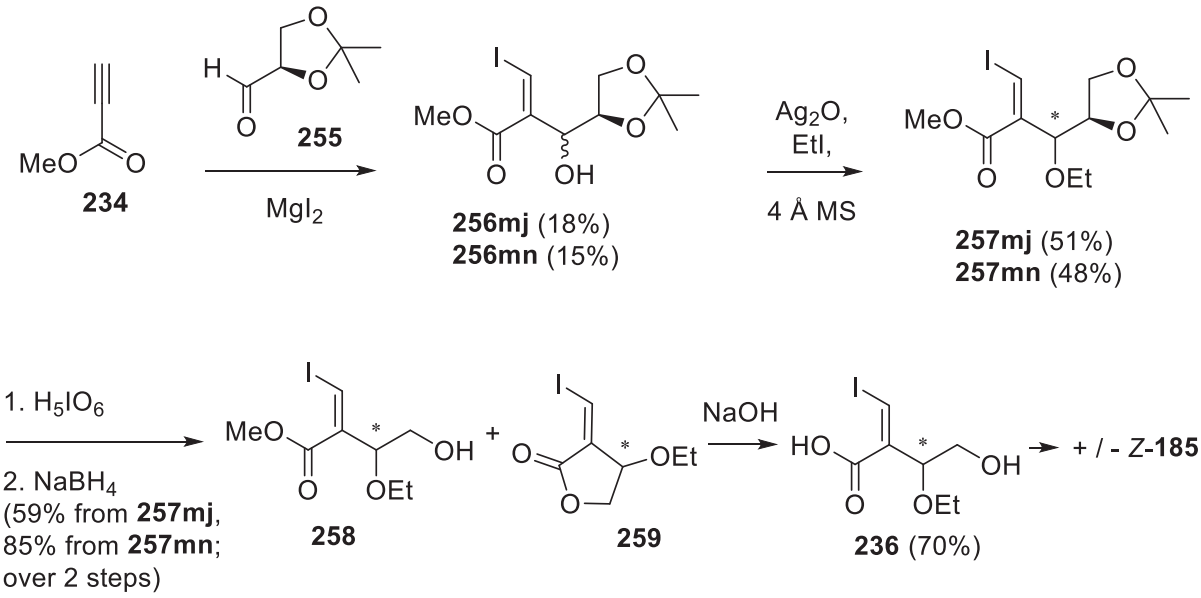
-TMSI from commercial source (same supplier as Ryu: TCI) *vs* freshly prepared (from reaction of I_2 in neat $(TMS)_2$, then distilled over copper wire).

-different temperature were examined: –78 °C, –60 °C and –40 °C.

None of the above-mentioned conditions resulted in formation of the desired product.

The above failures suggested that a catalytic asymmetric transformation was probably not applicable to our particular system (in my hands); we therefore considered carrying out a diastereoselective version of this transformation using a chiral aldehyde derivative. Aldehyde **255** (derived from D-mannitol *bis*-acetonide by oxidative cleavage),[133] could be coupled with methyl propiolate (**234**) under the conditions described above (Scheme 83, p. 81), in modest

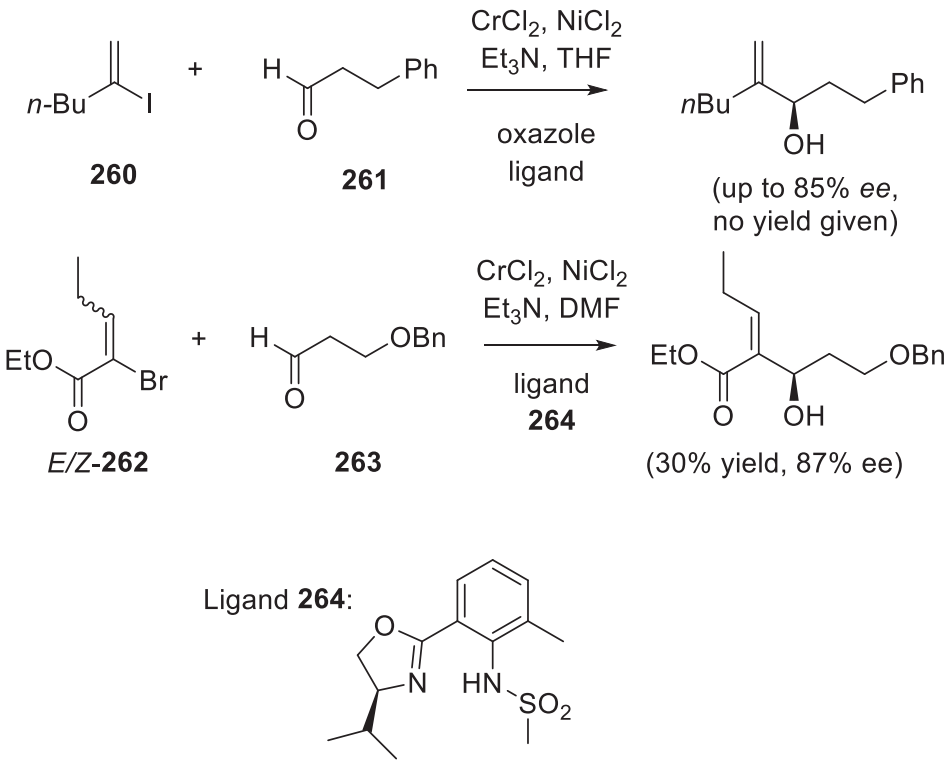
yields with low diastereoselectivity (1.2:1 dr, Scheme 91). Nevertheless, the diastereoisomers **256** could be separated and the following sequence independently carried out on each one. The usual *O*-ethylation conditions were used to obtain the ethyl ethers **257**. Deprotection / oxidative cleavage,[134] using periodic acid followed by reduction delivered an inseparable 1:3 mixture of the primary alcohol **258** and the corresponding lactone **259**. Hydrolysis delivered the hydroxyacid **236** and final cross-coupling with the hydroxyacid **236** obtained from the sequence starting from the major diastereoisomer gave a butenolide *Z*-**185** giving a positive specific rotation as the major enantiomer of aruncin B.



Scheme 91. Diastereoselective approach to aruncin B (*Z*-**2**).

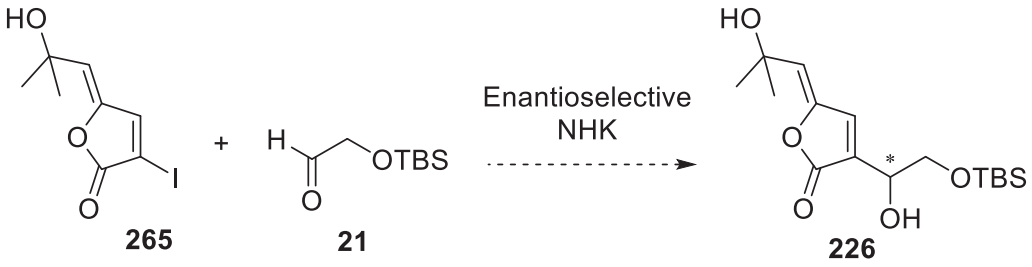
Unfortunately, this route did not help establishing the absolute configuration of aruncin B, the NMR data did not allow conformational analysis to establish the relative configuration of **256** and **257**, and derivatisation of the two latter compounds (e.g.: 3,5-dinitrobenzoate, various (poly)halobenzoate, Sanger's reagent) did not result in crystalline compounds for X-Ray crystallographic analysis.

In 2002, Kishi et al. reported the use of oxazole ligand (e.g. **264**, Scheme 92) for the enantioselective Nozaki-Hiyama-Kishi (NHK) coupling between, 2-iodo-hexene (**260**) and dihydrocinnamaldehyde (**261**) (Scheme 92).[135] In 2010, Horstmann et al. reported the use of these conditions for the coupling between an α-bromo-α,β-unsaturated ester **262** with the aldehyde **263**; interestingly, starting from an *E/Z*- mixture of bromide **262**, only the *E*- isomer reacted.[136]



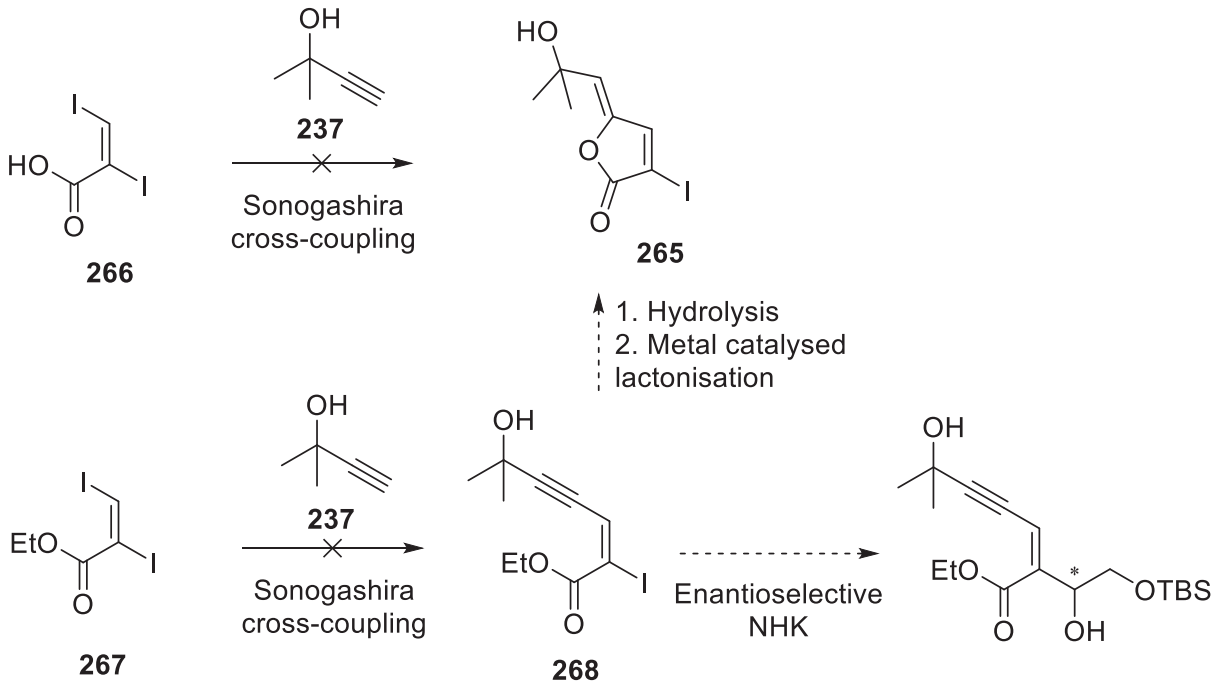
Scheme 92. Kishi's[135] first report of enantioselective NHK coupling and application to α-bromo-α,β-unsaturated by Horstmann.[136]

We were interested to establish whether the above method could be applied to the enantioselective synthesis of aruncin B (*Z*-**185**) by NHK coupling between an α-iodobutenolide **265** and the aldehyde **221** (Scheme 93).



Scheme 93. NHK approach to the enantioselective synthesis of aruncin B (*Z*-**185**).

In 2010, Pour reported that in the Sonogashira cross-coupling using methyl *E*-dibromoacrylate high selectivity for the coupling on the β-bromide was observed.[137] Other palladium-catalysed coupling between dihalo-acrylate or -acrylic acid and alkyne or alkynyl metals are reported with selectivity for the β-position.[138] These results suggested an intrinsic higher reactivity for the β-position. Therefore coupling of the *E*-diiodoacrylic acid **266**[139] with the alkyne **237** was attempted (Scheme 94), using some of the conditions described for the *Z*-**2** (Table 4), unfortunately none of them delivered useful amounts of butenolide **265**; at best, traces were observed in the crude mixture. The product **268** of the coupling between ethyl *E*-diiodoacrylate **267**[140] and the alkyne **237**, could be elaborated to the butenolide **268** *via* hydrolysis followed by metal-catalysed lactonisation. In principle, **268** could also be used for the enantioselective NHK step and the product could then be hydrolysed and lactonised. Unfortunately, attempted synthesis of **268** failed. Due to time constraints these sequences were not further studied.

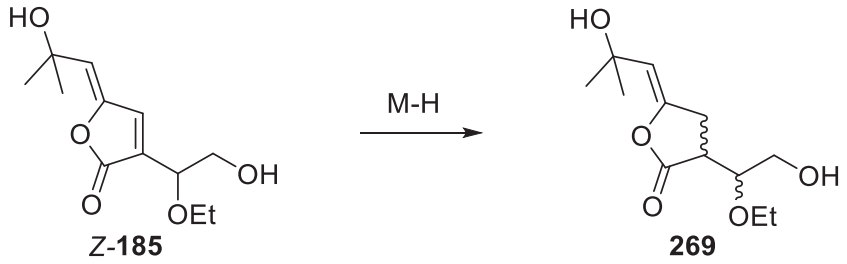


Scheme 94. Attempted synthesis of the NHK precursor.

5. Results and discussion: Synthesis of analogues for biological evaluation

5.1. Synthesis of α,β-saturated lactone analogues

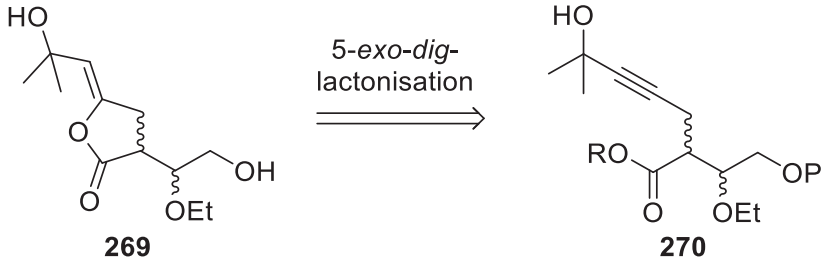
So as to establish whether the biological activity observed on aruncin B might be due to its potential Michael acceptor properties, we were interested in synthesising lactone **269** (Scheme 95), the α,β-saturated analogue of aruncin B. Direct reduction of aruncin B (*Z*-**185**) was attempted (L-selectride, $NaBH_4$ / $NiCl_2$)[141,142] but failed to deliver lactone **269**.



Z-**185** **269**

Scheme 95. Attempted synthesis of **269** by reduction of *Z*-**185**.

As an alternative synthetic route, we envisaged obtaining lactone **269** by a late-stage metal-catalysed (e.g., Ag or Au)[143,144] 5-*exo*-*dig*-lactonisation of an alkyne **270** (Scheme 96). This is closely related to the strategy used to obtain aruncin B (*Z*-**185**), but using the saturated version of enyne **230** (Scheme 82, p. 80).

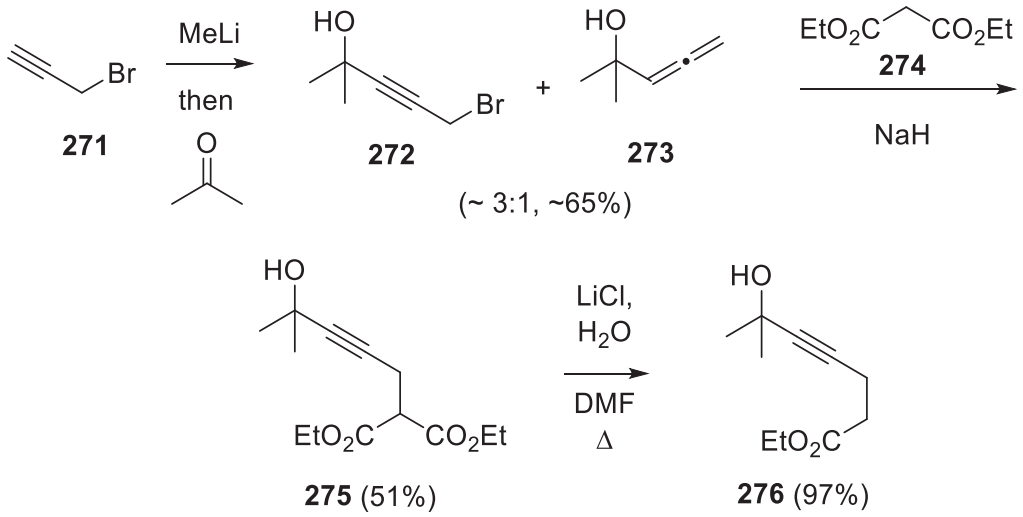


269 **270**

Scheme 96. Retrosynthesis of α,β-saturated aruncin B (**269**).

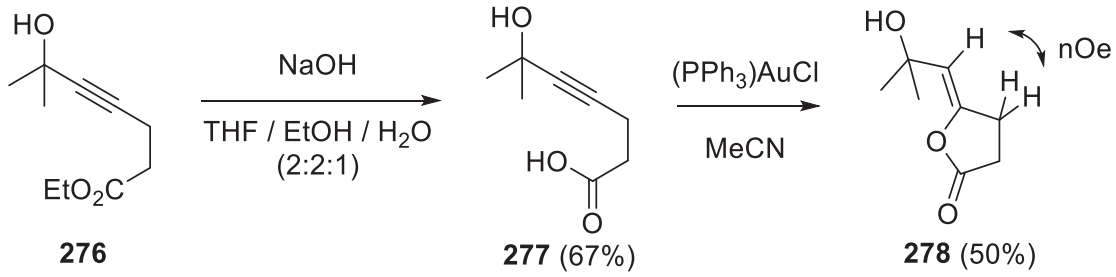
The synthesis of the precursor for the cyclisation commenced with propargyl bromide (**271**) (Scheme 97). Deprotonation of the latter using MeLi,[145] followed by electrophilic trapping

using acetone delivered bromoalkyne **272**, contaminated with inseparable amounts of allene **273**[146] resulting from Br-Li exchange on propargyl bromide (**271**) instead of deprotonation (Scheme 97). Nucleophilic attack of **272** by the conjugate base of diethyl malonate (**274**) gave the desired substituted malonate **275** and subsequent decarboxylation provided the mono-ester **276**.[147]



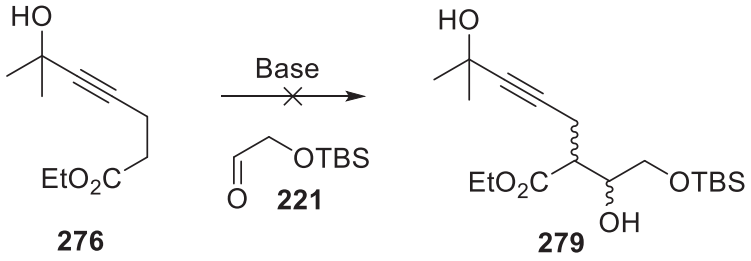
Scheme 97. Synthesis of mono-ester **276**.

In order to check the viability of the late stage lactonisation, we decided to attempt the cyclisation for the synthesis of compound **278** lacking the α-side chain (Scheme 98). Hydrolysis of **276**, followed by Au(I)-catalysed 5-*exo*-*dig*-lactonisation[144] of the carboxylic acid **277** delivered the model lactone **278**, as a single (*Z*-) geometric isomer.



Scheme 98. Synthesis of model lactone **278**.

Access to the desired lactone **269** was envisaged by α-functionalisation of mono-ester **276** *via* an aldol condensation with aldehyde **221** (Scheme 99); unfortunately, a variety of conditions failed to delivered significant quantities of the desired product **279**.

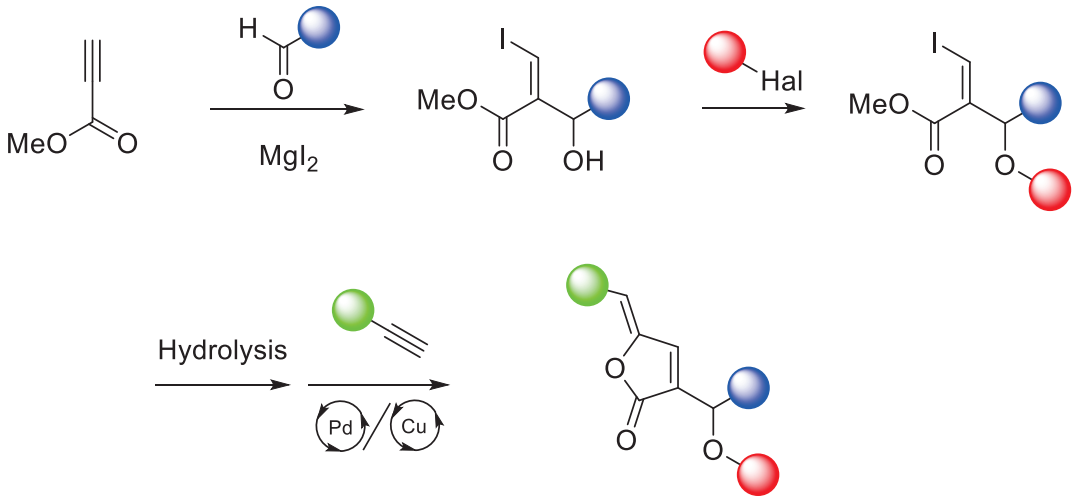


Scheme 99. Attempted synthesis of **279**.

Due to time constraints, the synthesis of **269** was not further explored and we decided to focus our efforts on the synthesis of other γ-alkylidenebutenolide analogues.

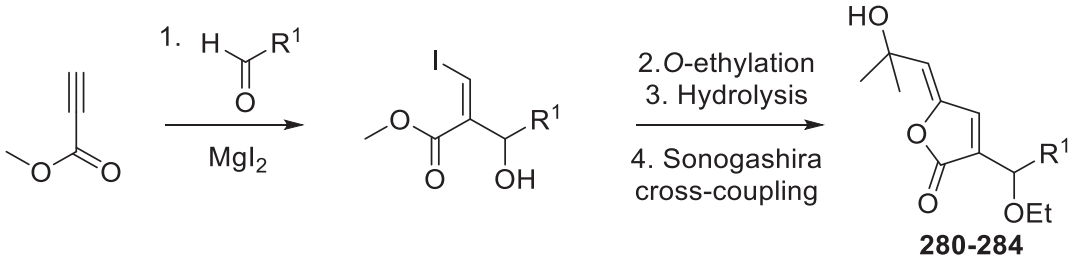
5.2. Synthesis of γ-alkylidenebutenolide analogues of aruncin B

We were planning to take advantage of the brevity and flexibility of our synthetic route towards aruncin B (*Z*-**185**, p. 81-83) for the synthesis of γ-alkylidenebutenolide analogues for biological evaluation. It appeared that applying the same synthetic sequence using different substrates (commercially available or prepared in a few steps) would rapidly generate a variety of derivatives for biological evaluation (Scheme 100).



Scheme 100. Application of the synthetic route for analogues synthesis.

Derivatives of the α-side-chain substituent were obtained by changing the aldehydes used in the β-iodo MBH reaction (Scheme 101, Table 5). Some of these vinyl iodides have already been reported using a similar β-iodo MBH reaction.[148] The rest of the sequence was followed as described for aruncin B. For the synthesis of **282** (R^1 = *t*-Bu) the hydrolysis was carried out using TMSOK in refluxing THF.

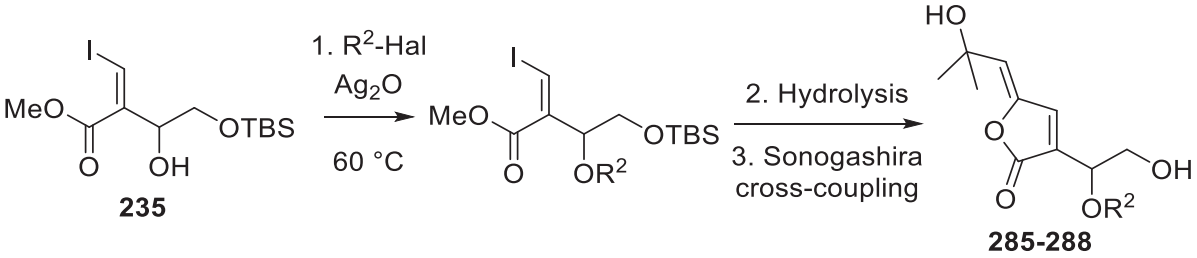


Scheme 101. Synthesis of α-side chain derivatives.

Entry	R^1	1. Yield (%)	2. Yield (%)	3. Yield (%)	4. Yield (%)	Product
1	CH_2OBn	52	59	71	53	**280**
2	Me	41	44	71	54	**281**
3	*t*-Bu	85	20	58	58	**282**
4	Ph	78	Quant.	75	52	**283**
5	*n*-C_8H_{17}	51	62	65	54	**284**

Table 5. α-side chain derivatives.

Derivatives of the *O*-ether substituent were obtained by simply changing the organohalide in the *O*-alkylation step (Scheme 102, Table 6).

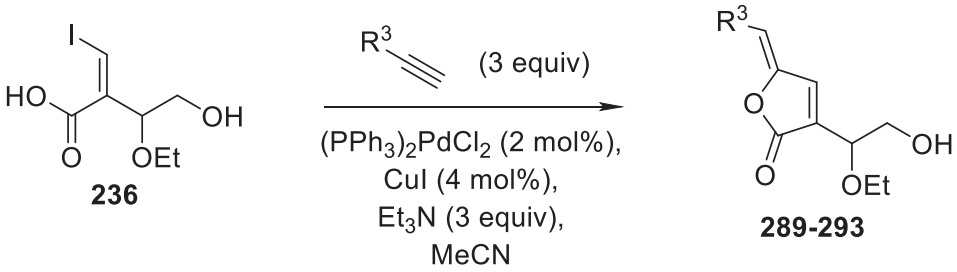


Scheme 102. Synthesis of *O*-alkyl derivatives.

Entry	R^2-Hal	1. Yield (%)	2. Yield (%)	3. Yield (%)	Product
1	No alkylation $R^2 = H$	-	60	42	**285**
2	MeI	77	98	67	**286**
3	*i*PrI	30	86	39	**287**
4	BnCl	46	64	52	**288**

Table 6. *O*-Alkyl derivatives.

The δ-substituent-analogues were obtained using different alkynes for the final cross-coupling, under the conditions previously described for the synthesis of aruncin B (Scheme 103, Table 7).



Scheme 103. Synthesis of δ-substituent-analogues.

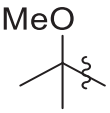
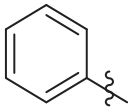
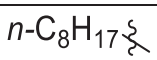
Entry	R^3 =	Yield (%)	Product
1		59	**289**
2		51	**290**
3		50	**291**
4		60	**292**
5		39	**293**

Table 7. δ-Substituent analogues.

The synthesis of these analogues demonstrated the efficiency and flexibility of our route to γ-alkylidenebutenolides.

5.3. Preliminary biological results

The above analogues are currently being tested against various cancer cell lines: jurkat T (as in the original publication),[6,7] but also against H460, MCF7 (human lung and breast cancer cell lines, respectively) and human T cells. These assays are being carried out by Frances Willenbrock and Christopher Towers (Cancer Research Centre, Oxford). Some early tests were also carried out by Laia Culleré (Department of Chemistry, Oxford).

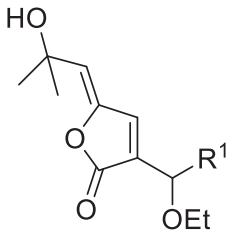
Preliminary results obtained for various compounds are briefly presented below; the values given in the tables correspond to the IC_{50} values in μM for the indicated cell line. These experiments have been carried out in duplicate or triplicate.

Data for the enantiomers of aruncin B ((+) *Z*-**185** and (–) *Z*-**185**), together with *E*-aruncin B (*E*-**185**) are discussed first (Table 8). The two enantiomers display the same level of activity, suggesting that the ether moiety is probably not directly involved in the binding of the compound with the target(s). The jurkat T values compared favourably with that originally reported[6] for the natural isolate (IC_{50}: 17 μg equating 70 μM). The configuration of the δ-alkylidene side chain also seems inconsequential to the activity of the compounds; this might be explained by isomerisation occurring once the compound had been injected in the cell medium.

Entry	Butenolide	Jurkat T	H460	MCF7
1	(+)-*Z*-**185**	9.6	11.7	11.3
2	(–)-*Z*-**185**	9.7	15.0	10.8
3	*E*-**185**	9.1	16.5	9.5

Table 8. IC_{50} (μM) for aruncin B isomers.

Derivatives at the α-side-chain substituent (Fig. 9), were tested against the three cell lines indicated above (Table 9). Although it is difficult to see a clear trend on which type of substituent affects the activity, butenolide **284** (Entry 5), featuring a long aliphatic side chain showed good activity against all three cell lines.



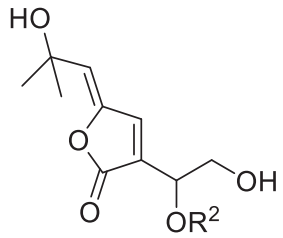
280-284

Figures 9. Derivatives at the α-side-chain substituent.

Entry	Butenolide	R^1	Jurkat T	H460	MCF7
1	**280**	CH_2OBn	22.5	>50	>50
2	**281**	Me	>50	>50	>50
3	**282**	*t*-Bu	>50	>50	>50
4	**283**	Ph	11.6	31.6	33.3
5	**284**	*n*-C_8H_{17}	2.9	12.8	12.4

Table 9. IC_{50} (μM) for derivatives of the α-side-chain substituent.

Change of the *O*-ether substituent does not affect significantly the IC_{50} values on the Jurkat T series (Fig. 10, Table 10). This suggests that the exact nature of the substituent is not crucial for the activity and this part of the molecule is probably not directly involved in the binding / interaction with the target(s) (also suggested by equivalent activity of (+) and (–)-*Z*-**185** (table 8, p. 100). In the two other cell lines it is difficult to see a clear trend.



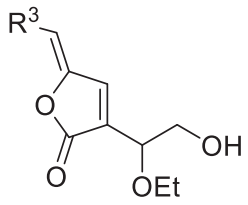
285-288

Figure 10. *O*-Alkyl derivatives.

Entry	Butenolide	R^2	Jurkat T	H460	MCF7
1	**285**	H	26.3	>50	>50
2	**286**	Me	8.6	12.6	31.3
3	**287**	*i*-Pr	23.0	36.4	>50
4	**288**	Bn	5.8	5.5	12.2

Table 10. IC_{50} (μM) for *O*-Alkyl derivatives.

The nature of the δ-alkylidene substituent (Fig. 11, Table 11) appeared to be crucial. Only the butenolide **291** (Entry 3) featuring a free alcohol showed some interesting activity. Compounds **289** and **290** (Entries 1, 2) featuring an δ-alkylidene substituent possessing similar steric character to aruncin B did not show significant activity. Entries 1-3 suggest that having a hydrogen bond donor substituent is critical for activity. Other substituents such as an aromatic ring or a long aliphatic chain, **292** and **293** respectively (Entries 4, 5), did not show activity.



289-293

Figure 11. δ-Substituent analogues.

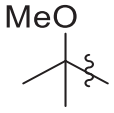
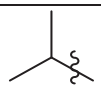
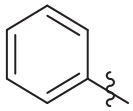
Entry	Butenolide	R^3 =	Jurkat T	H460	MCF7
1	**289**		>50	>50	>50
2	**290**		>50	>50	>50
3	**291**		3.6	5.9	12.5
4	**292**		>50	>50	>50
5	**293**		>50	>50	>50

Table 11. IC_{50} (μM) for δ-substituent analogues.

To summarise these observations, the exact nature of the α-side-chain substituent appeared to be important for the activity of the butenolide, but changes of the absolute configuration of the ether or the *O*-alkyl substituent does not seem to affect the observed activity. Although the change of the exocyclic geometry does not show a great importance in the activity of the butenolide, the δ-alkylidene substituent proved crucial for the activity of the butenolide, with the presence of a free hydroxy group apparently required.

The cytotoxic activity of these compound with human T cells is currently in progress.

6. Conclusion and outlook

Our original approach for the synthesis of aruncin B relying on an Achmatowicz reaction (2. Results and discussion: Early synthetic studies: Achmatowicz reaction) did not give satisfactory results, despite some closely related precedents. Oxidations of furanol derivatives often resulted in complex mixtures of various (over)-oxidation products, due to a lack of selectivity in the oxidation process. When the correct oxidation products were obtained, intrinsic preference for the linear 1,4-enedione was observed. A photooxygenation approach to the Achmatowicz reaction showed promise, but was unfortunately not reproducible.

The Achmatowicz approach was abandoned in favour of a sequence relying on formation of the key dihydropyranone ring by RCM, followed by the use of an ethoxyselenation–selenoxide elimination sequence for the installation of the sensitive exocyclic enol ether motif. The exact ordering of the post RCM events proved crucial for the success of this route. This strategy successfully provided the Na salts of the postulated structure of aruncin B, as well as a closely related regioisomeric ether. The free acids could not be obtained from these salts due to intrinsic acid sensitivity. This instability suggested that aruncin B was a compound of mistaken identity[149] and careful analysis of the analytical data suggested a better match for a *Z*-γ-alkyledenebutenolide. The only piece of data which contradicted this reassignment was the IR C=O stretch, but as discussed earlier (Figure 8, p. 65), the authors of the original publication could not locate the original spectrum.

The synthesis of the newly postulated structure was originally achieved using a related RCM / ethoxyselenation–selenoxide elimination sequence. This sequence enabled the establishment of the true structure of aruncin B, but unfortunately proved poorly reproducible. An alternative approach, based on β-iodo MBH followed by a *one-pot* Sonogashira cross-coupling–5-*exo*-

dig-lactonisation enabled a reliable access to the true structure of aruncin B. This sequence was also applied for the synthesis of aruncin B analogues for biological evaluation.

Our synthetic studies revealed the true structure of aruncin B, but also raised questions on its biological origins, suggesting that aruncin B may be an artefact of the isolation process. Our work aided the structural revision of other natural products isolated from rosaceae.[130] Although we have not heard back from him, we also provided enough material (10 mg of racemate and 5 mg of each enantiomer) to Prof. Kim in Korea, to pursue his investigations on the biological activity of aruncin B. More importantly, the synthetic route we designed enabled the preparation of sufficient amounts of aruncin B and analogues for biological evaluations in Oxford (currently ongoing).

We hope our studies will inspire further work on the synthesis of biologically active small oxacycles.

7. Experimental section

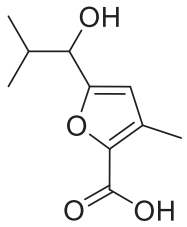
7.1. General information

Except where stated otherwise, all reactions were carried out under a nitrogen atmosphere. All reactions, except those conducted in the presence of H_2O, were carried out in flame-dried apparatus. CH_2Cl_2, toluene, MeOH, THF and Et_2O were degassed and dried over activated alumina under nitrogen.[150] "Degassed CH_2Cl_2" refers to CH_2Cl_2 further degassed by bubbling Argon through the solution for a minimum period of 30 min. EtOH was dried over 4 Å MS for at least 24 h.[151] Except where stated otherwise, commercially available reagents were used as received. "Freshly distilled" refers to distillation over CaH_2 using a short-path distillation apparatus under a nitrogen atmosphere or reduced pressure. Thin-layer chromatography (TLC) was carried out on aluminium-backed plates, pre-coated with silica (0.2 mm, 60 F254 nm), which were visualised by UV light (λ_{max} = 254 nm) and developed with basic potassium permanganate solution with heating. Flash column chromatography was carried out on Merck Silica-gel Geduran® Si 60 (43-63 μm) in the solvent systems indicated, applying head pressure by means of a low pressure nitrogen line (~ 0.5 atm). Petroleum ether refers to the fraction boiling between 30 °C - 40 °C. Melting points are uncorrected. Infra-red spectra were recorded neat using FT-IR apparatus and the intensity of the peaks are reported as s, m, w, br, denoting strong, medium, weak and broad, respectively. ^1H and ^{13}C spectra were recorded at 25 °C in $CDCl_3$, CD_3OD or C_6D_6. COSY, HSQC and where necessary NOESY and HMBC spectra were used to aid structure assignments. Data are expressed as chemical shifts (δ) in parts per million (ppm) relative to $CDCl_3$ (^1H δ 7.27 ppm, ^{13}C δ 77.0 ppm, respectively), CD_3OD (^1H δ 3.31 ppm, ^{13}C δ 49.2 ppm, respectively) or C_6D_6 (^1H δ 7.16 ppm, ^{13}C δ 128.4 ppm, respectively) as the internal standard on the δ scale. The multiplicity of each signal is reported as s, d, t, q, hept, br, m, denoting singlet, doublet, triplet, quartet, heptet broad and multiplet, respectively. Proton coupling constants *J* are reported to the nearest 0.5 Hz. H_{cis} and H_{trans} refer to the protons in *cis*

and *trans* position relative to the highest priority group (CIP rules), respectively. Low resolution mass spectra were obtained using electrospray ionisation (ESI). High resolution mass spectra were obtained by electrospray ionisation (ESI) using tetraoctylammonium bromide or sodium dodecyl sulfate as the lock mass; values are quoted as ratio of mass to charge (m/z) in Daltons.

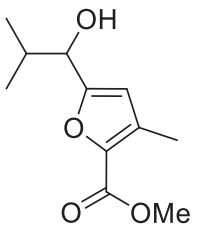
7.2. Synthesis of novel compounds

5-(1-Hydroxy-2-methylpropyl)-3-methylfuran-2-carboxylic acid (27):



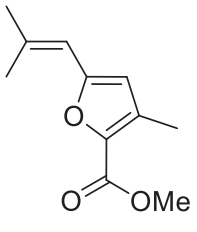
To a solution of freshly distilled *i*-Pr_2NH (1.22 g, 8.68 mmol, 2 equiv) in THF (14 mL) at −78 °C, was slowly added *n*-BuLi (3.5 mL, 2.5 M in hexanes, 8.75mmol, 2 equiv), then the reaction mixture was placed in an ice-bath. After 40 min, the reaction mixture was cooled to −78 °C and a solution of 3-methyl-2-furoic acid **25** (550 mg, 4.34 mmol, 1 equiv) in THF (2.5 mL) was added over 2 min. The solution turned yellow, then after 15 min neat isobutyraldehyde **26** (377 mg, 5.21 mmol, 1.2 equiv) was added dropwise at −78 °C. The solution turned colourless and the reaction mixture was allowed to warm to room temperature. After 30 min, the solution was quenched by addition of aq HCl (10 mL, 2 M) and extracted with Et_2O (3 x 10 mL). The organic layers were combined, washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, gradient elution: CH_2Cl_2 to 0.1% AcOH 2% MeOH in CH_2Cl_2) to give acid **27** (700 mg, 81%) as a yellow-orange oil: R_f 0.4 (0.1% AcOH 5% MeOH in CH_2Cl_2); IR (neat/cm^{-1}) 2964 w, 1678 s, 1536 w, 1444 m, 1292 m, 1174 s, 1021 m, 820 w; δ_H (200 MHz, $CDCl_3$) 6.28 (1H, s, C=CH), 4.46 (1H, d *J* 6, C<u>H</u>OH), 2.36 (3H, s, OC=CCH_3), 2.16-2.09 (1H, m, C<u>H</u>$(CH_3)_2$), 1.01-0.91 (6 H, m, CH$(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 163.9 (CO_2H), 160.1 (O<u>C</u>=CH), 138.1 (O<u>C</u>=CCH_3), 134.1 (OC=<u>C</u>CH_3), 111.8 (OC=<u>C</u>H), 73.0(CHOH), 32.9 (<u>C</u>H$(CH_3)_2$), 18.3 and 17.2 (CH(<u>C</u>$H_3)_2$), 11.5 (OC=C<u>C</u>H_3); LRMS (ESI^+): 221 ($[M+Na]^+$, 100%); HRMS (ESI^+): calcd for $C_{10}H_{14}O_4Na$ $[M+Na]^+$: 221.0784, found 221.0787.

Methyl 5-(1-hydroxy-2-methylpropyl)-3-methylfuran-2-carboxylate (ES-1):



To a solution of acid **27** (700 mg, 3.6 mmol, 1 equiv) in MeOH (7 mL) and toluene (35 mL) at 0 °C, was added $TMSCHN_2$ (2.15 mL, 2 M in Et_2O, 4.30 mmol, 1.2 equiv) dropwise. After 10 min the ice-bath was removed. After further 2h, the excess of $TMSCHN_2$ was quenched by dropwise addition of AcOH (until gas formation ceased) and concentrated under reduced pressure to give ester **ES-1** (700 mg, quant.). The crude product was used in the next step without further purification. R_f 0.5 (0.1% AcOH 5% MeOH in CH_2Cl_2); δ_H (200 MHz, $CDCl_3$) 6.21 (1H, s, OC=CH), 4.40 (1H, d *J* 6.5, C<u>H</u>OH), 3.85 (3H, s, OCH_3), 2.31 (3H, s, OC=CCH_3), 2.08 (1H, m, C<u>H</u>$(CH_3)_2$), 0.96 and 0.88 (2 x 3H, 2 x d *J* 7, CH(C<u>H</u>$_3)_2$); δ_C (100 MHz, $CDCl_3$) 160.1 (<u>C</u>O_2CH_3), 159.5 (O<u>C</u>=CH), 139.0 (O<u>C</u>=CCH_3), 132.1 (OC=<u>C</u>CH_3), 111.7 (OC=<u>C</u>H), 73.3 (CHOH), 51.5 (CO_2<u>C</u>H_3), 33.3 (<u>C</u>H$(CH_3)_2$), 18.7 and 17.6 (CH(<u>C</u>$H_3)_2$), 11.7 (OC=C<u>C</u>H_3); LRMS (ESI^+): 213 ($[M+H]^+$, 20%), 235 ($[M+Na]^+$, 100); HRMS (ESI^+): calcd for $C_{11}H_{16}NaO_4$ $[M+Na]^+$: 235.0941, found 235.0951.

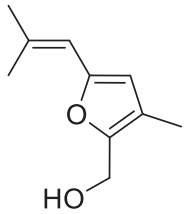
Methyl 3-methyl-5-(2-methylprop-1-en-1-yl)furan-2-carboxylate (ES-2):



A solution of the above crude ester **ES-1** (650 mg, 3.04 mmol, 1 equiv) and $TsOH.H_2O$ (650 mg, 3.42 mmol, 1.1 equiv) in toluene (65 mL) was refluxed for 30 min. After cooling to rt, the reaction mixture was washed with aq NaOH (10 mL, 15%) and water (10 mL), dried (Na_2SO_4)

and concentrated under reduced pressure to give olefin **ES-2** (500 mg, 85%). The crude product was used in the next step without further purification: R_f 0.8 (0.1% AcOH 5% MeOH in CH_2Cl_2); δ_H (200 MHz, $CDCl_3$) 6.07 (1H, s, OC=C<u>H</u>), 6.01 (1H, s, <u>H</u>C=C(CH_3)$_2$), 3.80 (3H, s, OCH_3), 2.26 (3H, s, OC=CCH_3), 1.94 and 1.85 (2 x 3H, 2 x s, HC=C(C<u>H</u>$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 159.8 (<u>C</u>O_2CH_3), 155.2 (O<u>C</u>=CH), 140.1 (O<u>C</u>=CCH_3), 137.3 (HC=<u>C</u>(CH_3)$_2$), 132.5 (OC=<u>C</u>CH_3), 113.7 (H<u>C</u>=C(CH_3)$_2$), 112.1 (OC=<u>C</u>H), 51.0 (OCH_3), 26.9 and 20.0 (HC=C(<u>C</u>H_3)$_2$), 11.3 (OC=C<u>C</u>H_3); LRMS (ESI^+): 195 ($[M+H]^+$, 55%), 217 ($[M+Na]^+$, 30), 411 ($[2M+Na]^+$, 100); HRMS (ESI^+): calcd for $C_{11}H_{14}NaO_3$ $[M+Na]^+$: 217.0835, found 217.0845.

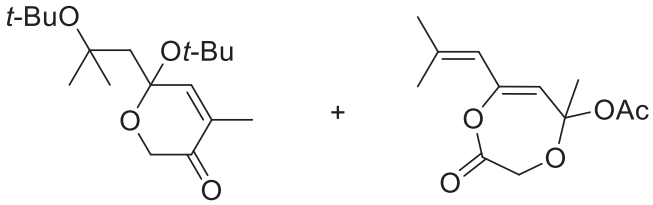
(3-Methyl-5-(2-methylprop-1-en-1-yl)furan-2-yl)methanol (3):



To a solution of the above crude olefin **ES-2** (100 mg, 0.51 mmol, 1 equiv) in THF (10 mL) at 0 °C, was added DIBAL-H (1.4 mL, 1 M in hexanes, 1.4 mmol, 2.8 equiv) dropwise. After 1 h, the reaction mixture was diluted with Et_2O (20 mL), and quenched by sequential addition of accurately measured: H_2O (56 µL), aq NaOH (56 µL, 15 %) and H_2O (140 µL). The reaction mixture was allowed to warm to rt. After 15 min, Na_2SO_4 was added and the mixture was stirred for a further 15 min, filtered and concentrated under reduced pressure to give furanol **3** (85 mg, quant.). The crude product was used in the next step without further purification: R_f 0.25 (20% Et_2O in petroleum ether); IR (neat/cm^{-1}) 3343 br, 2926 m, 2359 w, 1669 w, 1444 m, 1260 m, 995 s, 797m; δ_H (200 MHz, C_6D_6) 6.10 (1H, s, OC=CH), 5.91 (1H, s, <u>H</u>C=C(CH_3)$_2$), 4.29 (2H, s, C<u>H</u>$_2$OH), 1.87 and 1.67 (3H, s, HC=C(C<u>H</u>$_3$)$_2$), 1.76 (3H, s, OC=CCH_3); δ_C (100 MHz, C_6D_6) 152.3 (O<u>C</u>=CH), 148.1 (OC=<u>C</u>CH_3), 134.3 (HC=<u>C</u>(CH_3)$_2$), 118.5 (OC=<u>C</u>CH_3), 114.9 (OC=<u>C</u>H), 110.9 (H<u>C</u>=C(CH_3)$_2$), 55.0 (CH_2OH), 26.6 and 19.8 (HC=C(<u>C</u>H_3)$_2$), 9.3

(OC=C<u>C</u>H$_3$); LRMS (ESI$^+$): 149 ([M–OH]$^+$, 37%), 189 ([M+Na]$^+$, 100); HRMS (ESI$^+$): calcd for $C_{10}H_{14}O_2Na$ [M+Na]$^+$: 189.0892, not found.

6-(tert-butoxy)-6-(2-(tert-butoxy)-2-methylpropyl)-4-methyl-2H-pyran-3(6H)-one (31) / 5-Methyl-7-(2-methylprop-1-en-1-yl)-2-oxo-2,3-dihydro-5*H*-1,4-dioxepin-5-yl acetate (32):



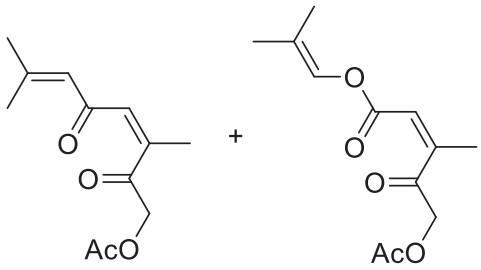
To a solution of furanol **3** (30 mg, 0.18 mmol, 1 equiv) in CH_2Cl_2 (5 mL) at –20 °C, was added $VO(acac)_2$ (0.5 mg, 0.2 μmol, 1 mol%) followed by *t*-BuOOH (80μL, 5.5 M in decanes, 0.45 mmol, 2.5 equiv). After 1 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL), quenched by addition of H_2O (5 mL) and stirred 5 min at 0 °C. The layers were separated and the aq layer was extracted with pre-cooled (~ 5 °C) CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with H_2O (2 x 5 mL), brine (2 x 5 mL), dried (Na_2SO_4) and concentrated under reduce pressure (water bath: 30 °C). The residue was dissolved in CH_2Cl_2 (5 mL) at 0 °C, and Et_3N (181 mg, 1.8 mmol, 10 equiv), Ac_2O (70 mg, 0.72 mmol, 4 equiv) and DMAP (9 mg, 0.07 mmol, 0.4 equiv) were successively added, then the ice-bath was removed. After 2 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with H_2O (3 x 10 mL), brine (2 x 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 25% Et_2O in petroleum ether). First eluted a colourless oil **31** (4.5 mg, 8%). Second eluted a colourless oil **32** (3 mg, 7%) a colourless oil.

Discernible data for **31**: R_f 0.35 (25% Et_2O in petroleum ether); IR (neat/cm^{-1}) 2979 m, 2930 w, 1692 s, 1364 s, 1243 w, 1195 s, 1178 m, 965 w, 882 w; δ_H (500 MHz, C_6D_6) 6.87 (1H, d *J*

1.5, HC=CCH$_3$), 4.81 and 4.22 (2 x 1H, 2 d *J* 17, OCH$_2$C=O), 2.56 and 2.48 (2 x 1H, d *J* 15, CH$_2$), 1.82 (3H, d *J* 1.5, HC=CCH$_3$), 1.32 (6H, s, 2 x C(CH$_3$)$_2$) 1.14 and 1.13 (2 x 9H, 2 x s, 2 x C(CH$_3$)$_3$); δ_c (125 MHz, C$_6$D$_6$) 194.5 (C=O), 141.9 (HC=CCH$_3$), 135.1 (HC=CCH$_3$), 101.1 (O–CH–O), 80.0, 79.9 and 78.7 (OC(CH$_3$)$_2$ + 2 x OC(CH$_3$)$_3$), 68.4 (OCH$_2$C=O), 44.8 (CH$_2$), 26.8 and 26.7 (2 x C(CH$_3$)$_3$), 27.6 and 25.0 (2 x C(CH$_3$)$_2$), 14.8 (OC=CCH$_3$).

Discernible data for **32**: R_f 0.25 (25% Et$_2$O in petroleum ether); IR (neat/cm^{-1}) 2925 m, 2852 w, 1800 s, 1746 s, 1455 w, 1372 m, 1233 s, 1048 m, 947 m; δ_H (500 MHz, C$_6$D$_6$) 5.52-5.50 (1H, m, HC=C(CH$_3$)$_2$), 4.74 (1H, s, OC=CH), 4.24 and 3.93 (2 x 1H, 2 x d *J* 11, OCH$_2$C=O), 1.73 and 1.48 (2 x 3H, 2 x s, HC=C(CH$_3$)$_2$), 1.53 (3H, s, OC(=O)CH$_3$), 0.88 (CCH$_3$); δ_c (125 MHz, C$_6$D$_6$) 179.3 and 170.3 (C=O and OC(=O)), 152.9 (OC=CH), 142.7 (HC=C(CH$_3$)$_2$), 114.2 (HC=C(CH$_3$)$_2$), 113.1 (O–C–O), 108.7 (OC=CH), 67.4 (OCH$_2$C=O), 27.6 and 20.7 (HC=C(CH$_3$)$_2$), 20.4 (OC(=O)CH$_3$), 19.8 (CCH$_3$).

***(Z)*-3,7-Dimethyl-2,5-dioxoocta-3,6-dien-1-yl acetate (33) / 2-Methylprop-1-en-1-yl *(Z)*-5-acetoxy-3-methyl-4-oxopent-2-enoate (34):**



To a solution of furanol **3** (22 mg, 0.13 mmol, 1 equiv) in CH$_2$Cl$_2$ (2.5 mL) at 0 °C was added *m*-CPBA (29 mg, 77%, 0.13 mmol, 1 equiv) portionwise. After the addition, TLC analysis showed no more starting material. The reaction mixture was quenched by addition of saturated aq Na$_2$SO$_3$. (2.5 mL). The layers were separated and the aq layer was extracted with CH$_2$Cl$_2$ (2 x 5 mL). The organic layers were combined, dried (Na$_2$SO$_4$) and concentrated under reduced pressure (water bath: 30 °C). The residue was dissolved in CH$_2$Cl$_2$ (1.3 mL) at 0 °C, and

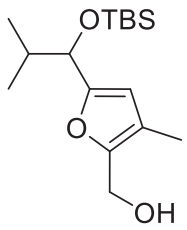
pyridine (52 µL, 0.65 mmol, 5 equiv), Ac_2O (307 µL, 3.25 mmol, 25 equiv) and DMAP (1.5 mg, 0.013 mmol, 0.1 equiv) were successively added and the ice-bath was removed. After 2 h, the reaction mixture was quenched by addition of saturated aq NH_4Cl (5 mL). The layers were separated and the aq layer was extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with saturated aq $CuSO_4$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The excess of Ac_2O was removed under *high vacuum* (~0.1 mBar). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 25% Et_2O in petroleum ether). First eluted a colourless oil, the dienedione **33** (4.5 mg, 16%). Second eluted a colourless oil, Bayer-Villiger by-product **34** (3 mg, 9%)

33: R_f 0.3 (20% Et_2O in petroleum ether); IR (neat/cm^{-1}) 2922 w, 2853 w, 1751 m, 1727 s, 1644 w, 1375 w, 1232 s, 1148 m, 1107 w, 1048 w; δ_H (500 MHz, C_6D_6) 5.66 (1H, m, $\underline{H}C=C(CH_3)_2$), 5.60-5.59 (1H, m, $\underline{H}C=CCH_3$), 4.87 (2H, s, $OCH_2C=O$), 2.01-1.99 (3H, m, $HC=C(C\underline{H}_3)(CH_3)$), 1.70 (3H, s, $OC(=O)CH_3$), 1.69-1.68 (3H, d *J* 1.5, $HC=CC\underline{H}_3$), 1.43-1.41 (3H, m, $HC=C(CH_3)(C\underline{H}_3)$); δ_c (125 MHz, C_6D_6) 202.1 and 188.0 (2 x C=O), 170.2 (OC(=O)), 158.8 ($HC=\underline{C}(CH_3)_2$), 152.5 ($HC=\underline{C}CH_3$), 128.8 ($H\underline{C}=CCH_3$), 123.9 ($H\underline{C}=C(CH_3)_2$), 66.9 ($O\underline{C}H_2C=O$), 27.7 and 21.0 ($HC=C(\underline{C}H_3)_2$), 20.7 ($HC=C\underline{C}H_3$), 20.3 ($OC(=O)CH_3$); LRMS (ESI^+): 225 ($[M+H]^+$, 100%), 247 ($[M+Na]^+$, 40), 471 ($[2M+Na]^+$, 70); HRMS (ESI^+): calcd for $C_{12}H_{16}O_4Na$ $[M+Na]^+$: 247.0941, found 247.0935.

34: R_f 0.15 (20% Et_2O in petroleum ether); IR (neat/cm^{-1}) 2933 w, 1747 s, 1722 s, 1625 s, 1443 m, 1374 m, 1230 s, 1114 m, 1046 m, 877 w; δ_H (500 MHz, C_6D_6) 7.02-7.00 ($O\underline{H}C=C(CH_3)_2$), 5.41-5.40 (1H, m, $\underline{H}C=CCH_3$), 4.74 (2H, s, $OCH_2C=O$), 1.67 (3H, s, $OC(=O)CH_3$), 1.58 (3H, d *J* 1.5, $HC=CC\underline{H}_3$), 1.56 and 1.32 (2 x 3H, 2 x m, $HC=C(C\underline{H}_3)_2$); δ_c (500 MHz, C_6D_6) 201.4 (C=O), 170.6 ($O\underline{C}(=O)CH_3$), 162.7 ($HCO\underline{C}(=O)CH$), 155.9 ($HC=\underline{C}CH_3$), 130.8 ($H\underline{C}=C(CH_3)_2$), 119.3 ($H\underline{C}=CCH_3$), 119.2 ($HC=\underline{C}(CH_3)_2$), 67.3 ($O\underline{C}H_2C=O$), 21.1 ($HC=C\underline{C}H_3$), 20.5 ($OC(=O)CH_3$), 20.0 and 16.2 ($HC=C(\underline{C}H_3)_2$); LRMS (ESI^+) 241 ($[M+H]^+$,

43%), 263 ([M+Na]$^+$, 100), 503 ([2M+Na]$^+$, 40); HRMS (ESI$^+$) calcd for $C_{12}H_{16}O_5Na$ [M+Na]$^+$: 263.0890, found 263.0884.

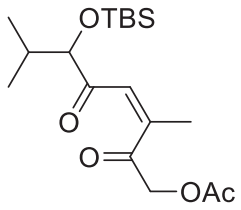
5-(1-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropyl)-3-methylfuran-2-yl)methanol (44):



To a solution of acid **27** (50 mg, 0.25 mmol, 1 equiv) and 2,6-lutidine (268 mg, 2.5 mmol, 10 equiv) in CH_2Cl_2 (2.5 mL) at 0 °C, was added neat TBDMSOTf (330 mg, 1.25 mmol, 5 equiv) dropwise. After 1 h, the reaction mixture was quenched by addition of H_2O (5 mL) and extracted with Et_2O (3 x 10 mL). The organic layers were combined, washed with H_2O (5 mL), aq HCl (5 mL, 0.3 M) and brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure, to give 170 mg of crude product (unstable over silica gel). This residue was dissolved in THF (6 mL) at 0 °C and DIBAL-H (0.75 mL, 1 M in hexanes, 0.75 mmol, 3 equiv) was added dropwise. After 30 min, the reaction mixture was diluted with Et_2O (15 mL) and quenched by sequential addition of accurately measured: H_2O (30 µL), aq NaOH (30 µL, 4M) and H_2O (75 µL). The reaction mixture was allowed to warm to rt. After 15 min, Na_2SO_4 (to saturation) was added and the mixture was stirred for a further 15 min, filtered and concentrated under reduced pressure. The residue (75 mg) was purified by column chromatography (SiO_2, dry loading, gradient elution: petroleum ether to 25% Et_2O in petroleum ether) to give protected secondary alcohol **44** (33 mg, 44% over two steps): R_f 0.25 (20% Et_2O in Petroleum ether); IR (neat/cm^{-1}) 3315 br, 2957 s, 2930 s, 2858 m, 1472 w, 1253 m, 1064 m, 857 s, 838 s, 776 s; δ_H (400 MHz, C_6D_6) 5.94 (1H, s, OC=C<u>H</u>), 4.33 (1H, d *J* 6.5, C<u>H</u>OTBS), 4.28 (2H, s, C<u>H</u>$_2$OH), 2.15 (1H, m, C<u>H</u>$(CH_3)_2$), 1.77 (3H, s, OC=CCH_3), 1.07 (3H, d *J* 6.5, CH(C<u>H</u>$_3$)(CH_3)), 0.99 (9H, s, SiC$(CH_3)_3$), 0.88 (3H, d *J* 6.5, CH(CH_3)(C<u>H</u>$_3$)), 0.07 and −0.02 (2 x 3H, 2 x s,

$Si(CH_3)_2$); δ_C (100 MHz, C_6D_6) 156.5 (O<u>C</u>=CH), 149.7 (O<u>C</u>=CCH_3), 118.3 (OC=<u>C</u>CH_3), 110.7 (OC=<u>C</u>H), 75.2 (<u>C</u>HOTBS), 55.9 (CH_2OH), 26.7 ($SiC(\underline{C}H_3)_3$), 19.6 ($\underline{C}(CH_3)_3$), 19.1 ($CH(\underline{C}H_3)_2$), 10.3 (OC=C<u>C</u>H_3), –4.0 and –4.5 ($Si(CH_3)_2$); LRMS (ESI^+): 321 ($[M+Na]^+$, 100%); HRMS (ESI^+): calcd for $C_{16}H_{30}O_3NaSi$ $[M+Na]^+$: 321.1856, found 321.1850.

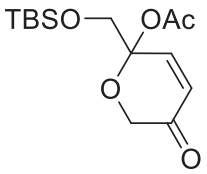
***(Z)*-6-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethyl-2,5-dioxooct-3-en-1-yl acetate (45):**



To a solution of protected secondary alcohol **44** (24 mg, 0.08 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at 0 °C was added *m*-CPBA (18 mg, 77%, 0.08 mmol, 1 equiv) portionwise. After the addition, TLC analysis showed no more starting material. The reaction mixture was quenched by addition of saturated aq Na_2SO_3 (2 mL). The layers were separated and the aq layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure (water bath: 30 °C). The residue was dissolved in CH_2Cl_2 (1 mL) at 0 °C, pyridine (32 µL, 0.40 mmol, 5 equiv), Ac_2O (189 µL, 2.0 mmol, 25 equiv) and DMAP (1 mg, 0.008 mmol, 0.1 equiv) were successively added and the ice-bath was removed. After 2 h, the reaction mixture was quenched by addition of saturated aq NH_4Cl (2 x 5 mL). The layers were separated and the aq was extracted with CH_2Cl_2 (10 mL). The organic layers were combined, washed with saturated aq $CuSO_4$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The excess of Ac_2O was removed under *high vacuum* (~0.1 mBar). The residue was purified by column chromotgraphy (SiO_2, gradient elution: petroleum ether to 15% Et_2O in petroleum ether) to give ene-1,4-dione **45** (3.6 mg, 13%): R_f 0.2 (20% Et_2O in petroleum ether); δ_H (500 MHz, C_6D_6) 6.34 (1H, d *J* 1.5, <u>H</u>C=CCH_3), 4.86-4.85 (2H, 2 x s, OCH_2C=O), 3.70 (1H, d *J* 6, C<u>H</u>OTBS), 1.82-1.75 (1H, m, C<u>H</u>$(CH_3)_2$), 1.71

(3H, d *J* 1.5, HC=CC<u>H</u>$_3$), 1.70 (3H, s, OC(=O)CH_3), 0.93 (9H, s, SiC(CH_3)$_3$), 0.87 and 0.81 (2 x 3H, 2x d *J* 7, HC=C(C<u>H</u>$_3$)$_2$), –0.04 and –0.06 (2 x 3H, 2 x s, Si(CH_3)$_2$); δ_c (500 MHz, C_6D_6) 202.4 and 200.8 (2 x C=O), , 170.3 (OC(=O)), 150.90 (HC=<u>C</u>CH$_3$), 123.1 (H<u>C</u>=CCH$_3$), 83.5 (<u>C</u>HOTBS), 66.9 (O<u>C</u>H$_2$C(=O)), 33.1 (<u>C</u>H(CH$_3$)$_2$), 26.3 (3 x SiC(<u>C</u>H$_3$)$_2$), 21.1 (HC=C<u>C</u>H$_3$), 20.4 (OC(=O)CH$_3$), 19.2 (HC=C(<u>C</u>H$_3$)(CH$_3$)), 18.7 (Si<u>C</u>(CH$_3$)$_3$), 17.9 (HC=C(CH$_3$)(<u>C</u>H$_3$)); LRMS (ESI$^+$): 379 ([M+Na]$^+$, 100%); HRMS (ESI$^+$): calcd for $C_{18}H_{32}O_5NaSi$ [M+Na]$^+$: 379.1611, found 379.1898.

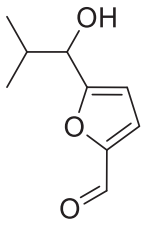
2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-oxo-5,6-dihydro-2*H*-pyran-2-yl acetate (50):



To a solution of (silyloxy)furanol **49**[29] (50 mg, 0.21 mmol, 1 equiv) in CH_2Cl_2 (4 mL) at 0 °C was added *t*-BuOOH (93 µL, 5.5 M in decanes, 0.52 mmol, 2.5 equiv). After 1 h, the reaction mixture was warmed to rt. After a further 3 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and quenched with water (5 mL). The layers were separated and the aq layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with H_2O (2 x 5 mL) and brine (2 x 5 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was acetylated using the procedure described above in CH_2Cl_2 (2.5 mL) with pyridine (84 µL, 1.05 mmol, 5 equiv), Ac_2O (496 µL, 5.25 mmol, 25 equiv) and DMAP (3 mg, 0.02 mmol, 0.1 equiv) for 2 h, to give crude 6-acetoxy-dihydropyranone **50** (50 mg, 80%). δ_H (400 MHz, $CDCl_3$) 7.23 (1H, d *J* 10.5, <u>H</u>C=CHC=O), 6.20 (1H, d *J* 10.5, HC=C<u>H</u>C=O), 4.57 and 4.26 (2 x 1H, 2 x d *J* 17, OCHH'C=O), 4.09 and 3.81 (2 x 1H, 2 x d *J* 10.5, C<u>HH</u>'OTBS), 2.06 (3H, s, OC(=O)CH$_3$), 0.87 (9H, s, SiC(CH$_3$)$_3$), 0.07 and 0.06 (2 x 3H, 2 x s, Si(CH$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 193.9 (C=O), 169.4 (OC=O), 145.0 (H<u>C</u>=CHC=O), 127.3 (HC=<u>C</u>HC=O), 98.8

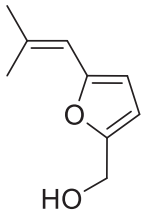
(O–C–O), 68.1 (OCH_2C=O), 66.2 ($\underline{C}H_2OTBS$), 25.7 ($SiC(CH_3)_3$), 21.4 ($OC(=O)CH_3$), 18.2 ($Si\underline{C}(CH_3)_3$), -5.43 ($Si(CH_3)_2$).

5-(1-Hydroxy-2-methylpropyl)furan-2-carbaldehyde (52):



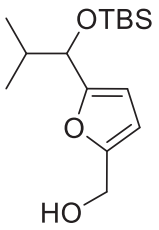
To a suspension of MeNHOMe.HCl (1.21 g, 12.4 mmol, 1.2 equiv) in THF (60 mL) at –20 °C, was slowly added *n*-BuLi (9.9 mL, 2.5 M in hexanes, 24.7 mmol, 2.4 equiv), after 30 min freshly distilled 2-furfural (**51**) (1.0 g, 10.3 mmol, 1 equiv) was added. After a further 15 min, *n*-BuLi (9.5 mL, 2.5 M in hexanes, 23.7 mmol, 2.3 equiv) was added. After a further 1 h, neat isobutyraldehyde (**26**) (3.0 g, 41.2 mmol, 4 equiv) was added and the reaction mixture was allowed to warm to rt. After 30 min, the reaction mixture was quenched by addition of saturated aq NH_4Cl (60 mL). The layers were separated and the aq layer was extracted with Et_2O (3 x 40 mL). The organic layers were combined, washed with brine (2 x 30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, dry loading, gradient elution: petroleum ether to 30% EtOAc in petroleum ether) to give a yellow-orange oil, furanal **52** (1.37 g, 78%): R_f 0.25 (25% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3392 br, 2960 m, 2934 m, 2873 w, 1716 w, 1669 m, 1468 m, 1193 m, 1013 s, 796 m, 771 m; δ_H (200 MHz, $CDCl_3$) 9.60 (1H, s, CHO), 7.23 (1H, d *J* 3.5, $\underline{H}C$=C–CHO), 6.49 (1H, d *J* 3.5, OC=CH), 4.55 (1H, d *J* 6, $C\underline{H}OH$), 2.27-2.10 (1 H, m, $C\underline{H}(CH_3)_2$), 1.02-0.93 (6H, m, $CH(C\underline{H}_3)_2$); δ_C (100 MHz, $CDCl_3$) 177.5 (C=O), 163.5 ($O\underline{C}$=CH), 151.94 (HC=$\underline{C}$–CHO), 122.6 ($H\underline{C}$=C–CHO), 109.3 (OC=$\underline{C}$H), 73.3 (CHOH), 32.9 ($\underline{C}H(CH_3)_2$), 18.3 and 17.2 ($CH(\underline{C}H_3)_2$)); LRMS (ESI^+): 169 ($[M+H]^+$, 20%), 191 ($[M+Na]^+$, 100), 335 (100); HRMS: not found.

(5-(2-Methylprop-1-en-1-yl)furan-2-yl)methanol (53):



A solution of furanal **52** (250 mg, 1.49 mmol, 1 equiv) and TsOH.H_2O (283 mg, 1.49 mmol, 1 equiv) in toluene (30 mL), was heated to reflux. After 30 min, the reaction mixture was cooled to rt, washed with aq NaOH (30 mL, 15%) and water (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in THF (13 mL) and MeOH (2.6 mL) at 0 °C, and $NaBH_4$ (59 mg, 1.6 mmol, 1.2 equiv) was added portionwise. After 30 min, the mixture was concentrated under reduced pressure, dissolved in water (20 mL) and EtOAc (20 mL), and the layers were separated and the aq layer extracted with EtOAc (2 x 20 mL). The organic layers were combined, washed with brine (2 x 20 mL), dried (Na_2SO_4) and concentrated under reduced pressure, to give furanol **53** (210 mg, 93%): R_f 0.25 (20% Et_2O in petroleum ether); IR (neat/cm^{-1}) 3447 br, 2932 m, 1683 m, 1617 m, 1382 m, 1018 s; δ_H (500 MHz, C_6D_6) 6.09-5.99 (3H, m, HC=C$(CH_3)_2$ and HC=C–O–C=CH), 4.25 (2H, s, CH_2OH), 1.86 and 1.65 (2 x 3H, 2 x s, HC=C(CH_3)$_2$); δ_C (125 MHz, C_6D_6) 152.7 and 152.0 (HC=C–O–C=CH), 133.6 (HC=$C$$(CH_3)_2$), 114.0, 107.7 and 107.2 (HC=C$(CH_3)_2$ and HC=C–O–C=CH), 56.4 ($C$$H_2$OH), 25.7 and 19.0 (HC=C($C$$H_3$)$_2$). LRMS ($ESI^+$): dec.

(5-(1-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropyl)furan-2-yl)methanol (54):

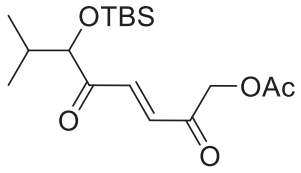


To a solution of furanal **52** (100 mg, 0.59 mmol, 1 equiv) in CH_2Cl_2 (5 mL) at rt, was added TBSCl (269 mg, 1.78 mmol, 3 equiv) and imidazole (163 mg, 2.38 mmol, 4 equiv). After 12 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and quenched by addition of H_2O (10 mL). The layers were separated and the aq layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by colomun chromatography (SiO_2, gradient elution: petroleum ether to 7.5 % Et_2O in petroleum ether) to give protected the silyloxyaldehyde (106 mg, 62%): R_f 0.4 (10 % Et_2O in petroleum ether); IR (neat/cm^{-1}) 2958 m, 2930 m, 2858 w, 1682 s, 1517 m, 1253 m, 1062 m, 854 s, 838 s, 776 s, 754 m, 671 w; δ_H (200 MHz, $CDCl_3$) 9.58 (1H, s, CHO), 7.21 (1H, d *J* 3.5 HC=C–CHO), 6.42 (1H, d *J* 3.5, OC=CH), 4.53 (1H, d *J* 5, CHOTBS), 2.05 (1H, m, CH(CH_3)$_2$), 0.92-0.88 (15H, m, CH(CH_3)$_2$ and SiC(CH_3)$_2$), 0.06 and –0.09 (2 x 3H, 2 x s, Si(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 177.4 (CHO), 164.7 (OC=CH), 151.7 (HC=C–CHO), 122.4 (OC=CH), 109.2 (HC=C–CHO), 73.8 (CHOTBS), 34.4 (CH(CH_3)$_2$), 25.7 (SiC(CH_3)$_3$), 18.6 and 17.1 (CH(CH_3)$_2$), 18.1 (SiC(CH_3)$_3$), –5.0 and –5.3 (Si(CH_3)$_2$); LRMS (ESI^+): 283 ($[M+H]^+$, 10%), 305 ($[M+Na]^+$, 100); HRMS: (ESI^+): calcd for $C_{15}H_{26}O_3NaSi$ $[M+Na]^+$: 305.1543, found 305.1538.

The above silyloxyaldehyde was dissolved in THF (6 mL) and MeOH (1.2 mL) at 0 °C, then $NaBH_4$ (17 mg, 0.45 mmol, 1.2 equiv) was added. After 15 min TLC analysis showed no starting material, the reaction mixture was diluted with EtOAc (20 mL) and quenched by addition of water (10 mL). The layers were separated and the aq layer was extracted with

EtOAc (2 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil alcohol **54** (100 mg, 94%, 58% over two steps): R_f 0.2 (20 % Et_2O in petroleum ether); IR (neat/cm^{-1}) 3346 br, 2957 m, 2930 m, 2858 w, 1471 w, 1252 m, 1064 s, 1008 m, 855 s, 837 s, 776 s, 670 w; δ_H (400 MHz, C_6D_6) 6.02 (1H, d *J* 3, OC=CH), 5.85 (1H, d *J* 3, OC=CH), 4.34 (1H, d *J* 6.5, C<u>H</u>OTBS), 4.22 (2H, s, C<u>H</u>$_2$OH), 2.14 (1H, m, C<u>H</u>$(CH_3)_2$), 1.05 (3H, d *J* 6.5, CH(C<u>H</u>$_3$)(CH_3)), 0.98 (9H, s, SiC$(CH_3)_3$), 0.86 (3H, d *J* 6.5, CH(CH_3)(C<u>H</u>$_3$)), 0.05 and –0.05 (2 x 3H, 2 x s, Si$(CH_3)_2$; δ_C (100 MHz, $CDCl_3$) 157.1 and 152.6 (HC=<u>C</u>–O–<u>C</u>=CH), 108.1 (OC=<u>C</u>H), 107.1 (OC=<u>C</u>H), 74.1 (C<u>H</u>OTBS), 57.6 (CH_2OH), 34.2 (<u>C</u>H$(CH_3)_2$), 25.8 (SiC$(CH_3)_2$), 18.8 (CH(<u>C</u>H$_3$)(CH_3)), 18.2 (Si<u>C</u>$(CH_3)_3$), 18.1 (CH(CH_3)(<u>C</u>H$_3$)), –4.9 and –5.2 (Si$(CH_3)_2$); LRMS (ESI$^+$): 307 ([M+Na]$^+$, 100%), 413 (97); HRMS: calcd for $C_{15}H_{28}O_3NaSi$: 307.1700, found 307.1698.

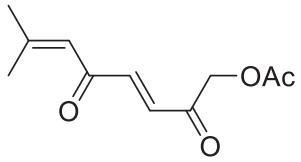
***E*-6-((*tert*-Butyldimethylsilyl)oxy)-7-methyl-2,5-dioxooct-3-en-1-yl acetate (*E*-55):**



Standard procedure of *m*-CPBA furanol oxidation / acetylation (see preparation of **45** p.115-116) was followed with furanol **54** (30 mg, 0.105 mmol). The residue was purified by column chromatography to give a colourless oil, the enedione ***E*-55** (11 mg, 25%): R_f 0.3 (20% Et_2O in petroleum ether); IR (neat/cm^{-1}) 2959 m, 2932 m, 2859 w, 1756 s, 1697 m, 1471 w, 1372 w, 1287 m, 1254 s, 1060 s, 839 s, 779 m, 674 w; δ_H (500 MHz, C_6D_6) 7.48 (1H, d *J* 16, <u>H</u>C=CH), 6.95 (1H, d *J* 16, HC=C<u>H</u>), 4.26 (2 x 1H, 2 x d *J* 17, C<u>H</u>$_2$OAc), 3.81 (1H, d *J* 6, C<u>H</u>OTBS), 1.98 (1H, m, C<u>H</u>$(CH_3)_2$), 1.68 (3H, s, OC(=O)CH_3), 0.98 (9H, s, SiC$(CH_3)_2$), 0.81 and 0.77 (2 x 3H, 2 x d *J* 7, CH(C<u>H</u>$_3$)$_2$), -0.04 and -0.07 (2 x 3H, 2 x s, Si$(CH_3)_2$); δ_C (125 MHz, C_6D_6) 199.3 and 191.2 (2 x C=O), 168.3 (OC=O), 132.3 (H<u>C</u>=CH) 131.3 (HC=<u>C</u>H), 82.3 (<u>C</u>H$_2$OAc), 66.6 (<u>C</u>HOTBS), 31.2 (<u>C</u>H$(CH_3)_2$), 24.7 (SiC(<u>C</u>H$_3$)$_3$), 18.7, 17.6, 17.1 and 16.3 (Si<u>C</u>$(CH_3)_3$,

OC(=O)$\underline{C}H_3$ and CH($\underline{C}H_3$)$_2$), −5.9 and −6.3 (Si(CH_3)$_2$); LRMS (ESI$^+$): 351 ([M+H]$^+$, 43%), 365 ([M+Na]$^+$, 100); HRMS (ESI$^+$): calcd for $C_{17}H_{30}O_5NaSi$ [M+Na]$^+$: 365.1755, found 365.1744.

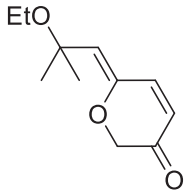
***(E)*-7-Methyl-2,5-dioxo-octa-3,6-dien-1-yl acetate (*E*-56):**



A solution of furanol **53** (40 mg, 0.26 mmol, 1 equiv) and rose Bengal (0.26 mg, 1 mg/mmol) in CH_2Cl_2 (1.6 mL) and MeOH (0.8 mL) was cooled to −78 °C. A balloon of dry O_2 was attached, and the gas was bubbled through the solution while the reaction mixture was irradiated using a 300 W tungsten lamp. After 4 h, TLC showed no more starting material, Me_2S (0.30 mL, 4 mmol, 15 equiv) was added, the reaction mixture was warmed to 0 °C. After 30 min, the reaction mixture was concentrated under reduced pressure and the resulting pink oil was dissolved in CH_2Cl_2 (1.3 mL) at 0 °C. Pyridine (105 µL, 1.3 mmol, 5 eq), Ac_2O (614 µL, 6.5 mmol, 25 eq) and DMAP (cat.) were successively added, and the ice-bath was removed. After 2 h, the reaction mixture was quenched by addition of saturated aq NH_4Cl (5 mL), the layers were separated and the aq layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with saturated aq $CuSO_4$ (10 mL) and brine (10mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 20% Et_2O in petroleum ether) to give a colorless oil, dienedione *E*-**56** (20 mg, 36%): R_f 0.3 (20% Et_2O in petroleum ether), IR (neat/cm^{-1}) 2936 w, 1751 s, 1621 m, 1602 m, 1375 m, 1229 s, 1176 m, 1051 m, 901 w, 782 w; δ_H (400 MHz, C_6D_6) 6.79 and 6.72 (2 x 1H, 2 x d *J* 16, $\underline{H}C=C\underline{H}$), 5.73 (1H, s, $\underline{H}C=C(CH_3)_2$), 4.30 (2H, s, $C\underline{H}_2OAc$), 2.06 (3H, s, $OC(=O)CH_3$), 1.73 and 1.42 (2 x 3H, 2 x s, $HC=C(C\underline{H}_3)_2$); δ_C (100 MHz, C_6D_6) 192.3 and 187.5 (2 x C=O), 169.2 (OC=O), 158.7 ($HC=\underline{C}(CH_3)_2$), 139.1

and 131.1 (H<u>C</u>=<u>C</u>H), 123.1 (H<u>C</u>=C(CH_3)$_2$), 67.3 (<u>C</u>H_2OAc), 27.1 (HC=C(<u>C</u>H_3)(CH_3)), 20.8 (OC(=O)CH_3), 19.6 (HC=C(CH_3)(<u>C</u>H_3)); LRMS (ESI$^+$): 211 ([M+H]$^+$, 25%), 233 ([M+Na]$^+$, 100); HRMS (ESI$^+$): calcd for $C_{11}H_{14}O_4Na$ [M+Na]$^+$: 233.0784, found 233.0783.

6-(2-Ethoxy-2-methylpropylidene)-2*H*-pyran-3(6*H*)-one (*Z*-60):

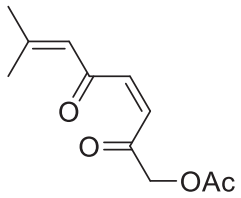


A solution of furanol **53** (50 mg, 0.33 mmol, 1 equiv) and rose Bengal (0.33 mg, 1 mg/mmol) in CH_2Cl_2 (2 mL) and MeOH (1 mL) was cooled to −78 °C. A balloon of dry O_2 was attached, and the gas was bubbled through the solution while the reaction mixture was irradiated using a 300 W tungsten lamp. After 4 h, TLC analysis showed no more starting material, Me_2S (0.38 mL, 5 mmol, 15 equiv) was added, the reaction mixture was warmed to 0 °C. After 30 min, the reaction mixture was concentrated under reduced pressure and the resulting pink oil was dissolved in dry EtOH (33 mL) at 0 °C, and TFA (37 mg, 0.33 mmol, 1 equiv) was added. The reaction mixture was allowed to warm to rt. After 14 h, the reaction mixture was concentrated under reduced pressure, the residue was dissolved in EtOAc (10 mL) and saturated aq $NaHCO_3$ (10 mL) was added, the layers were separated and the aqueous was extracted with EtOAc (2 x 10 mL). The organic layers were combined, washed with brine (2 x 5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 20% Et_2O in petroleum ether) to give a colourless oil, dihydropyranone *Z*-**60** (9 mg, 14%); R_f 0.3 (20% Et_2O in petroleum ether); IR (neat/cm^{-1}) 2976 m, 2929 w, 1686 s, 1583 w, 1326 w, 1269 m, 1206 m, 1120 m, 1070 s, 820 w; δ_H (500 MHz, $CDCl_3$) 6.94 (1H, d *J* 10, <u>H</u>C=CH–C=O), 6.06 (1H, d *J* 10, HC=C<u>H</u>–C=O), 5.19 (1H, s, OC=CH), 4.52 (2H, s, OCH_2C=O), 3.45 (2H, q *J* 7, $CH_3C\underline{H_2}O$), 1.44 (6H, s, C(CH_3)$_2$), 1.19

(3H, t *J* 7, C<u>H</u>$_3$CH$_2$O); δ_C (125 MHz, $CDCl_3$) 191.1 (C=O), 145.4 (O<u>C</u>=CH), 142.5 (HC=<u>C</u>H–CHO), 125.0 (OC=<u>C</u>H), 122.2 (H<u>C</u>=CH–CHO), 73.8 (O<u>C</u>(CH$_3$)$_2$), 70.1 (OCH$_2$C=O), 57.2 (CH$_3$<u>C</u>H$_2$O), 25.5 (C(<u>C</u>H$_3$)$_2$), 15.1 (<u>C</u>H$_3$CH$_2$O); LRMS (ESI$^+$) 151 ([M–EtO]$^+$, 100%), 197 ([M+H]$^+$, 10), 215 (90); HRMS (ESI$^+$) calcd for $C_9H_{11}O_2$ [M–EtO]$^+$: 151.0759, found 151.0752.

nOe experiments: irradiation at 5.19 (OC=CH) saw reciprocal signal enhancement at 6.94 (C<u>H</u>=CHC=O), 3.45 (CH$_3$C<u>H</u>$_2$O) and 1.44 (C(CH$_3$)$_2$) and irradiation at 6.06 (CH=C<u>H</u>C=O) saw reciprocal signal enhancement at 6.94 (C<u>H</u>=CHC=O).

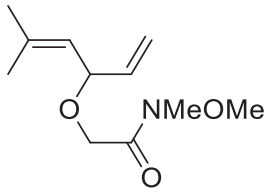
***(Z)*-7-Methyl-2,5-dioxoocta-3,6-dien-1-yl acetate (*Z*-56) :**



A solution of furanol **53** (50 mg, 0.33 mmol, 1 eq) and tetraphenylporphine (or methylene blue) (1 mg, cat.) in CH_2Cl_2 (3 mL) was cooled to −78 °C. A balloon of dry O_2 was attached, and the gas was bubbled through the solution while the reaction mixture was irradiated using a 300 W tungsten lamp. After 2 h, TLC analysis showed no more starting material. Me_2S (0.38 mL, 5 mmol, 15 equiv) was then added, the reaction mixture was warmed to 0 °C. After 30 min, the reaction mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2 (1.5 mL) at 0 °C, then pyridine (120 µL, 1.5 mmol, 5 equiv), Ac_2O (700 µL, 7.5 mmol, 25 equiv) and DMAP (cat.) were successively added and the reaction mixture was allowed to warm to rt. After 2 h, the reaction mixture was quenched by addition of saturated aq NH_4Cl (5 mL), the layers separated and the aq layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with saturated aq $CuSO_4$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography

(SiO_2, gradient elution: petroleum ether to 30% Et_2O in petroleum ether) to give a colorless oil, dienedione ***Z*-56** (8 mg, 11%): R_f 0.25 (20% Et_2O in petroleum ether); IR (neat/cm^{-1}) 2938 w, 2358 w, 1750 s, 1716 m, 1621 s, 1444 m, 1375 m, 1231 s, 1116 m, 1048 s, 855 w, 799 w; δ_H (500 MHz, C_6D_6) 5.75 (1H, d *J* 12.5, HC=CH), 5.68 (2 x 1H, m, HC=C<u>H</u> and <u>H</u>C=C$(CH_3)_2$), 4.68 (2H, s, C<u>H</u>$_2$OAc), 1.98 (3H, s, HC=C(C<u>H</u>$_3$)(CH_3)), 1.68 (3H, s, OC(=O)CH_3), 1.38 (3H, s, HC=C(CH_3)(C<u>H</u>$_3$)); δ_C (125 MHz, C_6D_6) 197.6 and 189.3 (2 x C=O), 170.1 (OC=O), 159.1 (HC=<u>C</u>$(CH_3)_2$), 136,2 and 135.7 (H<u>C</u>=<u>C</u>H), 123.5 (H<u>C</u>=C$(CH_3)_2$), 67.9 (<u>C</u>H_2OAc), 27.6 and 21.1 (HC=C(<u>C</u>$H_3)_2$), 20.2 (OC(=O)CH_3); LRMS (ESI^+): 211 ($[M+H]^+$, 22%), 233 ($[M+Na]^+$, 100). HRMS (ESI^+): calcd for $C_{11}H_{14}O_4Na$ $[M+Na]^+$: 233.0784, found 233.0782.

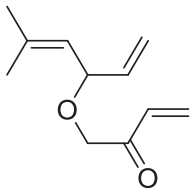
***N*-Methoxy-*N*-methyl-2-((5-methylhexa-1,4-dien-3-yl)oxy)acetamide (133):**



To a suspension of NaH (60% in mineral oil, 200 mg, 5.0 mmol, 1 equiv) in THF (1.5 mL) at 0 °C, was added 5-methylhexa-1,4-dien-3-ol **131**[57] (550 mg, 5.0 mmol, 1 equiv) and the reaction mixture was allowed to warm to rt. After 1h, 15-crown-5 (1.0 mL, 5.0 mmol, 1 equiv) and *n*Bu_4NI (60 mg, cat.) were added, followed by 2-bromo-*N*-methoxy-*N*-methylacetamide **132**[58] (900 mg, 5.0 mmol, 1 equiv) in THF (10 mL). After 12 h, the reaction mixture was quenched by addition of saturated aq NH_4Cl (15 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The organic layers were combined and washed with brine (2 x 15 mL), dried (Na_2SO_4) and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, dry loading, gradient elution: petroleum ether to 25% EtOAc in petroleum ether) to give a yellow oil, ether **133** (340 mg, 31%): R_f 0.3 (25% EtOAc in petroleum ether); IR (neat/cm^{-1}) 2971 w, 2936 w, 1679 s, 1443

m, 1425 m, 1082 m, 993 m, 924 w; δ_H (400 MHz, $CDCl_3$) 5.85-5.76 (1H, m, C<u>H</u>=CH_2), 5.25-5.15 (3 H, m, C<u>H</u>=$C(CH_3)_2$ and CH=C<u>H_2</u>), 4.67 (1H, m, OCH), 4.23 (2H, s, OCH_2), 3.66 (3H, s, $NOCH_3$), 3.17 (3H, s, NCH_3), 1.75 and 1.71 (2 x 3H, 2 s, CH=C(C<u>H_3</u>)$_2$); δ_C (100 MHz, $CDCl_3$) 137.5 (<u>C</u>H=CH_2), 137.2 (CH=<u>C</u>$(CH_3)_2$), 123.6 (<u>C</u>H=C$(CH_3)_2$), 116.4 (CH=<u>C</u>H_2), 77.6 (OCH), 64.3 (OCH_2), 61.3 ($NOCH_3$), 32.3 (NCH_3), 25.9 and 18.3 (CH=C(<u>C</u>H_3)$_2$); LRMS (ESI^+): 226 ($[M+Na]^+$, 55%), 446 ($[2M+Na]^+$, 100); HRMS (ESI^+) m/z: calcd for $C_{11}H_{19}O_3Na$: 236.1257 $[M+Na]^+$, found 236.1253.

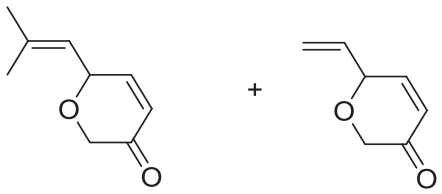
1-((5-Methylhexa-1,4-dien-3-yl)oxy)but-3-en-2-one (134):



To a solution of ether **133** (175 mg, 0.8 mmol, 1 equiv) in Et_2O (8 mL) at 0 °C, was added vinylmagnesium bromide (2.0 mL, 1.0 M in THF, 2.0 mmol, 2.5 equiv). After 15 min, technical grade acetone (0.5 mL) was added to the reaction mixture, followed after 10 min by saturated aq NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The organic layers were combined, washed with brine (2 x 15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 10% Et_2O in petroleum ether) to give a colourless oil, triene **134** (80 mg, 57%): R_f 0.4 (10% Et_2O in petroleum ether); IR (neat/cm^{-1}) 2977 w, 2916 w, 1700 s, 1615 m, 1402 m, 1095 s, 1063 m, 990 s, 924 m, 825 w; δ_H (500 MHz, C_6D_6) 6.50 (1H, dd *J* 17.5, 10, C(=O)CH), 6.21 (1H, dd *J* 17.5, 1.5, C(=O)CH=CH$_{trans}$<u>H</u>$_{cis}$), 5.79 (1H, ddd *J* 17, 10, 6, OCHC<u>H</u>=CH_2), 5.22-5.15 (3 x 1H, m, OCHCH= CH$_{trans}$<u>H</u>$_{cis}$, C<u>H</u>=C$(CH_3)_2$ and C(=O)CH=C<u>H</u>$_{trans}$H$_{cis}$), 5.01 (1H, dt *J* 10, 1.5, OCHCH=C<u>H</u>$_{trans}$H$_{cis}$), 4.48 (1H, m, OCH), 3.95 (2H, d *J* 3, OCH_2), 1.51 and 1.42 (2 x 3H, 2 x d *J* 1.5 and 1.0, CH=C(C<u>H_3</u>)$_2$); δ_C (125 MHz,

C_6D_6) 197.6 (C=O), 138.4 (OCH<u>C</u>H=CH_2), 137.2 (CH=<u>C</u>(CH_3)$_2$), 133.0 (C(=O)<u>C</u>H=CH_2), 127.4 (C(=O)CH=<u>C</u>H_2), 124.8 (<u>C</u>H=C(CH_3)$_2$), 116.0 (OCHCH=<u>C</u>H_2), 78.3 (OCH), 72.7 (OCH_2), 26.1 and 18.5 (CH=C(<u>C</u>H_3)$_2$); LRMS (ESI^+): 203 ($[M+Na]^+$, 57%), 383 ($[2M+Na]^+$, 100); HRMS (ESI^+) m/z: calcd for $C_{11}H_{16}O_2Na$: 203.1043 $[M+Na]^+$, found 203.1040.

6-(2-Methylprop-1-en-1-yl)-2*H*-pyran-3(6*H*)-one 135 / 6-Vinyl-2*H*-pyran-3(6*H*)-one 136:



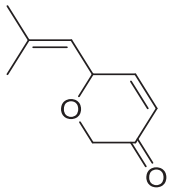
To a solution of triene **134** (80 mg, 0.45 mmol, 1 equiv) in degassed CH_2Cl_2 (90 mL) under an argon atmosphere, was added **GII** (19 mg, 0.022 mmol, 5 mol%). After 10 h at 40 °C, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (SiO_2, gradient elution: petroleum ether to 10% Et_2O in petroleum ether) to give a yellow oil (a mixture of enones **135** and **136** (45 mg, 3:1 by integration of C<u>H</u>=CHC=O signals, 60%).

Discernible data for **135**: R_f 0.3 (10% Et_2O in petroleum ether); δ_H (500 MHz, $CDCl_3$) 6.90 (1H, dd *J* 10.5, 2, C<u>H</u>=CHC=O), 6.15 (1H, dd *J* 10.5, 2, CH=C<u>H</u>C=O), 5.28 (1H, dt *J* 8.5, 1.5, C<u>H</u>=C(CH_3)$_2$), 5.03 (1H, dd 8.5, 2, OCH), 4.30 (1H, d *J* 16.5, OC<u>H</u>H'), 4.15 (1H, d *J* 16.5, OCH<u>H</u>'), 1.81-1.79 (2 x 3H, m, CH=C(C<u>H</u>$_3$)$_2$); δ_c (125 MHz, $CDCl_3$) 194.6 (C=O), 151.6 (<u>C</u>H=CHC=O), 139.7 (CH=<u>C</u>(CH_3)$_2$), 126.4 (CH=<u>C</u>HC=O), 120.7 (<u>C</u>H=C(CH_3)$_2$), 70.9 (OCH_2), 70.7 (OCH), 25.8 and 18.5 (CH=C(<u>C</u>H_3)$_2$).

Discernible data for **136**: δ_H (500 MHz, $CDCl_3$) 7.00 (1H, dd *J* 10.5, 2.5, C<u>H</u>=CHC=O), 6.18 (1H, dd *J* 10.5, 2, CH=C<u>H</u>C=O), 5.96-5.90 (1H, m, CH=CH$_{trans}$<u>H</u>$_{cis}$), 5.44-5.38 (2H, m, CH=C<u>H</u>$_{trans}$H$_{cis}$ and C<u>H</u>=CH_2), 4.87-4.86 (1H, m, OCH), 4.31 (1H, d *J* 16.5, OC<u>H</u>H'), 4.15

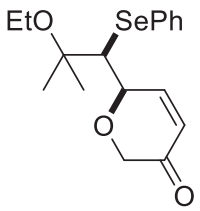
(1H, d *J* 16.5, OCHH'); δ_c (125 MHz, $CDCl_3$) 194.3 (C=O), 149.7 (CH=CHC=O), 133.7 ($CH=CH_2$), 126.9 (CH=CHC=O), 118.9 ($CH=CH_2$), 73.81 (OCH), 70.2 (OCH_2).

6-(2-Methylprop-1-en-1-yl)-2*H*-pyran-3(6*H*)-one (135):



To a solution of triene **134** (80 mg, 0.45 mmol, 1 equiv), in degassed CH_2Cl_2 (9 mL) under an argon atmosphere was added Grubbs I (40 mg, 0.044 mmol, 10 mol%). After 10 h at rt, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (SiO_2, gradient elution: pure petroleum ether to 10% Et_2O in petroleum ether) to give a yellow oil, the enone **135** (40 mg, 59%): IR (neat/cm^{-1}) 2973 w, 2917 w, 2850 w, 1694 s, 1381 w, 1233 w, 1152 w, 1092 m, 753 w; NMR data matched that found in the experiment described above; LRMS (ESI^+): 153 ($[M+H]^+$, 20%), 175 ($[M+Na]^+$, 95), 203 (98), 413 (100); HRMS (ESI^+) m/z: calcd for $C_9H_{12}O_2Na$: 175.0730 $[M+Na]^+$, found 175.0729.

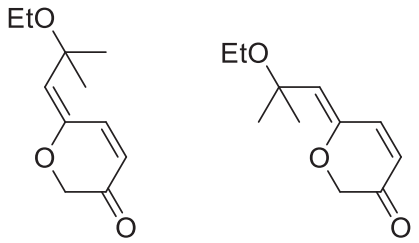
(*R)-6-((*S**)-2-Ethoxy-2-methyl-1-(phenylselanyl)propyl)-2*H*-pyran-3(6*H*)-one (137):**



To a solution of enone **135** (7.0 mg, 46 µmol, 1 equiv) in anhydrous EtOH (1 mL) at 0 °C, was added freshly distilled Et_3N (6.4 µL, 46 µmol, 1 equiv) followed by PhSeBr (12 mg, 51 µmol, 1.1 equiv) in a mixture of anhydrous EtOH (1 mL) and CH_2Cl_2 (0.2 mL). After 15 min the ice-bath was removed and after a further 1 h the reaction mixture was quenched by addition of saturated aq $NaHCO_3$ (5 mL) and extracted with Et_2O (3 x 5 mL). The organic layers were

combined, washed with brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 20% Et_2O in petroleum ether) to give a colourless oil, the ethoxyselenide **137** (5 mg, 30%); R_f 0.15 (10% Et_2O in petroleum ether); IR (neat/cm^{-1}) 2976 m, 2870 w, 1694 s, 1364 w, 1105 m, 1067 m, 741 m, 692 w; δ_H (200 MHz, $CDCl_3$) 7.60-7.57 (2H, m, SePh), 7.29-7.26 (3H, m, SePh), 7.07 (1H, dd *J* 10.5, 1.5, C<u>H</u>=CHC=O), 6.23 (1H, dd *J* 10.5, 2.5, CH=C<u>H</u>C=O), 5.08-5.07 (1H, m, OCH), 4.30 (1H, d *J* 16, OC<u>H</u>H'C=O), 4.12 (1H, dd *J* 16.5, 2, OCH<u>H</u>'C=O), 3.46-3.39 (2H, m, OC<u>H</u>$_2$CH$_3$), 3.31 (1H, d *J* 1.5, C<u>H</u>SePh), 1.43 and 1.33 (2 x 3H, 2 x s, C(C<u>H</u>$_3$)$_2$), 1.15 (3H, t *J* 7, OCH$_2$C<u>H</u>$_3$); δ_c (100 MHz, $CDCl_3$) 194.3 (C=O), 152.9 (<u>C</u>H=CHC=O), 134.0 (SePh), 131.3 (SePh), 129.2 (SePh), 127.7 (CH=<u>C</u>HC=O), 127.4 (SePh), 78.3 (O<u>C</u>(CH$_3$)$_2$), 73.9 (O<u>C</u>H), 71.6 (O<u>C</u>H$_2$C=O), 60.1 (O<u>C</u>H$_2$CH$_3$), 57.2 (<u>C</u>HSePh), 25.3 and 23.7 (C(<u>C</u>H$_3$)$_2$), 16.0 (OCH$_2$<u>C</u>H$_3$); LRMS (ESI$^+$): 130 (100%), 377 ([M+Na]$^+$, 70); HRMS (ESI$^+$) m/z: calcd for $C_{17}H_{22}O_3{}^{80}SeNa$: 377.0626 [M+Na]$^+$, found 377.0621.

***E*- and *Z*-6-(2-Ethoxy-2-methylpropylidene)-2*H*-pyran-3(6*H*)-one (60):**



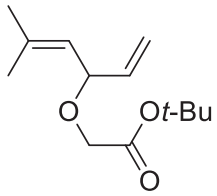
To a solution of ethoxyselenide **137** (10 mg, 28 µmol, 1 equiv) in CH_2Cl_2 (1 mL) and H_2O (0.05 mL) at 0 °C, was added pyridine (4.5 µL, 56 µmol, 2 equiv) followed by H_2O_2 (7.2 µL, 35 % in H_2O, 64 µmol, 3 equiv) and the reaction mixture was then allowed to warm to rt. After 20 min, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and the organic layer was washed with saturated aq $NaHCO_3$ (2 x 3 mL), water (3 x 3 mL) and brine (3 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: pure petroleum ether to 20% Et_2O in petroleum ether). First eluted a

colourless oil, the *E*-isomer **60** (1.5 mg, 27%) (which isomerises to the *Z*: after 12 h at rt in $CDCl_3$ a 4:1 mixture (by integration of C<u>H</u>=CHC=O signals) of *E/Z* isomers was observed). Second eluted a colourless oil, the *Z*-isomer **60** (1.5 mg, 27%) (no isomerisation observed under similar conditions).

E-isomer **60**: R_f 0.3 (20% Et_2O in petroleum ether); δ_H (500 MHz, $CDCl_3$) 8.07 (1H, d *J* 10.5, C<u>H</u>=CHC=O), 6.11 (1H, dd *J* 10.5, 1.5, CH=C<u>H</u>C=O), 5.45 (1H, d *J* 1.5, OC=C<u>H</u>), 4.48 (2H, s, OCH_2C=O), 3.41 (2H, q *J* 7, $CH_3C\underline{H}_2O$), 1.39 (6H, s, $C(C\underline{H}_3)_2$), 1.17 (3H, t *J* 7.0, $C\underline{H}_3CH_2O$); δ_c (125 MHz, $CDCl_3$) 193.2 (C=O), 146.7 (O<u>C</u>=CH), 138.1 (<u>C</u>H=CHC=O), 123.6 (CH=<u>C</u>HC=O), 122.7 (OC=<u>C</u>H), 74.1 ($O\underline{C}(CH_3)_2$), 72.1 ($O\underline{C}H_2C$=O), 57.9 ($CH_3\underline{C}H_2O$), 29.4 ($C(CH_3)_2$), 15.8 ($\underline{C}H_3CH_2O$); LRMS (ESI^+): 151 ($[M\text{-}CH_3CH_2O]^+$, 17 %), 197 ($[M+H]^+$, 4), 219 ($[M+Na]^+$, 38), 413 (100); HRMS (ESI^+) m/z: calcd for $C_9H_{11}O_2Na$: 151.0759 $[M+Na]^+$, found 151.0752.

Z-isomer **60**: analytical data corresponded to those previously reported

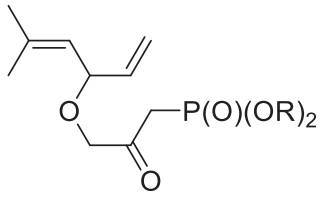
***tert*-Butyl 2-((5-methylhexa-1,4-dien-3-yl)oxy)acetate (140):**



A round bottom flask was charged with THF (50 mL) and vinylmagnesium bromide (100 mL, 1.0 M in THF, 100 mmol, 1.1 equiv). The solution was cooled to 0 °C, and a solution of prenal (8.61 mL, 90 mmol, 1 equiv) in THF (10 mL) was added *via* cannula over 20 min and the reaction mixture was allowed to warm to rt. After 1 h, the reaction mixture was quenched by addition of water (150 mL), the layers were separated and the aqueous was extracted with Et_2O (3 x 100 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure (maintained above 200 mbar) to give 16 g of a clear yellow oil, the volatile

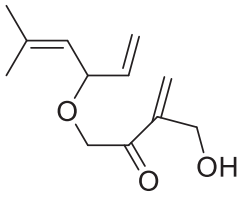
dienol **131** in residual THF (4:3 molar ratio; NMR data corresponded to those previously reported)[57]. The crude dienol **131** was dissolved in toluene (450 mL), pre-cooled (10 °C) and transferred into a 2-neck round bottom flask equipped with an overhead mechanical stirrer. Pre-cooled (10 °C) aq NaOH solution (450 mL, 30%) was added, the biphasic mixture was vigorously stirred (400 rpm) and *tert*-butyl bromoacetate (14.8 mL, 100 mmol, 1.1 equiv) was added in 3 portions (a 5 min time interval was left between each portion), followed by *n*-Bu_4NHSO_4 (2.78 g, 8.2 mmol, 0.09 equiv). After 60 h at rt, further *tert*-butyl bromoacetate (7.38 mL, 50 mmol, 0.55 equiv) was added. After a further 24 h, brine (450 mL) was added to the reaction mixture, the layers were separated and the aqueous was extracted with Et_2O (3 x 200 mL). The organic layers were combined, washed with brine (500 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The excess of *tert*-butyl bromoacetate was removed under *high vacuum* (~0.6 mbar) to give a yellow-orange oil, the ether **140** (19.0 g, 93%). The crude ester was used in the next step without further purification. An analytical sample was obtained by column chromatography (SiO_2, gradient elution: petroleum ether to 10% Et_2O in petroleum ether): R_f 0.3 (6% Et_2O in petroleum ether); IR (neat/cm^{-1}) 2979 w, 2932 w, 1747 m, 1368 m, 1223 m, 1160 m, 1115 s, 920 m, 850 w, 736 w; δ_H (400 MHz, $CDCl_3$) 5.85-5.76 (1H, m, $H_2C=C\underline{H}$), 5.30-5.15 (3 H, m, $(CH_3)_2C=C\underline{H}$ and $\underline{H_2}C=CH$), 4.66-4.63 (1H, m, OCH), 3.94 (2H, br. s, OCH_2), 1.77 and 1.70 (2 x 3H, 2 s, $(CH_3)_2C=C\underline{H}$), 1.47 (9H, s, $OC(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 170.0 (OC=O), 137.4 ($H_2C=\underline{C}H$), 136.8 ($(CH_3)_2\underline{C}=CH$), 123.4 ($(CH_3)_2C=\underline{C}H$), 116.4 ($H_2\underline{C}=CH$), 81.3 ($O\underline{C}(CH_3)_3$), 77.4 (OCH), 64.9 (OCH_2), 28.1 ($OC(\underline{C}H_3)_3$), 25.9 and 18.3 ($(\underline{C}H_3)_2C=CH$); LRMS (ESI^+): 249 ($[M+Na]^+$, 5%), 265 ($[M+K]^+$, 100); HRMS (ESI^+): calcd for $C_{13}H_{22}NaO_3$ $[M+Na]^+$: 249.14612 $[M+Na]^+$, found 249.14604.

Dimethyl (3-((5-methylhexa-1,4-dien-3-yl)oxy)-2-oxopropyl)phosphonate (141):



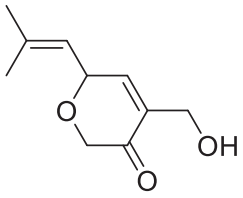
To a solution of dimethyl methylphosphonate (4.77 mL, 44 mmol, 2.2 equiv) in THF (80 mL) at −78 °C was added *n*-BuLi (16.8 mL, 2.5 M in hexanes, 42 mmol, 2.1 equiv). After 15 min, a solution of a portion of the above crude ether **140** (4.52 g, 20 mmol, 1 equiv) in THF (20 mL) was added *via* cannula over 20 min, then the cooling bath was removed and the reaction mixture was allowed to warm to rt. After 12 h, the reaction mixture was quenched by addition of saturated aq NH_4Cl (100 mL) and extracted with Et_2O (3 x 100 mL). The organic layers were combined, washed with brine (200 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give an orange oil, the phosphonate **141** (5.30 g, 96%) which was used in the next step without further purification. An analytical sample was obtained by column chromatography (SiO_2, gradient elution: petroleum ether to 80% EtOAc in pure petroleum ether): R_f 0.3 (80% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3470 br w, 1730 w, 1448 w, 1258 m, 1031 s; δ_H (400 MHz, $CDCl_3$) 5.78 (1H, ddd *J* 17, 10.5, 6.5, H_2C=C<u>H</u>), 5.26-5.11 (3H, m, <u>H</u>$_2$C=CH and (CH_3)$_2$C=C<u>H</u>), 4.53 (1 H, ddt *J* 9, 6.5, 1, OCH), 4.10 (1H, br d *J* 1, OCH_2), 3.78 (6H, d *J* 11.5, P(OCH_3)$_2$), 3.23 (1 H, dd *J* 21.5, 13.5, PC<u>H</u>H'), 3.17 (1 H, dd *J* 22, 13.5, PCH<u>H</u>'), 1.76 and 1.69 (2 x 3H, 2 x d *J* 1.5, (C<u>H</u>$_3$)$_2$C=CH); δ_C (100 MHz, $CDCl_3$) 200.7 (C=O), 137.7 ((CH_3)$_2$<u>C</u>=CH), 137.0 (H_2C=<u>C</u>H), 123.1 ((CH_3)$_2$C=<u>C</u>H), 116.6 (H_2<u>C</u>=CH), 78.1 (OCH), 72.8 (OCH_2), 53.1 (d *J* 6.5, P(OCH_3)$_2$), 53.0 (d *J* 6.5, P(OCH_3)$_2$), 37.2 (D *J* 129.5, PCH_2), 25.9 and 18.3 ((<u>C</u>H_3)$_2$C=CH); LRMS (ESI^+): 299 ([M+Na]$^+$, 100%); HRMS (ESI^+): calcd for $C_{12}H_{21}O_5NaP$: 299.1030 [M+Na]$^+$, found: 299.1019.

3-(Hydroxymethyl)-1-((5-methylhexa-1,4-dien-3-yl)oxy)but-3-en-2-one (142):



To a solution of a portion of the above crude phosphonate **141** (650 mg, 2.36 mmol, 1 equiv) in THF (24 mL) and H_2O (48 mL) at rt, were added formaldehyde (700 μL, 37% w/w aq solution, 9.44 mmol, 4 equiv) followed by K_2CO_3 (326 mg, 2.36 mmol, 1 equiv) in one portion. After 1 h, the reaction mixture was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 30% EtOAc in petroleum ether) to give a colourless oil, the triene **142** (270 mg, 53% over 2 steps): R_f 0.3 (30% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3459 br, 2974 m, 2930 m, 2361 m, 2341 w, 1721 s, 1082 s; δ_H (500 MHz, $CDCl_3$) 6.13 and 6.03 (2 x 1H, 2 x s, C=C$\underline{H}_2$), 5.81 (1H, ddd *J* 17, 10, 7, C$\underline{H}$=CH_2), 5.25-5.17 (3H, m, C=CH and CH=C$\underline{H}_2$), 4.57 (1H, m, OCH), 4.45 (2H, s, OCH_2), 4.33 (2H, d *J* 6, C$\underline{H}_2$OH), 2.31 (1H, t *J* 6.5, OH), 1.77 and 1.70 (2 x 3H, 2 x d *J* 1.5, ($C\underline{H}_3$)$_2$C=CH); δ_C (125 MHz, $CDCl_3$) 198.8 (C=O), 145.0 ($\underline{C}$=CH_2), 137.7 ((CH_3)$_2\underline{C}$=CH), 137.2 ($\underline{C}$H=CH_2), 125.4 (C=$\underline{C}H_2$), 123.3 ((CH_3)$_2$C=$\underline{C}$H), 116.7 (CH=$\underline{C}H_2$), 78.0 (OCH), 69.6 (OCH_2), 62.5 (CH_2OH), 25.9 and 18.3 (($\underline{C}H_3$)$_2$C=CH); LRMS (ESI^+): 233 ([M+Na]$^+$, 80%), 443 ([2M+Na]$^+$, 100); HRMS (ESI^+): calcd for $C_{12}H_{18}O_3Na$: 233.1148 [M+Na]$^+$, found 233.1144.

4-(Hydroxymethyl)-6-(2-methylprop-1-en-1-yl)-2*H*-pyran-3(6H)-one (143):

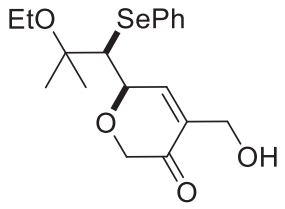


To a solution of triene **142** (113 mg, 0.54 mmol, 1 equiv) in degassed CH_2Cl_2 (10 mL, 0.054 M) was added Grubbs II (42 mg, 0.05 mmol, 10 mol%) at rt under an argon atmosphere. After 1 h,[a] argon was bubbled through the solution until the volume reduced to ~1 mL, and 2-methyl-2-butene (5 mL, 47 mmol, 87 equiv) was then added. After 12 h, the reaction mixture was concentrated and purified by column chromatography (SiO_2, gradient elution: petroleum ether to 30% EtOAc in petroleum ether) to give a brown oil, the dihydropyranone **143** (92 mg, 94%):[b] R_f 0.3 (30% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3440 br, 2917 w, 1684 s, 1447 w, 1377 m, 1115 m, 1017 w; δ_H (400 MHz, $CDCl_3$) 6.84 (1 H, s, C=C<u>H</u>), 5.30 (1 H, dsep *J* 8.5, 1.5, $(CH_3)_2C$=C<u>H</u>), 5.11 (1 H, br d *J* 8.5, OCH), 4.40-4.29 (3 H, m, C<u>H</u>$_2$OH + OC<u>H</u>H'), 4.14 (1 H, dd *J* 16.5, 2, OCH<u>H</u>'), 2.20-2.17 (1 H, m, OH), 1.81 and 1.79 (2 x 3H, 2 x d *J* 1.5, (C<u>H</u>$_3$)$_2$=CH); δ_C (100 MHz, $CDCl_3$) 195.5 (C=O), 146.6 (C=<u>C</u>H), 139.5 (<u>C</u>=CH), 135.6 ($(CH_3)_2$<u>C</u>=CH), 120.9 ($(CH_3)_2$C=<u>C</u>H), 71.2 (OCH), 70.7 (OCHH'), 60.3 (CH_2OH), 25.8 and 18.6 ($(\underline{C}H_3)_2$C=CH); LRMS (ESI^+): 183 ($[M+H]^+$, 10%), 205 ($[M+Na]^+$, 100), 387 ($[2M+Na]^+$, 18); HRMS (ESI^+): calcd for $C_{10}H_{14}O_3Na$: 205.0835 $[M+Na]^+$, found: 205.0835.

[a] ^{1}H NMR analysis at this stage indicated 9:1 dihydropyranone **143**: dihydropyranone **144** (discernible data for **144**: δ_H (400 MHz, $CDCl_3$) 6.94 (1H, dt *J* 2.5, 1.5, C=C<u>H</u>), 6.00-5.85 (1H, m, <u>H</u>$_{cis}$H$_{tans}$C=CH), 5.41 (1H, dt *J* 17.5, 1.5, H$_{cis}$<u>H</u>$_{tans}$C=CH), 5.35 (1H, dt *J* 10.5, 1.5, H$_{cis}$H$_{tans}$C=C<u>H</u>), 4.94-4.90 (1H, m, OCH).)

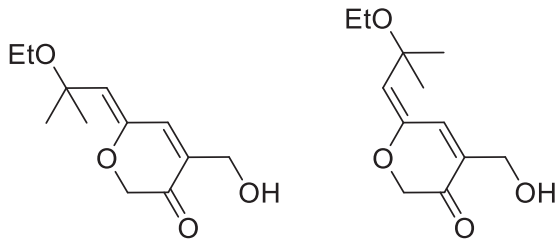
[b] On a larger scale (5 mmol), the reaction can be carried out at higher concentration (0.25 M) and lower catalyst loading (2 mol%) (reaction time 3 h), giving, after concentration and addition of 2-methyl-2-butene (9 equiv.) (reaction time 6 h) dihydropyranone **143** (82%).

(*R)-6-((*S**)-2-Ethoxy-2-methyl-1-(phenylselanyl)propyl)-4-(hydroxymethyl)-2H-pyran-3(6H)-one (145):**



To a solution of pyran **143** (185 mg, 1.0 mmol, 1 equiv) and Et_3N (140 μL, 1.0 mmol, 1 equiv.) in EtOH (10 mL) was added a solution of PhSeBr (260 mg, 1.1 mmol, 1.1 equiv) in a mixture of EtOH (10 mL) and CH_2Cl_2 (2 mL) over 10 min at 0 °C. After 15 min, the reaction mixture was allowed to warm to rt. After 90 min, the reaction mixture was quenched by addition of saturated aq $NaHCO_3$ (20 mL). The layers were separated and the aqueous was extracted with Et_2O (3 x 20 mL). The organic layers were combined, washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 30% EtOAc in petroleum ether) to give a yellow oil, the ethoxyselenide **145** (270 mg, 69%): R_f 0.3 (30% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3431 br, 2974 w, 1682 s, 1381 w, 1066 m, 742 m, 692 w; δ_H (500 MHz, $CDCl_3$) 7.60-7.57 (2 H, m, SePh), 7.29-7.26 (3 H, m, SePh), 6.92 (1 H, q *J* 1.5, C<u>H</u>=C), 5.15-5.14 (1 H, m, OCH), 4.40 (1 H, d *J* 14, C<u>H</u>H'OH), 4.31 (1 H, d *J* 16.5, OC<u>H</u>H'C=O), 4.25 (1 H, d *J* 14, CH<u>H</u>'OH), 4.12 (1 H, dd *J* 16.5, 2, OCH<u>H</u>'C=O), 3.47-3.36 (2 H, m, $CH_3C\underline{H}_2O$), 3.35 (1 H, d *J* 1.5, C<u>H</u>SePh), 2.11 (1 H, br. s, OH), 1.42 and 1.34 (2 x 3 H, 2 x s, $C(C\underline{H}_3)_2$), 1.15 (3 H, t *J* 7, $C\underline{H}_3CH_2O$); δ_C (125 MHz, $CDCl_3$) 195.1 (C=O), 148.0 (<u>C</u>H=C), 136.9 (CH=<u>C</u>), 134.2 (SePh), 131.3 (SePh), 129.2 (SePh), 127.5 (SePh), 78.2 ($O\underline{C}(CH_3)_2$), 74.1 (OCH), 71.3 ($O\underline{C}H_2C$=O), 60.3 (<u>C</u>HSePh), 60.3 (CH_2OH), 57.1 ($CH_3\underline{C}H_2O$), 25.4 and 23.8 ($C(\underline{C}H_3)_2$), 16.0 (<u>C</u>H_3CH_2O); LRMS (ESI^+): 407 ($[M+Na]^+$, 100%); HRMS (ESI^+) m/z: calcd for $C_{18}H_{24}O_4{}^{80}SeNa$: 407.0732 $[M+Na]^+$, found: 407.0730.

***E*- and *Z*-6-(2-Ethoxy-2-methylpropylidene)-4-(hydroxymethyl)-2H-pyran-3(6H)-one (146):**



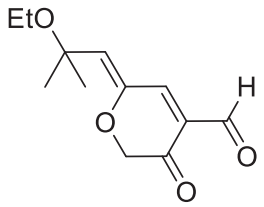
To a solution of ethoxyselenide **145** (10 mg, 26 μmol, 1 equiv) in CH_2Cl_2 (1 mL) and water (50 μL) at 0 °C, was added pyridine (4.2 μL, 52 μmol, 2 equiv.), followed by H_2O_2 (6.7 μL, 35 % in H_2O, 78 μmol, 3 equiv). After 20 min, the reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with saturated aq $NaHCO_3$ (3 x 5 mL) and brine (5mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 40% EtOAc in petroleum ether). First eluted a colourless oil, the *E*-isomer **146** (1.0 mg, 17%). Second eluted a colourless oil, the *Z*-isomer **146** (1.8 mg, 30%).

E-isomer **146**: R_f 0.5 (40% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3412 br, 2976 m, 2930 w, 1677 s, 1390 w, 1267 m, 1071 m; δ_H (500 MHz, $CDCl_3$) 8.05-8.04 (1 H, m, C<u>H</u>=C), 5.44 (1 H, s, OC=C<u>H</u>), 4.47 (2 H, s, OCH_2C=O), 4.42 (2 H, s, CH_2OH), 3.42 (2 H, q *J* 7, $CH_3C\underline{H}_2O$), 1.40 (6 H, s, $C(\underline{C}H_3)_2$), 1.19 (3 H, t *J* 7, $C\underline{H}_3CH_2O$); δ_C (125 MHz, $CDCl_3$) 193.8 (C=O), 146.8 (O<u>C</u>=CH), 134.0 (OC=<u>C</u>H), 133.3 (CH=<u>C</u>), 122.8 (<u>C</u>H=C), 74.1 ($O\underline{C}(CH_3)_2$), 71.8 ($O\underline{C}H_2C$=O), 60.2 (CH_2OH), 57.9 ($CH_3\underline{C}H_2O$), 29.4 ($C(\underline{C}H_3)_2$), 15.8 ($\underline{C}H_3CH_2O$); LRMS (ESI^+): 249 ($[M+Na]^+$, 100%); HRMS (ESI^+) m/z: calcd for $C_{12}H_{18}O_4Na$: 249.1097 $[M+Na]^+$, found: 249.1094.

Z-isomer **146**: R_f 0.4 (40% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3429 br, 2976 m, 2930 w, 1678 s, 1330 w, 1153 m, 1068 m; δ_H (500 MHz, $CDCl_3$) 6.94 (1 H, t *J* 1, C<u>H</u>=C), 5.21 (1

H, s, OC=C<u>H</u>), 4.52 (2 H, s, $OCH_2C=O$), 4.42-4.40 (2 H, m, CH_2OH), 3.44 (2 H, q *J* 7, $CH_3C\underline{H}_2O$), 1.44 (6 H, s, $C(CH_3)_2$), 1.20 (3 H, t *J* 7, $C\underline{H}_3CH_2O$); δ_C (125 MHz, $CDCl_3$) 192.7 (C=O), 146.7 (O<u>C</u>=CH), 139.3 (OC=<u>C</u>H), 132.9 (CH=<u>C</u>), 126.0 (<u>C</u>H=C), 74.1 (O<u>C</u>$(CH_3)_2$), 71.0 (O<u>C</u>$H_2C=O$), 59.6 (CH_2OH), 58.2 ($CH_3\underline{C}H_2O$), 26.6 ($C(\underline{C}H_3)_2$), 16.2 ($\underline{C}H_3CH_2O$); LRMS (ESI^+): 249 ($[M+Na]^+$, 100%), 475 ($[2M+Na]^+$, 13); HRMS (ESI^+) m/z: calcd for $C_{12}H_{18}O_4Na$: 249.1097 $[M+Na]^+$, found: 249.1093.

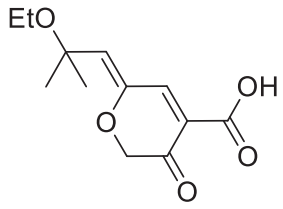
***Z*-6-(2-Ethoxy-2-methylpropylidene)-3-oxo-3,6-dihydro-2H-pyran-4-carbaldehyde (147):**



To a solution of ethoxyselenide **146** (75 mg, 0.2 mmol, 1 equiv) in CH_2Cl_2 (4 mL) at 0 °C, was added $NaHCO_3$ (67 mg, 0.8 mmol, 4 equiv.) followed by Dess-Martin periodinane (204 mg, 0.48 mmol, 2.4 equiv). After 1 h, the reaction mixture was quenched by addition of saturated aq $NaHCO_3$ (10 mL). The layers were separated and the aqueous was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with water (5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 10 % Et_2O in petroleum ether) to give a colourless oil, the ketoaldehyde **147** (15 mg, 34%): R_f 0.3 (10 % Et_2O in petroleum ether); IR (neat/cm^{-1}) 2976 w, 2360 s, 2340 m, 1688 s, 1579 m, 1274 w, 1089 w, 1068 w, 750 s; δ_H (200 MHz, $CDCl_3$) 10.13 (1 H, s, CHO), 7.55 (1 H, s, C<u>H</u>=C), 5.76 (1 H, s, OC=C<u>H</u>), 4.57 (2 H, s, $OCH_2C=O$), 3.46 (2 H, t *J* 7, $CH_3C\underline{H}_2O$), 1.47 (6 H, s, $C(CH_3)_2$), 1.20 (3 H, q *J* 7, $C\underline{H}_3CH_2O$); δ_C (125 MHz, $CDCl_3$) 190.6 and 186.1 (C=O and CHO), 147.0 (O<u>C</u>=CH), 145.3 (<u>C</u>H=C), 137.1 (OC=<u>C</u>H), 126.6 (CH=<u>C</u>), 75.4 (O<u>C</u>$(CH_3)_2$), 70.8 (O<u>C</u>$H_2C=O$), 58.6

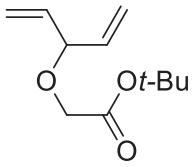
($CH_3\underline{C}H_2O$), 26.0 ($C(\underline{C}H_3)_2$), 16.1 ($\underline{C}H_3CH_2O$); LRMS (ESI^+): 246 ($[M+Na]^+$, 100%); HRMS (ESI^+) m/z: calcd for $C_{12}H_{16}O_4Na$: 247.0940 $[M+Na]^+$, found: 249.0937.

***Z*-6-(2-Ethoxy-2-methylpropylidene)-3-oxo-3,6-dihydro-2H-pyran-4-carboxylic acid (148):**



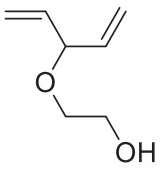
To a solution of ketoaldehyde **147** (40 mg, 0.18 mmol, 1 equiv) in pyridine (8 mL) was added CrO_3 (100 mg, 1.0 mmol, 5.5 equiv) at rt. After 12 h, the reaction mixture was filtered through Florisil®, washing through with EtOAc / AcOH (98:2, 20 mL). The filtrate was concentrated under reduced pressure and dried under *high vacuum* (~ 0.6 mBar). The residue was dissolved in EtOAc (10 mL) and washed with 2 M aq HCl (10 mL), saturated aq $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution from pure petroleum ether to 20% Et_2O in petroleum ether) to give a colourless oil, the ketoacid **148** (2 mg, 4%): R_f 0.3 (20 % Et_2O in petroleum ether); IR (neat/cm^{-1}) 2955 m, 2921 s, 2851 m, 2360 s, 2341 m, 1719 w, 1675 w, 1079 w; δ_H (500 MHz, $CDCl_3$) 7.43 (1 H, s, CH=C), 5.35 (1 H, s, OC=CH), 4.56 (2 H, s, $OCH_2C{=}O$), 3.46 (2 H, q *J* 7, $CH_3C\underline{H}_2O$), 1.45 (6 H, s, $C(CH_3)_2$), 1.20 (3 H, t *J* 7, $C\underline{H}_3CH_2O$); δ_C (125 MHz, $CDCl_3$) 190.5 (CO_2H), 147.3 ($O\underline{C}$=CH), 143.2 ($\underline{C}$H=C), 128.6 (OC=$\underline{C}$H), 124.4 (CH=$\underline{C}$), 75.0 ($O\underline{C}(CH_3)_2$), 71.3 ($O\underline{C}H_2C{=}O$), 58.4 ($CH_3\underline{C}H_2O$), 29.7 ($C(\underline{C}H_3)_2$), 16.2 ($\underline{C}H_3CH_2O$; LRMS (ESI^+) / $(ESI)^-$: dec.

***tert*-Butyl 2-(penta-1,4-dien-3-yloxy)acetate (155):**



To a solution of 1,4-divinyl carbinol (**153**) (504 mg, 6 mmol, 1 equiv) in benzene (30 mL) and NaOH (30 mL, 30 %) were added *tert*-butyl bromoacetate (**139**) (990 µL, 6.6 mmol, 1.1 equiv) and *n*-Bu_4NHSO_4 (60 mg, cat.). The reaction mixture was vigorously stirred at rt. After 10 h, the reaction mixture was diluted with brine (30 mL) and Et_2O (20 mL). The layers were separated and the aqueous was extracted with Et_2O (2 x 20 mL). The organics were combined washed with brine (30 mL), dried (Na_2SO_4) and concentrated. The residue was dried under *high vacuum* to give ether **155** (1.2 g, quant.): R_f 0.4 (10 Et_2O in petroleum ether); IR (neat/cm^{-1}) 2980 w, 1749 s, 1162 m, 1129 s; δ_H (400 MHz, $CDCl_3$) 5.82 (2 H, ddd *J* 17, 10.5, 6.5, $\underline{H}C=CH_2$), 5.31-5.22 (4 H, m, $HC=C\underline{H_2}$), 4.34-4.31 (1 H, m, OCH), 3.97 (2 H, s, $OCH_2C=O$), 1.47 (9 H, s, $OC(CH_3)_3$); δ_c (100 MHz, $CDCl_3$) 169.7 (OC=O), 136.7 ($H\underline{C}=CH_2$), 117.5 ($HC=\underline{C}H_2$), 82.1 ($O\underline{C}H_2C=O$), 81.4 ($O\underline{C}(CH_3)_3$), 65.5 (OCH), 28.1 ($OC(\underline{C}H_3)_3$); LRMS (ESI^+): 221 ($[M+Na]^+$, 100%); HRMS (ESI^+): calcd for $C_{11}H_{18}O_3Na$: 221.1148 $[M+Na]^+$, found: 221.1142.

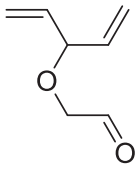
2-(Penta-1,4-dien-3-yloxy)ethan-1-ol (ES-3):



To a suspension of $LiAlH_4$ (400 mg, 10.6 mmol, 2 equiv) in Et_2O (30 mL) at 0 °C, was added ether **155** (1.05 g, 5.3 mmol, 1 equiv) in Et_2O (20 mL) over 10 min. The reaction mixture was allowed to warmed to rt. After 2 h, the reaction mixture was cooled down to 0 °C, then water

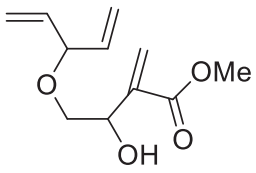
(400 µL), aq NaOH (400 µl, 4 M) and water (1.2 mL) were sequentially added. After 15 min, Na_2SO_4 was added, and the reaction mixture was stirred further 15 min. The reaction mixture was filtered and concentrated to give alcohol **ES-3** (650 mg, 96 %), which was used in the next step without further purification: R_f 0.2 (20 % Et_2O in petroleum ether); IR (neat/cm^{-1}) 3406 br, 2930 m, 2866 m, 1417 m, 1097 s, 1059 s, 991 s, 926 w; δ_H (400 MHz, $CDCl_3$) 5.77-5.68 (2 H, m, $\underline{H}C=CH_2$), 5.21-5.13 (4 H, m, $HC=C\underline{H}_2$), 4.17-4.10 (1 H, m, OCH), 3.70-3.65 (2H, m, $C\underline{H}_2OH$), 3.50-3.46 (2 H, m, $OC\underline{H}_2$), 2.19 (1 H, br. s, OH); δ_C (100 MHz, $CDCl_3$) 137.3 ($H\underline{C}=CH_2$), 116.9 ($HC=\underline{C}H_2$), 82.3 (OCH), 69.3 (OCH_2), 61.2 (CH_2OH); LRMS (ESI^+): 151 ($[M+Na]^+$, 100%); HRMS (ESI^+): calcd for $C_{17}H_{12}O_2Na$: 151.0730 $[M+Na]^+$, found: 151.0725.

2-(Penta-1,4-dien-3-yloxy)acetaldehyde (156):



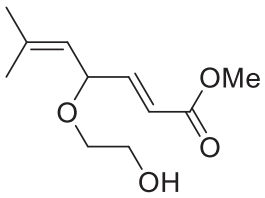
To a solution of oxalyl chloride (232 µL, 2.74 mmol, 2 equiv) in CH_2Cl_2 (4 mL) were successively added DMSO (387 µL, 5.47 mmol, 4 equiv) in CH_2Cl_2 (0.5 mL) and alcohol **ES-3** (175 mg, 1.37 mmol, 1 equiv) in CH_2Cl_2 (2 mL), at −78 °C. After 30 min. Et_3N (950 µL, 6.83 mmol, 5 equiv) was added at this temperature. After 1 h, the reaction mixture was allowed to warm to rt. After 2 h, the reaction mixture was diluted with CH_2Cl_2 (15 mL), washed with 2 M HCl (3 x 10 mL), saturated aq. $NaHCO_3$ (2 x 10 mL) and brine (15mL), dried (Na_2SO_4) and concentrated to afford crude aldehyde (155 mg, ~44%) contaminated with $MeSCH_2Cl$ **157** (~25 mol%). The unstable aldehyde **156** was used next step without purification: IR (neat/cm^{-1}) 2928 w, 1736 s, 1264 m, 1113 s, 1005 m, 934 m; δ_H (400 MHz, $CDCl_3$) 9.74 (1 H, s, CHO), 5.86-5.78 (2 H, m, $\underline{H}C=CH_2$), 5.33-5.26 (5 H, m, $HC=C\underline{H}$), 5.29-5.28 (1 H, m, OCH), 4.08 (1 H, s, $OCH_2C=O$); δ_C (100 MHz, $CDCl_3$) 201.1 (CHO), 136.4 ($\underline{H}C=CH_2$), 118.0 ($HC=C\underline{H}_2$), 82.9 (OCH), 73.5 ($O\underline{C}H_2C=O$); LRMS (ESI^+): dec.

Methyl 3-hydroxy-2-methylene-4-(penta-1,4-dien-3-yloxy)butanoate (158):



To a mixture of the above crude aldehyde **156** (155 mg, ~1.2 mmol) and methyl acrylate (335 µL, 3.6 mmol, 3 equiv) were added quinuclidine (35 mg, 0.3 mmol, 0.25 equiv) and MeOH (37 µL, 0.9 mmol, 0.75 equiv) at rt. After 12 h, the reaction mixture was directly purified by flash chromatography (SiO_2, gradient elution from pure petroleum ether to 15 % EtOAc in petroleum ether) to give adduct **158** (75 mg, 26% over 2 steps) as a yellow oil: R_f 0.25 (20 EtOAc in petroleum ether); IR (neat/cm^{-1}) 3491 br, 2953 w, 1718 s, 1632 w, 1440 m, 1291 m, 1087 s, 930 m; δ_H (400 MHz, $CDCl_3$) 6.24 (1 H, s, C=C<u>H</u>H'), 5.95 (1 H, t *J* 1.5, C=CH<u>H</u>'), 5.71 (2 H, dddd *J* 17, 10.5, 9.5, 7, <u>H</u>C=CH_2), 5.21-5.12 (4 H, m, HC=C<u>H</u>$_2$), 4.65-4.63 (1 H, m, C<u>H</u>OH), 4.18-4.15 (1H, m, OCH), 3.70 (3 H, s, CO_2CH_3), 3.62 (1 H, dd *J* 9.5, 3.5, OC<u>H</u>H'), 3.28 (1 H, dd *J* 10.0, 7.5, OCH<u>H</u>'), 2.91 (1 H, br. s, OH); δ_C (100 MHz, $CDCl_3$) 166.4 (<u>C</u>O_2CH_3), 139.1 (<u>C</u>=CH_2), 137.1 (H<u>C</u>=CH_2), 126.6 (C=<u>C</u>H_2), 117.0 (HC=<u>C</u>H_2), 82.3 (OCH), 71.6 (CHOH), 69.5 (OCH_2), 51.8 (CO_2<u>C</u>H_3); LRMS (ESI^+): 213 ($[M+H]^+$, 15%), 235 ($[M+Na]^+$, 100); HRMS (ESI^+): calcd for $C_{11}H_{16}O_4Na$: 235.0941 $[M+Na]^+$, found: 235.0936.

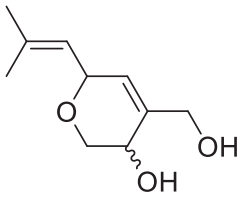
Methyl (E)-4-(2-hydroxyethoxy)-6-methylhepta-2,5-dienoate (161):



To a suspension of $LiAlH_4$ (60 mg, 1.6 mmol, 2 equiv) in Et_2O (3 mL) at 0 °C, was added a solution of ether **140** (175 mg, 0.8 mmol, 1 equiv) in Et_2O (5 mL), the reaction mixture was then allowed to warm to rt. After 1 h, the reaction mixture was cooled down to 0 °C, then water

(60 µL), aq NaOH (60 µl, 4 M) and water (180 µL) were sequentially added. After 15 min, Na_2SO_4 was added, and the reaction mixture was stirred further 15 min. The reaction mixture was filtered and concentrated to give alcohol. The residue was dissolved in CH_2Cl_2 (0.7 mL), methyl acrylate (328 µL, 3.6 mmol, 4.5 equiv) was added and the solution heated to 40 °C. A solution of **GII** (30 mg, 0.036 mmol, 5 mol%) in CH_2Cl_2 (0.7 mL) was added over 12 h using a syringe pump. Then, N_2 was flushed through the solution until the volume reached approx. 1 mL and the resulting solution directly purified by column chromatography (SiO_2, gradient elution: from pure petroleum ether to 40% EtOAc in petroleum ether) to give *E*–α–β unsaturated ester **161** (53 mg, 35%) as a colourless oil: R_f 0.3 (40% EtOAc in petroleum ether); δ_H (400 MHz, $CDCl_3$) 6.81 (1H, dd *J* 16, 5.5, C<u>H</u>=CHCO$_2$ CH$_3$), 5.98 (1H, dd *J* 16, 1.5, CH=C<u>H</u>CO$_2$CH$_3$), 5.07-5.02 (1H, m, C<u>H</u>=C(CH$_3$)$_2$), 4.68-4.64 (1H, m, OCH), 3.74-3.71 (5H, m, OCH$_3$ and C<u>H</u>$_2$OH), 3.58-3.46 (2H, m, C<u>H</u>$_2$OCH), 2.21 (1H, br s, OH), 1.75 and 1.70 (2 x 3 H, 2 x d *J* 1, 2 x CH$_3$); δ_C (400 MHz, $CDCl_3$) 166.8 (CO_2Me), 146.9 (<u>C</u>H=CHCO$_2$Me), 138.0 (CH=<u>C</u>Me$_2$), 122.4 (<u>C</u>H=C (CH$_3$)$_2$), 120.20 (CH=<u>C</u>HCO$_2$CH$_3$), 75.7 (O<u>C</u>H), 69.3 (<u>C</u>H$_2$OCH), 61.9 (<u>C</u>H$_2$OH), 51.6 (O CH$_3$), 25.6 and 18.4 (2 x CH$_3$); LRMS (ESI$^+$): 237 ([M+Na]$^+$, 65%), 451 ([2M+Na]$^+$, 100); HRMS (ESI$^+$): calcd for C_{11} $H_{18}O_4Na$: 237.1097 [M+Na]$^+$, found 237.1097.

4-(Hydroxymethyl)-6-(2-methylprop-1-en-1-yl)-3,6-dihydro-2*H*-pyran-3-ol (164):



To a vigorously stirred solution of hydroxymethyldihydropyranone **143** (770 mg, 4.23 mmol, 1 equiv) in THF (53 mL) at −78 °C, was added DIBAL-H (8.46 mL, 1.0 M in hexanes, 8.46 mmol, 2 equiv). After 10 min, saturated aq Rochelle's salt (50 mL) was added, the biphasic

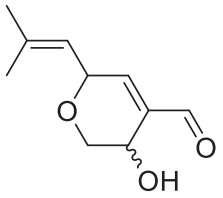
mixture was vigorously stirred and allowed to warm to rt. After 1 h, the layers were separated and the aq layer was extracted with EtOAc (5 x 50 mL). The organic layers were combined, washed with brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil, the diol **164** (750 mg, 96%). The crude diol was used in the next step without purification.

In a separate experiment using dihydropyranone **143** (480 mg, 2.64 mmol) the resulting crude diol **164** was purified by column chromatography for characterisation purposes (SiO_2, gradient elution: 50% EtOAc in petroleum ether to EtOAc) to give a 3:1 mixture (by integration of OCH δ_H signals, 4.82 and 4.69 ppm, respectively) of inseparable diastereoisomers of diol **164** (300 mg, 62 %): R_f 0.25 (75% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3363 br, 2922 m, 2854 w, 1146 w, 1377 w, 1118 m, 1082 m, 1063 s, 1030 m; LRMS (ESI^+): 207 ($[M+Na]^+$, 45%), 391 ($[2M+Na]^+$, 100); HRMS (ESI^+): calcd for $C_{10}H_{16}O_3Na$: 207.0992 $[M+Na]^+$, found 207.0993.

Discernible data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 5.64 (1H, s, C=CH), 5.18-5.16 (1H, m, $(CH_3)_2C=C\underline{H}$), 4.82 (1H, d *J* 8.5, OCH), 4.17 (3 H, br s, $C\underline{H}_2OH$ and $C\underline{H}OH$), 3.97-3.93 (2 H, m, $OC\underline{H}H'$ + $CHO\underline{H}$), 3.58-3.55 (2H, m, $CH\underline{H}'$ + $CH_2O\underline{H}$), 1.73-1.70 (6 H, m, $(C\underline{H}_3)_2C=CH$); δ_C (100 MHz, $CDCl_3$) 137.5 ($\underline{C}=CH$), 136.6 ($(CH_3)_2\underline{C}=CH$), 127.7 ($C=\underline{C}H$), 122.1 ($(CH_3)_2C=\underline{C}H$), 70.4 (OCH), 67.5 (OCH_2), 64.0 (CH_2OH), 63.4 (CHOH), 25.7 and 18.2 ($(\underline{C}H_3)_2C=CH$).

Discernible data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 5.64 (1H, s, C=CH), 5.15-5.12 (1H, m, $(CH_3)_2C=C\underline{H}$), 4.69 (1 H, d *J* 8.5, OCH), 4.17 (2 H, br s, $C\underline{H}_2OH$), 3.93-3.89 (3H, m, $C\underline{H}O\underline{H}$ + $OC\underline{H}H'$), 3.67 (1H, dd *J* 12, 2.5, $OCH\underline{H}'$), 1.73-1.70 (6 H, m, $(C\underline{H}_3)_2C=CH$); δ_C (100 MHz, $CDCl_3$) 137.6 ($\underline{C}=CH$), 136.5 ($(CH_3)_2\underline{C}=CH$), 128.3 ($C=\underline{C}H$), 123.1 ($(CH_3)_2C=\underline{C}H$), 71.5 (OCH), 70.5 (OCH_2), 64.0 (CH_2OH), 62.9 (CHOH), 25.7 and 18.2 $(CH_3)_2C=\underline{C}H$).

3-Hydroxy-6-(2-methylprop-1-en-1-yl)-3,6-dihydro-2*H*-pyran-4-carbaldehyde (165):



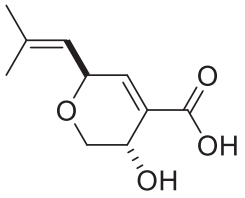
To a solution of the above crude diol **164** (750 mg, 4.08 mmol theoretical, 1 equiv) in CH_2Cl_2 (40 mL) at rt, was added TEMPO (64 mg, 0.41 mmol, 10 mol%) followed by $PhI(OAc)_2$ (1.58 g, 4.9 mmol, 1.2 equiv) at rt. After 2 h, the reaction mixture was directly purified by column chromatography (SiO_2, gradient elution: petroleum ether to 40% EtOAc in petroleum ether). First eluted a yellow oil which slowly solidified, the major diastereoisomer of hydroxyaldehyde **165mj** (320 mg, 42% over 2 steps). Second eluted a yellow oil, the minor diastereoisomer of hydroxyaldehyde **165mn** (215 mg, 28% over 2 steps).

165mj: R_f 0.4 (40% EtOAc in petroleum ether): Mp: 72-74° C. IR (neat/cm^{-1}) 3443 br, 2970 w, 2916 w, 2860 w, 1686 s, 1447 w, 1377 w, 1173 m, 1117 m, 1084 m, 1059 m; δ_H (500 MHz, $CDCl_3$) 9.49 (1H, s, CHO), 6.72 (1H, d *J* 2, C=CH), 5.20 (1H, ddq *J* 8.5, 3, 1.5, $(CH_3)_2C=C\underline{H}$), 5.09 (1H, dt *J* 8.5, 2, OCH), 4.64 (1H, br t *J* 5.5, C<u>H</u>OH), 4.11 (1H, dd *J* 11.5, 5, OC<u>H</u>H'), 3.59 (1H, dd *J* 11.5, 6.5, OCH<u>H</u>'), 3.16 (1H, br s, OH), 1.80-1.79 (6H, m, $(C\underline{H}_3)_2C=CH$); δ_C (125 MHz, $CDCl_3$) 193.5 (CHO), 151.4 (C=<u>C</u>H), 139.6 and 139.5 ($(CH_3)_2\underline{C}=CH$ and <u>C</u>=CH), 119.9 ($(CH_3)_2C=\underline{C}H$), 71.5 (OCH), 67.0 (OCH_2), 60.9 (CHOH), 25.8 and 18.6 ($(\underline{C}H_3)_2C=CH$); LRMS (ESI^+): 205 ($[M+Na]^+$, 100%), 387 ($[2M+Na]^+$, 15); HRMS $(ESI)^+$: calcd for $C_{10}H_{14}O_3Na$: 205.0835 $[M+Na]^+$, found 205.0837.

165mn: R_f 0.3 (40% EtOAc in petroleum ether): IR (neat/cm^{-1}) 3444 br, 2970 w, 2913 w, 2853 w, 1687 s, 1447 w, 1377 w, 1260w, 1177 m, 1113 m, 1082 m, 1060 m; δ_H (500 MHz, $CDCl_3$) 9.51 (1H, s, CHO), 6.72 (1H, d *J* 2, C=CH), 5.25 (1H, ddq *J* 8.5, 3, 1.5, $(CH_3)_2C=C\underline{H}$), 4.96 (1H, dt *J* 8.5, 2, OCH), 4.43 (1H, q *J* 2, C<u>H</u>OH), 4.07 (1H, dd *J* 12.5, 2, OC<u>H</u>H'), 3.71 (1H, dd

J 12.5, 2.5, OCHH'), 2.59 (1H, br s, OH), 1.80 and 1.79 (2 x 3H, 2 x d *J* 1.5, $(CH_3)_2C$=CH); δ_C (125 MHz, $CDCl_3$) 192.5 (CHO), 151.6 (C=CH), 139.3 and 139.0 ($(CH_3)_2C$=CH and C=CH), 120.6 ($(CH_3)_2C$=CH), 71.8 (OCH), 69.4 (OCH_2), 59.6 (CHOH), 25.8 and 18.5 ($(CH_3)_2C$=CH); LRMS (ESI^+): 205 ($[M+Na]^+$, 100%), 387 ($[2M+Na]^+$, 70); HRMS $(ESI)^+$: calcd for $C_{10}H_{14}O_3Na$: 205.0835 $[M+Na]^+$, found 205.0836.

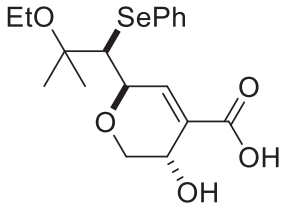
(3*S,6*S**)-3-Hydroxy-6-(2-methylprop-1-en-1-yl)-3,6-dihydro-2*H*-pyran-4-carboxylic acid (168):**



A solution of hydroxyaldehyde **165mj** (105 mg, 0.58 mmol, 1 equiv) and $AgNO_3$ (148 mg, 0.87 mmol, 1.5 equiv) in EtOH / H_2O (1:1, 10 mL) was heated to 40 °C. A solution of NaOH (140 mg, 3.5 mmol, 6 equiv) in H_2O (10 mL) was added over 90 min *via* syringe pump. Following addition, the reaction mixture was stirred for 1 h at 40 °C, then cooled to rt. The reaction mixture was filtered, then acidified to pH 2-3 using aq HCl (1 M) and extracted with EtOAc (5 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a brown oil, the carboxylic acid **168** (130 mg, quant.) which was used in the next step without further purification: R_f 0.4 (30% EtOAc / 1% AcOH in petroleum ether); IR (neat/cm^{-1}) 3450 br, 2974 w, 2917 m, 2361 w, 1711 s, 1446 s, 1376 s,1227 m, 1083 m; δ_H (500 MHz, $CDCl_3$) 7.02 (1H, d *J* 2.5, C=CH), 5.21 (1H, dt *J* 8.5, 1.5, $(CH_3)_2C$=CH), 5.03 (1H, d *J* 8.5, OCH), 4.52-4.50 (1H, m, CHOH), 4.07 (1H, dd *J* 12, 4.5, OCHH′), 3.69 (1H, dd *J* 12, 5.5, OCHH′), 1.78-1.77 (6 H, m, $(CH_3)_2C$=CH); δ_C (125 MHz, $CDCl_3$) 170.4 (CO_2H), 145.0 (C=CH), 139.4 ($(CH_3)_2C$=CH), 129.2 (C=CH), 119.7 ($(CH_3)_2C$=CH), 70.9 (OCH), 66.7 (OCH_2), 61.3 (CHOH), 25.8 and 18.5 ($(CH_3)_2C$=CH); LRMS (ESI^+): 221 ($[M+Na]^+$, 100%),

(ESI$^-$): 197 ([M-H]$^-$, 100); HRMS (ESI$^+$): calcd for $C_{10}H_{14}O_4Na$: 221.0784 [M+Na]$^+$, found 221.0783.

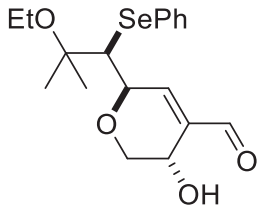
(3*S,6*R**)-6-((*S**)-2-Ethoxy-2-methyl-1-(phenylselanyl)propyl)-3-hydroxy-3,6-dihydro-2*H*-pyran-4-carboxylic acid (169):**



To a solution of carboxylic acid **168** (60 mg, 0.3 mmol, 1 equiv.) in EtOH (12 mL) at 0 °C, was added K_2CO_3 (83 mg, 0.6 mmol, 2 equiv) followed by a solution of PhSeBr (142 mg, 0.6 mmol, 2 equiv.) in CH_2Cl_2 (3 mL). The reaction mixture was allowed to warm to rt over 3 h. After 12 h at rt, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in water (10 mL), acidified to pH 2-3 using 1 M aq HCl and extracted with EtOAc (5 x 10 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified using a short chromatographic column (SiO_2, gradient elution: petroleum ether to 30% EtOAc / 0.6% AcOH in petroleum ether) to give a colourless oil, the ethoxyselenide **169** (30 mg, 25%): R_f 0.5 (30% EtOAc / 1% AcOH in petroleum ether); IR (neat/cm^{-1}) 3460 br, 2974 m, 2928 m, 2870 w, 2360 s, 2341 m, 1696 s, 1477 m, 1236 m, 1067 s, 739 s, 691 m; δ_H (500 MHz, $CDCl_3$) 7.63-7.56 (2H, m, SePh), 7.29-7.24 (3H, m, SePh), 7.16 (1H, s, C=CH), 5.01 (1H, br s, OCH), 4.72-4.70 (1H, m, C<u>H</u>OH), 4.25 (1H, dd *J* 11, 6, OC<u>H</u>H′CHOH), 3.47-3.32 (3H, m, $CH_3C\underline{H}_2O$ and OCH<u>H</u>′CHOH), 3.25-3.24 (1H, m, SeCH), 1.41 and 1.29 (2 x 3H, 2 x s, $C(CH_3)_2$), and 1.14 (3H, t *J* 7, $C\underline{H}_3CH_2O$); δ_C (125 MHz, $CDCl_3$) 170.1 (CO_2H), 146.5 (C=<u>C</u>H), 134.4, 131.5, 131.4 and 129.1 (SePh), 127.5 (<u>C</u>=CH), 78.3 (O<u>C</u>$(CH_3)_2$), 74.6 (OCH), 68.0 (O<u>C</u>H_2CHOH), 61.8 (CHOH), 60.6 ($CH_3\underline{C}H_2O$), 57.1 (SeCH), 25.3 and 23.6 (C(<u>C</u>$H_3)_2$) and 15.9 (<u>C</u>H_3CH_2O); LRMS (ESI$^+$): 423

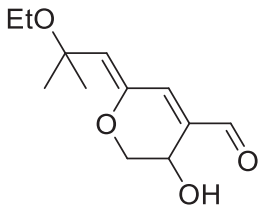
([M+Na]$^+$, 100 %), (ESI$^-$): 399 ([M-H]$^-$, 100); HRMS (ESI$^-$) m/z: calcd for $C_{18}H_{23}O_5{}^{80}Se$: 399.0716 [M–H]$^-$, found 399.0711.

(3*S,6*R**)-6-((*S**)-2-Ethoxy-2-methyl-1-(phenylselanyl)propyl)-3-hydroxy-3,6-dihydro-2*H*-pyran-4-carbaldehyde (170):**



To a solution of hydroxyaldehyde **165mj** (20 mg, 0.11 mmol, 1 equiv) in EtOH (4 mL) at 0 °C, was added Et_3N (17 µL, 0.12 mmol, 1.1 equiv), followed by a solution of PhSeBr (28 mg, 0.12 mmol, 1.1 equiv) in CH_2Cl_2 (1.5 mL). After 2 h, CH_2Cl_2 (10 mL) and aq HCl (10 mL, 1 M) were added and the biphasic mixture was stirred for 25 min at rt. The layers were then separated and the aqueous was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 20% Et_2O in petroleum ether) to give an orange oil, the ethoxyselenide **170** (35 mg, 83%): R_f 0.3 (30% Et_2O in petroleum ether); IR (neat/cm^{-1}) 3525 br, 2974 s, 2924 m, 2874 m, 1676 s, 1117 m, 1064 s, 743 w; δ_H (500 MHz, $CDCl_3$) 9.41 (1H, s, CHO), 7.53 (2H, s, SePh), 7.27-7.26 (3H, m, SePh), 6.84 (1H, s, C=CH), 5.05 (1H, q *J* 2, OCH), 4.80 (1H, ddt *J* 10, 5.5, 2, C<u>H</u>OH), 4.24 (1H, dd *J* 11, 6, OC<u>H</u>H′), 3.59 (1H, d *J* 1.5, OH), 3.52-3.35 (3H, m, OCH<u>H</u>′ and $CH_3C\underline{H}_2O$), 3.32 (1H, d *J* 2, C<u>H</u>SePh), 1.43 and 1.32 (6 H, s, $(CH_3)_2C$), 1.14 (3H, t *J* 7.0, $C\underline{H}_3CH_2O$); δ_C (125 MHz, $CDCl_3$) 193.8 (CHO), 152.9 (C=<u>C</u>H), 141.0 (C=CH), 134.0, 131.3, 129.2 and 127.5 (SePh), 78.0 ($CH_3CH_2O\underline{C}$), 75.4 (OCH), 67.8 (OCH_2), 61.8 (CHOH), 60.3 (CHSePh), 57.2 ($CH_3\underline{C}H_2O$), 25.3 and 23.8 ($(\underline{C}H_3)_2C$), 16.0 ($\underline{C}H_3CH_2O$); LRMS: dec.

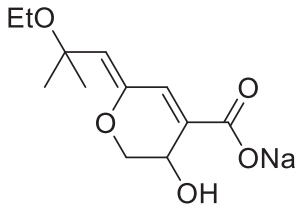
(*Z*)-6-(2-Ethoxy-2-methylpropylidene)-3-hydroxy-3,6-dihydro-2*H*-pyran-4-carbaldehyde (*Z*-171):



To a solution of aldehyde **165mj** (30 mg, 0.16 mmol, 1 equiv) in EtOH (7 mL) at 0 °C, was added Et_3N (26 μL, 0.18 mmol, 1.1 equiv) followed by a solution of PhSeBr (42 mg, 0.18 mmol, 1.1 equiv) in CH_2Cl_2 (2 mL). After 2 h, CH_2Cl_2 (15 mL) and aq HCl (15 mL, 1 M) were added and the biphasic mixture was stirred for 25 min at rt. The layers were then separated and the aqueous was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue (65 mg) was dissolved in MeOH (3 mL) and H_2O (1.5 mL) at 0 °C, then $NaIO_4$ (73 mg, 0.32 mmol, 2 equiv) and $NaHCO_3$ (27 mg, 0.32 mmol, 2 equiv) were added. The reaction mixture was slowly allowed to warm to rt. After 15 h, saturated aq $NaHCO_3$ (10 mL) was added and the aq layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 40% EtOAc in petroleum ether) to give a colorless oil, the *Z*-enol ether **171** (15 mg, 40%): R_f 0.3 (30% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3420 br, 2975 w, 2360 s, 2341 s, 1683 m, 1159 w, 1068 w, 669 m, 652 s; δ_H (400 MHz, $CDCl_3$) 9.51 (1H, s, CHO), 6.77 (1H, s, C=CH), 5.25 (1H, s, OC=CH), 4.64 (1H, t *J* 3.5, C<u>H</u>OH), 4.14 (1H, dd *J* 12, 3.5, OC<u>H</u>H′), 3.94 (1H, dd *J* 12, 3.5, OCH<u>H</u>′), 3.43 (1H, q *J* 7.0, $CH_3C\underline{H}_2O$), 1.44 (6 H, s, $(CH_3)_2C$), 1.17 (3H, t *J* 7, $C\underline{H}_3CH_2O$); δ_C (100 MHz, $CDCl_3$) 191.8 (CHO), 147.5 (O<u>C</u>=CH), 142.3 (C=<u>C</u>H), 135.5 (<u>C</u>=CH), 128.4 (OC=<u>C</u>H), 75.1

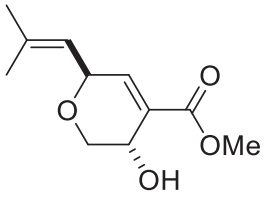
($CH_3CH_2O\underline{C}$), 69.9 (OCH_2), 59.4 (CHOH), 58.2 ($CH_3\underline{C}H_2O$), 26.4 and 26.3 ($(\underline{C}H_3)_2C$), 16.1 ($\underline{C}H_3CH_2O$); LRMS (ESI^+): 249 ($[M+Na]^+$,100%); HRMS (ESI^+): calcd for $C_{12}H_{18}O_4Na$: 249.1097 $[M+Na]^+$, found 249.1098.

Sodium 6-(2-ethoxy-2-methylpropylidene)-3-hydroxy-3,6-dihydro-2*H*-pyran-4-carboxylate (*Z*-173):



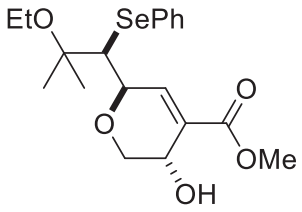
To a solution of $AgNO_3$ (5.6 mg, 0.033 mmol, 1.5 equiv) in H_2O (680 µL), was added NaOH (2 mg, 0.044 mmol, 2 equiv) in H_2O (120 µL). The reaction mixture was stirred for 5 min, then decanted. The supernatant was removed by syringe, and the solid was washed with H_2O (3 x 800 µL). H_2O (360 µL) and enol ether **171** (5 mg, 0.022 mmol, 1 equiv) in EtOH (200 µL) were added to the solid residue, followed by NaOH (4.0 mg, 0.088 mmol, 4 equiv) in H_2O (240 µL). After 3.5 h, the reaction mixture was diluted with EtOH (2 mL), filtered and concentrated to give the crude sodium carboxylate *Z*-**173** (10 mg, quant): IR (neat/cm^{-1}) 3430 br, 2480 br, 2360 s, 2341 m, 1620 s, 1422 m, 1337 w, 1119 w, 823 w, 669 w; δ_H (500 MHz, CD_3OD) 6.71 (1H, s, C=CH), 4.84 (1H, s, OC=CH), 4.52 (1H, t *J* 3.5, CHOD), 4.00 (1H, dd *J* 11, 3.5, $C\underline{H}H'$), 3.91 (1H, dd *J* 11, 3.5, $CH\underline{H}'$), 3.46 (2H, q *J* 7, $CH_3C\underline{H}_2O$), 1.41 (6 H, s, $(CH_3)_2C$), 1.14 (3H, t *J* 7, $C\underline{H}_3CH_2O$); δ_c (125 MHz, CD_3OD) 173.9 (CO_2Na), 150.7 ($O\underline{C}$=CH), 135.6 ($\underline{C}$=CH), 130.9 (C=$\underline{C}$H), 119.9 (OC=$\underline{C}$H), 76.7 ($CH_3CH_2O\underline{C}$), 71.7 (OCH_2), 63.5 (CHOD), 59.4 ($CH_3\underline{C}H_2O$), 27.7 ($(\underline{C}H_3)_2C$), 16.6 ($\underline{C}H_3CH_2O$); LRMS (ESI^+): 265 ($[M+H]^+$, 100%), (ESI^-): 241 ($[M-Na]^-$, 100); HRMS (ESI^-): calcd for $C_{12}H_{17}O_5$: 241.1082 $[M-Na]^-$, found 241.1083.

Methyl (3*S,6*S**) 3-hydroxy-6-(2-methylprop-1-en-1-yl)-3,6-dihydro-2*H*-pyran-4-carboxylate (ES-4):**



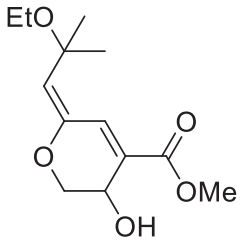
To a solution of a portion of the above crude carboxylic acid **168** (60 mg, 0.30 mmol, 1 equiv) in toluene (2.7 mL) and MeOH (0.6 mL) at 0 °C was added $TMSCHN_2$ (0.18 mL, 2.0 M in Et_2O, 0.36mmol, 1.2 equiv). After 10 min, the reaction mixture was allowed to warm to rt. After 1 h, the reaction mixture was quenched by addition of AcOH (~0.1 mL, until N_2 formation ceased) and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 30% EtOAc in petroleum ether) to give a yellow oil, the hydroxy ester **ES-4** (20 mg, 31%): R_f 0.3 (30% EtOAc in petroleum ether); IR (neat/cm^{-1}) 2979 s, 2930 m, 1722 s, 1438 m, 1379 w, 1256 s, 1092 s, 969 w; δ_H (500 MHz, $CDCl_3$) 6.87 (1H, d *J* 2.5, C=CH), 5.19 (1H, ddt *J* 8.5, 2.5, 1.5, $(CH_3)_2C=C\underline{H}$), 4.98 (1H, br d *J* 8.5, OCH), 4.51 (1H, br s, C<u>H</u>OH), 4.07 (1H, dd *J* 12, 4.5, OC<u>H</u>H′), 3.81 (3H, s, CO_2CH_3), 3.63 (1H, dd *J* 12, 6, OCH<u>H</u>′), 3.16 (1H, d *J* 3.5, OH), 1.77 and 1.76 (2 x 3 H, 2 x s, $(C\underline{H}_3)_2C=CH$); δ_C (125 MHz, $CDCl_3$) 166.4 ($\underline{C}O_2CH_3$), 142.5 (C=<u>C</u>H), 138.8 ($(CH_3)_2\underline{C}=CH$), 129.8 (<u>C</u>=CH), 120.3 ($(CH_3)_2C=\underline{C}H$), 70.9 (OCH), 66.9 (OCH_2), 61.5 (CHOH), 52.0 ($CO_2\underline{C}H_3$) 25.8 and 18.4 ($(\underline{C}H_3)_2C=CH$)); LRMS (ESI^+): 235 ($[M+Na]^+$, 100%); HRMS (ESI^+): calcd for $C_{11}H_{16}O_4Na$: 235.0940 $[M+Na]^+$, found 235.0942.

Methyl (3*S,6*R**)-6-((*S**)-2-ethoxy-2-methyl-1-(phenylselanyl)propyl)-3-hydroxy-3,6-dihydro-2*H*-pyran-4-carboxylate (ES-5):**



To a solution hydroxy ester **ES-4** (10 mg, 47 μmol, 1 equiv) in EtOH (2 mL) at 0 °C, was added Et_3N (11 μL, 75 μmol, 1.5 equiv) followed by a solution of PhSeBr (18 mg, 75 μmol, 1.5 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C. After 1 h, the reaction mixture was quenched by addition of saturated aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 3 mL). The organic layers were combined, washed with saturated aq $NaHCO_3$ (5 mL), brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 20% EtOAc in petroleum ether) to give a brown oil, the selenide **ES-5** (18 mg, 92%): R_f 0.5 (30% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3744 w, 2361 s, 2341 s, 1717 w, 679 m; δ_H (500 MHz, $CDCl_3$) 7.56-7.54 (2H, m, SePh), 7.26-7.23 (3H, m, SePh), 6.97 (1H, t *J* 1.5, C=CH), 4.96-4.95 (1H, m, OCH), 4.71-4.68 (1H, m, C<u>H</u>OH), 4.24 (1H, dd *J* 11, 6, OC<u>H</u>H′), 3.81 (3H, s, CO_2CH_3), 3.67 (1H, d *J* 2, CHO<u>H</u>), 3.44-3.31 (3H, m, $CH_3C\underline{H}_2O$ and OCH<u>H</u>′), 3.24 (1H, d *J* 1.5, SeCH), 1.41 and 1.30 (2 x 3H, 2 x s, $(CH_3)_2C$), and 1.13 (3H, t *J* 7, $C\underline{H}_3CH_2O$); δ_C (125 MHz, $CDCl_3$) 166.4 ($\underline{C}O_2CH_3$), 143.8 (C=<u>C</u>H), 134.3, 131.6, 131.5 and 129.0 (SePh), 127.3 (<u>C</u>=CH), 78.2 ($CH_3CH_2O\underline{C}$), 74.5 (OCH), 68.1 (OCH_2), 61.9 (CHOH), 60.6 (SeCH), 57.0 ($CH_3\underline{C}H_2O$), 51.9 ($C(O_2\underline{C}H_3)$, 25.3 and 23.8 ($(\underline{C}H_3)_2C$) and 15.9 ($\underline{C}H_3CH_2O$); LRMS (ESI^+): 437 ($[M+Na]^+$, 100%); HRMS (ESI^+): calcd for $C_{19}H_{26}O_5{}^{80}SeNa$: 437.0838 $[M+Na]^+$, found 437.0837.

Methyl (*E*)-6-(2-ethoxy-2-methylpropylidene)-3-hydroxy-3,6-dihydro-2*H*-pyran-4-carboxylate (175):

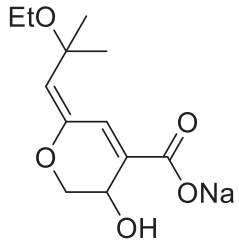


To a solution of selenide **ES-5** (9.0 mg, 22 μmol, 1 equiv) in CH_2Cl_2 (1 mL) and H_2O (50 μL) at 0 °C were added pyridine (3.6 μL, 44 μmol, 2 equiv) and H_2O_2 (5.7 μL, 35% aq solution, 66 μmol, 3 equiv). After 2 h, the reaction mixture was diluted with CH_2Cl_2 (5mL) and the organic layer was washed with saturated aq $NaHCO_3$ (3 x 5 mL) and brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 40% EtOAc in petroleum ether) to give a 76:24 (by integration of C=CH δ_H signals, 8.03 and 7.04 ppm, respectively) mixture of *E* / *Z* enol ether **175** (3.0 mg, 54%), which isomerizes to the *Z*-isomer over time: R_f 0.3 (30% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3463 br, 2975 m, 2927 m, 2873 w, 1715 s, 1633 w, 1604 m, 1438 m, 1242 s, 1221 s, 1150 m, 1098 s, 1066 s, 1009 m; LRMS (ESI^+): 211 ($[M\text{-}EtO]^+$, 85%), 279 ($[M+Na]^+$, 100), 535 ($[2M+Na]^+$, 65). HRMS (ESI^+): calcd for $C_{13}H_{20}O_5Na$: 279.1203, found 279.1204.

Data for *E*-**175**: δ_H (500 MHz, CD_3OD) 8.03 (1H, s, C=CH), 5.30 (1H, s, OC=CH), 4.48-4.47 (1H, m, C<u>H</u>OD), 4.10 (1H, dd *J* 12, 1.5, OC<u>H</u>H′), 3.85-3.84 (1H, m, OCH<u>H</u>′), 3.81 (3H, s, CO_2CH_3), 3.41 (1H, qd *J* 7.0, $CH_3C\underline{H}_2O$), 1.36 (6 H, s, $(CH_3)_2C$), 1.15 (3H, t *J* 7.0, $C\underline{H}_3CH_2O$); δ_C (125 MHz, CD_3OD) 167.8 ($\underline{C}O_2CH_3$), 149.4 (O<u>C</u>=CH), 131.6 (C=<u>C</u>H), 129.3 (<u>C</u>=CH), 122.3 (OC=<u>C</u>H), 75.6 ($CH_3CH_2O\underline{C}$), 72.4 (OCH_2), 62.1 (CHOD), 59.0 ($CH_3\underline{C}H_2O$), 52.7 ($CO_2\underline{C}H_3$) 30.1 (($\underline{C}H_3)_2C$), 16.1 ($\underline{C}H_3CH_2O$).

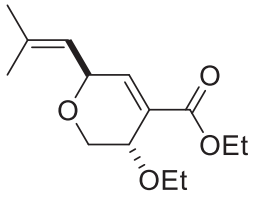
Discernible data for *Z*-**175**: δ_H (500 MHz, CD_3OD) 7.04 (1H, s, C=CH), 5.10 (1H, s, OC=CH), 4.50 (1H, t *J* 2, CHOD), 4.21 (1H, dd *J* 12, 1.5, OCHH'), 3.80 (1H, s, OCH_3), 3.47 (1H, qd *J* 7, 1.5, OCH_2CH_3), 1.43 and 1.42 (2 x 3H, 2 x s, $(CH_3)_2C$); δ_C (125 MHz, CD_3OD) 136.4 (C=<u>C</u>H), 128.5 (<u>C</u>=CH), 124.9 (OC=<u>C</u>H), 76.7 ($CH_3CH_2O\underline{C}$), 61.5 (CHOD), 59.5 ($CH_3\underline{C}H_2O$), 27.3 (($\underline{C}H_3)_2C$).

Sodium (*E*)-6-(2-ethoxy-2-methylpropylidene)-3-hydroxy-3,6-dihydro-2*H*-pyran-4-carboxylate (*E*-173):



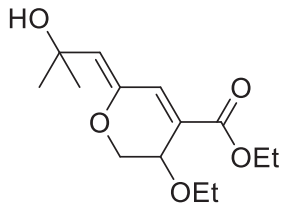
To a solution of enol ether **175** (3.0 mg, 12 μmol, 1 equiv) in THF (0.4 mL) and EtOH (0.4 mL) was added NaOH (1.4 mg, 36 μmol, 3 equiv) in H_2O (0.2 mL) at 0 °C. After 3 h, the reaction mixture was warmed up to rt. After 12 h, the reaction mixture was concentrated under reduced pressure to give crude sodium carboxylate **173** (5 mg, quant.) as a 85:15 mixture of *E* : *Z*-**173** (by integration of C=CH δ_H signals, 7.62 and 6.72 ppm, respectively): IR (neat/cm^{-1}) 3427 br, 2980 m, 2361 w, 2078 w, 1623 s, 1572 m, 1399 s, 1116 m, 823 m; LRMS (ESI^+): 265 ($[M+H]^+$, 100%), (ESI^-): 241 ($[M-Na]^-$, 100); HRMS (ESI^-): calcd for $C_{12}H_{17}O_5$: 241.1082, found 241.1080. Data for *E*-**173**: δ_H (500 MHz, CD_3OD) 7.62 (1H, s, C=CH), 5.10 (1H, s, OC=CH), 4.51-4.49 (1H, m, C<u>H</u>OD), 3.90-3.89 (2H, m, CHH′), 3.43-3.38 (3H, m, $CH_3C\underline{H}_2O$), 1.38 and 1.36 (2 x 3H, 2 x s, $(CH_3)_2$), 1.15 (3H, t *J* 7, $C\underline{H}_3CH_2O$); δ_c (125 MHz, CD_3OD) 174.2 (CO_2Na), 150.9 (O<u>C</u>=CH), 136.7 (<u>C</u>=CH), 125.9 (C=<u>C</u>H), 118.4 (OC=CH), 75.4 ($CH_3CH_2O\underline{C}$), 71.6 (OCH_2), 64.1 (CHOD), 58.4 ($CH_3\underline{C}H_2O$), 30.1 and 30.0 ($(CH_3)_2$), 16.4 ($\underline{C}H_3CH_2O$).

Ethyl (3*S,6*S**)-3-ethoxy-6-(2-methylprop-1-en-1-yl)-3,6-dihydro-2H-pyran-4-carboxylate (180):**



In a glass vial shielded from light, a solution of hydroxyaldehyde **165mj** (30 mg, 0.16 mmol, 1 equiv) in EtI (3 mL, 37 mmol, 231 equiv) was added Ag_2O (250 mg, 0.96 mmol, 6 equiv). The reaction mixture was heated to 60 °C for 53 h, 4 Å MS (100 mg) was added after 5 h. The reaction mixture was then filtered and concentrated. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 15% Et_2O in petroleum ether) to give ethyl ester **180** (22 mg, 50%); R_f 0.4 (25% Et_2O in petroleum ether); IR (neat/cm^{-1}) 2975 m, 2930 w, 2873 w, 1718 s, 1447 w, 1375 w, 1251 s, 1093 s; δ_H (500 MHz, $CDCl_3$) 6.89 (1H, d *J* 3, CH=C), 5.27-5.25 (1H, m, C<u>H</u>=C$(CH_3)_2$), 5.05 (1H, dd *J* 9, 3, OCH), 4.28-4.21 (2H, m, $CO_2C\underline{H}_2CH_3$), 4.08 (1H, t *J* 2.5, C<u>H</u>OEt), 3.88 (1H, dd *J* 12.5, 3, OC<u>H</u>H′CHOEt), 3.82 (1H, dd *J* 12.5, 3, OCH<u>H</u>′CHOEt), 3.73-3.63 (3H, m, CHOC<u>H</u>$_2$CH$_3$), 1.76 (6H, br s, C$(CH_3)_2$), 1.32 (3H, t *J* 7.5, $CO_2CH_2C\underline{H}_3$), 1.23 (3H, t J 7.5, $CHOCH_2C\underline{H}_3$); δ_c (125 MHz, $CDCl_3$) 165.7 (<u>C</u>$O_2CH_2CH_3$), 142.4 (<u>C</u>H=C), 138.6 (<u>C</u>$(CH_3)_2$), 128.4 (CH=<u>C</u>), 119.8 (<u>C</u>H=C$(CH_3)_2$), 69.5 (OCH), 68.0 ($OCH_2\underline{C}HOEt$), 65.6 ($CHO\underline{C}H_2CH_3$), 63.7 ($O\underline{C}H_2CHOEt$), 60.7 ($CO_2\underline{C}H_2CH_3$), 25.9 and 18.4 (C($\underline{C}H_3)_2$), 15.6 ($CHOCH_2\underline{C}H_3$) and 14.2 ($CO_2CH_2\underline{C}H_3$); LRMS (ESI^+): 209 ($[M\text{-}EtO]^+$, 50%), 277 ($[M+Na]^+$, 100), 531 ($[2M+Na]^+$, 60); HRMS (ESI^+) m/z: calcd for $C_{14}H_{22}O_4Na$: 277.1410 $[M+Na]^+$, found 277.1411.

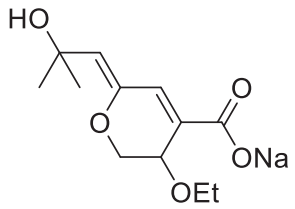
Ethyl (*Z*)-3-ethoxy-6-(2-hydroxy-2-methylpropylidene)-3,6-dihydro-2H-pyran-4-carboxylate (182):



To a solution of diethyl ether ester **180** (13 mg, 0.051 mmol, 1 equiv) in CH_3CN / H_2O (5:1, 5.5 mL) at rt was added PhSeBr (18 mg, 0.077 mmol, 1.5 equiv). After 15 h, the reaction mixture was quenched by addition of saturated aq $NaHCO_3$ (5 mL) and the aq layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 30% EtOAc in petroleum ether) to give a yellow oil, hydroxyselenide **181** (17 mg, 80%): δ_H (400 MHz, CDCl3). 7.54-7.51 (2H, m, SePh), 7.25-7.23 (3H, m, SePh), 6.51 (1H, d *J* 1.5, CH=C), 5.06-5.01 (1H, m, OCH), 4.41-4.36 (2H, m, OC<u>H</u>H′C<u>H</u>OEt), 4.21 (2H, q *J* 7, $CO_2C\underline{H}_2CH_3$), 3.73-3.67 (3H, m, OCH<u>H</u>′CHOC<u>H</u>$_2CH_3$), 3.15 (1H, d *J* 2, C<u>H</u>SePh), 3.13 (1H, s, OH), 1.55 and 1.48 (2 x 3H, 2 s, $C(CH_3)_2$) and 1.29-1.19 (6H, m, $CO_2CH_2C\underline{H}_3$ and $CHOCH_2C\underline{H}_3$); LRMS (ESI^+): 451 ($[M+Na]^+$, 100%); HRMS (ESI^+): calcd for $C_{20}H_{28}O_5{}^{80}SeNa$: 451.0994, found 451.0994. The resulting oil was dissolved in CH_2Cl_2 (7.5 mL) and H_2O (0.375 mL) at 0 °C, then pyridine (10.3 µL, 0.14 mmol, 2 equiv) and H_2O_2 (18 µL, 35 % in H_2O, 0.21 mmol, 3 equiv.) were added. After 3 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was washed with saturated aq $NaHCO_3$ (3 x 20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 30% EtOAc in petroleum ether) to give a colorless oil, enol ether **182** (7 mg, 51% over two steps): R_f 0.3 (30% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3658

w, 2980 s, 2889 m, 1741 w, 1382 m, 1152 m, 1074 w, 955 m; δ_H (500 MHz, $CDCl_3$) 6.99 (1H, s, CH=C), 5.18 (1H, s, OC=CH), 4.46 (1H, dd *J* 12, 1, OCHH'CHOEt), 4.31-4.23 (3H, m, CHOEt and $CO_2CH_2CH_3$), 3.85 (1H, dd *J* 12, 2, OCHH'CHOEt), 3.74-3.60 (3H, m, $CHOCH_2CH_3$ and COH), 1.41 and 1.40 (2 x 3H, 2 s, $C(CH_3)_2$), 1.33 (3H, t *J* 7, $CO_2CH_2CH_3$) and 1.24 (3H, t *J* 7.5, $CHOCH_2CH_3$); δ_c (125 MHz, $CDCl_3$) 165.4 ($CO_2CH_2CH_3$), 146.6 (OC=CH), 134.9 (CH=C), 126.0 (OC=CH), 125.4 (CH=C), 70.6 (COH), 68.5 (OCH_2CHOEt), 67.3 (CHOEt), 65.3 ($CHOCH_2CH_3$), 60.9 ($CO_2CH_2CH_3$), 30.2 and 30.1 ($C(CH_3)_2$) 15.5 ($CHOCH_2CH_3$) and 14.2 ($CO_2CH_2CH_3$); LRMS (ESI^+): 253 ($[M\text{-}OH]^+$, 95 %), 293 ($[M+Na]^+$, 100), 563 ($[2M+Na]^+$, 20); HRMS (ESI^+) m/z: calcd for $C_{14}H_{22}O_5Na$: 293.1359 $[M+Na]^+$, found 293.1360.

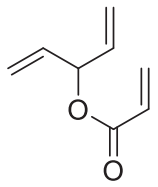
Sodium (*Z*)-3-ethoxy-6-(2-hydroxy-2-methylpropylidene)-3,6-dihydro-2H-pyran-4-carboxylate (183):



To a solution of enol ether **182** (8 mg, 0.03 mmol, 1 equiv) in THF (0.4 mL) and EtOH (0.4 mL) at 0 °C was added NaOH (3.6 mg, 0.09 mmol, 3 equiv) in H_2O (0.2 mL). After 3 h, the reaction mixture was allowed to warm to rt. After 12 h, the reaction mixture was concentrated under reduced pressure and dried under *high vacuum* (~ 0.6 mBar) to give a sticky brown solid, crude sodium carboxylate **183** (12 mg, quant.); IR (neat/cm^{-1}) 3399 br, 2974 w, 2362 w, 1621 s, 1570 m, 1401 m, 1348 m, 1117 m, 1103 m, 824 w; δ_H (500 MHz, CD_3OD) 6.74 (1H, s, CH=C), 5.00 (1H, s, OC=CH), 4.39-4.37 (2H, m, OCHH'CHOEt and CHOEt), 3.76 (1H, dd *J* 12, 2.5, OCHH'CHOEt), 3.71-3.64 (2H, m, $CHOCH_2CH_3$), 1.42 and 1.41 (2 x 3H, 2 s, $C(CH_3)_2$) and 1.18 (3H, t *J* 7, $CHOCH_2CH_3$); δ_c (125 MHz, CD_3OD) 174.0 (CO_2Na), 148.8 (OC=CH),

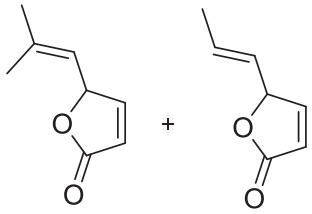
133.9 (CH=C), 131.9 (CH=C), 123.2 (OC=CH), 71.6 (COD), 70.2 (CHOEt), 69.8 (OCH_2CHOEt), 65.8 ($CHOCH_2CH_3$), 30.2 and 30.2 ($C(CH_3)_2$) and 16.0 ($CHOCH_2CH_3$); LRMS (ESI^+): 265 ($[M+H]^+$, 100%), (ESI^-): 241 ($[M-Na]^-$, 100); HRMS (ESI^-) m/z: calcd for $C_{12}H_{17}O_5$: 241.1082 $[M-Na]^-$, found 241.1081.

Penta-1,4-dien-3-yl acrylate 215:



To a solution of acrolein (370 µl, 5.5 mmol, 1.1 equiv) in Et_2O (50 mL) at 0 °C, was added vinylmagnesium bromide (5.0 mL, 1.0 M in THF, 1 equiv). After 20 min, acryloyl chloride (490 µL, 6 mmol, 1.2 equiv) was added. After 30 min, the reaction mixture was quenched by addition of saturated aq $NaHCO_3$ (50 mL), the layers were separated and the aq layer was extracted with Et_2O (2 x 50 mL). The organic layers were combined, washed with saturated aq $NaHCO_3$ (2 x 50 mL) and brine (50 mL), dried and concentrated under reduced pressure (200 mBar). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 4% Et_2O in petroleum ether) to give a volatile colourless liquid, triene **215** (600 mg, 87%): R_f 0.5 (4% Et_2O in petroleum ether); IR (neat/cm^{-1}) dec. ; δ_H (400 MHz, $CDCl_3$) 6.46 (1H, dd *J* 17.5, 1.5, C(=O)CH=C$H_{cis}H_{trans}$), 6.17 (1H, dd *J* 17.5, 10.5, C(=O)CH), 5.92-5.84 (3 H, m, OCH($CH=CH_2$)$_2$ and C(=O)CH=$CH_{cis}H_{trans}$), 5.80 (1H, ddt *J* 7.5, 6, 1, OCH), 5.26 (2 H, dt *J* 17, 1, OCH(CH=C$H_{cis}H_{trans}$)$_2$), 5.18 (2H, dt *J* 10.5, 1, OCH(CH=$CH_{cis}H_{trans}$)$_2$); δ_c (100 MHz, $CDCl_3$) 165.1 (OC=O), 134.9 (OCH(CH=CH_2)$_2$), 131.0 (C(=O)CH=CH_2), 128.5 (C(=O)CH=CH_2), 117.6 (OCH(CH=CH_2)$_2$), 75.1 (OCH); LRMS (ESI^+): dec.

5-(2-Methylprop-1-en-1-yl)furan-2(5H)-one 216 and (*E*)-5-(prop-1-en-1-yl)furan-2(5*H*)-one 217:



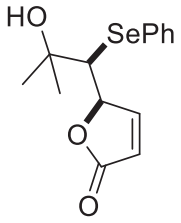
To a solution of triene **215** (600 mg, 4.3 mmol, 1 equiv) in CH_2Cl_2 (150 mL) and 2-methyl-2-butene (11 mL, 104 mmol, 24 equiv) at rt was added Grubbs II (183 mg, 0.22 mmol, 5 mol%). After 72 h, activated charcoal (9 g) was added. After a further 24 h, the reaction mixture was filtered through Celite®, and the filter cake was washed with Et_2O (150 mL). The filtrate was concentrated under reduce pressure (200 mBar) and the residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 30% Et_2O in petroleum ether) to give an orange-brown oil, a mixture of lactone **216** and the corresponding mono-methyl olefin containing lactone **217**[117] (480 mg, 80 %, 10:1 by ^1H NMR analysis of C<u>H</u>=CHC=O peaks): R_f 0.3 (30% Et_2O in petroleum ether); IR (neat/cm^{-1}) 3484 br w, 2928 br w, 1756 s, 1161 w, 1084 w, 1017 w, 813 m, 751 m.

Data for furanone **216**: δ_H (400 MHz, $CDCl_3$) 7.33 (1H, dd *J* 5.5, 1.5, C<u>H</u>=CHC=O), 6.12-6.10 (1H, m, CH=C<u>H</u>C=O), 5.73 (1H, d *J* 9, OCH), 4.95–4.91 (1H, m, C<u>H</u>=C(CH_3)$_2$), 1.82 and 1.79 (2 x 3H, 2 x s, CH=C(C<u>H</u>$_3$)$_2$); δ_c (100 MHz, $CDCl_3$) 173.3 (OC=O), 155.7 (<u>C</u>H=CHC=O), 141.3 CH=<u>C</u>(CH_3)$_2$), 121.2 (CH=<u>C</u>HC=O), 117.7 (<u>C</u>H=C(CH_3)$_2$), 80.4 (OCH), 25.8 and 18.5 (CH=C(<u>C</u>H_3)$_2$); LRMS (ESI^+): 299 ($[2M+Na]^+$, 55%), 161 ($[M+Na]^+$, 100), 139 ($[M+H]^+$, 20); HRMS (ESI^+) m/z: calcd for $C_8H_{10}O_2Na$ $[M+Na]^+$: 161.0573 $[M+Na]^+$, found 161.0573.

Discernable data for mono-methyl olefin **217**[117]: δ_H (400 MHz, $CDCl_3$) 7.38 (1H, dd *J* 5.5, 1.5, C<u>H</u>=CHC=O), 6.13-6.11 (1H, m, CH=C<u>H</u>C=O), 5.93 (1H, qdd *J* 15, 6.5, 0.5, CH=C<u>H</u>CH_3), 5.40 (1H, br d *J* 8, OCH), 5.35-5.28 (1H, m, C<u>H</u>=CHCH_3), 1.75 (3H, dd *J* 6.5, 1, CH_3); δ_c (100

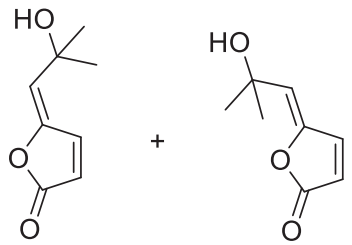
MHz, $CDCl_3$) 155.3 (CH=CHC=O), 124.5 (CH=CHCH$_3$), 121.3 (CH=CHC=O), 83.9 (OCH), 17.8 (CH_3); LRMS (ESI$^+$): 147 ([M+Na]$^+$, 100%).

(*R)-5-((*S**)-2-Hydroxy-2-methyl-1-(phenylselanyl)propyl)furan-2(5*H*)-one 219:**



To a solution of the above mixture of olefins (**216 / 217**, 10:1, 40 mg, 0.29 mmol, 1 equiv) in CH_3CN / H_2O (5:1, 9 mL) at rt was added PhSeBr (101 mg, 0.43 mmol, 1.5 equiv). After 15 h, the reaction mixture was quenched by addition of saturated aq $NaHCO_3$ (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 30% EtOAc in petroleum ether) to give a yellow oil, hydroxyselenide **219** (60 mg, 66%)**:** R_f 0.3 (30% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3450 br, 1754 s, 1477 w, 1338 w, 1155 m, 1105 m, 892 w, 825 m, 803 m, 733 w; δ_H (400 MHz, $CDCl_3$) 7.52-7.48 (2H, m, SePh), 7.30-7.23 (3H, m, SePh), 7.11 (1H, dd *J* 5.5, 1.5, CH=CHC=O), 6.24 (1H, dd *J* 5.5, 2, CH=CHC=O), 5.58 (1H, q *J* 1.5, OCH), 3.31 (1 H, br d *J* 1, SeCH), 2.50 (1H, br s, OH), 1.53 and 1.50 (2 x 3H, 2 x s, C(CH_3)$_2$); δ_c (400 MHz, $CDCl_3$) 172.9 (OC=O), 155.5 (CH=CHC=O), 134.4, 130.1, 129.3 and 128.0 (SePH), 123.1 (CH=CHC=O), 81.5 (OCH), 73.2 (OC(CH$_3$)$_2$), 63.4 (SeCH), 29.3 and 27.3 (C(CH$_3$)$_2$); LRMS (ESI$^+$): 335.0 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) m/z: calcd for $C_{14}H_{16}O_3{}^{80}SeNa$: 335.0157 [M+Na]$^+$, found 335.0157.

***E*- and *Z*-5-(2-Hydroxy-2-methylpropylidene)furan-2(5*H*)-one 220:**



To a solution of hydroxyselenide **219** (23 mg, 0.073 mmol, 1 equiv) in a mixture of CH_2Cl_2 (4 mL) and H_2O (0.2 mL) at 0 °C, were added pyridine (12 μL, 0.146 mmol, 2 equiv) and H_2O_2 (19 μL, 35 % in H_2O, 0.22 mmol, 3 equiv). After 1 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was washed with saturated aq $NaHCO_3$ (3 x 20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 80% Et_2O in petroleum ether). First eluted, a colourless oil, *E*-enol ether **220** (3.0 mg, 26%). Second eluted, a colourless oil, *Z*-enol ether **220** (3.0 mg, 26%).

E-enol **220**: R_f 0.3 (60% Et_2O in petroleum ether); IR (neat/cm^{-1}) 3456 br, 1746 s, 1555 w, 1229 w, 1104 m, 819 s; δ_H (500 MHz, $CDCl_3$): 8.20 (1H, d *J* 5.5, C<u>H</u>=CHC=O), 6.20 (1H, dd *J* 5.5, 1.5, CH=C<u>H</u>C=O), 5.84 (1H, d *J* 1.5, OC=CH), 1.50 (6H, s, $C(CH_3)_2$); δ_c (125 MHz, $CDCl_3$) 169.3 (OC=O), 149.3 (O<u>C</u>=CH), 142.6 (<u>C</u>H=CHC=O), 122.5 (CH=<u>C</u>HC=O), 120.4 (OC=<u>C</u>H), 71.3 (O<u>C</u>$(CH_3)_2$), 31.9 (C(<u>C</u>$H_3)_2$) ; LRMS (ESI^+): 137 ($[M\text{-}OH]^+$, 10%), 177 ($[M+Na]^+$, 100); HRMS (ESI^+) m/z: calcd for $C_8H_{10}O_3Na$: 177.0522 $[M+Na]^+$, found 177.0533.

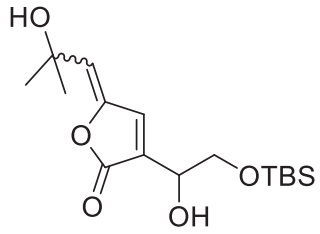
nOe experiements: irradiation at 8.20 (C<u>H</u>=CHC=O) saw reciprocal signal enhancement at 6.20 (CH=C<u>H</u>C=O) and 1.50 ($C(CH_3)_2$), and irradiation at 5.84 (OC=CH) saw reciprocal signal enhancement at 1.50 ($C(CH_3)_2$).

Z-enol **220**: R_f 0.25 (60% Et_2O in petroleum ether); IR (neat/cm^{-1}) 3440 br, 1772 m, 1746 s, 1558 w, 1222 w, 1148 m, 1104 m, 1068 w, 917 m; δ_H (500 MHz, $CDCl_3$) 7.34 (1H, d *J* 5.5,

C<u>H</u>=CHC=O), 6.18 (1H, dd *J* 5.5, 0.5, CH=C<u>H</u>C=O), 5.84 (1H, br s, OC=CH), 1.53 (6H, s, $C(CH_3)_2$); δ_c (125 MHz, $CDCl_3$) 169.2 (OC=O), 147.3 (O<u>C</u>=CH), 144.8 (<u>C</u>H=CHC=O), 123.3 (CH=<u>C</u>HC=O), 119.0 (OC=<u>C</u>H), 70.7 (O<u>C</u>$(CH_3)_2$), 30.2 (C(<u>C</u>$H_3)_2$); LRMS (ESI^+): 137 ([M-OH]$^+$, 25%), 177 ([M+Na]$^+$, 100); HRMS (ESI^+) m/z: calcd for $C_8H_{10}O_3Na$: 177.0522 [M+Na]$^+$, found 177.0533.

nOe experiements: irradiation at 7.34 (C<u>H</u>=CHC=O) saw reciprocal signal enhancement at 6.18 (CH=C<u>H</u>C=O) and 5.84 (OC=CH).

3-(2-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxyethyl)-5-(2-hydroxy-2-methylpropylidene) furan-2(5*H*)-one (226):



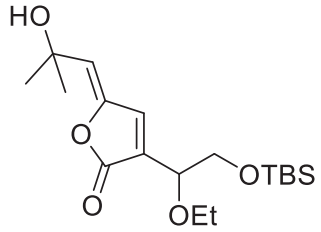
To a solution of olefins **216** / **217** (45 mg, 10:1, 0.33 mmol, 1.1 equiv) and 2-((*tert*-butyldimethylsilyl)oxy)acetaldehyde (**221**)[122] (52 mg, 0.3 mmol, 1 equiv) in EtOH (720 µL) at rt, were added TMEDA/MgI_2 (120 µL, 0.25 M in EtOH, 10 mol%) followed by DMAP (60 µL, 0.5 M in EtOH, 10 mol%). After 15 h, the reaction mixture was quenched by addition of H_2O (5 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, gradient elution: petroleum ether to 50% EtOAc in petroleum ether) to give a yellow oil, impure butenolide **15** (15 mg, *E*:*Z* = 2:5, by ^{1}H NMR analysis of the C<u>H</u>=CC=O peaks, ~15%): R_f 0.3 (50% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3424 br, 2930 w, 1749 s, 1464 w, 1362 w, 1254 m, 1114 m, 837 s, 779 m; LRMS (ESI^+): 351 ([M+Na]$^+$,

100%), 329 ([M+H]$^+$, 35); HRMS (ESI$^+$) m/z: calcd for $C_{16}H_{28}O_5SiNa$: 351.1598 [M+Na]$^+$, found 351.1600.

Discernible data for *E*-isomer **226**: δ_H (500 MHz, C_6D_6) 8.17 (1H, br s, C<u>H</u>=CC=O), 6.16 (1H, d *J* 5.5, OC=CH), 4.67-4.65 (1H, m, C<u>H</u>OH), 3.93 (1H, dd *J* 10.5, 3.5, C<u>H</u>H′OTBS), 3.61 (1H, dd *J* 10.5, 6, CH<u>H</u>′OTBS), 2.89 (1H, br, OH), 1.28 (6H, s, $C(CH_3)_2$), 0.88 (9H, s, $SiC(CH_3)_3$), –0.01 (6H, s, $Si(CH_3)_2$); δ_c (125 MHz, C_6D_6) 169.1 (OC=O), 144.6 (OC=<u>C</u>H), 138.0 (<u>C</u>H=CC=O), 69.0 (CHOH), 66.3 (CH_2OTBS), 30.5 ($C(\underline{C}H_3)_2$), 26.4 ($SiC(\underline{C}H_3)_3$), 18.8 ($Si\underline{C}(CH_3)_3$), –5.1 ($Si(CH_3)_2$).

Discernible data for *Z*-isomer **226**: δ_H (500 MHz, C_6D_6) 6.82 (1H, br s, C<u>H</u>=CHC=O), 5.41-5.39 (1H, m, OC=CH), 4.55–4.51 (1H, m, CHOH), 3.86 (1H, dd *J* 10.5, 3.5, C<u>H</u>H′OTBS), 3.53 (1H, dd *J* 10.5, 6.5, CH<u>H</u>′OTBS), 2.74 (1H, br, OH), 1.31 (6H, s, $C(CH_3)_2$), 0.87 (9H, s, $SiC(CH_3)_3$), –0.03 (6H, s, $Si(CH_3)_2$); δ_c (125 MHz, C_6D_6) 168.4 (OC=O), 140.2 (<u>C</u>H=CC=O), 123.2 (OC=CH), 68.8 (CHOH), 66.2 (CH_2OTBS), 30.6 ($C(CH_3)_2$), 26.3 ($SiC(\underline{C}H_3)_3$), 18.8 ($Si\underline{C}(CH_3)_3$, –5.0 ($Si(CH_3)_2$).

(*Z*)-3-(2-((*tert*-Butyldimethylsilyl)oxy)-1-ethoxyethyl)-5-(2-hydroxy-2-methylpropylidene) furan-2(5*H*)-one (229):

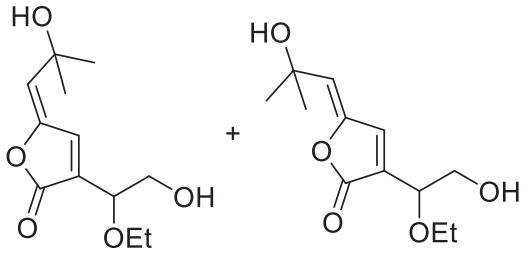


To a solution of the above butenolide **226** (15 mg, 0.05 mmol, 1 equiv) in EtI (2 mL, 25 mmol, 500 equiv) at rt, was added Ag_2O (25 mg, 0.125 mmol, 2.5 equiv) and 4 Å MS (15 mg). After 72 h, the reaction mixture was filtered through Celite®. The filter cake was washed with Et_2O (10 mL) and the filtrate was concentrated. ^{1}H NMR analysis of the δ 5.5-5.4 ppm region of the

residue indicated a 1:1 mixture of **226** / **229**. The residue was redissolved in EtI (2 mL, 25 mmol, 500 equiv), and Ag_2O (25 mg, 0.125 mmol, 2.5 equiv) and 4 Å MS (15 mg) were added. After 24 h, the reaction mixture was filtered through Celite®. The filter cake was washed with Et_2O (10 mL) and the filtrate concentrated. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 30% EtOAc in petroleum ether) to give a colourless oil, ethyl ether **229** (6 mg, 37%): R_f 0.3 (30% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3473 br, 2930 m, 1766 s, 1255 m, 1113 m, 837 s, 778 m, 679 w; δ_H (500 MHz, $CDCl_3$) 7.22 (1H, d *J* 1, C<u>H</u>=C), 5.43 (1H, s, OC=CH), 4.31–4.29 (1H, m, C<u>H</u>OEt), 3.85 (1H, dd *J* 11, 6, C<u>H</u>H′OTBS), 3.72 (1H, dd *J* 11, 6, CH<u>H</u>′OTBS), 3.61–3.55 (1H, m, OC<u>H</u>$_2$CH$_3$), 2.46 (1H, br s, OH), 1.52 (6H, s, C(CH$_3$)$_2$), 1.22 (3H, t *J* 7, OCH$_2$C<u>H</u>$_3$), 0.88 (9H, s, SiC(CH$_3$)$_3$), 0.05 (6H, s, Si(CH$_3$)$_2$); δ_c (125 MHz, $CDCl_3$) 168.4 (OC=O), 146.3 (O<u>C</u>=CH), 140.4 (<u>C</u>H=C(C=O)), 132.0 (CH=<u>C</u>(C=O)), 122.5 (OC=<u>C</u>H), 75.2 (<u>C</u>HOEt), 70.7 (COH), 65.9 (O<u>C</u>H$_2$CH$_3$), 64.7 (CH$_2$OTBS), 30.3 (C(CH$_3$)$_2$), 25.8 (SiC(<u>C</u>H$_3$)$_3$), 18.3 (Si<u>C</u>(CH$_3$)$_3$), 15.8 (OCH$_2$<u>C</u>H$_3$), –5.4 (Si(<u>C</u>H$_3$)$_2$); LRMS (ESI$^+$): 379 ([M+Na]$^+$, 100%), 357 ([M+H]$^+$, 23); HRMS (ESI$^+$) m/z: calcd for $C_{18}H_{32}O_5SiNa$ [M+Na]$^+$: 379.1911, found 379.1914.

nOe experiements: irradiation at 7.22 (C<u>H</u>=C(C=O)) saw reciprocal signal enhancement at 5.43 (OC=CH), 4.31–4.29 (C<u>H</u>OEt), 3.85 (C<u>H</u>H′OTBS) 3.72 (CH<u>H</u>′OTBS) and 3.61–3.55 (OC<u>H</u>$_2$CH$_3$).

(*Z*)-3-(1-Ethoxy-2-hydroxyethyl)-5-(2-hydroxy-2-methylpropylidene)furan-2(5*H*)-one (*Z*-185, aruncin B) and (*E*)-3-(1-ethoxy-2-hydroxyethyl)-5-(2-hydroxy-2-methylpropylidene)furan-2(5*H*)-one (*E*-185):



To a solution of butenolide **229** (4.5 mg, 13 μmol, 1 equiv) in THF (1 mL) at 0 °C was added TBAF (20 μL, 1.0 M in THF, 1.5 equiv). After 1 h, the reaction mixture was warmed to rt and stirred for 2 h. The reaction mixture was quenched by addition of H_2O (3 mL) and extracted with EtOAc (3 x 3mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 60% EtOAc in petroleum ether). First eluted a colourless oil *E*-aruncin B *E*-**185** (2.0 mg, 65%). Second eluted colourless oil aruncin B *Z*-**185**[6] (0.7 mg, 23%).

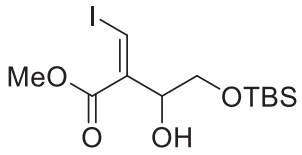
E-aruncin B: R_f 0.3 (50% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3390 br, 2923 m, 1746 s, 1628 w, 1108 m, 1061 m, 969 m, 783 w; δ_H (500 MHz, CD_3OD) 8.13–8.12 (1H, m, CH=C), 5.90 (1H, s, OC=CH), 4.29–4.27 (1H, m, C<u>H</u>OEt), 3.76 (1H, dd *J* 11.5, 4, C<u>H</u>H′OH), 3.65 (1H, dd *J* 11.5, 6, CH<u>H</u>′OH), 3.60–3.56 (2H, m, OC<u>H</u>$_2$CH$_3$), 1.42 (6 H, s, C(CH$_3$)$_2$), 1.23 (3H, t *J* 7, OCH$_2$C<u>H</u>$_3$); δ_c (125 MHz, CD_3OD) 170.4 (OC=O), 149.3 (O<u>C</u>=CH), 139.9 (<u>C</u>H=C(C=O)), 133.3 (CH=<u>C</u>(C=O)), 125.2 (OC=<u>C</u>H), 77.0 (<u>C</u>HOEt), 71.6 ((CH$_3$)$_2$<u>C</u>OH), 66.8 (O<u>C</u>H$_2$CH$_3$), 64.3 (<u>C</u>H$_2$OH), 31.7 (C(CH$_3$)$_2$), 15.8 (OCH$_2$<u>C</u>H$_3$); LRMS (ESI$^+$): 265 ([M+Na]$^+$, 100%), 243 ([M+H]$^+$, 10); HRMS (ESI$^+$) m/z: calcd for $C_{12}H_{18}O_5Na$: 265.1046 [M+Na]$^+$, found 265.1046.

Z-aruncin B: R_f 0.25 (50% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3408 br, 2924 m, 2853 w, 1755 s, 1667 w, 1108 m, 1058 m, 1025 m, 787 w; δ_H (500 MHz, CD_3OD) 7.46–7.45 (1H,

m, CH=C), 5.54 (1H, s, OC=CH), 4.28–4.26 (1H, m, CHOEt), 3.76 (1H, dd *J* 11.5, 4, CHH′OH), 3.65 (1H, dd *J* 11.5, 6, CHH′OH), 3.59–3.55 (2H, m, OCH_2CH_3), 1.50 (6 H, s, $C(CH_3)_2$), 1.22 (3H, t *J* 7, OCH_2CH_3); δ_c (125 MHz, CD_3OD) 170.8 (OC=O), 147.5 (OC=CH), 143.0 (CH=C(C=O)), 132.3 (CH=C(C=O)), 124.9 (OC=CH), 76.8 (CHOEt), 71.3 ($(CH_3)_2COH$), 66.8 (OCH_2CH_3), 64.3 (CH_2OH), 30.3 ($C(CH_3)_2$), 15.8 (OCH_2CH_3); LRMS (ESI^+): 265 ($[M+Na]^+$, 100%), 243 ($[M+H]^+$, 5%); HRMS (ESI^+): calcd for $C_{12}H_{18}O_5Na$: 265.1046 $[M+Na]^+$, found 265.1046.

nOe experiements: irradiation at 7.22 (CH=C(C=O)) saw reciprocal signal enhancement at 5.54 (OC=CH), 4.28-4.26 (CHOEt), 3.76 (CHH′OH) 3.65 (CHH′OH) and 3.59-3.55 (OCH_2CH_3).

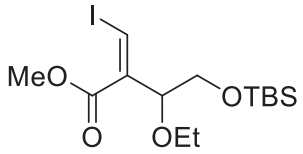
Methyl (*Z*)-4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-(iodomethylene)butanoate (234):



In a Schlenk tube, Mg turnings (875 mg, 36 mmol, 3 equiv) were dry-stirred overnight under N_2.[152] The resulting dark grey powder was suspended in Et_2O (12 mL) at 0 °C and I_2 (9.14 g, 36 mmol, 3 equiv) was added. The suspension was allowed to warm to rt over 3 h, under vigorous stirring, then cooled to –20 °C. A solution of 2-((*tert*-butyldimethylsilyl)oxy)acetaldehyde (**221**) (2.08 g, 12 mmol, 1 equiv.) in CH_2Cl_2 (18 mL) was added to the cooled suspension. After 5 min, methyl propiolate (**234**) (7.3 mL, 36 mmol, 3 equiv) was added. The reaction mixture was allowed to warm to rt over 1 h then quenched by addition of saturated aq $NaHCO_3$ / Na_2SO_3 (3:1, 50 mL), followed by EtOAc (50 mL). The layers were separated and the aqueous was extracted with EtOAc (2 x 50 mL). The organic layers were combined, washed with brine (100 mL), dried (Na_2SO_4) and concentrated under

reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 9 % EtOAc in petroleum ether) to give a brown oil, the *Z*-iodoester **235** (4.46 g, 96%): R_f 0.4 (15% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3344 br, 2926 m, 1741 s, 1661 m, 1613 w, 1069 m, 1028 m; δ_H (400 MHz, $CDCl_3$) 7.37 (1H, d *J* 1.5, CHI), 4.55-4.51 (1H, m, CHOH), 3.83 (3H, s, OCH_3), 3.81-3.79 (1H, m, OC<u>H</u>H'), 3.51 (1H, dd *J* 10, 6.5, OCH<u>H</u>'), 3.01 (1H, d *J* 5, OH), 0.89 (9H, s, $SiC(CH_3)_3$), 0.07 and 0.06 (6H, 2 x s, $Si(CH_3)_2$); δ_c (101 MHz, $CDCl_3$) 166.0 (<u>C</u>O_2CH_3), 142.2 (<u>C</u>=CHI), 87.4 (CHI), 73.8 (CHOH), 65.9 (OCH_2), 51.9 (CO_2<u>C</u>H_3), 25.8 ($SiC(\underline{C}H_3)_3$), 18.2 ($Si\underline{C}(CH_3)_3$), −5.4 ($Si(\underline{C}H_3)_2$); LRMS (ESI^+): 409 ($[M+Na]^+$, 100%); HRMS (ESI^+) m/z: calcd for $C_{12}H_{23}O_4INaSi$: 409.0303 $[M+Na]^+$, found 409.0302.

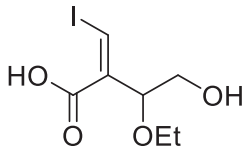
Methyl (*Z*)-4-((*tert*-butyldimethylsilyl)oxy)-3-ethoxy-2-(iodomethylene)butanoate (ES-6):



A glass vial was charged with a solution of iodoacrylate **235** (600 mg, 1.55 mmol, 1 equiv) in EtI (2 mL), Ag_2O (900 mg, 3.9 mmol, 2.2 equiv) and powdered 4 Å MS (600 mg). The vial was sealed, shielded from light using aluminium foil and heated at 40 °C for 12 h. After cooling to rt, the reaction was diluted with Et_2O (15 mL), filtered over celite and concentrated (N_2 sparge). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 3% Et_2O in petroleum ether) to give a yellow oil, the ethyl ether **ES-6** (320 mg, 50%): R_f 0.3 (4% Et_2O in petroleum ether); IR (neat/cm^{-1}) 2929 m, 1731 s, 1468 w, 1435 w, 1253 m, 1198 m, 1110 s, 837 s; δ_H (500 MHz, $CDCl_3$) 7.14 (1H, d *J* 1, CHI), 4.22-4.19 (1H, m, C<u>H</u>OEt), 3.82 (3H, s, OCH_3), 3.69-3.62 (2H, m, $OC\underline{H}_2CH_3$), 3.57 (1H, dd *J* 9.5, 7, OC<u>H</u>H'), 3.46 (1H, dd *J* 9.5, 7, OCH<u>H</u>'), 1.19 (2H, t *J* 7, $OCH_2C\underline{H}_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.05 (6H, s, $Si(C\underline{H}_3)_2$); δ_c (125 MHz, $CDCl_3$) 166.4 (<u>C</u>O_2CH_3), 143.1 (<u>C</u>=CHI), 85.7 (CHI), 82.2

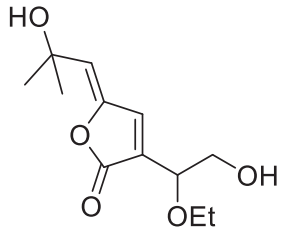
(CHOEt), 65.7 (OCH_2CH_3), 65.5 (OCH_2), 51.9 (CO_2CH_3), 25.8 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 15.2 (OCH_2CH_3), −5.34 and −5.41 ($Si(CH_3)_2$); LRMS (ESI^+): 437 ($[M+Na]^+$, 100%), 415 ($[M+H]^+$, 40); HRMS (ESI^+) m/z: calcd for $C_{14}H_{27}O_4INaSi$: 437.0616 $[M+Na]^+$, found 437.0614.

(*Z*)-3-Ethoxy-4-hydroxy-2-(iodomethylene)butanoic acid 236:



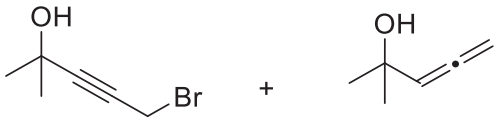
To a solution of ethyl ether **ES-6** (250 mg, 0.6 mmol, 1 equiv) in MeOH (0.6 mL) and H_2O (0.12 mL) at rt was added KOH (270 mg, 4.8 mmol, 8 equiv) at rt. After 12 h, the reaction mixture was diluted with H_2O (25 mL) and the aq. layer extracted with Et_2O (2 x 25 mL). The ethereal layers were discarded and $KHSO_4$ (830 mg, 6 mmol, 10 equiv) was added to the aq layer. The aq layer (~pH 3) was extracted with EtOAc (3 x 30 mL), the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give the sensitive hydroxy acid **236** as a yellow-brown oil, which slowly crystallised (150 mg, 87%): Mp 90-92° C; IR (neat/cm^{-1}) 3391 br, 2891 m, 1691 s, 1590 m, 1279 m, 1208 s, 1118 s, 1057 s, 855 m, 732 s; δ_H (400 MHz, $CDCl_3$) 7.47 (1H, d *J* 0.5, CHI), 4.33-4.31 (1H, m, CHOEt), 3.75 (1H, td *J* 11.5, 4, OCHH'), 3.64-3.57 (1H, m, OCHH'), 3.50-3.38 (2H, m, OCH_2CH_3), 1.22 (3H, t *J* 7, OCH_2CH_3); δ_c (100 MHz, $CDCl_3$) 169.1 (CO_2H), 140.7 (C=CHI), 89.2 (CHI), 81.8 (CHOEt), 65.6 (OCH_2CH_3), 64.9 (CH_2OH), 15.2 (OCH_2CH_3); LRMS (ESI^-): 285 ($[M-H]^-$, 100%); HRMS (ESI^-) m/z: calcd for $C_7H_{10}O_4I$: 284.9629 $[M-H]^-$, found 284.9626.

(*Z*)-3-(1-Ethoxy-2-hydroxyethyl)-5-(2-hydroxy-2-methylpropylidene)furan-2(5*H*)-one (*Z*-185):



To a solution of the hydroxy acid **236** (380 mg, 1.33 mmol, 1 equiv) in MeCN (8 mL) at rt was successively added $Pd(PPh_3)_2Cl_2$ (10 mg, 0.014 mmol, 1 mol%), CuI (5 mg, 0.028 mmol, 2 mol%) and freshly distilled Et_3N (0.6 mL, 4.1 mmol, 3 equiv). After 15 min, freshly distilled 2-methyl-3-butyn-2-ol (**237**) (400 μL, 2 mmol, 1.5 equiv) was added. After 12 h, the reaction mixture was diluted with EtOAc (20 mL) and filtered through celite. The filter cake was washed with EtOAc (20 mL) and the combined filtrates were concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, gradient elution: petroleum ether to 80% EtOAc in petroleum ether) gave a yellow oil, butenolide *Z*-**185** (200 mg, 60%). R_f 0.25 (50% EtOAc in petroleum ether): IR (neat/cm^{-1}) 3408 br, 2924 m, 2853 w, 1755 s, 1667 w, 1108 m, 1058 m, 1025 m, 787 w; IR (KBr disc/cm^{-1}) C=O: 1756 s; UV (MeOH) λ_{max} (log ε): 275.6 (4.21); δ_H (400 MHz, CD_3OD) 7.46 (1H, d *J* 1, C=CH), 5.54 (1H, s, OC=CH), 4.28–4.26 (1H, m, C<u>H</u>OEt), 3.76 (1H, dd *J* 11.5, 4, C<u>H</u>H'OD), 3.64 (1H, dd *J* 11.5, 6, CH<u>H</u>'OD), 3.57 (2H, q *J* 7.5, OC<u>H</u>$_2$CH$_3$), 1.50 (6 H, s, $(CH_3)_2$), 1.22 (3H, t, *J* 7, $OCH_2C\underline{H}_3$); δ_C (100 MHz, CD_3OD) 170.8 (OC=O), 147.5 (O<u>C</u>=CH), 143.0 (C=<u>C</u>H), 132.3 (<u>C</u>=CH), 124.9 (OC=<u>C</u>H), 76.8 (<u>C</u>HOEt), 71.3 ($(CH_3)_2COD$), 66.8 ($O\underline{C}H_2CH_3$), 64.3 (CH_2OD), 30.3 ($(CH_3)_2C$), 15.8 ($OCH_2\underline{C}H_3$); LRMS (ESI^+): 265 ($[M+Na]^+$, 100%), 243 ($[M+H]^+$, 5%); HRMS (ESI^+) m/z: calcd for $C_{12}H_{18}O_5Na$: 265.1046 $[M+Na]^+$, found 265.1046.

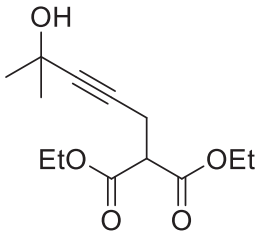
5-Bromo-2-methylpent-3-yn-2-ol (272) and 2-methylpenta-3,4-dien-2-ol (273):



To a solution of propargyl bromide (**271**) (110 μL, 80% in toluene, 1 mmol, 1 equiv) in Et_2O (10 mL) at –78 °C, was added MeLi (0.65 mL, 1.55 M in Et_2O, 1.0 mmol, 1 equiv). After 15 min, freshly distilled acetone (0.37 mL, 5 mmol, 5 equiv) was added. After 1 h, the reaction mixture was quenched by addition of saturated aq NH_4Cl (10 mL). The layers were separated and the aq layer was extracted with Et_2O (3 x 10 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure (>200 mBar). The residue was purified by column chromatography (SiO_2, gradient elution petroleum ether to 30% Et_2O in petroleum ether) to give a colorless oil, alkynol **272** contaminated with the corresponding allenol **273**[146] impurity (115 mg, ~ 65%, ~ 3:1 by integration of CH_2 and $H_2C{=}C{=}C\underline{H}$-C respectively): R_f 0.3 (30% Et_2O in petroleum ether); IR (neat/cm^{-1}) 3450 br, 1350 m, 1250 s, 1209 s, 1166 s, 950 s; δ_H (400 MHz, $CDCl_3$) 3.93 (2H, s, CH_2Br); 1.52 (6H, s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 91.2 and 71.2 ($CH_2\underline{C}\underline{C}$), 65.2 ($O\underline{C}(CH_3)_2$), 31.1 ($OC(\underline{C}H_3)_2$), 14.2 ($CH_2Br$); LRMS ($ESI^+$): dec.

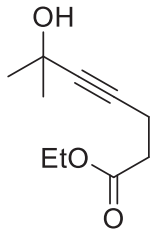
Discernible data for allenol **273**[146]: δ_H (400 MHz, $CDCl_3$): 5.35 (1H, t *J* 6.5, $H_2C{=}C{=}C\underline{H}$-C), 4.89 and 4.88 (2 x 1H, 2 x s, $H_2C{=}C{=}C$); δ_C (100 MHz, $CDCl_3$) 205.3 ($H_2C{=}\underline{C}{=}C$), 100.2 ($H_2C{=}C{=}\underline{C}H$), 78.4 ($H_2\underline{C}{=}C{=}CH$), 28.5 ($OC(\underline{C}H_3)_2$).

Diethyl 2-(4-hydroxy-4-methylpent-2-yn-1-yl)malonate (275):



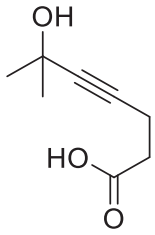
To a solution of diethyl malonate (**274**) (210 mg, 1.3 mmol, 2 equiv) in THF (4.5 mL) at 0 °C was added portion-wise NaH (55 mg, 60% in mineral oil, 1.3 mmol, 2 equiv). After 30 min, alkynol **272** (115 mg, 0.65 mmol, 1 equiv) in THF (2 mL) was added and the reaction mixture was allowed to warm to rt. After 12 h, the reaction mixture was quench by addition of saturated aq NH_4Cl (10 mL) and the aq layer was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 30% EtOAc in petroleum ether) to give a yellow oil, malonate **275** (85 mg, 51%): R_f 0.3 (30% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3450 br, 1731 s, 1350 m, 1225 m, 1163 s, 1075 m, 900 m, 850 w; δ_H (400 MHz, $CDCl_3$) 4.22 (6H, qt *J* 7, 1.5, $CH(CO_2C\underline{H}_2CH_3)_2$), 3.53 (1H, td *J* 8, 1.5, $C\underline{H}(CO_2CH_2CH_3)_2$, 2.77 (2H, dd *J* 8, 1.5, $C\underline{H}_2CC$), 2.13 (1H, br s, OH), 1.46 (6H, d *J* 1.5, $C(CH_3)_2$), 1.28 (6H, td *J* 7, 1.5, $CH(CO_2CH_2C\underline{H}_3)_2$); δ_C (100 MHz, $CDCl_3$) 168.0 (OC=O), 87.2 and 78.0 ($CH_2\underline{C}\underline{C}$), 65.0 ($O\underline{C}(CH_3)_2$), 61.7 ($CH(CO_2\underline{C}H_2CH_3)_2$), 51.4 ($\underline{C}H(CO_2CH_2CH_3)_2$), 31.4 ($C(\underline{C}H_3)_2$), 18.6 ($\underline{C}H_2CC$), 14.1 ($CH(CO_2CH_2\underline{C}H_3)_2$); LRMS ($ESI^+$): 239 ($[M–OH]^+$, 18%), 279 ($[M+Na]^+$, 100); HRMS ($ESI^+$) m/z: calcd for $C_{13}H_{20}O_5Na$ $[M+Na]^+$: 279.1203, found 279.1203.

Ethyl 6-hydroxy-6-methylhept-4-ynoate (276):



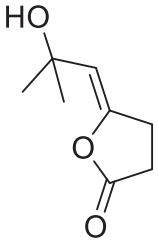
To a solution of malonate **275** (200 mg, 0.78 mmol, 1 equiv) in DMF (8 mL), was added H_2O (28 μL, 1.56 mmol, 2 equiv) and LiCl (164 mg, 3.9 mmol, 5 equiv). The reaction mixture was heated to 160 °C for 90 min (until gas formation ceased). After cooling to rt, the reaction mixture was concentrated under reduced pressure (~ 1 mBar, 40 °C). The residue was dissolved in Et_2O (10 mL) and washed with H_2O (5 x 10 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil, mono ester **276** (140 mg, 97%) which was used next step without further purification: IR (neat/cm^{-1}) 3400 br, 1733 s, 1370 m, 1237 m, 1164 s, 1040 m, 952 m, 800 w; δ_H (400 MHz, $CDCl_3$) 4.15 (2H, q *J* 7, $CO_2C\underline{H}_2CH_3$), 2.50 (4H, br s, CH_2CH_2), 2.07 (1H, br s, OH), 1.48 (6H, s, $C(CH_3)_2$), 1.27 (3H, t *J* 7, $CO_2CH_2C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 172.0 (OC=O), 85.7 and 80.4 (CC), 65.1 ($O\underline{C}(CH_3)_2$), 60.6 ($CO_2\underline{C}H_2CH_3$), 33.6 ($\underline{C}H_2CO_2CH_2CH_3$), 31.6 ($C(\underline{C}H_3)_2$), 14.6 ($CC\underline{C}H_2$), 14.2 ($CO_2CH_2\underline{C}H_3$); LRMS ($ESI^+$): 167 ($[M-OH]^+$, 30%), 207 ($[M+Na]^+$, 100) ; HRMS ($ESI^+$) m/z: calcd for $C_{10}H_{16}O_3Na$ $[M+Na]^+$: 207.0992, found 207.0994.

6-Hydroxy-6-methylhept-4-ynoic acid (277):



To a solution of the above mono-ester **276** (140 mg, 0.76 mmol, 1 equiv) in THF / EtOH / H_2O (2:2:1, 7.5 mL) at 0 °C was added NaOH (152 mg, 3.8 mmol, 5 equiv) and the reaction mixture was allowed to warm to rt. After 12 h, H_2O (15 mL) and Et_2O (15 mL) were added. The layers were separated and the ethereal layer was discarded. The aq layer was acidified (pH 2-3) by dropwise addition of aq HCl (1 M), extracted with EtOAc (3 x 15 mL); the organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil, acid **277** (80 mg, 67%): IR (neat/cm^{-1}) 3400 br, 1712 s, 1365 w, 1242 m, 1159 s, 948 m, 912 m, 853 w, 732 s, 648 w; δ_H (400 MHz, $CDCl_3$) 7.42 (1H, br s, CO_2H), 2.59-2.48 (4 H, m, $C\underline{H}_2C\underline{H}_2CO_2H$), 1.48 (6H, s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 177.4 (OC=O), 85.7 and 80.2 (CC), 65.4 ($O\underline{C}(CH_3)_2$), 33.3 ($\underline{C}H_2CO_2H$), 31.4 ($C(\underline{C}H_3)_2$), 14.3 ($CC\underline{C}H_2$); LRMS (ESI^-): 155 ($[M–H]^-$, 100%); HRMS (ESI^-) m/z: calcd for $C_8H_{11}O_3$ $[M–H]^-$: 155.0714, found 155.0713.

(*Z*)-5-(2-Hydroxy-2-methylpropylidene)dihydrofuran-2(3*H*)-one (278):



To a solution of the above acid **277** (40 mg, 0.25 mmol, 1 equiv) in CH_3CN (2.5 mL) at rt was added K_2CO_3 (4 mg, 0.025 mmol, 10 mol%), followed by $(PPh_3)AuCl$ (12 mg, 0.025, 10

mol%). After 12 h, the reaction mixture was diluted with H_2O (10 mL) and exctrated with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 40% EtOAc in petroleum ether) to give a colourless oil, lactone **278** (20 mg, 50%): R_f 0.3 (40% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3400 br, 1713 s, 1688 s, 1620 s, 1441 w, 1400 w, 1382 w, 1210 w, 1164 w, 1116 m; δ_H (500 MHz, C_6D_6) 4.43 (1H, q *J* 2, OC=CH), 2.29 (1H, br s, OH), 1.80-1.75 (2H, m, $C\underline{H}_2CH_2C=O$), 1.63-1.59 (2H, m, $CH_2C\underline{H}_2C=O$), 1.41 and 1.40 (2 x 3H, 2 x 3, $C(CH_3)_2$); δ_C (125 MHz, C_6D_6) 174.1 (OC=O), 146.8 ($O\underline{C}$=CH), 113.0 (OC=$\underline{C}$H), 70.1 ($O\underline{C}(CH_3)_2$), 31.1 ($C(\underline{C}H_3)_2$), 26.7 ($CH_2\underline{C}H_2C=O$), 25.5 ($\underline{C}H_2CH_2C=O$); LRMS (ESI^+): 139 ($[M–OH]^+$, 95%), 179 ($[M+Na]^+$, 100); HRMS (ESI^+) m/z: calcd for $C_8H_{12}O_3Na$ $[M+Na]^+$: 179.0679, found 179.0680.

nOe experiments: irradiation at 4.43 (OC=CH) saw reciprocal signal enhancement at 1.80-1.75 ($C\underline{H}_2CH_2C=O$) and 1.41-1.40 ($C(CH_3)_2$).

General procedure for β-iodo MBH:

In a Schlenk tube, Mg turnings (100 mg, 4.0 mmol, 1 equiv) were dry-stirred overnight under N_2.[152] The resulting dark grey powder was suspended in Et_2O (4 mL) at 0 °C and I_2 (1.0 g, 4.0 mmol, 1 equiv) was added. The suspension was allowed to warm to rt over 3 h, under vigorous stirring, then cooled to –20 °C. A solution of aldehyde (4.0 mmol, 1 equiv.) in CH_2Cl_2 (6 mL) was added to the cooled suspension. After 5 min, methyl propiolate (0.35 mL, 4.0 mmol, 1 equiv) was added. The reaction mixture was allowed to warm to rt over 1 h then quenched by addition of saturated aq $NaHCO_3$ / Na_2SO_3 (3:1, 10 mL), followed by EtOAc (10 mL) and the biphasic mixture was vigorously stirred. After 10 min, the layers were separated and the aqueous was extracted with EtOAc (2 x 10 mL). The organic layers were combined, washed

with brine (25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether / EtOAc) to give the *Z*-iodoester.

General procedure for *O*-alkylation:

A glass vial was charged with a solution of *Z*-iodoester (N mmol, 1 equiv.) in the desired alkyl halide (N x 2.5 mL), Ag_2O (2.5 equiv.) and powdered 4 Å MS (1 mg per mg of substrate). The vial was sealed, shielded from light using aluminium foil and heated at 60 °C for 12 h. After cooling to rt, the reaction mixture was diluted with Et_2O (N x 15 mL), filtered through Celite® and concentrated (N_2 sparge). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether / Et_2O) to give the ether.

General procedure for hydrolysis:

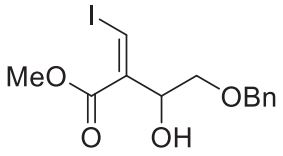
To a solution of ether (N mmol, 1 equiv) in MeOH (N x 1 mL) and H_2O (N x 0.2 mL) at 0 °C was added KOH (8 equiv) and the reaction mixture was allowed to warm to rt. After 12 h, the reaction mixture was diluted with H_2O (N x 20 mL) and the aq layer extracted with Et_2O (2 x (N x 20) mL). The ethereal layers were discarded and $KHSO_4$ (10 equiv) was added to the aqueous. The aq layer (~ pH 3) was extracted with EtOAc (3 x (N x 30) mL), the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give the hydroxy acid, which was used in the next step without further purification.

General procedure for final cross-coupling:

To a solution of the hydroxy acid (N mmol, 1 equiv) in MeCN (N x 10 mL) at rt were successively added $Pd(PPh_3)_2Cl_2$ (2 mol%), CuI (4 mol%) and freshly distilled Et_3N (3 equiv). After 15 min, alkyne (3 equiv) was added. After 12 h, the reaction mixture was diluted with EtOAc (N x 20 mL) and filtered through Celite®. The filter cake was washed with EtOAc (N x 20 mL) and the combined filtrates were concentrated under reduced pressure. Purification of

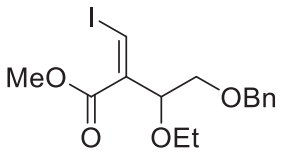
the residue by column chromatography (SiO_2, gradient elution: petroleum ether / EtOAc) gave the butenolide.

Methyl (*Z*)-4-(benzyloxy)-3-hydroxy-2-(iodomethylene)butanoate (ES-7):



Standard procedure for β-iodo MBH was followed with 2-(benzyloxy)acetaldehyde (600 mg, 4 mmol, 1 equiv). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 9% EtOAc in petroleum ether) to give a yellow oil, iodoacrylate **ES-7** (760 mg, 52%): R_f 0.3 (9% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3439 br, 1719 s, 1452 w, 1433 w, 1310 m, 1200 s, 1175 m, 1099 s, 1063 s, 736 s; δ_H (400 MHz, $CDCl_3$) 7.39-7.29 (6H, m, Ph and CHI), 4.69 (1H, dddd *J* 7, 5, 3.5, 1.5, C<u>H</u>OH), 4.56 (2H, 2 x s, OC<u>H</u>$_2$Ph), 3.79 (3H, s, CO_2CH_3), 3.67 (1H, dd *J* 9.5, 3.5, C<u>H</u>H'OCH$_2$Ph), 3.44 (1H, dd *J* 9.5, 7, CH<u>H</u>'OCH$_2$Ph), 2.94 (1H, d *J* 4.5, OH); δ_C (100 MHz, $CDCl_3$) 166.0 (OC=O), 142.3 (<u>C</u>=CHI), 137.4 (*ipso*Ph), 128.5, 127.9 and 127.8 (Ph), 87.5 (C=<u>C</u>HI), 73.4 (<u>C</u>H$_2$Ph), 72.7 (<u>C</u>H$_2$OCH$_2$Ph), 72.6 (<u>C</u>HOH), 51.9 (CO_2<u>C</u>H$_3$); LRMS (ESI^+): dec.

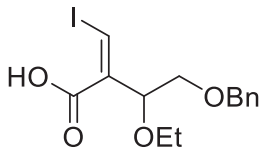
Methyl (*Z*)-4-(benzyloxy)-3-ethoxy-2-(iodomethylene)butanoate (ES-8):



Standard *O*-alkylation procedure was used using EtI with **ES-7** (380 mg, 1.05 mmol). The residue was purified by chromatography (SiO_2, gradient elution: petroleum ether to 2% Et_2O in petroleum ether) to give a yellow oil, ethyl ether **ES-8** (240 mg, 59%): R_f 0.5 (4% Et_2O in

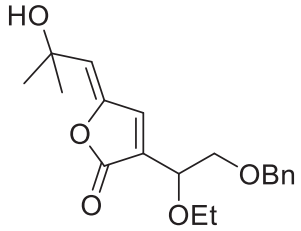
petroleum ether); IR (neat/cm^{-1}) 1726 s, 1452 w, 1433 w, 1304 m, 1279 m,1198 m, 1174 m,1098 s, 737 m, 698 m; δ_H (400 MHz, $CDCl_3$) 7.38-7.28 (5H, m, Ph), 7.21 (1H, d *J* 1, CHI), 4.59 and 4.56 (2H, 2 x d *J* 12, $OC\underline{H}_2Ph$), 4.37 (1H, ddd *J* 6, 4.5, 1, $C\underline{H}OCH_2CH_3$) 3.77 (3H, s, CO_2CH_3), 3.61-3.45 (4H, m, $C\underline{H}_2OCH_2Ph$ and $CHOC\underline{H}_2CH_3$), 1.22 (3H, t *J* 7, $OCH_2C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 166.3 (OC=O), 142.6 ($\underline{C}$=CHI), 138.0 (*ipso*Ph), 128.3, 127.6 and 127.6 (Ph), 86.1 (C=$\underline{C}$HI), 80.6 ($\underline{C}HOCH_2CH_3$) 73.4 ($\underline{C}H_2Ph$), 72.2 ($\underline{C}H_2OCH_2Ph$), 65.5 ($O\underline{C}H_2CH_3$), 51.9 ($CO_2\underline{C}H_3$), 15.3 ($OCH_2\underline{C}H_3$); LRMS (ESI^+) 413 ($[M+Na]^+$, 100%); HRMS (ESI^+) m/z: calcd for $C_{15}H_{19}O_4INa$ $[M+Na]^+$: 413.0220, found 413.0252.

(*Z*)-4-(benzyloxy)-3-ethoxy-2-(iodomethylene)butanoic acid (ES-9):



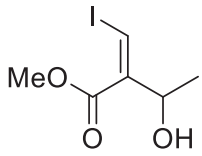
Standard hydrolysis procedure was followed with **ES-8** (220 mg, 0.59 mmol) to give a yellow sticky oil, iodoacrylic acid **ES-9** (150 mg, 71%): IR (neat/cm^{-1}) 3450 br, 1701 s, 1453 w, 1367 w, 1213 m, 1096 s, 736 m, 698 m; δ_H (400 MHz, $CDCl_3$) 7.44 (1H, d *J* 1, CHI), 7.39-7-7.29 (5H, m, Ph), 4.60 (2H, s, $C\underline{H}_2Ph$), 4.39 (1H, ddd *J* 5.5, 4.5, 1, $C\underline{H}OCH_2CH_3$), 3.66-3.45 (4H, m, $OC\underline{H}_2CH_3$ and $C\underline{H}_2OCH_2Ph$), 1.23 (3H, t *J* 7, $OCH_2C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 169.0 (OC=O), 141.2 ($\underline{C}$=CHI), 137.5, 128.4, 127.8 and 127.7 (Ph), 89.6 (CHI), 80.5 ($\underline{C}HOCH_2CH_3$), 73.5 ($O\underline{C}H_2Ph$), 72.2 ($O\underline{C}H_2CH_3$), 65.7 ($\underline{C}H_2OCH_2Ph$), 15.2 ($OCH_2\underline{C}H_3$); LRMS (ESI^-): 375 ($[M-H]^-$, 100%), (ESI^+): 399 ($[M+Na]^+$, 100%); HRMS (ESI^-) m/z: calcd for $C_{14}H_{16}O_4I$ $[M-H]^-$: 375.0099, found 375.0097.

(*Z*)-3-(2-(Benzyloxy)-1-ethoxyethyl)-5-(2-hydroxy-2-methylpropylidene)furan-2(5*H*)-one (280):



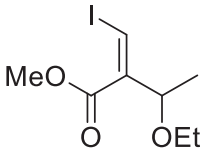
Standard cross-coupling procedure was followed with the above crude acid **ES-9** (75 mg, 0.20 mmol) and 2-methyl-3-butyn-2-ol (58 μL, 0.60 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 80% EtOAc in petroleum ether) to give a yellow oil, butenolide **280** (35 mg, 53%): R_f 0.3 (80% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3449 br, 1756 s, 1395 m, 1252 w, 1096 s, 614 m, 699 w, 676 w; δ_H (400 MHz, $CDCl_3$) 7.37-7.28 (5H, m, Ph), 7.25 (1H, d *J* 1, CH=C(C=O)), 5.44 (1H, s, OC=CH), 4.59 (2H, s, OC$\underline{H}_2$Ph), 4.43 (1H, ddd *J* 5.5, 3.5, 1, C$\underline{H}$OCH_2CH_3), 3.73 (1H, d *J* 10.5, 3.5, C$\underline{H}$H'OCH_2Ph), 3.65-3.53 (3H, m, CH$\underline{H}$'OCH_2Ph and OC$\underline{H}_2$CH_3), 1.52 (6H, s, OC(CH_3)$_2$), 1.24 (3H, t *J* 7, OCH_2C$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 168.3 (OC=O), 146.1 (O$\underline{C}$=CH), 140.5 ($\underline{C}$H=C(C=O)), 137.8, 131.5, 128.3 and 127.7 (CH=$\underline{C}$(C=O) and Ph), 122.8 (OC=CH), 73.5 ($\underline{C}$HOCH_2CH_3), 73.4 (O$\underline{C}$$H_2$Ph), 70.7 ($\underline{C}$$H_2OCH_2$Ph), 70.6 (O$\underline{C}$(C$H_3$)$_2$), 65.8 (OC$H_2CH_3$), 30.2 (C($\underline{C}$$H_3$)$_2$), 15.4 (OC$H_2CH_3$); LRMS ($ESI^+$): 355 ($[M+Na]^+$, 100%); HRMS ($ESI^+$) m/z: calcd for $C_{19}H_{24}O_5Na$ $[M+Na]^+$: 355.1516, found 355.1514.

Methyl (*Z*)-3-hydroxy-2-(iodomethylene)butanoate (ES-10):



Standard procedure for β-iodo MBH was followed using acetaldehyde (224 μL, 4.0 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 9% EtOAc in petroleum ether) to give a yellow oil, iodoacrylate **ES-10** (420 mg, 41%): R_f 0.3 (9% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3439 br, 1719 s, 1435 w, 1288 m, 1204 m, 1177 w, 1134 w, 1067 w; δ_H (400 MHz, $CDCl_3$) 7.20-7.18 (1H, m, CHI), 4.61 (1H, d *J* 6.5, C<u>H</u>OH), 3.85 (3H, s, CO_2CH_3), 2.59 (1H, br s, OH), 1.37 (3H, d *J* 6.5, CHC<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 166.7 (OC=O), 147.5 (<u>C</u>=CHI), 84.6 (CHI), 70.4 (CHOH), 52.0 (CO_2<u>C</u>H_3), 22.3 (CH<u>C</u>H_3); LRMS (ESI^+): 279 ($[M+Na]^+$, 100%); HRMS (ESI^+) m/z : calcd for $C_6H_9O_3INa$: 278.9489 $[M+Na]^+$, found 278.9489.

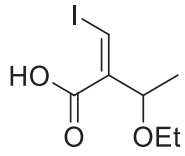
Methyl (*Z*)-3-ethoxy-2-(iodomethylene)butanoate (ES-11):



Standard *O*-alkylation procedure was used using EtI with **ES-10** (210 mg, 1.05 mmol). The residue was purified by chromatography (SiO_2, gradient elution: petroleum ether to 2% Et_2O in petroleum ether) to give a yellow oil, ethyl ether **ES-11** (130 mg, 44%): R_f 0.5 (4% Et_2O in petroleum ether); IR (neat/cm^{-1}) 1730 s, 1433 w, 1371 w, 1387 w, 1283 m, 1200 m, 1175 m, 1117 m, 1092 m, 1012 w, 851 s; δ_H (400 MHz, $CDCl_3$) 7.02 (1H, br t *J* 1.5, CHI), 4.22 (1H, qt *J* 6.5, 1.5, C<u>H</u>OCH_2CH_3), 3.83 (1H, d *J* 1.5, CO_2CH_3), 3.51 (1H, dqd *J* 9, 7, 1.5, CHOC<u>H</u>H'CH_3), 3.41 (1H, dqd *J* 9, 7, 1.5, CHOCH<u>H</u>'CH_3), 1.32 (1H, dd *J* 6.5, 1.5, CHC<u>H</u>$_3$),

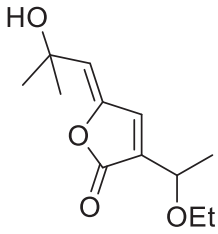
1.19 (1H, td *J* 7, 1.5, $OCH_2C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 166.7 (OC=O), 147.0 ($\underline{C}$=CHI), 83.1 (C=$\underline{C}$HI), 77.3 ($\underline{C}HOCH_2CH_3$), 64.6 ($CHO\underline{C}H_2CH_3$), 52.0 ($CO_2\underline{C}H_3$), 21.4 ($CH\underline{C}H_3$), 15.3 ($OCH_2\underline{C}H_3$); LRMS: (ESI^+): 307 ($[M+Na]^+$, 100%); HRMS (ESI^+) m/z : calcd for $C_8H_{14}O_3I$: 284.9982 $[M+H]^+$, found 284.9983.

(*Z*)-3-Ethoxy-2-(iodomethylene)butanoic acid (ES-12):



Standard hydrolysis procedure was followed with ethyl ether **ES-11** (110 mg, 0.39 mmol) to give a yellow sticky oil, iodoacrylic acid **ES-12** (75 mg, 71%): IR (neat/cm^{-1}) 3051 br, 1702 s, 1285 w, 1190 m, 1110 m, 850 w, 710 w; δ_H (400 MHz, $CDCl_3$) 9.96 (1H, br. s, CO_2H), 7.35 (1H, d *J* 1, CHI), 4.29 (1H, qd *J* 6.5, 1, $C\underline{H}OCH_2CH_3$), 3.57-3.38 (2H, m, OCH_2CH_3), 1.36 (3H, d *J* 6.5, $OCHC\underline{H}_3$), 1.21 (3H, t *J* 7, $CH_2C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 170.1 (OC=O), 144.7 ($\underline{C}$=CHI), 87.4 (CHI), 77.5 ($C\underline{H}OCH_2CH_3$), 64.7 ($O\underline{C}H_2CH_3$), 21.5 ($OCH\underline{C}H_3$), 15.2 ($OCH_2\underline{C}H_3$); LRMS (ESI^-): 269 ($[M-H]^-$, 100%); HRMS (ESI^-) m/z: calcd for $C_7H_{10}O_3I$ $[M-H]^-$: 268.9680, found 268.9679.

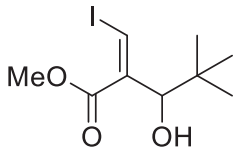
(*Z*)-3-(1-ethoxyethyl)-5-(2-hydroxy-2-methylpropylidene)furan-2(5*H*)-one (281):



Standard cross-coupling procedure was followed with the above crude acid **ES-12** (55 mg, 0.20 mmol) and 2-methyl-3-butyn-2-ol (58 µL, 0.60 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 80% EtOAc in petroleum ether) to

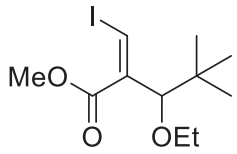
give a yellow oil the butenolide **281** (25 mg, 54%): R_f 0.3 (40% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3427 br, 1760 s, 1372 w, 1240 w, 1173 m, 1109 m, 977 m, 780 w; δ_H (400 MHz, $CDCl_3$) 7.16 (1H, d *J* 1, CH=C(C=O)), 5.42 (1H, s, OC=CH), 4.32 (1H, qd *J* 6.5, 1, C<u>H</u>OCH$_2$CH$_3$), 3.56-3.45 (2H, m, OC<u>H</u>$_2$CH$_3$), 2.58 (1H, br s, OH), 1.51 (6H, s, C(C<u>H</u>$_3$)$_2$), 1.40 (3H, d *J* 6.5, CHC<u>H</u>$_3$), 1.21 (3H, t *J* 7, OCH$_2$C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 168.4 (OC=O), 146.1 (O<u>C</u>=CH), 138.7 (<u>C</u>H=C(C=O)), 135.6 (CH=<u>C</u>(C=O)), 122.4 (OC=<u>C</u>H), 70.6 (O<u>C</u>(CH$_3$)$_2$), 69.9 (<u>C</u>HOCH$_2$CH$_3$), 64.8 (O<u>C</u>H$_2$CH$_3$), 30.2 (C(<u>C</u>H$_3$)$_2$), 20.4 (CH<u>C</u>H$_3$), 15.4 (OCH$_2$<u>C</u>H$_3$); LRMS: (ESI$^+$): 249 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) m/z: calcd for $C_{12}H_{18}O_4Na$: 249.1097 [M+Na]$^+$, found 249.1098.

Methyl (*Z*)-3-hydroxy-2-(iodomethylene)-4,4-dimethylpentanoate (ES-13):



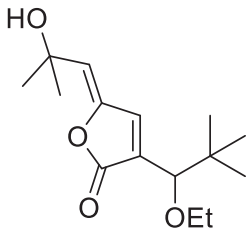
Standard procedure for β-iodo MBH was followed using pivaldehyde (433 μL, 4 mmol, 1 equiv)). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 9% EtOAc in petroleum ether) to give a yellow oil, iodoacrylate **ES-13**[148] (1.01 g, 85%): R_f 0.3 (5% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3500 br, 1715 s, 1435 w, 1300 m, 1202 m, 1047 m, 1015 w; δ_H (400 MHz, $CDCl_3$) 7.08 (1 H, d *J* 1, CHI), 4.25 (1H, d *J* 1, C<u>H</u>OH), 3.83 (3H, s, CO_2CH_3), 0.90 (9H, s, C(CH$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 168.0 (OC=O), 145.3 (<u>C</u>=CHI), 85.7 (C=<u>C</u>HI), 82.6 (CHOH), 52.0 (CO_2<u>C</u>H$_3$), 36.1 (<u>C</u>(CH$_3$)$_3$), 25.5 (C(<u>C</u>H$_3$)$_3$); LRMS (ESI$^+$): 321 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) m/z : calcd for $C_9H_{15}O_3INa$: 320.9958 [M+Na]$^+$, found 320.9958.

Methyl (*Z*)-3-ethoxy-2-(iodomethylene)-4,4-dimethylpentanoate (ES-14):



Standard *O*-alkylation procedure was used using EtI with **ES-13** (500 mg, 1.7 mmol). The residue was purified by chromatography (SiO_2, gradient elution: petroleum ether to 2% Et_2O in petroleum ether) to give a yellow oil the ethyl ether **ES-14** (110 mg, 20%): R_f 0.5 (1% Et_2O in petroleum ether); IR (neat/cm^{-1}) 1722 br, 1481 w, 1433 w, 1296 m, 1277 m, 1196 m, 1171 m, 1103 s, 1074 m, 1039 w; δ_H (400 MHz, $CDCl_3$) 6.97 (1H, t *J* 1, CHI), 3.91 (1H, d *J* 1, C<u>H</u>OCH_2CH_3), 3.80 (1H, br s, CO_2CH_3), 3.49 (1H, dqd *J* 9.5, 7, 1, OC<u>H</u>H'CH_3), 3.30 (1H, dqd *J* 9.5, 7, 1, OCH<u>H</u>'CH_3), 1.15 (1H, td *J* 7, 1, $OCH_2C\underline{H}_3$), 0.85 (9H, d *J*, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 167.8 (OC=O), 144.1 (<u>C</u>=CHI), 88.1 (<u>C</u>HOCH_2CH_3), 84.7 (C=<u>C</u>HI), 65.1 (CHO<u>C</u>H_2CH_3), 51.8 ($CO_2\underline{C}H_3$), 36.0 (<u>C</u>$(CH_3)_3$), 21.4 (C(<u>C</u>$H_3)_3$), 15.3 ($OCH_2\underline{C}H_3$); LRMS: dec.

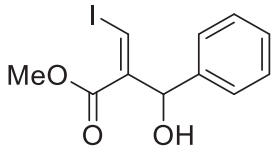
(*Z*)-3-(1-ethoxy-2,2-dimethylpropyl)-5-(2-hydroxy-2-methylpropylidene)furan-2(5*H*)-one (282):



To a solution of ester **ES-14** (50 mg, 0.15 mmol, 1 equiv) in THF (1 mL) was added TMSOK (29 mg, 0.23 mmol, 1.5 equiv) at rt. After 12 h, TLC analysis indicated some starting material remaining, further TMSOK (29 mg, 0.23 mmol, 1.5 equiv) was added and the reaction mixture heated at 60 °C. After 24 h, Et_2O (10 mL) and H_2O (10 mL) were added and the layers

separated; the etheral layer was discarded. The aq layer was acidified by addition of $KHSO_4$ (100 mg, 0.75 mmol, 5 equiv), and extracted with EtOAc (3 x 10 mL). The organic layers, were combined, dried (Na_2SO_4) and concentrated to give crude acid as a yellow oil (30 mg). Standard cross-coupling procedure was followed with the crude acid (30 mg) and 2-methyl-3-butyn-2-ol (44 µL, 0.45 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 80% EtOAc in petroleum ether) to give a yellow oil, butenolide **282** (15 mg, 58%): R_f 0.5 (40% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3437 br, 1760 s, 1365 w, 1238 w, 1163 m, 1100 m, 1021 m, 945 w, 919 w; δ_H (400 MHz, $CDCl_3$) 7.16 (1H, d *J* 1, C<u>H</u>=C(C=O)), 5.42 (1H, s, OC=CH), 3.90 (1H, d *J* 1, C<u>H</u>OCH_2CH_3), 3.43 (1H, dq *J* 9.5, 7, OC<u>H</u>H'CH_3), 3.31 (1H, dq *J* 9.5, 7, OCH<u>H</u>'CH_3), 2.52 (1H, br s, OH), 1.54 (6H, s, $C(CH_3)_2$), 1.15 (3H, t *J* 7, $OCH_2C\underline{H}_3$), 0.92 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 169.5 (OC=O), 146.3 (O<u>C</u>=CH), 140.4 (<u>C</u>H=C(C=O)), 133.5 (CH=<u>C</u>(C=O)), 122.1 (OC=<u>C</u>H), 80.9 (<u>C</u>HOCH_2CH_3), 70.7 (O<u>C</u>$(CH_3)_2$), 65.6 (O<u>C</u>H_2CH_3), 36.1 (<u>C</u>$(CH_3)_3$), 30.3 (C(<u>C</u>$H_3)_2$), 25.5 (C(<u>C</u>$H_3)_3$), 15.2 ($OCH_2\underline{C}H_3$); LRMS (ESI^+): 279 ($[M+H]^+$, 40%), 291 ($[M+Na]^+$, 100); HRMS (ESI^+) m/z: calcd for $C_{15}H_{24}O_4Na$ $[M+Na]^+$: 291.1567, found 291.1567.

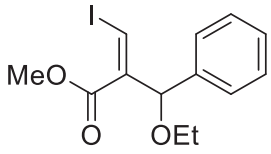
Methyl (*Z*)-2-(hydroxy(phenyl)methyl)-3-iodoacrylate (ES-15):



Standard procedure for β-iodo MBH was followed using freshly distilled benzaldehyde (406 µL, 4.0 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 9% EtOAc in petroleum ether) to give a yellow oil, iodoacrylate **ES-15** (998 mg, 78%): IR (neat/cm^{-1}) 3436 br, 1715 s, 1434 w, 1317 m, 1283 m, 1202 m, 822 w, 765 w, 700 m; δ_H (400 MHz, $CDCl_3$) 7.39-7.31 (5H, m, Ph), 7.29 (1H, t *J* 1.5, CHI), 5.56 (1H, dd *J*

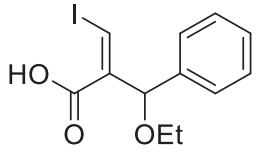
5.5, 1.5, C<u>H</u>OH), 3.74 (1H, d *J* 1.5, CO_2CH_3), 2.87 (1H, d *J* 5.5, OH); δ_C (100 MHz, $CDCl_3$) 166.3 (OC=O), 145.1 (<u>C</u>=CHI), 140.0, 128.7, 128.3 and 126.5 (Ph), 87.2 (CHI), 76.0 (CHOH), 51.9 (CO_2CH_3); LRMS (ESI^+): 341.0 ($[M+Na]^+$, 100%); HRMS (ESI^+) m/z: calcd for $C_{11}H_{11}O_3INa$ $[M+Na]^+$: 340.9645, found 340.9644.

Methyl (*Z*)-2-(ethoxy(phenyl)methyl)-3-iodoacrylate (ES-16):



Standard *O*-alkylation procedure was used using EtI with **ES-15** (500 mg, 1.45 mmol). The crude ether **ES-16** (550 mg, quant.) was used in the next step without further purification: IR (neat/cm^{-1}) 1731 s, 1453 w, 1433 w, 1283 m, 1255 m, 1201 m, 1026 m; δ_H (500 MHz, $CDCl_3$) 7.37-7.29 (5H, m, Ph), 7.10 (1H, d *J* 1.5, CHI), 5.17 (1H, d *J* 1.5, C<u>H</u>OCH_2CH_3), 3.74 (3H, s, CO_2CH_3), 3.51-3.45 (2H, m, OC<u>HH</u>'CH_3), 1.20 (3H, t *J* 7, $OCH_2C\underline{H}_3$); δ_C (125 MHz, $CDCl_3$) 166.3 (OC=O), 145.1 (<u>C</u>=CHI), 138.4 (*ipso*Ph), 128.5, 128.3 and 127.5 (Ph), 85.3 (CHI), 82.3 (<u>C</u>HOCH_2CH_3), 64.9 (O<u>C</u>H_2CH_3), 51.8 ($CO_2\underline{C}H_3$), 15.2 ($OCH_2\underline{C}H_3$); LRMS (ESI^+): 369 ($[M+Na]^+$, 100%); HRMS (ESI^+) m/z: calcd for $C_{13}H_{15}O_3INa$ $[M+Na]^+$: 368.9958, found 368.9957.

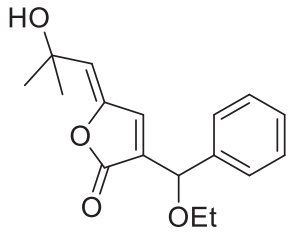
(*Z*)-2-(Ethoxy(phenyl)methyl)-3-iodoacrylic acid (ES-17):



Standard hydrolysis procedure was followed with **ES-16** (550 mg, 1.6 mmol) to give a yellow sticky oil, iodoacrylic acid **ES-17** (400 mg, 75%): IR (neat/cm^{-1}) 3500 br, 1699 s, 1454 w, 1398 w, 1262 m, 1188 m, 1072 s, 756 m, 699 m; δ_H (400 MHz, $CDCl_3$) 7.39-7.29 (1H, 6H, Ph

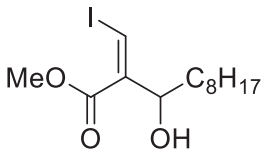
and CHI), 5.21 (1H, d *J* 1.5, C<u>H</u>OCH$_2$CH$_3$), 3.56-3.44 (2H, m, OC<u>H$_2$</u>CH$_3$), 1.22 (3H, t *J* 7, OCH$_2$C<u>H$_3$</u>); 169.3 (OC=O), 143.1 (<u>C</u>=CHI), 138.1 (*ipso*Ph), 128.6, 128.4 and 127.4 (Ph), 89.3 (C=<u>C</u>HI), 82.2 (<u>C</u>HOCH$_2$CH$_3$), 65.0 (O<u>C</u>H$_2$CH$_3$), 15.1 (OCH$_2$<u>C</u>H$_3$); LRMS (ESI$^-$): 331 ([M–H]$^-$, 100%); HRMS (ESI$^-$) m/z: calcd for $C_{12}H_{12}O_3I$ [M–H]$^-$: 330.9837, found 330.9835.

(*Z*)-3-(Ethoxy(phenyl)methyl)-5-(2-hydroxy-2-methylpropylidene)furan-2(5*H*)-one (283):



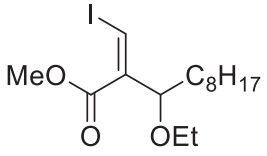
Standard cross-coupling procedure was followed with the above crude acid **ES-17** (66 mg, 0.20 mmol) and 2-methyl-3-butyn-2-ol (58 µL, 0.60 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 80% EtOAc in petroleum ether) to give a yellow oil, butenolide **283** (30 mg, 52%): R_f 0.5 (40% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3447 br, 1759 s, 1454 w, 1362 w, 1163 m, 1047 m, 914 w, 700 m; δ_H (400 MHz, $CDCl_3$) 7.47-7.30 (5H, m, Ph), 7.16 (1H, d *J* 1, CH=C(C=O)), 5.40 (1H, s, OC=CH), 5.21 (1H, d *J* 1, C<u>H</u>OCH$_2$CH$_3$), 3.52 (2H, q *J* 7, OC<u>H$_2$</u>CH$_3$), 2.49 (1H, br s, OH) 1.49 and 1.48 (2 x 3H, 2 x s, OC(CH$_3$)$_2$), 1.24 (3H, t *J* 7, OCH$_2$C<u>H$_3$</u>); δ_C (100 MHz, $CDCl_3$) 167.9 (OC=O), 146.1 (O<u>C</u>=CH), 138.6 (*ipso*Ph), 138.5 (<u>C</u>H=C(C=O)), 134.4 (CH=<u>C</u>(C=O)), 128.7, 128.3 and 126.9 (Ph), 122.9 (OC=<u>C</u>H), 75.6 (<u>C</u>HOCH$_2$CH$_3$), 70.6 (O<u>C</u>(CH$_3$)$_2$) , 64.9 (O<u>C</u>H$_2$CH$_3$), 31.0 and 30.2 (C(<u>C</u>H$_3$)$_2$), 15.2 (OCH$_2$<u>C</u>H$_3$); LRMS (ESI$^+$): 311 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) m/z: calcd for $C_{17}H_{20}O_5Na$ [M+Na]$^+$: 311.1254, found 311.1253.

Methyl (*Z*)-3-hydroxy-2-(iodomethylene)undecanoate (ES-18):



Standard procedure for β-iodo MBH was followed using nonaldehyde (686 μL, 4.0 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 9% EtOAc in petroleum ether) to give a yellow oil, iodoacrylate **ES-18** (720 mg, 51%): R_f 0.3 (5% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3462 br, 1717 s, 1458 s, 1435 m, 1306 m, 1200 s, 1175 m, 1067 w; δ_H (400 MHz, $CDCl_3$) 7.14 (1H, d *J* 1, CHI), 4.40 (1H, tdd *J* 7.5, 6, 1, C<u>H</u>OH), 3.85 (3H, s, CO_2CH_3), 2.40 (1H, br d *J* 6.5, OH), 1.65-1.57 (2H, m, C<u>H</u>$_2$(CH_2)$_6CH_3$), 1.31-1.26 (12H, br m, CH_2(C<u>H</u>$_2$)$_6CH_3$), 0.87 (3H, d *J* 7, CH_2(CH_2)$_6$C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 166.8 (OC=O), 146.8 (<u>C</u>=CHI), 84.7 (C=<u>C</u>HI), 75.0 (CHOH), 52.0 (CO_2<u>C</u>H_3), 36.1 (<u>C</u>H$_2$(CH_2)$_6CH_3$), 31.8, 29.4, 29.3, 29.2, 25.5 and 22,6 (CH_2(<u>C</u>H$_2$)$_6CH_3$), 14.1 (CH_2(CH_2)$_6$<u>C</u>H_3); LRMS: dec.

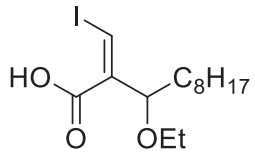
Methyl (*Z*)-3-ethoxy-2-(iodomethylene)undecanoate (ES-19):



Standard *O*-alkylation procedure was used using EtI with **ES-18** (360 mg, 1.02 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 2% Et_2O in petroleum ether) to give a yellow oil, ethyl ether **ES-19** (240 mg, 62%): R_f 0.5 (1% Et_2O in petroleum ether); IR (neat/cm^{-1}) 1732 s, 1456 w, 1433 w, 1342 w, 1298 m, 1198 m, 1173 m, 1098 m; δ_H (400 MHz, $CDCl_3$) 6.94 (1H, br s, CHI), 4.02 (1H, dd *J* 7.5, 5, C<u>H</u>OCH_2CH_3), 3.82 (3H, s, CO_2CH_3), 3.55 (1H, dq *J* 9.5, 7, CHOC<u>H</u>H'CH_3), 3.35 (1H, dq *J*

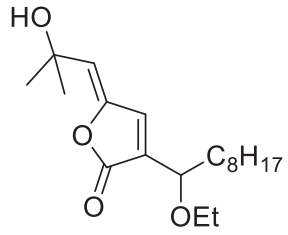
9, 7, CHOCHH'CH_3), 1.63-1.50 (2H, m, CH_2(CH_2)$_6CH_3$), 1.43-1.36 (12H, br m, CH_2(CH_2)$_6CH_3$), 1.18 (3H, t *J* 7, OCH_2CH_3), 0.88 (3H, t *J* 6.5, CH_2(CH_2)$_6$CH_3); δ_C (100 MHz, $CDCl_3$) 166.9 (OC=O), 146.4 (C=CHI), 82.8 (C=CHI), 81.9 (CHOCH_2CH_3), 64.9 (CHOCH_2CH_3), 52.0 (CO_2CH_3), 35.5 (CH_2(CH_2)$_6CH_3$), 31.8, 29.4, 29.3, 29.2, 25.5 and 22.6 (CH_2(CH_2)$_6CH_3$), 15.2 (OCH_2CH_3), 14.1 (CH_2(CH_2)$_6$CH_3). LRMS: dec

(*Z*)-3-Ethoxy-2-(iodomethylene)undecanoic acid (ES-20):



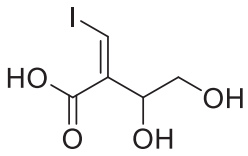
Standard hydrolysis procedure was followed with **ES-19** (240 mg, 0.63 mmol) to give a yellow sticky oil, iodoacrylic acid **ES-20** (150 mg, 65%): IR (neat/cm^{-1}) 3500 br, 1700 s, 1462 w, 1381 m, 1264 w, 1157 m, 1094 m, 953 w, 722 w; δ_H (400 MHz, $CDCl_3$) 7.27 (1H, s, CHI), 4.08 (1H, t *J* 6.5, CHOCH_2CH_3), 3.59 (1H, dq 8.5, 7, OCHH'CH_3), 3.48-3.36 (1H, m, OCHH'CH_3), 1.62 (2H, q *J* 7, CH_2(CH_2)$_6CH_3$), 1.43-1.26 (12H, br m, CH_2(CH_2)$_6CH_3$), 1.22 (3H, t *J* 7, OCH_2CH_3), 0.88 (3H, t *J* 7, CH_2(CH_2)$_6$CH_3); δ_C (100 MHz, $CDCl_3$) 168.9 (OC=O), 143.3 (C=CHI), 87.6 (C=CHI), 82.5 (CHOCH_2CH_3), 65.2 (CHOCH_2CH_3), 35.2 (CH_2(CH_2)$_6CH_3$), 31.8, 31.8, 29.4, 29.3, 29.2, 25.5 and 22.6 (CH_2(CH_2)$_6CH_3$), 15.1 (OCH_2CH_3), 14.1 (CH_2(CH_2)$_6$CH_3); LRMS (ESI^-): 367 ([M–H]$^-$, 100%); HRMS (ESI^-) m/z: calcd for $C_{14}H_{24}O_3I$ [M–H]$^-$: 367.0776, found 367.0773.

(*Z*)-3-(1-Ethoxynonyl)-5-(2-hydroxy-2-methylpropylidene)furan-2(5*H*)-one (284):



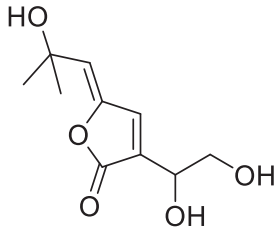
Standard cross-coupling procedure was followed with the above crude acid **ES-20** (73 mg, 0.20 mmol) and 2-methyl-3-butyn-2-ol (58 μL, 0.60 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 80% EtOAc in petroleum ether) to give a yellow oil, butenolide **284** (35 mg, 54%): R_f 0.5 (40% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3422 br, 1759 s, 1466 w, 1375 w, 1240 w, 1163 m, 1029 m, 979 m, 945 w, 782 w, 722 w; δ_H (500 MHz, $CDCl_3$) 7.14 (1H, d *J* 1, CH=C(C=O)), 5.41 (1H, s, OC=CH), 4.19 (1H, ddd *J* 7.5, 4.5, 1, C<u>H</u>OCH_2CH_3), 3.52 (1H, dq *J* 9.5, 7, OC<u>H</u>H'CH_3), 3.45 (1H, dq *J* 9.5, 7, OCH<u>H</u>'CH_3), 2.49 (1H, br s, OH), 1.76-1.69 (1H, m, C<u>H</u>H'$(CH_2)_6CH_3$), 1.67-1.60 (1H, m, CH<u>H</u>'$(CH_2)_6CH_3$), 1.53 (6H, s, $C(CH_3)_2$), 1.32-1.26 (12H, br m, $CH_2(C\underline{H}_2)_6CH_3$), 1.21 (3H, t *J* 7, $OCH_2C\underline{H}_3$), 0.88 (3H, t *J* 7, $CH_2(CH_2)_6C\underline{H}_3$); δ_C (125 MHz, $CDCl_3$) 168.6 (OC=O), 146.2 (O<u>C</u>=CH), 138.5 (<u>C</u>H=C(C=O)), 135.0 (CH=<u>C</u>(C=O)), 122.2 (OC=<u>C</u>H), 74.0 (<u>C</u>HOCH_2CH_3), 70.6 (O<u>C</u>$(CH_3)_2$), 65.3 (O<u>C</u>H_2CH_3), 34.8 (<u>C</u>$H_2(CH_2)_6CH_3$), 31.8, 31.0, 30.3, 29.5, 29.4, 29.2, 25.2 and 22.6 ($CH_2(\underline{C}H_2)_6CH_3$ and $C(\underline{C}H_3)_2$), 15.4 ($OCH_2\underline{C}H_3$), 14.1 ($CH_2(CH_2)_6\underline{C}H_3$); LRMS ($ESI^+$): 347 ($[M+Na]^+$, 100%); HRMS ($ESI^+$) m/z: calcd for $C_{19}H_{32}O_4Na$ $[M+Na]^+$: 347.2193, found 347.2193.

(*Z*)-3,4-Dihydroxy-2-(iodomethylene)butanoic acid (ES-21):



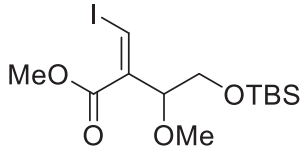
Standard hydrolysis procedure was followed with **235** (100 mg, 0.25 mmol) to give a brown sticky oil, iodoacrylic acid **ES-21** (40 mg, 60%): IR (neat/cm^{-1}) 3368 br, 1699 s, 1393 m, 1266 m, 1203 s, 1072 m, 722 w; δ_H (400 MHz, CD_3OD) 7.18 (1H, d *J* 1.5, CHI), 4.48 (1H, ddd *J*, 6.5, 4.0, 1.5, C<u>H</u>OD), 3.67 (1H, dd *J* 11.5, 4, C<u>H</u>H'OD), 3.49 (1H, dd *J* 11.5, 6.5, CH<u>H</u>'OD); δ_C (100 MHz, CD_3OD) 169.6 (CO_2D), 147.5 (<u>C</u>=CHI), 84.1 (C=<u>C</u>HI), 75.7 (CHOD), 66.4 (CH_2OD); LRMS (ESI^-): dec.

(*Z*)-3-(1,2-Dihydroxyethyl)-5-(2-hydroxy-2-methylpropylidene)furan-2(5*H*)-one (285):



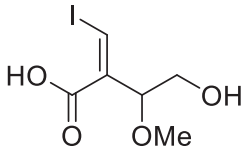
Standard cross-coupling procedure was followed with the above crude acid **ES-21** (40 mg, 0.15 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: 50% EtOAc in petroleum ether to EtOAc) to give a yellow oil, butenolide **285** (14 mg, 42%): R_f 0.2 (EtOAc); IR (neat/cm^{-1}) 3364 br, 1751 s, 1364 w, 1252 w, 1167 m, 1070 m, 1026 m, 919 w; δ_H (500 MHz, CD_3OD) 7.43 (1H, d *J* 1.5, CH=C(C=O)), 5.51 (1H, s, OC=CH), 4.54-4.52 (1H, m, C<u>H</u>OD), 3.76 (1H, dd *J* 11.5, 4, C<u>H</u>H'OD), 3.65 (1H, dd *J* 11.5, 6, CH<u>H</u>'OD), 1.49 (6 H, s, $C(CH_3)_2$); δ_C (125 MHz, CD_3OD) 170.6 (OC=O), 147.4 (O<u>C</u>=CH), 142.1 (<u>C</u>H=C(C=O)), 134.5 (CH=<u>C</u>(C=O)), 124.5 (OC=<u>C</u>H), 71.2 (O<u>C</u>$(CH_3)_2$), 68.9 (CHOD), 65.6 (CH_2OD), 30.3 (C(<u>C</u>$H_3)_2$); LRMS (ESI^+): dec.

Methyl (*Z*)-4-((*tert*-butyldimethylsilyl)oxy)-2-(iodomethylene)-3-methoxybutanoate (ES-22):



Standard *O*-alkylation procedure was used using MeI with **235** (150 mg, 0.40 mmol). The residue was purified by chromatography (SiO_2, gradient elution: petroleum ether to 2% Et_2O in petroleum ether) to give a yellow oil, methyl ether **ES-22** (120 mg, 77%): R_f 0.5 (4% Et_2O in petroleum ether); IR (neat/cm^{-1}) 1732 m, 1462 w, 1433 w, 1252 m, 1198 m, 1109 s, 835 s, 777 s; δ_H (400 MHz, $CDCl_3$) 7.17 (1H, d *J* 1, CHI), 4.11 (1H, ddd *J* 6, 4.5, 1, C<u>H</u>OCH_3), 3.82 (3H, s, CO_2CH_3), 3.70 (1H, dd *J* 10.5, 4.5, C<u>H</u>H'OTBS), 3.63 (1H, dd *J* 10.5, 6, CH<u>H</u>'OTBS), 3.35 (3H, s, CHOC<u>H</u>$_3$), 0.88 ($SiC(CH_3)_3$), 0.04 (6H, s, $Si(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 166.2 (<u>C</u>O_2CH_3), 141.9 (<u>C</u>=CHI), 86.5 (C=<u>C</u>HI), 84.1 (<u>C</u>HOCH_3), 65.5 (CH_2OTBS), 57.8 (CHO<u>C</u>H_3), 51.9 (CO_2<u>C</u>H_3), 25.8 ($SiC(\underline{C}H_3)_3$), 18.3 ($Si\underline{C}(CH_3)_3$), −5.33 ($Si(CH_3)_2$). LRMS (ESI^+): dec.

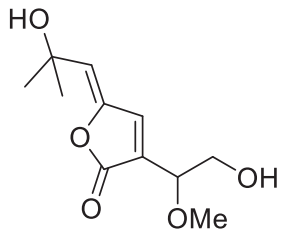
(*Z*)-4-Hydroxy-2-(iodomethylene)-3-methoxybutanoic acid (ES-23):



Standard hydrolysis procedure was followed with methyl ether **ES-22** (60 mg, 0.15 mmol) to give a brown sticky oil, iodoacrylic acid **ES-23** (40 mg, 98%): IR (neat/cm^{-1}) 3401 br, 1703 s, 1272 w, 1190 m, 1110 s, 1054 s, 838 m, 722 w, 676 w; δ_H (400 MHz, $CDCl_3$) 7.45 (1H, d *J* 1, CHI), 4.23 (1H, ddd *J* 7, 3.5, 1, C<u>H</u>OCH_3), 3.80 (1H, dd *J* 12, 3.5, C<u>H</u>H'OH), 3.62 (1H, dd *J* 12, 7, CH<u>H</u>'OH), 3.39 (3H, s, CHOC<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 169.0 (CO_2H), 139.8 (<u>C</u>=CHI),

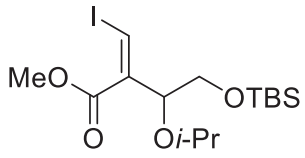
90.0 (C=CHI), 83.6 (CHOCH$_3$), 64.7 (CH$_2$OH), 57.6 (OCH$_3$); LRMS (ESI$^-$): 271 ([M–H]$^-$, 100%); HRMS (ESI$^-$) m/z: calcd for $C_6H_8O_4I$ [M–H]$^-$: 270.9473, found 270.9471.

(*Z*)-3-(2-Hydroxy-1-methoxyethyl)-5-(2-hydroxy-2-methylpropylidene)furan-2(5*H*)-one (286):



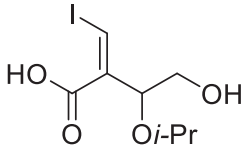
Standard cross-coupling procedure was followed with the above crude acid **ES-23** (40 mg, 0.15 mmol). The residue was purified by column chromatography (SiO$_2$, gradient elution: petroleum ether to 80% EtOAc in petroleum ether) to give a yellow oil, butenolide **286** (22 mg, 67%): R_f 0.3 (80% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3404 br, 1753 s, 1667 w, 1462 w, 1364 w, 1242 w, 1165 m, 1113 m, 1055 m, 980 w, 914 w; δ_H (400 MHz, CDCl$_3$) 7.27 (1H, s, CH=C(C=O)), 5.47 (1H, s, OC=CH), 4.24 (1H, ddd *J* 6, 3.5, 1.5, CHOCH$_3$), 3.86 (1H, d *J* 12, CHH'OH), 3.67 (1H, dd *J* 12, 5.5, CHH'OH), 3.42 (3H, s, OCH$_3$), 2.64 and 2.44 (2 x 1H, 2 br s, 2 x OH), 1.52 (6H, s, OC(CH$_3$)$_2$); δ_C (100 MHz, CDCl$_3$) 168.5 (OC=O), 146.0 (OC=CH), 140.8 (CH=C(C=O)), 130.3 (CH=C(C=O)), 123.4 (OC=CH), 76.6 (CHOCH$_3$), 70.6 (OC(CH$_3$)$_2$), 63.5 (CH$_2$OH), 57.8 (OCH$_3$), 30.2 (C(CH$_3$)$_2$); LRMS (ESI$^+$): 251 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) m/z: calcd for $C_{11}H_{16}O_5Na$ [M+Na]$^+$: 251.0890, found 251.0892.

Methyl (*Z*)-4-((*tert*-butyldimethylsilyl)oxy)-2-(iodomethylene)-3-isopropoxybutanoate (ES-24):



Standard *O*-alkylation procedure was used using *i*-PrI with **235** (150 mg, 0.4 mmol). The residue was purified by chromatography (SiO_2, gradient elution: petroleum ether to 2% Et_2O in petroleum ether) to give a yellow oil, isopropyl ether **ES-24** (50 mg, 30%): R_f 0.5 (4% Et_2O in petroleum ether); IR (neat/cm^{-1}) 1732 m, 1254 w, 1198 w, 1175 w, 1117 s, 1088 m, 837 s, 777 s; δ_H (400 MHz, $CDCl_3$) 7.15-7.14 (1H, m, CHI), 4.29 (1H, ddd *J* 6.5, 5, 1, C<u>H</u>OCH$(CH_3)_2$), 3.82 (1H, s, CO_2CH_3), 3.67-3.56 (3H, m, C<u>H</u>$_2$OTBS and CHOC<u>H</u>$(CH_3)_2$), 1.16 and 1.13 (2 x 3H, 2 x d *J* 6, CH(C<u>H</u>$_3)_2$), 0.88 (9H, s, SiC$(CH_3)_3$), 0.04 (6H, s, Si$(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 166.5 (OC=O), 144.1 (<u>C</u>=CHI), 85.5 (C=<u>C</u>HI), 79.7 (<u>C</u>HOCH$(CH_3)_2$), 70.9 (CHO<u>C</u>H$(CH_3)_2$), 66.0 (<u>C</u>H$_2$OTBS), 51.8 (CO_2CH_3), 25.8 (SiC(<u>C</u>H$_3)_3$), 23.0 and 21.6 (CH(<u>C</u>H$_3)_2$), 18.3 (Si<u>C</u>$(CH_3)_3$), –5.42 (Si$(CH_3)_2$); LRMS (ESI^+): dec.

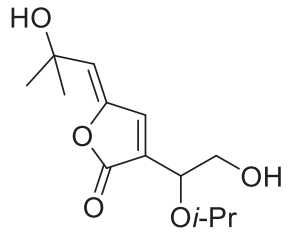
(*Z*)-4-Hydroxy-2-(iodomethylene)-3-isopropoxybutanoic acid (ES-25):



Standard hydrolysis procedure was followed with isopropyl ether **ES-24** (50 mg, 0.12 mmol) to give a brown sticky oil, impure iodoacrylic acid **ES-25** (30 mg, ~86%): discernible data: IR (neat/cm^{-1}) 3500 br, 1703 s, 1463 w, 1382 m, 1255 m, 1180 m, 1110 s, 836 s, 778 m; δ_H (400 MHz, $CDCl_3$) 7.47 (1H, d *J* 1, CHI), 4.44-4.40 (1H, m, C<u>H</u>OCH$(CH_3)_2$), 3.76-3.54 (3H, m, CH_2OH and CHOC<u>H</u>$(CH_3)_2$), 1.21-1.14 (6 H, m, CHOCH(C<u>H</u>$_3)_2$); δ_C (100 MHz, $CDCl_3$) 169.1

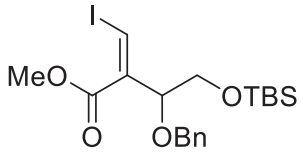
(CO_2H), 141.3 (C=CHI), 89.6 (C=CHI), 79.2 ($CHOCH(CH_3)_2$), 71.3 ($CHOCH(CH_3)_2$), 65.1 (CH_2OH), 23.1 and 21.5 ($CH(CH_3)_2$); LRMS (ESI^+): dec.

(*Z*)-3-(2-Hydroxy-1-isopropoxyethyl)-5-(2-hydroxy-2-methylpropylidene)furan-2(5*H*)-one (287):



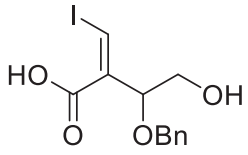
Standard cross-coupling procedure was followed with the above crude acid **ES-25** (30 mg, 0.15 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 80% EtOAc in petroleum ether) to give a yellow oil, butenolide **287** (10 mg, 39%): R_f 0.3 (80% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3421 br, 1757 s, 1381 w, 1164 w, 1121 m, 1030 m, 976 m; δ_H (500 MHz, $CDCl_3$) 7.25 (1H, d *J* 1, CH=C(C=O)), 5.45 (1H, s, OC=CH), 4.43 (1H, ddd *J* 5.5, 3.5, 1, $CHOCH(CH_3)_2$), 3.84-3.80 (1H, ddd *J* 11, 6.5, 3.5, CHH'OH), 3.71 (1H, hept *J* 6, $CHOCH(CH_3)_2$), 3.64-3.60 (1H, ddd *J* 11, 6.5, 5.5, CHH'OH), 2.47 (1H, br s, $(CH_3)_2COH$), 2.22 (1H, t *J* 6.5, CH_2OH), 1.53 and 1.52 (2 x 3H, 2 x s, $OC(CH_3)_2$), 1.22 and 1.19 (2 x 3H, 2 x d *J* 6, $OCH(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 168.4 (OC=O), 146.2 (OC=CH), 140.5 (CH=C(C=O)), 132.0 (CH=C(C=O)), 123.0 (OC=CH), 72.3 ($CHOCH(CH_3)_2$), 71.4 ($CHOCH(CH_3)_2$) 70.7 ($OC(CH_3)_2$), 64.2 (CH_2OH), 30.3 ($C(CH_3)_2$), 23.1 and 21.91 ($CHOCH(CH_3)_2$); LRMS (ESI^+): 279 ($[M+Na]^+$, 100%); HRMS (ESI^+) m/z: calcd for $C_{13}H_{20}O_5Na$ $[M+Na]^+$: 271.1203, found 279.1203.

Methyl (*Z*)-3-(benzyloxy)-4-((*tert*-butyldimethylsilyl)oxy)-2-(iodomethylene)butanoate (ES-26):



Standard *O*-alkylation procedure was used using BnCl with **235** (300 mg, 0.80 mmol). The residue was purified by chromatography (SiO_2, gradient elution: petroleum ether to 2% Et_2O in petroleum ether) to give a yellow oil, benzyl ether **ES-26** (170 mg, 46%): R_f 0.5 (4% Et_2O in petroleum ether); IR (neat/cm^{-1}) 1732 s, 1454 w, 1254 m, 1130 m, 845 s, 777 m, 735 w, 696 w; δ_H (400 MHz, $CDCl_3$) 7.39-7.28 (5H, m, Ph), 7.23 (1H, d *J* 1, CHI), 4.64 (1H, d *J* 12, C<u>H</u>H'Ph), 4.46 (1H, d *J* 12, CH<u>H</u>'Ph), 4.34 (1H, ddd *J* 6, 5, 1, C<u>H</u>OBn), 3.82 (3H, s, CO_2CH_3), 3.77-3.68 (2H, m, C<u>H</u>$_2$OTBS), 0.88 (9H, s, $SiC(CH_3)_3$), 0.04-0.03 (2 x 3H, 2 x s, $Si(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 166.3 (OC=O), 142.6 (<u>C</u>=CHI), 137.7 (*ipso*Ph), 128.6, 128.4 and 127.7 (Ph), 86.5 (CHI), 81.5 (<u>C</u>HOCH$_2$Ph), 71.5 (O<u>C</u>H$_2$Ph), 65.7 (<u>C</u>H$_2$OTBS), 51.9 (CO_2CH_3), 25.8 (SiC(<u>C</u>H$_3$)$_3$), 18.3 (Si<u>C</u>(CH$_3$)$_3$), -5.38 and -5.46 ($Si(CH_3)_2$); LRMS (ESI^+): 499 ($[M+Na]^+$, 100%); HRMS (ESI^+) m/z: calcd for $C_{19}H_{29}O_4INaSi$ $[M+Na]^+$: 499.0772, found 499.0769.

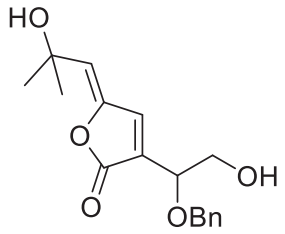
(*Z*)-3-(Benzyloxy)-4-hydroxy-2-(iodomethylene)butanoic acid (ES-27):



Standard hydrolysis procedure was followed with benzyl ether **ES-26** (150 mg, 0.38 mmol) to give a colorless solid, iodoacrylic acid **ES-27** (70 mg, 64%): Mp 85-87 °C; IR (neat/cm^{-1}) 3450 br, 1699 s, 1454 w, 1209 m, 1101 s, 1070 s, 837 m, 698 m; δ_H (400 MHz, CD_3OD) 7.37-7.27 (5H, m, Ph), 7.17 (1H, d *J* 1, CHI), 4.61 (1H, d *J* 11.5, OC<u>H</u>H'Ph), 4.46 (1H, d *J* 1, OCH<u>H</u>'Ph),

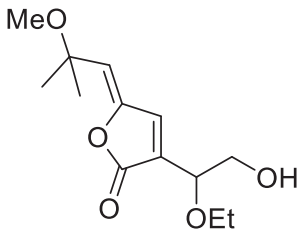
4.29 (1H, ddd *J* 6.5, 4, 1, C<u>H</u>OCH$_2$Ph), 3.68 (1H, dd *J* 12, 4, C<u>H</u>H'OD), 3.61 (1H, dd *J* 12, 6.5); δ_C (100 MHz, CD_3OD) 169.5 (OC=O), 145.4 (<u>C</u>=CHI), 139.4, 129.5, 129.3 and 129.0 (Ph), 85.3 (CHI), 83.8 (C<u>H</u>OCH$_2$Ph), 72.7 (OCH$_2$Ph), 65.5 (CH_2OD); LRMS (ESI^-): 346 ($[M-H]^-$, 100%); HRMS (ESI^-) m/z: calcd for $C_{12}H_{12}O_4I$ $[M-H]^-$: 346.9786, found 346.9785.

(*Z*)-3-(1-(Benzyloxy)-2-hydroxyethyl)-5-(2-hydroxy-2-methylpropylidene)furan-2(5*H*)-one (288):



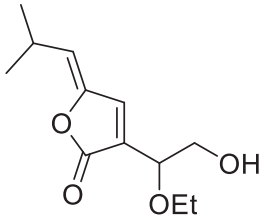
Standard cross-coupling procedure was followed with the above crude acid **ES-27** (55 mg, 0.10 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 80% EtOAc in petroleum ether) to give a yellow oil, butenolide **288** (25 mg, 52%): R_f 0.3 (60% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3396 br, 1755 s, 1361 w, 1165 w, 1103 m, 1028 m, 1028 m, 979 w, 740 w, 699 w; δ_H (400 MHz, $CDCl_3$) 7.39-7.34 (5H, m, Ph), 7.30 (1H, d *J* 1, CH=C(C=O)), 5.46 (1H, s, OC=CH), 4.63 (1H, d *J* 11.5, OC<u>H</u>H'Ph), 4.54 (1H, d *J* 11.5, OCH<u>H</u>'Ph), 4.46 (1H, ddd *J* 5, 3.5, 1, C<u>H</u>OCH$_2$Ph), 3.89-3.84 (1H, br m, C<u>H</u>H'OH), 3.73-3.68 (1H, br m, CH<u>H</u>'OH), 2.64 and 2.45 (2 x 1H, 2 x br s, 2 x OH), 1.52 (6H, s, C(CH$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 169.0 (OC=O), 146.0 (O<u>C</u>=CH), 140.9 (<u>C</u>H=C(C=O)), 137.1 (Ph), 130.6 (CH=<u>C</u>(C=O)), 128.6, 128.2 and 127.8 (Ph), 123.5 (OC=<u>C</u>H), 74.3 (C<u>H</u>OCH$_2$Ph), 72.0 (O<u>C</u>H$_2$Ph), 70.6 (O<u>C</u>(CH$_3$)$_2$), 63.7 (CH_2OH), 30.2 (C(<u>C</u>H$_3$)$_2$); LRMS (ESI^+): 327 ($[M+Na]^+$, 100%); HRMS (ESI^+) m/z: calcd for $C_{17}H_{20}O_5Na$ $[M+Na]^+$: 327.1203, found 327.1201.

(*Z*)-3-(1-Ethoxy-2-hydroxyethyl)-5-(2-methoxy-2-methylpropylidene)furan-2(5*H*)-one (289):



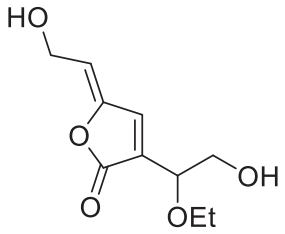
Standard cross-coupling procedure was followed with the crude acid **236** (40 mg, 0.14 mmol) and 3-methoxy-3-methylbut-1-yne (53 μL, 0.42 mmol). The residue was purified by column chromatography (SiO_2, gradient elution from petroleum ether to 40% EtOAc in petroleum ether) to give a yellow oil, butenolide **289** (21 mg, 59%): R_f 0.3 (40% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3433 br, 1759 s, 1170 w, 1106 m, 1068 s, 1021 m, 973 w, 860 w; δ_H (500 MHz, $CDCl_3$) 7.27 (1H, br s, CH=C(C=O)), 5.32 (1H, s, OC=CH), 4.35 (1H, ddd *J* 6, 3.5, 1.5, C<u>H</u>OCH_2CH_3), 3.87 (1H, dd *J* 11, 6, C<u>H</u>H'OH), 3.69-3.55 (3H, m, O<u>C</u>H_2CH_3 and CH<u>H</u>'OH), 3.26 (3H, s, OCH_3), 2.20 (1H, br s, OH), 1.50 (6H, s, $OC(CH_3)_2$), 1.26 (3H, t *J* 7, $OCH_2C\underline{H}_3$); δ_C (125 MHz, $CDCl_3$) 169.0 (OC=O), 147.3 (O<u>C</u>=CH), 140.7 (<u>C</u>H=C(C=O)), 131.1 (CH=<u>C</u>(C=O)), 121.6 (OC=<u>C</u>H), 75.3 ($(CH_3)_2\underline{C}OCH_3$), 74.7 (<u>C</u>HO$CH_2CH_3$), 65.7 (O<u>C</u>$H_2CH_3$), 63.8 ($CH_2OH$), 51.0 ($OCH_3$), 26.4 and 26.3 ($C(\underline{C}H_3)_2$), 15.4 ($OCH_2CH_3$); LRMS ($ESI^+$): 279 ($[M+Na]^+$, 100%); HRMS ($ESI^+$) m/z: calcd for $C_{13}H_{20}O_5Na$ $[M+Na]^+$:279.1203, found 279.1203.

(*Z*)-3-(1-Ethoxy-2-hydroxyethyl)-5-(2-methylpropylidene)furan-2(5*H*)-one (290):



Standard cross-coupling procedure was followed with the crude acid **236** (40 mg, 0.14 mmol) and 3-methylbut-1-yne (43 μL, 0.42 mmol). The residue was purified by column chromatography (SiO_2, gradient elution from petroleum ether to 40% EtOAc in petroleum ether) to give a yellow oil, butenolide **290** (16 mg, 51%): R_f 0.3 (40% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3456 br, 1753 s, 1466 w, 1302 m, 1106 m, 1059 m, 1021 m, 965 m, 781 w; δ_H (500 MHz, $CDCl_3$) 7.25 (1H, d *J* 1, CH=C(C=O)), 5.17 (1H, d *J* 9.5, OC=CH), 4.35 (1H, ddd *J* 6, 3.5, 1, C<u>H</u>OCH_2CH_3), 3.85 (1H, ddd *J* 11.5, 7, 3.5, C<u>H</u>H'OH), 3.68-3.53 (3H, m, CH<u>H</u>'OH and O<u>C</u>H_2CH_3), 3.01 (1H, dh *J* 9.5, 6.5, C<u>H</u>$(CH_3)_2$), 2.22-2.18 (1H, m, OH), 1.25 (3H, t J *7*, $OCH_2C\underline{H}_3$), 1.11 and 1.10 (2 x 3H, 2 x d *J* 6.5, CH$(C\underline{H}_3)_2$); δ_C (125 MHz, $CDCl_3$) 169.3 (OC=O), 146.7 (O<u>C</u>=CH), 139.7 (<u>C</u>H=C(C=O)), 130.9 (CH=<u>C</u>(C=O)), 124.2 (OC=<u>C</u>H), 74.7 (<u>C</u>HOCH_2CH_3), 65.6 (O<u>C</u>H_2CH_3), 64.0 (CH_2OH), 26.5 (<u>C</u>H$(CH_3)_2$), 22.5 and 22.5 (CH$(\underline{C}H_3)_2$), 15.4 ($OCH_2\underline{C}H_3$); LRMS (ESI^+): 181 ($[M–EtO]^+$, 35%), 249 ($[M+Na]^+$, 100); HRMS (ESI^+) m/z: calcd for $C_{12}H_{19}O_4$ $[M+H]^+$:227.1278, found 277.1280.

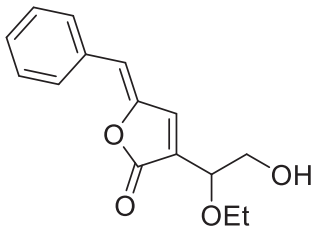
(*Z*)-3-(1-Ethoxy-2-hydroxyethyl)-5-(2-hydroxyethylidene)furan-2(5*H*)-one (291):



Standard cross-coupling procedure was followed with the crude acid **236** (40 mg, 0.14 mmol) and prop-2-yn-1-ol (25 μL, 0.42 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 80% EtOAc in petroleum ether) to give a yellow oil, butenolide **291** (15 mg, 50%): R_f 0.3 (80% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3421 br, 1768 s, 1439, w, 1376 w, 1175 m, 1102 s, 1069 s, 975 m, 725 w, 696 w; δ_H (500 MHz, $CDCl_3$) 7.32 (1H, d *J* 1, CH=C(C=O)), 5.48 (1H, t *J* 7, OC=CH), 4.52 (2H, dd *J* 7, 4, OC=CHC<u>H</u>$_2$OH), 4.36 (1H, ddd *J* 5, 3.5, 1, C<u>H</u>OCH_2CH_3), 3.87 (1H, ddd *J* 11.5, 6.5, 3.5, C<u>H</u>H'OH), 3.69-3.64

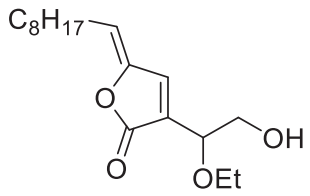
(1H, m, OCHCHH'OH), 3.63-3.52 (2H, m, OCH_2CH_3), 2.20 (1H, br t *J* 7, $OC=CHCH_2OH$), 1.84 (1H, br t *J* 6.5, $OCHCH_2OH$), 1.25 (3H, t *J* 7, OCH_2CH_3); δ_C (125 MHz, $CDCl_3$) 168.4 (OC=O), 148.3 (OC=CH), 139.3 (CH=C(C=O)), 132.8 (CH=C(C=O)), 113.9 (OC=CH), 74.8 ($CHOCH_2CH_3$), 65.7 (OCH_2CH_3), 63.8 ($OCHCH_2OH$), 57.3 ($OC=CHCH_2OH$), 15.4 (OCH_2CH_3); LRMS (ESI^+): 237 ($[M+Na]^+$, 100%); HRMS (ESI^+) m/z: calcd for $C_{10}H_{14}O_5Na$ $[M+Na]^+$:237.0733, found 237.0734.

(*Z*)-5-Benzylidene-3-(1-ethoxy-2-hydroxyethyl)furan-2(5*H*)-one (292):



Standard cross-coupling procedure was followed with the crude acid **236** (50 mg, 0.17 mmol) and phenylacetylene (56 μL, 0.51 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 40% EtOAc in petroleum ether) to give a yellow oil, butenolide **292** (27 mg, 60%): R_f 0.3 (40% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3462 br, 1749 s, 1608 w, 1451 w, 1355 w, 1109 m, 1054 m, 1014 m, 938 w, 759 w, 692 m; δ_H (400 MHz, $CDCl_3$) 7.79-7.76 (2H, m, Ph), 7.45 (1H, d *J* 1, CH=C(C=O)), 7.43-7.32 (3H, m, Ph), 6.06 (1H, s, OC=CH), 4.42 (1H, ddd *J* 6, 3.5, 1, $CHOCH_2CH_3$), 3.89 (1H, br s, CHH'OH), 3.71-3.56 (3H, m, CHH'OH and $CHOCH_2CH_3$), 2.26 (1H, br s, OH), 1.27 (3H, t *J* 7, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 169.3 (OC=O), 147.2 (OC=CH), 141.2 (CH=C(C=O)), 132.8 (CH=C(C=O)), 130.6, 130.2, 129.3 and 128.8 (Ph), 114.3 (OC=CH), 74.8 ($CHOCH_2CH_3$), 65.7 (OCH_2CH_3), 64.0 (CH_2OH), 15.4 (OCH_2CH_3); LRMS (ESI^+): 215 ($[M–EtO]^+$, 30%), 283 ($[M+Na]^+$, 100); HRMS (ESI^+) m/z : calcd for $C_{15}H_{16}O_4Na$: 283.0941 $[M+Na]^+$, found 283.0940.

(*Z*)-3-(1-Ethoxy-2-hydroxyethyl)-5-nonylidenefuran-2(5*H*)-one (293):



Standard cross-coupling procedure was followed with the crude acid **236** (25 mg, 0.9 mmol) and 1-decyne (46 μL, 0.27 mmol). The residue was purified by column chromatography (SiO_2, gradient elution: petroleum ether to 20% EtOAc in petroleum ether) to give a yellow oil, butenolide **293** (10 mg, 39%): R_f 0.3 (30% EtOAc in petroleum ether); IR (neat/cm^{-1}) 3454 br, 1763 s, 1459 w, 1377 w, 1109 m, 1016 m, 976 m, 779 w; δ_H (500 MHz, $CDCl_3$) 7.27 (1H, d *J* 1, CH=C(C=O)), 5.32 (1H, t *J* 8, OC=CH), 4.36-4.34 (1H, m, C<u>H</u>OCH_2CH_3), 3.87-3.83 (1H, br m, C<u>H</u>H'OH), 3.64-3.62 (1H, m, CH<u>H</u>'OH), 3.62-3.49 (2H, m, O<u>C</u>H_2CH_3), 2.39 (2H, d *J* 8, OC=CHC<u>H</u>$_2(CH_2)_6CH_3$), 2.23 (1H, t *J* 6.5, OH), 1.50-1.27 (12H, br m, $CH_2(C$<u>H</u>$_2)_6CH_3$), 1.25 (3H, t *J* 7, OCH_2C<u>H</u>$_3$), 0.89 (3H, t *J* 7, $CH_2(CH_2)_6C$<u>H</u>$_3$); δ_C (125 MHz, $CDCl_3$) 169.3 (OC=O), 148.3 (O<u>C</u>=CH), 139.4 (<u>C</u>H=C(C=O)), 130.8 (CH=<u>C</u>(C=O)), 117.9 (OC=<u>C</u>H), 74.7 (<u>C</u>HOCH_2CH_3), 65.8 (O<u>C</u>H_2CH_3), 64.0 (OCH<u>C</u>H_2OH), 31.80, 29.3, 29.3, 29.2, 29.0 and 22.6 ($CH_2(\underline{C}H_2)_6CH_3$), 26.5 ($\underline{C}H_2(CH_2)_6CH_3$), 15.4 ($OCH_2\underline{C}H_3$), 14.1 ($CH_2(CH_2)_6\underline{C}H_3$); LRMS ($ESI^+$): 251 ($[M–EtO]^+$, 50%), 319 ($[M+Na]^+$, 100); HRMS ($ESI^+$) m/z : calcd for $C_{17}H_{29}O_4$: 297.2060 $[M+H]^+$, found 297.2061.

7.3. Viability assays

The following protocol was provided by Frances Willenbrock. The assays were carried out by the latter and Christopher Towers. Some early tests were also carried out by Laia Culleré.

The cytotoxic effect of the compounds was analysed by obtaining the total number of live and dead cells per well of a 96-well plate, using Hoechst 33342 and propidium iodide staining. Adherent cells (H460, MCF7, SK-OV3) were seeded the night before addition of compound whereas suspension cells (Jurkat A3, KMS-12-BM and T-cells) were seeded the same day, all at cell densities of 1500-5000 cells/well. Cells were incubated in the presence of compound for three cell cycles and then stained and counted using a Celigo imaging cytometer. The IC50 (the compound concentration at which cell viability is 50% of that of the control) value for each compound was determined from a plot of viable cells, expressed as a percentage of control cell count, against log[compound] in Graphpad Prism using the equation:

$y = 100/(1 + 10^{(m(\log IC50 - x))})$ in which m is the Hill slope.

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9. Appendices

9.1. Appendix 1: Ru alkene metathesis catalysts

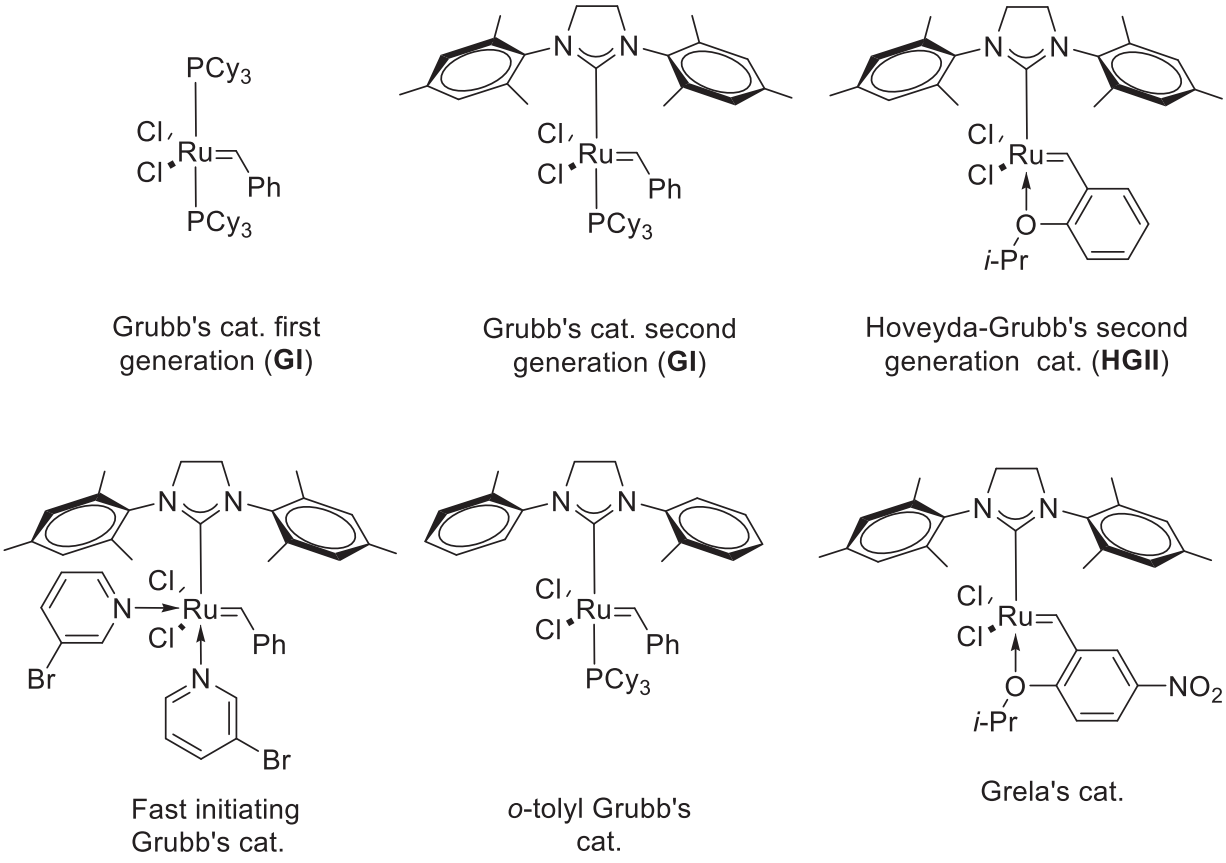

Figure 12. Ru alkene metathesis catalysts.

9.3. Appendix 2: Published work:

-A review article on "*Recent applications in natural product synthesis of dihydrofuran and -pyran formation by ring-closing alkene metathesis*" has been published:

Jacques, R.; Pal, R.; Parker, N. A.; Sear, C. E.; Smith, P. W.; Ribaucourt, A.; Hodgson, D. M. *Org. Biomol. Chem.* **2016**, ***14***, 5875-5893. (DOI:10.1039/C6OB00593D).

-A communication on "*Total Synthesis and Structural Revision of the Cytotoxin Aruncin B*" has been published:

Ribaucourt, A.; Hodgson, D. M. *Org. Lett.* **2016**, *18*, 4364-4367. (DOI:10.1021/acs.orglett.6b02120)

The originally submitted manuscript follows.

Total Synthesis and Structural Revision of the Cytotoxin Aruncin B

Aubert Ribaucourt and David M. Hodgson*

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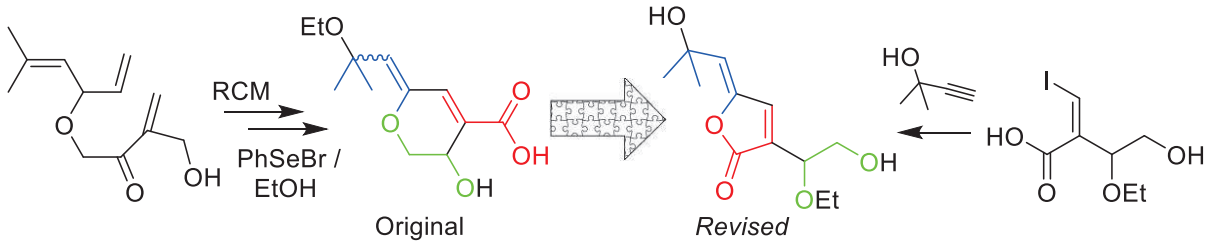
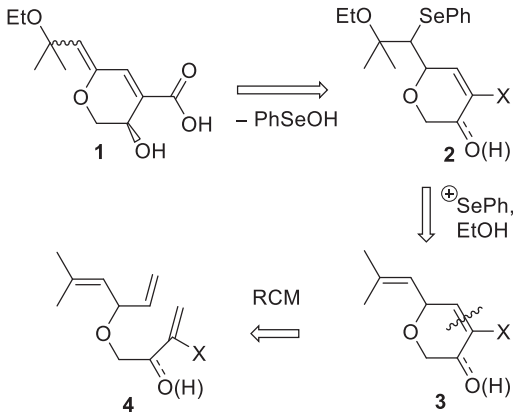


ABSTRACT: The sodium salts *E*-**15** and *Z*-**15** of the originally proposed dihydropyran acid structure of the cytotoxin aruncin B (**1**) were prepared by ring-closing metathesis of an α-hydroxymethyl enone **8**, followed by ethoxyselenation–selenoxide elimination strategies to stereoselectively install either the *E*- or *Z*-exocyclic enol ether motif. Acid sensitivity of these salts, together with inconsistencies in the spectral data suggested a significant structural misassignment of the natural product. A β-iodo Morita-Baylis-Hillman reaction to give *Z*-iodo ester **24**, followed by Sonogashira cross-coupling–5-*exo*-*dig* lactonization provided concise access to a *Z*-γ-alkylidenebutenolide **18**, which possessed data corresponding to that originally reported for aruncin B.

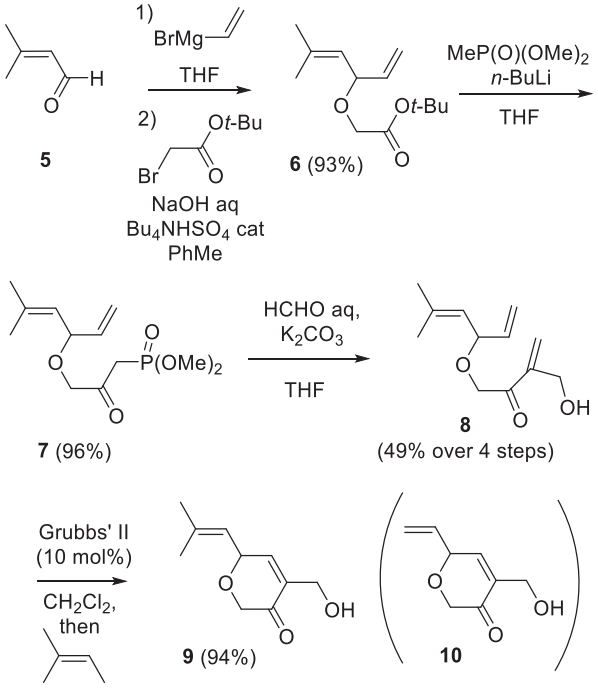
In 2011, Woo and co-workers reported cytotoxicity-directed isolation of extracts from the plant *Aruncus dioicus* var. *kamtschaticus*, obtained from the Korean island Ulleungdo, which enabled discovery of the monoterpenoid (+)-aruncin B (**1**) (Scheme 1, 29 mg from 6.9 kg of aerial parts).[1] Studies indicated inhibition of Bcl-2 antiapoptotic proteins, with selective cytotoxicity for malignant tumour cells over normal human T cells suggesting potential as an antitumor agent.[1b]

The structure of aruncin B was assigned using spectroscopic methods (NMR, MS, UV and IR) and shows interesting features: an enol ether with a unique cross-conjugated pattern, along with a potentially acid-labile tertiary allylic ethyl ether coexisting with carboxylic acid functionality. Exocyclic double bond geometry and absolute configuration were not established. The intriguing structure and biological activity make aruncin B (**1**) an attractive target for synthesis. Late-stage installation of the potentially sensitive enol ether motif was envisaged, using an ethoxyselenation–selenoxide elimination sequence[2] (Scheme 1, **3**→**2**→**1**). The precursor dihydropyran-containing core **3** would be formed by ring-closing alkene metathesis (RCM) of a triene **4**. Appropriate ring and side-chain (X) oxidation levels for this strategy would be established through experimentation.



Scheme 1. Structure of aruncin B (**1**) assigned by Woo and co-workers,[1] and retrosynthetic analysis.

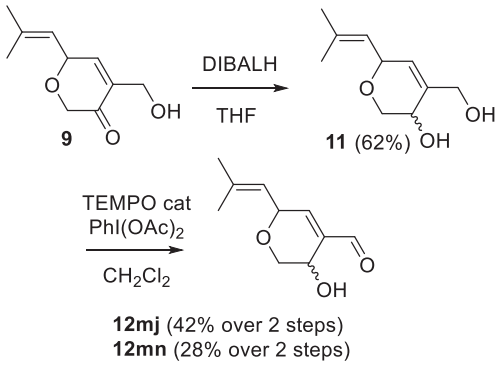
The synthesis of the postulated structure began with 1,2-addition of vinylmagnesium bromide to prenal (**5**) (Scheme 2), followed by *O*-alkylation of the resulting crude dienol[3] with *tert*-butyl bromoacetate, under phase transfer conditions,[4] to give ester **6**. Following phosphonation,[5] phosphonate **7** underwent the Villieras variant of the Horner-Wadsworth-Emmons reaction[6] to give, after purification by column chromatography (the first required in this sequence), α-hydroxymethyl enone **8**. RCM[7] of the latter using Grubbs' II catalyst gave hydroxymethyldihydropyranone **9**. ~10% of undesired dihydropyranone **10** was originally obtained as an inseparable RCM by-product, due to metathetical involvement of the *gem*-dimethyl substituted alkene; this issue was overcome by subsequent addition of excess 2-methyl-2-butene.[8]



Scheme 2. Synthesis of hydroxymethyldihydropyranone **9**.

Hydroxymethyldihydropyranone **9** contains all the core carbon atoms of aruncin B. Reduction using DIBALH,[9] gave a diol **11** (Scheme 3, 3:1 dr) from which the primary alcohol was selectively oxidized to the hydroxyaldehyde **12** through TEMPO catalysis;[10] no ketone

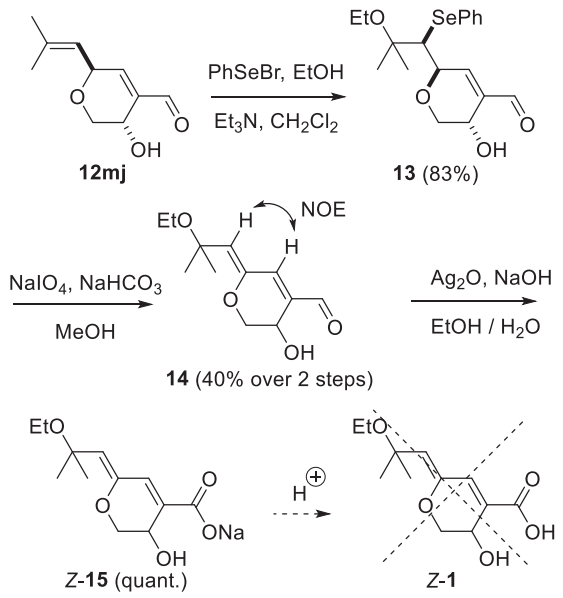
was observed. For analytical convenience the hydroxyaldehyde **12** diastereoisomers were separated at this stage, and subsequent chemistry was carried out on the major (*trans*-**11**) diastereoisomer.



Scheme 3. Redox adjustment.

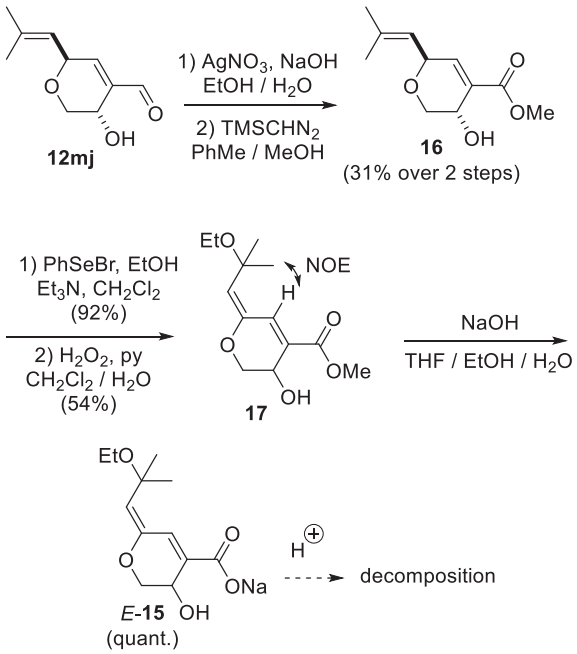
Ethoxyselenation[2] occurred selectively at the electron-rich olefin of the hydroxyaldehyde 12mj, to give the ethoxyselenide 13 as a single diastereoisomer (Scheme 4).[12] Periodate oxidation,[13] of the crude ethoxyselenide **13** followed by selenoxide elimination gave the desired enol ether **14** as the *Z*-isomer. The *E*-isomer was observed in the crude mixture[14] but not isolated; it is suspected to be the initial product from *syn* elimination, but isomerization of the double bond occurs rapidly (possibly by reversible conjugate addition at the δ-position of the dienal) to deliver the *Z*-isomer, likely favored due to minimization of allylic strain. Final chemoselective oxidation of the aldehyde to the carboxylic acid was anticipated to be achievable using freshly prepared silver oxide under alkaline conditions.[15] While this proceeded smoothly to deliver the Na–salt *Z*-**15** of the originally assigned structure, all attempts to obtain the free acid from *Z*-**15** led only to complete and rapid decomposition. For example, mild acidification conditions, such as pH 6 buffer solution, addition of accurately measured 1

equiv of HCl (at −78 °C), or carboxylic acid-supported ion-exchange resins all proved unsuccessful.



Scheme 4. Ethoxyselenation–selenoxide elimination sequence, final oxidation and attempted acidification.

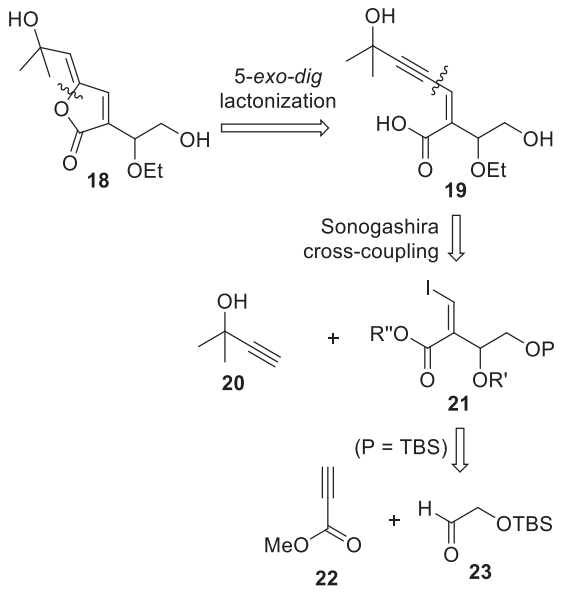
Since enol ether geometry of aruncin B had not been established in the isolation paper,[1a] we were interested in seeing whether the *E*-isomer would possess different acid stability character and correspond to the natural product. It was considered that switching from an aldehyde to a slightly less electron-withdrawing group, such as an ester, might retard isomerisation and thereby enable the access to the *E*-configured exocyclic unsaturation. Oxidation[16] of hydroxyaldehyde **12mj**, then esterification using $TMSCHN_2$ delivered hydroxy ester **16** (Scheme 5). Ethoxyselenation as before, followed by hydrogen peroxide-induced oxidation[17] of the resulting selenide gave the *E*-enol ether **17**, which exhibited greater configurational stability than enol ether **14**. Saponification of *E*-enol ether **17** delivered the *E*-Na–salt *E*-**15** which, however, possessed the same sensitivity to acid as previously found with *Z*-Na–salt *Z*-**15**.



Scheme 5. Synthesis of the Na-salt *E*-**15**.

Our above studies suggested that acid **1** is intrinsically unstable, due to the coexistence of tertiary allylic ether and carboxylic acid functionality: acid-induced loss of EtOH, assisted by the enol ether, leads to decomposition. While UV data supported the presence of a γ-alkoxy-α,β,γ,δ–unsaturated carboxyl motif,[18,19] acid sensitivity, together with inconsistencies in the ^{1}H and ^{13}C NMR data between **1** and the two Na-salts (*Z*-**15** and *E*-**15**)[20] indicated that a structural revision was necessary. Detailed analysis of the data suggested that, in particular, a better match for the originally assigned ring CH_2 would be as a primary alcohol,[21] rather than an (enol) ether. Further inspection of the original structure assignment of aruncin B (**1**)[1a] indicated that the site of etherification was not determined unambiguously and, based on the ^{13}C NMR data, a structure featuring tertiary allylic alcohol and the ethyl ether of a secondary alcohol would be a more reasonable alternative.[22] These considerations led us to consider a *Z*[23]-γ-alkylidenebutenolide **18** (Scheme 6) as being more consistent with available data.[24] The γ-alkylidenebutenolide motif is present in several natural products,[25] including novaxenicin D[26] and an oxidised tirucallane triterpenoid[27] which possess *E*-γ-(hydroxy)isobutylidene and *Z*-γ-

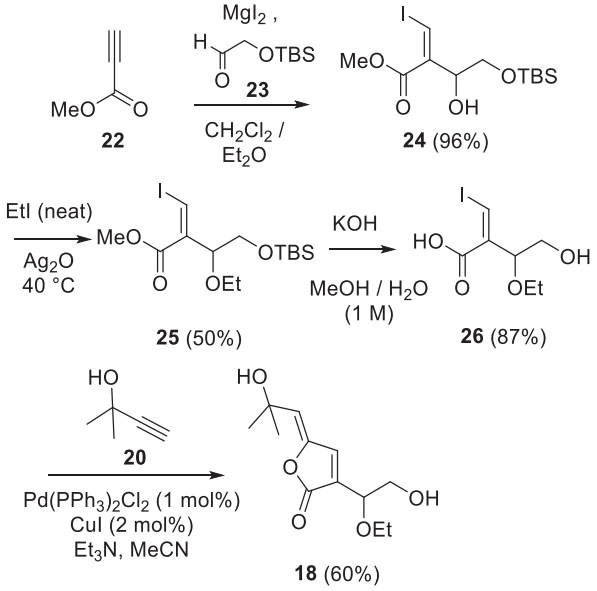
(methoxy)isobutylidene substitution, respectively. However, the α-dioxygenated side-chain has not previously been observed. While many routes to γ-alkylidenebutenolides are known,[25] we were attracted to a Sonogashira cross-coupling–5-*exo-dig* lactonization sequence[28] (**20**+**21**→**19**→**18**, Scheme 6) due to its functional group tolerance, stereocontrol and brevity. The *Z*-vinyl iodide substrate **21** bearing the requisite α-dioxygenated side-chain could be prepared via a β-iodo-Morita-Baylis-Hillman (MBH) reaction.[29]



Scheme 6. New postulated structure of aruncin B (butenolide **18**) and retrosynthetic plan.

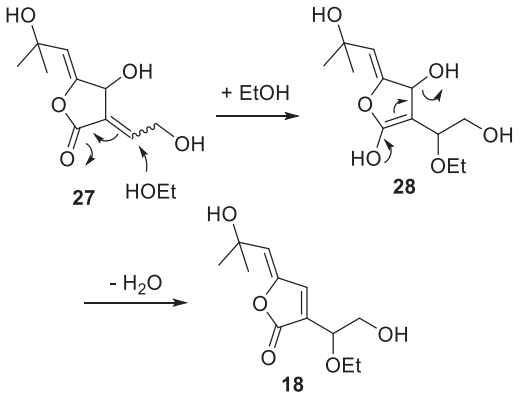
The synthesis starts with methyl propiolate (**22**) and the aldehyde **23**.[30] The β-iodo-MBH reaction was carried out using *in situ* generated MgI_2 as iodide source,[31] giving *Z*-iodoester **24** (Scheme 7). This powerful one-step transformation installs the dioxygenated side chain and sets the *Z*-vinyl iodide functionality necessary for the subsequent cross-coupling. *O*-Ethylation of the secondary alcohol was achieved using Ag_2O in neat EtI, to give the ether **25**. Subsequent saponification of the methyl ester was accompanied by desilylation to give the desired cross-coupling substrate *Z*-iodoacid **26**. The Sonogashira cross-coupling–5-*exo-dig* lactonization sequence could be achieved in the presence of free alcohol functionality in both partners, and

with as little as 1 mol% $Pd(PPh_3)_2Cl_2$ and 2 mol% CuI (~1 mmol scale, leading to 200 mg of *Z*-butenolide **18**). To our delight, the spectroscopic data of synthetic γ-alkylidenebutenolide **18** corresponded to that reported for the originally isolated aruncin B.[20,32]



Scheme 7. Synthesis of the correct structure of aruncin B: butenolide **18**.

Enantiopure samples of (+)- and (–)-aruncin B were obtained from *Z*-butenolide **18** by semi-prep HPLC. The specific rotation values found for the synthetic materials ($[\alpha]_D^{25}$ + / – 90 (*c* 1.0 in MeOH)) were significantly higher than that reported for the natural isolate ($[\alpha]_D^{20}$ + 27 (*c* 0.1 in MeOH)).[1b] This discrepancy suggests that the originally isolate may not be enantiopure, but rather partially enantioenriched. An intriguing structural feature of the correct structure of aruncin B is the ethoxy group at the β'-position. Interestingly, aruncin B was isolated by EtOH extraction of the aerial plant parts. The possibility of low enantiomeric enrichment and unusual presence of the ethoxy group could indicate that butenolide **18** is an artefact of the isolation process, resulting from a modestly diastereoselective conjugate addition of EtOH to a α-(2-hydroxyethylidene)-γ-lactone **27**,[33] followed by loss of water (Scheme 8).



Scheme 8. Potential origin of butenolide **18**.

In summary, RCM followed by ethoxyselenation–selenoxide elimination proved a viable strategy to (ethoxy)isobutylidene-substituted dihydropyranols, which was applied in stereocontrolled syntheses of the Na–salts of the *Z*- and *E*-isomers of the originally postulated structure of aruncin B (**1**). However, the free acids could not be obtained from these Na–salts. This instability, together with inconsistencies in the collected analytical data led to the conclusion that aruncin B has been misidentified.[34] An alternative butenolide **18** structure has been proposed and synthesized in four-steps, through β-iodo-MBH reaction and Sonogashira cross coupling–lactonization. The data for butenolide **18** match with that originally reported for aruncin B. With the true structure of the natural product and a concise and flexible synthetic approach to it both established, studies can now be undertaken to probe in more detail the biological activity of aruncin B and analogues.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett

Experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra for all reported compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(11) Assigned according to ring $^{3}J_{\text{H-H}}$ values, see SI.

(12) Acidic work-up was used to deprotect small amounts of the corresponding diethyl acetal of **13** formed during the course of the reaction.

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9.3. Crystal data and structure refinement for 172

The following cristal data and structure refinement has been provided by Amber L. Thompson.

Table 1. Crystal data and structure refinement for DIA0268.

Identification code	global	
Empirical formula	C25 H26 N2 O9 Se1	
Formula weight	577.45	
Temperature	100 K	
Wavelength	0.68890 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 21.316(13) Å	α= 90°.
	b = 15.347(10) Å	β= 99.26(8)°.
	c = 8.083(8) Å	γ = 90°.
Volume	2610(3) $Å^3$	
Z	4	
Density (calculated)	1.470 Mg/m^3	
Absorption coefficient	1.494 mm^{-1}	
F(000)	1184.000	
Crystal size	0.10 x 0.01 x 0.01 mm^3	
Theta range for data collection	1.592 to 36.207°.	
Index ranges	-30<=h<=36, -26<=k<=25, -12<=l<=13	
Reflections collected	39129	
Independent reflections	12045 [R(int) = 0.200]	
Completeness to theta = 25.345°	98.4 %	
Absorption correction	None	
Max. and min. transmission	. and .	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5472 / 148 / 383	
Goodness-of-fit on F^2	1.0771	
Final R indices [I>2sigma(I)]	R1 = 0.0756, wR2 = 0.2046	
R indices (all data)	R1 = 0.1155, wR2 = 0.3117	
Largest diff. peak and hole	0.80 and -1.10 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DIA0268. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	7093	4449	8130	77
C(2)	7573	4479	9543	79
C(3)	7678	5411	10181	61
C(4)	7718	6020	8725	64
C(5)	7543	5744	7144	66
C(6)	7308	4842	6700	73
O(7)	8301	5429	11235	69
C(8)	8335	5766	12786	62
O(9)	7887	5914	13453	70
C(10)	9005	5905	13577	61
C(11)	9124	6237	15219	64
C(12)	9733	6386	15949	67
C(13)	10255	6239	15141	72
C(14)	10124	5914	13529	69
C(15)	9518	5753	12715	66
N(16)	9864	6734	17705	86
O(17)	9417	6832	18431	101
O(18)	10414	6903	18283	117
N(19)	10659	5726	12628	82
O(20)	11190	5898	13363	122
O(21)	10548	5379	11286	114
C(22)	7918	6920	9061	76
O(23)	8052	7217	10470	83
C(24)	6781	4816	5215	77
Se(25)	6067	5527	5641	78
C(26)	5853	6069	3444	83
C(27)	6306	6535	2767	79
C(28)	6140	6914	1168	98
C(29)	5542	6815	327	116
C(30)	5092	6354	1021	128
C(31)	5248	5970	2583	102

C(32)	6672	3946	4329	83
C(33)	6250	4105	2565	107
C(34)	6420	3260	5280	94
O(35)	7318	3695	4038	72
C(36)	7409	2849	3371	74
C(37)	8117	2745	3290	80
C(132)	6485	3837	4699	83
C(133)	6103	3888	2880	96
C(134)	6118	3448	5876	81
O(135)	7055	3302	4643	77
C(136)	7431	3472	3352	85
C(137)	7958	2781	3496	72

Table 3. Bond lengths [Å] and angles [°] for DIA0268.

O(1)-C(2)	1.406	C(24)-Se(25)	1.949
O(1)-C(6)	1.442	C(24)-C(32)	1.516
C(2)-C(3)	1.525	C(24)-H(241)	0.970
C(2)-H(21)	0.976	C(24)-Se(25)	1.949
C(2)-H(22)	0.983	C(24)-C(132)	1.657
C(3)-C(4)	1.516	C(24)-H(242)	0.971
C(3)-O(7)	1.458	Se(25)-C(26)	1.947
C(3)-H(31)	0.974	C(26)-C(27)	1.384
C(4)-C(5)	1.340	C(26)-C(31)	1.372
C(4)-C(22)	1.459	C(27)-C(28)	1.409
C(5)-C(6)	1.497	C(27)-H(271)	0.931
C(5)-H(51)	0.918	C(28)-C(29)	1.355
C(6)-C(24)	1.506	C(28)-H(281)	0.932
C(6)-H(61)	0.973	C(29)-C(30)	1.381
O(7)-C(8)	1.347	C(29)-H(291)	0.927
C(8)-O(9)	1.190	C(30)-C(31)	1.385
C(8)-C(10)	1.485	C(30)-H(301)	0.923
C(10)-C(11)	1.406	C(31)-H(311)	0.934
C(10)-C(15)	1.406	C(32)-C(33)	1.578
C(11)-C(12)	1.356	C(32)-C(34)	1.456
C(11)-H(111)	0.924	C(32)-O(35)	1.484
C(12)-C(13)	1.397	C(33)-H(331)	0.962
C(12)-N(16)	1.500	C(33)-H(332)	0.959
C(13)-C(14)	1.381	C(33)-H(333)	0.963
C(13)-H(131)	0.931	C(34)-H(341)	0.958
C(14)-C(15)	1.375	C(34)-H(342)	0.951
C(14)-N(19)	1.476	C(34)-H(343)	0.952
C(15)-H(151)	0.924	O(35)-C(36)	1.430
N(16)-O(17)	1.207	C(36)-C(37)	1.528
N(16)-O(18)	1.218	C(36)-H(361)	0.974
N(19)-O(20)	1.221	C(36)-H(362)	0.973
N(19)-O(21)	1.197	C(37)-H(371)	0.961
C(22)-O(23)	1.217	C(37)-H(372)	0.964
C(22)-H(221)	0.930	C(37)-H(373)	0.959

C(132)-C(133)	1.563
C(132)-C(134)	1.453
C(132)-O(135)	1.474
C(133)-H(1331)	0.964
C(133)-H(1332)	0.965
C(133)-H(1333)	0.960
C(134)-H(1341)	0.953
C(134)-H(1342)	0.957
C(134)-H(1343)	0.957
O(135)-C(136)	1.437
C(136)-C(137)	1.535
C(136)-H(1361)	0.974
C(136)-H(1362)	0.970
C(137)-H(1371)	0.962
C(137)-H(1372)	0.957
C(137)-H(1373)	0.957

C(2)-O(1)-C(6)	110.777
O(1)-C(2)-C(3)	110.715
O(1)-C(2)-H(21)	107.9
C(3)-C(2)-H(21)	109.4
O(1)-C(2)-H(22)	109.4
C(3)-C(2)-H(22)	109.6
H(21)-C(2)-H(22)	109.9
C(2)-C(3)-C(4)	109.814
C(2)-C(3)-O(7)	106.666
C(4)-C(3)-O(7)	106.409
C(2)-C(3)-H(31)	110.9
C(4)-C(3)-H(31)	111.8
O(7)-C(3)-H(31)	111.1
C(3)-C(4)-C(5)	120.284
C(3)-C(4)-C(22)	119.379
C(5)-C(4)-C(22)	120.271
C(4)-C(5)-C(6)	123.451
C(4)-C(5)-H(51)	117.9
C(6)-C(5)-H(51)	118.7
C(5)-C(6)-O(1)	109.386
C(5)-C(6)-C(24)	113.145
O(1)-C(6)-C(24)	109.669
C(5)-C(6)-H(61)	107.3
O(1)-C(6)-H(61)	108.8
C(24)-C(6)-H(61)	108.5
C(3)-O(7)-C(8)	117.234
O(7)-C(8)-O(9)	124.655
O(7)-C(8)-C(10)	111.011
O(9)-C(8)-C(10)	124.312
C(8)-C(10)-C(11)	118.242
C(8)-C(10)-C(15)	122.254
C(11)-C(10)-C(15)	119.441
C(10)-C(11)-C(12)	119.108
C(10)-C(11)-H(111)	119.6
C(12)-C(11)-H(111)	121.3
C(11)-C(12)-C(13)	123.233
C(11)-C(12)-N(16)	119.471
C(13)-C(12)-N(16)	117.294
C(12)-C(13)-C(14)	116.367
C(12)-C(13)-H(131)	122.2
C(14)-C(13)-H(131)	121.4
C(13)-C(14)-C(15)	123.237
C(13)-C(14)-N(19)	118.757
C(15)-C(14)-N(19)	118.006
C(10)-C(15)-C(14)	118.588
C(10)-C(15)-H(151)	120.9
C(14)-C(15)-H(151)	120.5
C(12)-N(16)-O(17)	117.540
C(12)-N(16)-O(18)	117.425
O(17)-N(16)-O(18)	125.032
C(14)-N(19)-O(20)	116.556
C(14)-N(19)-O(21)	118.611
O(20)-N(19)-O(21)	124.715
C(4)-C(22)-O(23)	123.103
C(4)-C(22)-H(221)	117.7

O(23)-C(22)-H(221)	119.2	C(33)-C(32)-O(35)	107.833
C(6)-C(24)-Se(25)	110.346	C(34)-C(32)-O(35)	109.081
C(6)-C(24)-C(32)	115.943	C(32)-C(33)-H(331)	109.5
Se(25)-C(24)-C(32)	120.827	C(32)-C(33)-H(332)	109.0
C(6)-C(24)-H(241)	102.0	H(331)-C(33)-H(332)	109.7
Se(25)-C(24)-H(241)	102.5	C(32)-C(33)-H(333)	109.8
C(32)-C(24)-H(241)	101.9	H(331)-C(33)-H(333)	109.6
C(6)-C(24)-Se(25)	110.346	H(332)-C(33)-H(333)	109.2
C(6)-C(24)-C(132)	115.431	C(32)-C(34)-H(341)	110.3
Se(25)-C(24)-C(132)	105.965	C(32)-C(34)-H(342)	109.6
C(6)-C(24)-H(242)	108.1	H(341)-C(34)-H(342)	109.7
Se(25)-C(24)-H(242)	108.5	C(32)-C(34)-H(343)	109.6
C(132)-C(24)-H(242)	108.2	H(341)-C(34)-H(343)	109.1
C(24)-Se(25)-C(26)	98.777	H(342)-C(34)-H(343)	108.5
Se(25)-C(26)-C(27)	120.398	C(32)-O(35)-C(36)	118.725
Se(25)-C(26)-C(31)	118.572	O(35)-C(36)-C(37)	107.823
C(27)-C(26)-C(31)	121.027	O(35)-C(36)-H(361)	109.2
C(26)-C(27)-C(28)	119.249	C(37)-C(36)-H(361)	109.7
C(26)-C(27)-H(271)	120.2	O(35)-C(36)-H(362)	109.2
C(28)-C(27)-H(271)	120.6	C(37)-C(36)-H(362)	110.4
C(27)-C(28)-C(29)	119.374	H(361)-C(36)-H(362)	110.4
C(27)-C(28)-H(281)	120.3	C(36)-C(37)-H(371)	108.9
C(29)-C(28)-H(281)	120.4	C(36)-C(37)-H(372)	109.0
C(28)-C(29)-C(30)	120.886	H(371)-C(37)-H(372)	109.3
C(28)-C(29)-H(291)	119.2	C(36)-C(37)-H(373)	109.3
C(30)-C(29)-H(291)	119.9	H(371)-C(37)-H(373)	109.7
C(29)-C(30)-C(31)	120.542	H(372)-C(37)-H(373)	110.8
C(29)-C(30)-H(301)	120.4	C(24)-C(132)-C(133)	108.128
C(31)-C(30)-H(301)	119.1	C(24)-C(132)-C(134)	115.537
C(30)-C(31)-C(26)	118.910	C(133)-C(132)-C(134)	112.521
C(30)-C(31)-H(311)	120.3	C(24)-C(132)-O(135)	103.267
C(26)-C(31)-H(311)	120.8	C(133)-C(132)-O(135)	107.821
C(24)-C(32)-C(33)	108.169	C(134)-C(132)-O(135)	108.936
C(24)-C(32)-C(34)	115.376	C(132)-C(133)-H(1331)	109.2
C(33)-C(32)-C(34)	112.571	C(132)-C(133)-H(1332)	109.7
C(24)-C(32)-O(35)	103.179	H(1331)-C(133)-H(1332)	109.7

C(132)-C(133)-H(1333)	109.5	O(135)-C(136)-H(1361)	110.1
H(1331)-C(133)-H(1333)	109.5	C(137)-C(136)-H(1361)	110.0
H(1332)-C(133)-H(1333)	109.1	O(135)-C(136)-H(1362)	109.4
C(132)-C(134)-H(1341)	108.9	C(137)-C(136)-H(1362)	109.8
C(132)-C(134)-H(1342)	109.3	H(1361)-C(136)-H(1362)	109.6
H(1341)-C(134)-H(1342)	109.2	C(136)-C(137)-H(1371)	109.3
C(132)-C(134)-H(1343)	109.8	C(136)-C(137)-H(1372)	109.7
H(1341)-C(134)-H(1343)	109.7	H(1371)-C(137)-H(1372)	109.0
H(1342)-C(134)-H(1343)	110.0	C(136)-C(137)-H(1373)	110.3
C(132)-O(135)-C(136)	118.700	H(1371)-C(137)-H(1373)	109.6
O(135)-C(136)-C(137)	107.839	H(1372)-C(137)-H(1373)	108.9

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for DIA0268. 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}
O(1)	89	56	82	0	2	-4
C(2)	99	53	84	2	8	1
C(3)	77	48	59	4	12	2
C(4)	87	52	58	-3	24	-5
C(5)	71	65	62	-3	14	-8
C(6)	79	64	75	-14	7	3
O(7)	77	66	66	-5	14	6
C(8)	85	47	55	3	16	7
O(9)	80	75	55	4	16	10
C(10)	68	45	69	1	9	3
C(11)	75	51	68	3	17	6
C(12)	79	48	73	-9	7	-1
C(13)	69	52	95	-3	12	2
C(14)	69	57	83	2	21	3
C(15)	85	44	72	3	18	6
N(16)	83	72	99	-24	2	6
O(17)	94	106	101	-43	13	10
O(18)	84	132	129	-60	-1	-5
N(19)	78	74	99	-5	27	3
O(20)	79	129	164	-56	36	-13
O(21)	91	160	91	-16	22	16
C(22)	106	67	57	-1	22	-17
O(23)	127	63	62	-8	21	-22
C(24)	87	57	84	-9	-1	3
Se(25)	75	61	99	4	17	-2
C(26)	74	68	101	3	-1	4
C(27)	77	69	90	2	13	3
C(28)	120	75	95	14	8	-5
C(29)	120	87	124	27	-30	-9
C(30)	111	115	138	30	-36	-17
C(31)	81	89	130	28	-6	-6

C(32)	83	65	96	-16	0	-4
C(33)	102	64	134	-23	-44	-10
C(34)	89	66	130	-24	24	-16
O(35)	86	50	77	0	3	-2
C(36)	90	50	82	-1	12	-6
C(37)	90	63	85	-3	9	3
C(132)	83	65	96	-16	0	-4
C(133)	126	40	109	1	-23	-12
C(134)	78	59	102	-23	4	-5
O(135)	99	53	80	2	16	2
C(136)	101	63	91	13	20	-4
C(137)	78	58	77	-8	8	-19

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for DIA0268.

	x	y	z	U(eq)
H(21)	7964	4258	9211	95
H(22)	7451	4109	10432	95
H(31)	7346	5586	10811	74
H(51)	7559	6137	6296	79
H(61)	7666	4508	6428	88
H(111)	8788	6349	15779	77
H(131)	10670	6354	15652	86
H(151)	9449	5561	11618	80
H(221)	7949	7277	8146	91
H(241)	6958	5161	4397	93
H(242)	6944	5056	4256	93
H(271)	6717	6591	3358	94
H(281)	6442	7222	688	117
H(291)	5437	7051	-737	139
H(301)	4682	6303	454	153
H(311)	4947	5639	3028	123
H(331)	6156	3556	2006	161
H(332)	6478	4471	1905	161
H(333)	5860	4390	2710	161
H(341)	6442	2709	4736	142
H(342)	6658	3236	6380	142
H(343)	5989	3385	5363	142
H(361)	7278	2408	4111	89
H(362)	7159	2803	2256	89
H(371)	8172	2259	2579	120
H(372)	8342	2633	4402	120
H(373)	8271	3266	2838	120
H(1331)	5995	3307	2480	143
H(1332)	6358	4169	2152	143
H(1333)	5722	4219	2887	143

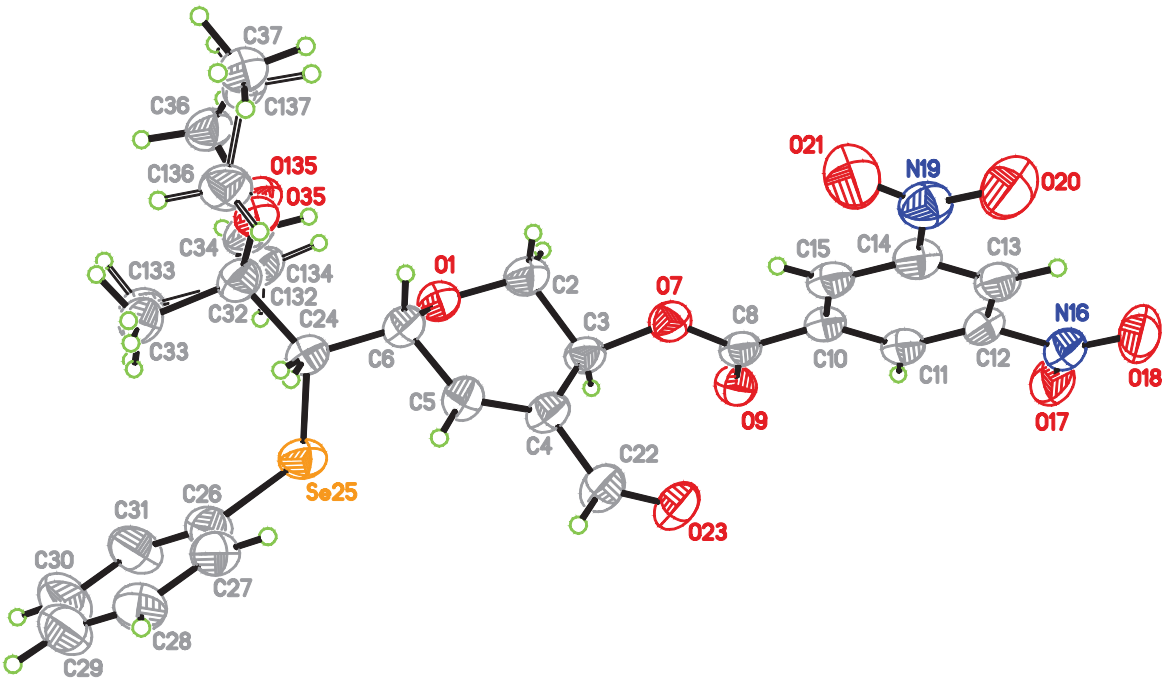
H(1341)	5953	2903	5439	121
H(1342)	6389	3353	6924	121
H(1343)	5776	3827	6030	121
H(1361)	7166	3438	2253	101
H(1362)	7618	4048	3512	101
H(1371)	8196	2856	2592	108
H(1372)	7772	2211	3425	108
H(1373)	8236	2836	4546	108

Table 6. Hydrogen bonds for DIA0268 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(2)-H(22)...C(136)#1	0.98	2.56	3.501(12)	160
C(5)-H(51)...O(9)#2	0.92	2.53	3.196(12)	130
C(6)-H(61)...O(20)#3	0.97	2.50	3.405(12)	155
C(22)-H(221)...O(23)#4	0.93	2.34	3.244(12)	163
C(24)-H(241)...O(9)#2	0.97	2.51	3.392(12)	150
C(24)-H(242)...O(9)#2	0.97	2.57	3.392(12)	142
C(34)-H(342)...O(1)	0.95	2.43	3.103(12)	128
C(134)-H(1342)...O(1)	0.96	2.36	2.963(12)	121

Symmetry transformations used to generate equivalent atoms:

#1 x,y,z+1 #2 x,y,z-1 #3 -x+2,-y+1,-z+2 #4 x,-y+3/2,z-1/2



Displacement ellipsoids drawn at 30% probability for clarity.