Reductive transformations mediated by samarium(II) iodide: the enabling use of H$_2$O as an additive

A thesis submitted to The University of Manchester for the degree of Doctor of Philosophy
In the faculty of Engineering and Physical Sciences

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Brice Sautier

School of Chemistry
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Abstract

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Brice Sautier
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2013

Reductive transformations mediated by samarium(II) iodide: the enabling use of H\textsubscript{2}O as an additive

The use of H\textsubscript{2}O as an additive in SmI\textsubscript{2}-mediated reductive processes provides access to new transformations and previously inaccessible chemical space.

The cyclisation of radicals derived from the selective mono-reduction of Meldrum’s acid derivatives was further investigated and the scope of the methodology expanded to cyclisation cascades.

The first general methodology for the reduction of amide-type carbonyls under single electron transfer conditions was developed and applied to the mono-reduction of barbituric acid derivatives, providing an unprecedented direct access to the corresponding hemiaminals with a good degree of stereocontrol. The intermediate acyl-type radicals were in addition successfully exploited in stereoselective radical cyclisations.

The hemiaminals derived from mono-reduction and cyclisation of barbituric acid derivatives have been exploited as N-acyliminium equivalents, affording hydouracils with an excellent degree of regio- and stereoselectivity.

Efforts towards the synthesis of the azulene framework of pseudolaric acid B using a model substrate are also described.
Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Part of this work has been published in peer reviewed journals:


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“One need only believe in two things:

One self, sometimes:

And Science, always.”
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## Abbreviations

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<thead>
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<td>Ac</td>
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<td>µL</td>
<td>microlitre</td>
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<td>µmol</td>
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</tr>
<tr>
<td>anal</td>
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<td>APCI</td>
<td>atmospheric pressure chemical ionisation</td>
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<td>dr</td>
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<td>electron</td>
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<td>ee</td>
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<td>NMO</td>
<td>N-methylmorpholine N-oxide</td>
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<tr>
<td>NMR</td>
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<td>Nu</td>
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<tr>
<td>p</td>
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<td>P</td>
<td>protecting group</td>
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</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
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<tr>
<td>PTSA</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>Py.</td>
<td>pyridine</td>
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<tr>
<td>q</td>
<td>quadruplet</td>
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<td>quant.</td>
<td>quantitative</td>
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<td>quintuplet</td>
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<td>racemic</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
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<td>Definition</td>
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<tr>
<td>s</td>
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<td>t</td>
<td>tert-Butyl</td>
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<tr>
<td>t</td>
<td>triplet</td>
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<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
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<td>TBAHSO$_4$</td>
<td>tetrabutylammonium bisulfate</td>
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<td>TBDPS</td>
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<td>TBS</td>
<td>tert-butylidimethylsilyl</td>
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<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
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<td>THF</td>
<td>tetrahydrofuran</td>
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<td>THP</td>
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<td>thin layer chromatography</td>
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<td>trimethylsilyl</td>
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<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
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</table>
Introduction

1. Introduction to samarium(II) iodide

Samarium(II) iodide (SmI$_2$) is a single electron transfer reagent introduced by Kagan in 1977 (sometimes referred to as Kagan’s reagent).$^{1,2}$ It has since grown into one of the most valuable and versatile reducing agents available to organic chemists, typically displaying a high degree of regio-, chemo- and stereoselectivity, resulting in its extensive use in the development of new synthetic transformations and methodologies as well as in complex total syntheses.$^3$-$^6$

One of the most important features of SmI$_2$ is the possibility to control its reactivity by the use of additives, allowing for fine tuning of its reduction potential (figure 1:1).$^6$-$^8$ This behaviour is fundamental to the modern use of the reagent, enabling access to specific transformations unique to SmI$_2$. The change in reduction potential arises from coordination of the additives to the metal centre,$^9$-$^{11}$ typically displacing not only the coordinated solvent but also both iodides to the outer sphere to allow access to more reactive Sm(II)–additive complexes.$^{12,13}$

![Figure 1:1 – Influence of additives on the reduction potential of SmI$_2$](image)

Amongst the numerous additives that can be used with SmI$_2$, H$_2$O has emerged as an atypical ligand, displaying an atypical reactivity when compared to other proton sources. The use of low equivalents of H$_2$O was indeed shown to accelerate a broad range of SmI$_2$-mediated reactions, whilst larger amounts (over 20 equivalents) also gradually increase the reduction potential of the system.$^7$-$^{14}$ Studies by Hilmersson and Flowers on the rates of reaction of SmI$_2$ with proton donors showed that although H$_2$O behaved similarly to alcohols at low concentration (lower than 8 equivalents),$^{14,15}$ it had a far higher affinity for
samarium than other proton sources and triggered a dramatic increase in the rates of reaction upon the use of higher concentrations.\textsuperscript{14}

2. SmI\textsubscript{2}–ROH mediated reduction of carbonyls

2.1. Aldehydes and ketones

2.1.1. Reduction

The ability of SmI\textsubscript{2} to reduce aldehydes and ketones when used in conjunction with a proton source was demonstrated very early on.\textsuperscript{2} This transformation however has seldom been used for direct access to alcohols, as numerous other reagents are available to efficiently mediate these reactions.\textsuperscript{6} Mechanistic studies have nonetheless been carried out by Flowers to uncover the impact of the proton source on the rate of reduction of ketones, showing a linear relationship between the acidity of the alcohol additive used and the rate of ketone reduction.\textsuperscript{14}

Useful applications of the SmI\textsubscript{2}–ROH system for the reduction of ketones have also been reported. Keck described the highly efficient synthesis of 1,3-\textit{anti}-diols from β-hydroxy-ketones\textsuperscript{16,17} during which reduction is directed by coordination of samarium(II) to the hydroxyl group through a 6-membered transition state, and successfully applied the strategy to the total synthesis of epothilones B and D.\textsuperscript{18} Further work by Flowers later highlighted the influence of the reaction’s solvent on the diastereoisomeric ratios obtained (scheme 2.1.1:1).\textsuperscript{19}

\begin{align*}
\text{Scheme 2.1.1:1 – Diastereoselective reduction of β-hydroxy-ketones}
\end{align*}

Additional work by Keck on β-amino-ketones demonstrated the strong influence of protecting groups on the reaction outcome, triggering a complete switch in diastereoselectivity (scheme 2.1.1:2).\textsuperscript{20}
Although the direct reduction of ketones and aldehydes is rarely carried out using \( \text{SmI}_2 \), considerable interest has been devoted to exploiting the ketyl radical formed during these transformations in bond-forming processes.  

### 2.1.2. Pinacol coupling

Intramolecular \( \text{SmI}_2-\text{ROH} \) mediated pinacol couplings have been efficiently used to access complex target molecules. Both 5- and 6-membered carbocycles were shown to be accessible, affording complex systems with a typically high degree of selectivity arising from coordination of both oxygen centres to samarium(II)/(III) in the transition state.

Molander reported that keto-aldehydes 8 underwent pinacol coupling in moderate to good yields, usually with an excellent level of diastereoselectivity (scheme 2.1.2:1).

```
        \begin{center}
          \includegraphics[width=\textwidth]{pinacol_coupling.png}
        \end{center}
```

Scheme 2.1.2:1 – Diastereoselective pinacol couplings

Molander also obtained similar results with analogously activated diketones using \( t-\text{BuOH} \) as the proton source. In addition, the use of an oxazolidinone moiety was also described, affording cyclopentadiol 11 in moderate yield as a single enantiomer starting from optically active keto-aldehyde 10 (Scheme 2.1.2:2).
Scheme 2.1.2:2 – Enantioselective pinacol coupling

This methodology was also efficiently applied to the synthesis of bridged polycyclic targets. As part of studies towards taxoids, Arseniyadis reported the use of a SmI$_2$–MeOH mediated pinacol coupling to access the bicycle 13 in excellent yield (Scheme 2.1.2:3).$^{23}$

Scheme 2.1.2:3 – Pinacol coupling towards the synthesis of taxoids

SmI$_2$–t-BuOH mediated couplings have also been employed in carbohydrate chemistry. Adinolfi et al. used this strategy to access the 5-membered core of caryose with very high diastereoselectivity albeit in moderate yield (Scheme 2.1.2:4).$^{24}$ Guidot et al. followed the same strategy in their synthesis of a myo-inositol analogue.$^{25}$ The interesting influence of protecting groups on the reaction outcome was demonstrated by Carpintero et al. as part of their efforts towards fucopyranoside analogues. Pinacol coupling of dialdehyde 17 afforded opposite cis:trans ratios when switching from benzyl protecting groups to the bulkier tert-butyldiphenylsilyl groups (Scheme 2.1.2:4).$^{26,27}$

Scheme 2.1.2:4 – Application to the synthesis of carbohydrates
The diastereoselective synthesis of trans-decalins was described by Matsuda, affording cis-vicinal diol 22 in moderate yield as a single isomer (Scheme 2.1.2:5). The strong effect of the additive chosen on stereocontrol was highlighted by the alternative use of HMPA, yielding the trans-vicinal diol as the sole product of the reaction. An identical approach using SmI$_2$–t-BuOH was followed by Anies et al. for the formal total synthesis of forskolin.

![Scheme 2.1.2:5 – Application to the synthesis of trans-decalins](image)

**2.1.3. Ketyl-olefin coupling**

The trapping of the ketyl radical intermediate with an olefin acceptor has evolved into one of the most prominent uses of SmI$_2$-mediated carbonyl reduction, with a strong focus on cyclisation reactions. SmI$_2$–ROH systems have successfully been used for the synthesis of various carbocycle ring sizes and this strategy has been efficiently applied towards the synthesis of natural products.

Although activated olefins are usually preferred, the use of unactivated acceptors has also been exploited for the synthesis of 5- and 6-membered rings. Molander reported the highly diastereoselective synthesis of cyclopentanols from β-keto esters using terminal alkenes as the radical acceptor. The use of a TMS substituted alkyne was also shown to be suitable for the reaction (scheme 2.1.3:1). In an approach towards (±)-erigerol, Pancrazi also used a TMS protected alkyne as part of a SmI$_2$–t-BuOH mediated 6-exo-dig cyclisation strategy to access the trans-decalin core skeleton (scheme 2.1.3:1). Kurozumi’s synthesis of isocarbacyclin also exploited the same acceptor to access the 5,5-fused bicyclic core of the molecule via cyclisation of an aldehyde-derived ketyl radical.
Scheme 2.1.3:1 – Trapping of ketyl radicals using unactivated acceptors

The use of allenes as acceptors has also been reported by Gillmann, but remains scarce despite the reasonable yields and selectivity obtained in this seminal account (scheme 2.1.3:2).\textsuperscript{32}

Scheme 2.1.3:2 – Use of allenes as the radical acceptor

The use of activated olefins, usually $\alpha,\beta$-unsaturated esters, however predominates and has been exploited to access small and medium sized rings. Although not wide-spread, access to 3- and 4-membered carbocycles using conjugated esters as the radical acceptor has been successfully investigated, usually affording the desired cyclic targets with a good degree of stereocontrol. Guibé reported that the diastereoselective synthesis of cyclopropanols from $\delta$-oxo-$\alpha,\beta$-unsaturated esters proceeded in good to excellent yields using the SmI$_2$–t-BuOH
The use of MeOH as the proton source was on the other hand described by Procter to access functionalised cyclobutanols (scheme 2.1.3:3).34

![Scheme 2.1.3:3 – Synthesis of 3- and 4-membered rings](image)

Cyclopropanols were also accessed by Armesto using aryl-substituted olefins, typically affording 38 in moderate yield with a high degree of stereocontrol (scheme 2.1.3:4).35,36

![Scheme 2.1.3:4 – Synthesis of cyclopropanols using aryl-substituted olefins](image)

The highly diastereoselective synthesis of 5-membered rings was also reported by Molander (scheme 2.1.3:5). The use of a thioester as the α-activating group was also reported but resulted in complete loss of stereoselectivity in the cyclisation.22 Enholm also described the synthesis of functionalised carbocycles starting from carbohydrate derivatives,37 including an approach to anguidine featuring a 5-<i>exo</i>-trig cyclisation onto a β-substituted, α,β-unsaturated ester (scheme 2.1.3:5).38
Scheme 2.1.3:5 – Synthesis of 5-membered rings

Trapping of ketyl radicals with activated olefins has widely been used to access 6-membered rings, particularly for the synthesis of tetrahydropyrans (vide infra), and the methodology has been applied to the synthesis of various natural products. Stereoselective access to decalin skeletons has also been reported and such a reaction was key to Little’s synthesis of the cis-decalin core of an arteannuin B analogue (scheme 2.1.3:6). A noteworthy feature of this transformation was the use of an α,β-unsaturated ketone as the ketyl radical precursor, which undergoes 6-exo-trig cyclisation selectively as opposed to conjugate reduction. Matsuda also exploited this strategy in an approach to the cis-decalin skeleton of vinigrol, as well as for the synthesis of trans-decalin systems (scheme 2.1.3:6).
The use of SmI$_2$–ROH mediated cyclisations to access tetrahydropyrans was first reported by Nakata for the iterative synthesis of trans-fused polyethers, a template common to many marine natural products. Nakata’s strategy allowed for high yielding, diastereoselective reactions whilst giving access to easily functionalisable precursors to a subsequent cyclisation substrate (scheme 2.1.3:7).

Scheme 2.1.3:7 – Iterative synthesis of trans-fused polyethers

The reaction is proposed to proceed via an 11-membered transition state 59 in which chelation between samarium(III) and the ester carbonyl controls the stereochemical outcome of the transformation (figure 2.1.3:1).

Figure 2.1.3:1 – Proposed transition state for the synthesis of trans-fused polyethers

Since this initial report, this strategy has been used in the synthesis of several natural products containing a tetrahydropyran motif. Nakata applied it to the total synthesis of mucocin and pyranicin, two cytotoxic agents containing a THP ring (scheme 2.1.3:8). Interestingly, the second aldehyde present in 60 remained untouched under the reaction conditions, only reacting in the presence of a large excess of SmI$_2$ or upon prolonged exposure to the reagent system. A possible explanation to this behaviour lies in the pre-
coordination of samarium(II), thus increasing the reactivity of the proximal aldehyde. An alternative mechanistic pathway would involve reversible electron transfer as proposed by Curran for the reduction of carbonyl groups, upon which only one of the two possible ketyl radicals would undergo cyclisation.

![Scheme 2.1.3:8 – Application to natural products containing isolated THP rings](image)

The synthesis of naturally occurring polyethers has also been carried out by exploiting this methodology, as in Yamamoto’s approaches to and total synthesis of the neurotoxin gambierol. Nakata also took advantage of the SmI$_2$–MeOH system in an approach to brevetoxin B (scheme 2.1.3:9).

![Scheme 2.1.3:9 – Application to naturally occurring polyethers](image)

However, Nakata later reported a total synthesis of brevetoxin B relying on a bidirectional approach, during which SmI$_2$-mediated concomitant tetrahydropyran and oxepane formation afforded with complete stereocontrol (scheme 2.1.3:10). The synthesis of oxepanes had previously been demonstrated and used by Nakata for the iterative synthesis...
of polyethers. The diastereoselectivity of the reaction is again proposed to arise from coordination to samarium(III) via a 12-membered transition state analogous to that suggested for the formation of 6-membered rings (see figure 2.1.3:1).

Scheme 2.1.3:10 – Bidirectional heterocycle formation

In addition to esters, conjugated lactones have also been used by Procter as ketyl-olefin acceptors for the synthesis of cyclobutanols during studies towards pestalotiopsin A. The outcome of the reaction was found to be strongly influenced by the configuration of the double bond in the starting material (scheme 2.1.3:11).

Scheme 2.1.3:11 – Synthesis of cyclobutanols using a conjugated lactone acceptor

In a subsequent report, Procter described the use of a silicon handle to exert greater control on the reaction’s stereochemical outcome, culminating in complete stereocontrol when a large directing silyl group was used (scheme 2.1.3:12).
Although uncommon, the use of a conjugated ketone acceptor has also been investigated. Hsu reported the synthesis of a variety of spiranes in such a fashion, affording the desired spirocycles in moderate to good yield (scheme 2.1.3:13).\textsuperscript{56} In addition, Arimoto exploited a 7-endo-trig ketyl-olefin coupling onto a conjugated ketone in an approach towards the synthesis of eranecines, obtaining 85 as a single diastereoisomer (scheme 2.1.3:13).\textsuperscript{57} A similar 7-exo-trig cyclisation has also been described by Lee as part of an approach towards guanacastepene A.\textsuperscript{58}

Hsu:

\[
\begin{align*}
82 & \quad \overset{\text{Sml}_2(2 \text{ eq})}{\text{Sml}_2-\text{MeOH}} \quad \text{THF, 0 °C} \quad \text{n = 0, 1, 2} \quad \text{m = 1, 2} \\
& \quad \overset{\text{83}}{\text{up to 75% yield}} \\
\end{align*}
\]

Arimoto:

\[
\begin{align*}
84 & \quad \overset{\text{Sml}_2(20 \text{ eq})}{\text{Sml}_2-\text{tBuOH (100:1)}} \quad \text{THF, 0 °C} \quad \text{n = 0, 1, 2} \\
& \quad \overset{\text{85}}{\text{up to 16:1 dr}} \\
\end{align*}
\]

Scheme 2.1.3:13 – Use of a conjugated ketone acceptor

Sulfones and sulfoxides have also been used to activate alkenes, and chiral sulfoxides employed successfully to induce enantioselective cyclisations. Nakata described the use of (E)- and (Z)-β-alkoxyvinylsulfones as an efficient method to control the stereoselectivity of Sml\textsubscript{2}-mediated tetrahydropyran syntheses (scheme 2.1.3:14). Good degrees of selectivity were likewise obtained when starting from acyclic starting materials.\textsuperscript{59} Procter also reported moderate to good cyclisation yields for the diastereoselective formation of cyclobutanols when using vinyl sulfones as the radical acceptor.\textsuperscript{34}
The use of chiral sulfoxides in SmI$_2$–MeOH mediated ketyl-olefin couplings has been pioneered by Lee, who reported highly efficient chirality transfer in the synthesis of tetrahydropyrans (scheme 2.1.3:15).$^{60,61}$ Nakata also described the use of this strategy to control the stereochemistry of the newly formed ring in the synthesis of fused polyethers.$^{62,63}$

Even though cyclisation reactions hold a prominent position, SmI$_2$–ROH mediated intermolecular ketyl-olefin couplings have also been successfully attempted, usually displaying exquisite levels of selectivity. A striking example of SmI$_2$’s ability to effect high stereocontrol through coordination even under intermolecular reaction conditions has been reported by Little in an approach to phorbol’s skeleton (scheme 2.1.3:16).$^{64}$ Coupling of 98 and 99 give 101 was obtained as a single diastereoisomer, albeit in moderate yield, via the proposed transition structure 100 in which samarium(III) plays a key role in defining the stereochemical outcome by complexing all but one oxygen centre in the molecules. The essential role of complexation was confirmed by replacing the
benzoyloxyethyl side chain by a cyanomethyl substituent, leading to 104 after treatment with SmI$_2$–t-BuOH (scheme 2.1.3:16).

Scheme 2.1.3:16 – Effect of complexation on stereocontrol

Excellent degrees of stereocontrol can also be obtained on simpler substrates by using α-hydroxy ketones, as demonstrated by Matsuda. The observed stereocontrol can be explained by a chelation controlled transition state such as 107 (scheme 2.1.3:17).

Scheme 2.1.3:17 – Chelation controlled intermolecular ketyl-olefin coupling

Enantioselective intermolecular couplings have also been achieved by using either a chiral template or a chiral ligand system. Fukuzawa described the use of $N$-methylephedrinyl acceptors for the synthesis of chiral γ-butyrolactones, affording moderate to high yield and typically excellent enantiomeric excess (scheme 2.1.3:18). Moreover, Mikami reported that the use of (R)-BINAP as a chiral ligand resulted in ketyl-olefin coupling with moderate ee despite low chemical yields (scheme 2.1.3:18).
2.1.4. Other ketyl radical acceptors

Although olefins are the most common radical acceptor used to trap ketyl radicals in SmI$_2$–ROH mediated reactions, other functional groups have been exploited in an identical fashion.

The possibility of using nitrile acceptors was demonstrated early on by Molander, and cyclisation proceeded with excellent diastereoselectivity despite disappointing yields (scheme 2.1.4:1). In a later report, Molander described an efficient procedure for this transformation when assisted by irradiation with visible light.

Oximes have also been used as efficient acceptors, as reported by Naito in the synthesis of heterocyclic amino-alcohols, providing a reasonable degree of diastereoselectivity (scheme 2.1.4:2). Giese exploited a ketyl-oxime cyclisation for the synthesis of trehazolin, affording 124 in excellent yield as a single diastereoisomer (scheme 2.1.4:2).
Finally, intermolecular couplings with chiral sulfinylimines have also been used to access enantiopure β-amino alcohols, proceeding in high yield and affording 127 with excellent diastereo- and enantioselectivity (scheme 2.1.4:3).71

Scheme 2.1.4:3 – Ketyl-sulfinylimine couplings

2.2. Other carbonyl compounds

2.2.1. Activated carboxylic acid derivatives

Although general Sml₂–ROH mediated reductions of carboxyls were until recently limited to aldehyde and ketones, the efficient reduction of activated carboxylic acid derivatives to alcohols under mild conditions using Sml₂–H₂O had been demonstrated by Kamochi in 1993 (scheme 2.2.1:1). Despite being exclusively limited to aromatic substrates, the procedure was shown to accommodate a large variety of functional groups.72
Scheme 2.2.1: Reduction of activated carboxylic acid derivatives

2.2.2. Lactones

In 2008, Procter reported the first \( \text{SmI}_2 \)-mediated reduction of lactones to their corresponding diols (scheme 2.2.2:1). Prior to this report, the reduction of unactivated aliphatic esters was thought to lie beyond the scope of \( \text{SmI}_2 \) reductions. The reaction was shown to be selective for 6-membered lactones over other ring-sized lactones and acyclic esters (scheme 2.2.2:2).

Scheme 2.2.2:1 - \( \text{SmI}_2-\text{H}_2\text{O} \) mediated reduction of 6-membered lactones

The selectivity for 6-membered lactones is proposed to arise from the rate of the initial electron transfer to the lactone carbonyl. The stability of the resulting ketyl radical is believed to result from anomeric stabilisation from the neighbouring oxygen lone pairs, which would be most pronounced in 6-membered ring systems. This hypothesis is supported by theoretical calculations of relative reaction energies for the initial electron transfer, showing a decrease in reaction energy for the 6-membered system compared to
larger and smaller rings. The mechanism of this transformation is thought to proceed via activation of the lactone carbonyl by SmI$_2$ followed by single electron transfer to give the anomerically stabilised pseudo-axial radical 138. A second electron transfer followed by protonation then gives rise to hemiacetal 141, in equilibrium with aldehyde 142. A second series of electron transfers and protonations then affords diol 144 (scheme 2.2.2.3).

These unusual ketyl radicals were subsequently exploited by Procter in ketyl-olefin couplings. The cyclisation of lactones bearing a tethered alkene at the $\alpha$ position afforded cyclopentanones with a moderate to good degree of stereoselectivity from a range of unactivated and activated olefins (scheme 2.2.2.4). The presence of an $\alpha$-ester substituent was found to prevent the collapse of the hemiketal intermediate obtained after cyclisation, avoiding over-reduction to cyclopentanols. Similarly, the use of tethered acceptors at the $\delta$ position efficiently gave access to cycloheptanols, albeit with typically low diastereoselectivity when using alkenes as the radical trap (scheme 2.2.2.4).
Following up on these successful cyclisations, Procter then reported cyclisation cascades exploiting the intermediate cycloheptanone obtained after the initial 7-membered ring formation, starting from cis-lactones bearing two tethered acceptors. High sequence integrity was observed in these cascades, as predicted by theoretical calculations showing a difference in relative reaction energy in favour of the 7-exo-trig cyclisation. The importance of the cis-configuration was ascertained by attempting the cascade sequence with a trans-configured system, which only underwent a single cyclisation to give a cyclopentanol product. Both alkenes and alkynes were used as the second radical acceptor, affording the 5,7-fused bicycles products in good to excellent yields with a good degree of diastereoselectivity (scheme 2.2.2:5).\(^{75}\)

![Scheme 2.2.2:5 – Cyclisation cascades](image)

The use of allenes as the first radical acceptor was subsequently investigated, and such substrates shown to efficiently undergo cyclisations and cyclisation cascades – starting from either cis- or trans-lactones – with moderate to excellent diastereocontrol (scheme 2.2.2:6).\(^ {76}\)

![Scheme 2.2.2:6 – Cyclisation cascades using allenes as the first radical acceptor](image)
2.2.3. The SmI$_2$–H$_2$O–amine system

In 2011 and 2012, Procter described the use of SmI$_2$–H$_2$O–amine systems for the highly efficient reduction of unactivated esters, carboxylic acids and lactones (scheme 2.2.3:1). These reports were the first account of a general method for the SmI$_2$-mediated reduction of carboxylic acid derivatives, and opened access to a chemical space that was thought to be inaccessible to SmI$_2$-mediated transformations.

The SmI$_2$–H$_2$O–amine system has yet to be extensively used for the generation of ketyl-radical anions from carboxylic acid derivatives for use in ketyl-olefin cyclisations, but the potential to do so is striking.
Chapter 1 — Meldrum’s acid: \( \text{SmI}_2-\text{H}_2\text{O} \) mediated cyclisations and cyclisation cascades

1.1. Introduction to Meldrum’s acid

Meldrum’s acid is a common, versatile building block in organic synthesis.\(^{80-84}\) It was first synthesised by Meldrum in 1908,\(^{85}\) but incorrectly assigned as β-lactone 164. It then took 40 years before Davidson and Bernhardt identified its structure as a cyclic diester, 2,2-dimethyl-1,3-dioxane-4,6-dione 163 (figure 1.1:1).\(^{86}\)

![Meldrum's acid](image)

Figure 1.1:1 – Meldrum’s acid

A characteristic feature at the origin of this misassignment is the strong acidity it exhibits, with a measured pKa of 4.83 - 4.93 in water,\(^{87}\) similar to that of acetic acid (pKa 4.75). The peculiar acidity of Meldrum’s acid stands out even more when compared to the corresponding diketone (figure 1.1:2), having a lower pKa than dimedone although diketones usually display higher acidity than related diesters.\(^{88,89}\)

![Acidity of some acyclic/cyclic diketones and their corresponding diesters](image)

Figure 1.1:2 – Acidity of some acyclic/cyclic diketones and their corresponding diesters (pKa in DMSO)

The origin of this acidity has been attributed to the less stable \( E \)-conformation both ester groups are forced to adopt in the cyclic structure, which has been predicted by Wiberg et al. to result in a 9.7 kcal mol\(^{-1}\) increase in energy compared to the \( Z \) conformer. Such a difference in energy amounts to the loss of \( \sim 7 \) pKa units, and is in accordance with the experimentally measured difference in acidity.\(^{90}\) Simultaneous studies by Houk used
dipolar moments to estimate the energy difference between the $E$ and $Z$ conformers, obtaining a similar value with a calculated difference of 9.2 kcal mol$^{-1}$.\textsuperscript{91} Despite these consistent results obtained using two different approaches (molecular orbitals in one case, steric and electrostatics in the other), Gao more recently reported that the contribution of the enforced $E$-conformation to the acidity had been overestimated, and suggested that stabilisation of the enolate anion of Meldrum’s acid by the anomeric effect provided a significant contribution to the acidity of Meldrum’s acid (scheme 1.1:1).\textsuperscript{92} Gao’s computational studies – based on the calculation of the Gibbs free energy difference between the $E$ and $Z$ ester conformations rather than the difference in enthalpy – indeed predict a contribution of 3.4 kcal mol$^{-1}$ per $E$ ester, amounting to only 60% of the observed 11.6 kcal mol$^{-1}$ increase in acidity.

\begin{center}
\[ \begin{array}{c}
\text{165} \quad \text{166} \\
\text{Z conformation} \quad \text{E conformation}
\end{array} \]
\end{center}

\begin{center}
\[ \begin{array}{c}
\text{167} \quad \text{168} \\
\text{9.2 kcal mol}^{-1} \\
\text{3.8 kcal mol}^{-1}
\end{array} \]
\end{center}

Scheme 1.1:1 – Conformational energy difference between $E$ and $Z$ ester conformations (as calculated by Houk)

The unique acidity of Meldrum’s acid has long been exploited in organic synthesis. In particular, it is an extremely versatile pro-nucleophile which, after addition, provides a reactive handle for further functionalization.\textsuperscript{81,82}

\section*{1.2. Previous work: SmI$_2$–H$_2$O mediated reduction of Meldrum’s acid}

In 2009, following on from work done in the Procter group on the selective reduction of 6-membered lactones over other lactones and acyclic diesters,\textsuperscript{73} the group reported the selective reduction of cyclic 1,3-diesters using SmI$_2$–H$_2$O.\textsuperscript{93} This methodology, which was the first reported for the direct mono-reduction of such a system, was shown to be compatible with a wide range of mono- and di-substituted alkyl Meldrum’s acids (table 1.2:1).
In addition, the reduction of Meldrum’s acid was completely selective over that of acyclic-1,3-diesters (scheme 1.2:1).

This selectivity is proposed to have its roots in the rate of the initial electron transfer to the ester carbonyl, which results in a radical anion stabilised by the anomeric effect. As shown by theoretical calculations, this stabilisation appears to promote the reduction step by reducing the energy barrier from ~102-114 kJ mol⁻¹ for acyclic esters to ~50 kJ mol⁻¹ for the 1,3-cyclic system (relative reaction energies). The mechanism of these reductions is thought to proceed via activation of the ester by coordination with samarium(II) and subsequent electron transfer, followed by protonation of the intermediate obtained to give...
The half chair conformation of the ketyl radical is supported by theoretical calculations. The radical is then in a pseudoaxial position, benefiting from the aforementioned anomeric stabilisation. Hemiacetal 178 is then obtained through a second electron transfer and quench of the resulting anion by water. The equilibrium with aldehyde 179 then allows further reduction and a third electron transfer gives the ketyl radical, which can be quenched after a fourth and final electron transfer before collapsing of 181 finally reveals β-hydroxy-acid 182. Further reduction of an unactivated acid such as 182 was not expected based on literature reports (SmI$_2$–H$_2$O has only been reported to reduce activated aryl carboxylic acids). It is proposed that the reduction of 182 cannot be achieved because of its inability to give rise to cyclic intermediates, thus preventing the essential continuous anomeric stabilisation of the ketyl radical which makes these reductions viable under SmI$_2$–H$_2$O conditions due to the higher entropy of the system. This mechanism is also supported by reduction experiments in D$_2$O, after which the carbon supporting the hydroxyl group is doubly deuterated (scheme 1.2:2).

![Scheme 1.2:2 - Proposed reduction mechanism of cyclic 1,3-diesters](#)

Prior to this report, the reduction of Meldrum’s acid derivatives to their β-hydroxy-acid counterparts typically had to be achieved through a four-step sequence, as described by Polla et al. (scheme 1.2:3).  

![Scheme 1.2:3 – Typical method for the reduction of Meldrum’s acid derivatives to β-hydroxy-acids](#)
1.3. SmI$_2$–H$_2$O mediated cyclisations of Meldrum’s acid derivatives

1.3.1. 5-exo-Trig cyclisations

Building on the mono-reduction of cyclic-1,3-diesters, it was hypothesised that intramolecular trapping of the first radical anion intermediate (cf. 175, scheme 1.2:2) could lead to cyclisation adducts when starting from suitably substituted Meldrum’s acids. The use of an olefin as the radical acceptor was attempted and 5-exo-trig cyclisation upon treatment with SmI$_2$–H$_2$O indeed successfully achieved, affording cyclopentanols (table 1.3.1:1). To the best of our knowledge, this was the first report of the addition of radicals generated by single electron reduction of ester carbonyls to olefins. The stereoselectivity of the reaction was assessed after esterification and oxidation of the obtained cyclopentanols in order to simplify the diastereoisomeric mixture. The relative stereochemistry of the major diastereoisomer was confirmed by X-ray crystallographic analysis (see scheme 1.3.1:3). The use of an excess of SmI$_2$ to reduce the cyclopentanone intermediates in situ is advantageous as they proved to be prone to decarboxylation.

![Scheme 1.3.1:1](image)

<table>
<thead>
<tr>
<th>$\text{R}^1$</th>
<th>$\text{R}^2$</th>
<th>$\text{188}$</th>
<th>$\text{189}$ (2 steps)</th>
<th>$\text{dr}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>92%</td>
<td>74%</td>
<td>1 : 2</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>94%</td>
<td>73%</td>
<td>2.5 : 1</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>66%</td>
<td>65%</td>
<td>5 : 1</td>
</tr>
</tbody>
</table>

Table 1.3.1:1 – Radical cyclisations

Based on these initial results, work was undertaken to explore the scope and selectivity of these cyclisations. It was proposed that the ketal unit could be modified to improve the diastereoselectivity of the reaction by exerting greater control over the transition structure. Meldrum’s acid derivatives were therefore synthesised following the procedure described by Zhang$^{96}$ (scheme 1.3.1:1), and then used for the preparation of cyclisation substrates.
These compounds can easily be accessed from Meldrum’s acid through a three step sequence (scheme 1.3.1:2). Knoevenagel condensation with a suitable aldehyde followed by reduction of the resulting alkylidene 194 with NaBH₄, and subsequent alkylation with an alkyl bromide affords the desired substrate 196. Alkyl bromides such as 199 were prepared according to the procedure reported by Wong et al. (scheme 1.3.1:2). ⁹⁷

Scheme 1.3.1:1 – Zhang’s synthesis of Meldrum’s acid derivatives

Pleasingly, it was indeed found that varying the ketal unit had an effect on the diastereoisomeric ratios observed in the cyclisation reaction (scheme 1.3.1:3, table 1.3.1:2). ⁹⁸ The greatest impact on the stereochemical outcome of the cyclisation was obtained by using an acetophenone-derived ketal unit 200c.
Scheme 1.3.1:3 – Effect of the ketal unit on the diastereoselectivity

Table 1.3.1:2 – Effect of the ketal unit on the diastereoselectivity

These results also provided strong evidence supporting our proposed mechanistic pathway for the cyclisation. Such an influence of the ketal unit on the stereoselectivity of the cyclisation can only arise from cyclisation of the first radical anion before the collapse of the ketal, and is consistent with the isolation of cyclopentanone when using limiting SmI₂ for the reaction (pathway A). The alternative cyclisation mechanism (pathway B), in which cyclisation occurs from the second radical anion generated after the collapse of the cyclic diester, therefore appears unlikely. Cyclisation through an anionic mechanism is highly improbable, as the reaction occurs in the presence of a large excess of H₂O which would cause rapid protonation of the anion generated (H₂O has been shown to coordinate to samarium, resulting in quick intramolecular proton transfer). Furthermore, the addition of carbonyl-derived samarium carbanions to olefins is, to the best of our knowledge, unprecedented.
Scheme 1.3.1:4 – Proposed cyclisation pathway

To rationalise the selectivity observed during these cyclisations, we propose that the initial electron transfer gives rise to the formation of a pseudo-axial radical anion due to the anomeric effect, that can exist in both conformations 212 and 213 (see scheme 1.3.1:5). When R¹ = Me, the conformational similarity between the starting materials as well as between the radical anions leads us to believe that either intermediate is energetically accessible. However, only 212 can undergo cyclisation as the formation of a trans-bicyclic system from 213 appears highly unlikely. Radical 213 must therefore undergo inversion for cyclisation to occur, thus providing the pseudo-equatorial radical 214. Cyclisation of 212 through a favoured anti transition state 219 gave the major diastereoisomer 223. Radical 214, on the other hand, cannot give rise to a well-defined anti transition structure. We nevertheless believe that cyclisation of 214 through transition state 221, which would give the major diastereoisomer 223, is still favoured over that of 222 which takes place in a well-defined syn transition state. When R¹ = Ph, the improved selectivity in the cyclisation can be explained by the greater conformational control exerted by the phenyl group over the cyclisation substrate, which strongly favours radical 212 (scheme 1.3.1:5).
To further improve the diastereoselectivity of the cyclisation, the impact of temperature was investigated. As radical transformations are known to typically proceed with improved stereocontrol at lower temperature,\textsuperscript{108} it was decided to carry out the reaction at 0 °C. This change unexpectedly led to a decrease in selectivity, whereas an increase in temperature resulted in greater diastereoselectivity (table 1.3.1:3).

Scheme 1.3.1:5 – Proposed origin of the selectivity of the cyclisation
The reason behind this peculiar effect of the temperature remains unclear. Although most radical cyclisations are irreversible, it has been shown that stabilised radicals sometimes undergo reversible cyclisation. In such a case, thermodynamic control would indeed lead to higher diastereoselectivity, despite being unlikely for the present transformation. Temperature indeed has no influence on the cyclisation onto a terminal olefin, failing to improve stereocontrol, while the primary radical formed in this case would be the most likely to undergo reversible cyclisation due to the absence of any stabilising substituent. Epimerisation of the obtained cyclopentanol product upon heating has also been considered, but this would not be consistent with the influence displayed by the ketal unit on the reaction’s stereochemical outcome.

1.3.2. Attempted access to other ring sizes

To further expand our understanding of the scope of these cyclisations, it was decided to look at the formation of other ring sizes. To that end, substrates bearing appropriate acceptors for 4-, 6- and 7-exo-trig cyclisation were prepared (see scheme 1.3.2.:1) and subjected to the standard reaction conditions, adding SmI₂ to the reaction mixture over 30 min. However, the use of unactivated olefin acceptors only led to straight reduction of the Meldrum’s acid moiety to the corresponding β-hydroxy-acids. Activation of the olefin gave identical results when using 6- and 7-exo-trig starting materials (table 1.3.2:1).
Speculating that over-reduction of the Meldrum’s acid moiety was observed because the ketyl radical formed was too short-lived to cyclise, the reaction conditions were modified and cyclisation attempted again with SmI$_2$ addition carried out over 3 h. Although this had no effect on the formation of 7-membered rings, again yielding the previously observed β-hydroxy-acid, 4- and 6-exo-trig substrates displayed alternative behaviours. 4-exo-Trig substrate 231 on the one hand gave 195, resulting from the loss of cinnamyl radical 234. Such a fragmentation was not unexpected, resulting not only in the formation of a highly stabilised radical 234, but also of a stable samarium enolate 233 (scheme 1.3.2:2). On the other hand, 6-membered cyclised compound 235 was pleasingly observed after treatment of 229e under these revised conditions (scheme 1.3.2:3). Unfortunately, several shortcomings limited the impact of this result. 235 was indeed obtained as a complex mixture of diastereoisomers along with a by-product, of which only the major diastereoisomer could be separated after esterification and oxidation. The reaction also suffered from reproducibility issues, associated with typically modest conversion and
yield. In addition, the use of unactivated olefins unsurprisingly only resulted in β-hydroxy-acid formation, limiting the scope of the reaction.

**Scheme 1.3.2:2 – Radical fragmentation**

**Scheme 1.3.2:3 – 6-exo-Trig cyclisation**

### 1.4. SmI₂–H₂O mediated cyclisation cascades of Meldrum’s acid derivatives

#### 1.4.1. Proof of concept

In the work on 5-exo-trig cyclisations, the intermediate ketones obtained after cyclisation were reduced to the corresponding alcohols. The possibility of using a second intramolecular radical acceptor to trap the ketyl radical formed during the reduction of the ketone was envisioned. This would then lead to bicyclic compounds. Substrates suitable for such a cyclisation cascade were easily synthesised by double alkylation of Meldrum’s acid or a derivative (scheme 1.4.1:1) and treated with SmI₂–H₂O. Pleasingly, double cyclisation indeed occurred, affording the products 241 as single diastereoisomers, the
stereochemistry of which was confirmed by X-ray crystallographic analysis of 241a (table 1.4.1:1).

![Scheme 1.4.1:1 – Synthesis of symmetrical cascade substrates](image)

**Table 1.4.1:1 – Cyclisation cascades of symmetrical substrates**

<table>
<thead>
<tr>
<th>239</th>
<th>241</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Ar</td>
</tr>
<tr>
<td>239a</td>
<td>Me</td>
</tr>
<tr>
<td>239b</td>
<td>Me</td>
</tr>
<tr>
<td>239c</td>
<td>Ph</td>
</tr>
</tbody>
</table>

<sup>a</sup>Work undertaken by J. M. Oliveira. <sup>b</sup>Work undertaken by B. Sautier.

Based on this initial success, it was decided to explore the scope offered by these cyclisation cascades by synthesising substrates bearing two differentiated side chains. The cyclisation of such substrates would allow symmetrical starting materials to be converted to asymmetrical products in a single process with a single reagent. However, although the synthesis of disubstituted, symmetrical Meldrum’s acid derivatives was extremely straightforward, obtaining non-symmetrical substrates proved to be quite challenging.

### 1.4.2. Substrate synthesis

Due to the higher reactivity of mono-alkylated Meldrum’s acid derivatives compared to the unsubstituted cyclic diester, direct mono-alkylation is not possible. However, alternative
methods have been devised to circumvent this limitation, the most common being the use of Knoevenagel condensations. Unfortunately, the use of unhindered aliphatic aldehydes in this methodology is typically unsuccessful due to the formation of \textit{bis}-adducts of Meldrum’s acid (scheme 1.4.2:1).\textsuperscript{112-114} Another widespread method involves the trapping of the intermediate alkylidene using a competing nucleophile, thus preventing Michael addition of a second molecule of Meldrum’s acid, before releasing the nucleophile in a subsequent step (scheme 1.4.2:2).\textsuperscript{112-114}

![Scheme 1.4.2:1 – Limitation of the Knoevenagel condensation](image)

Thioalkylation of Meldrum’s acid was therefore attempted using a suitable aldehyde \textsuperscript{246}. Surprisingly though, this method failed to deliver the expected product \textsuperscript{247}. Successful control reactions using an aliphatic aldehyde suggested that starting materials like \textsuperscript{246} were unsuitable for this methodology, although the reason behind this incompatibility remains unclear (scheme 1.4.2:3).

![Scheme 1.4.2:2 – Alkylidene trapping and release strategy](image)

![Scheme 1.4.2:3 – Attempted thioalkylation](image)

As mono-alkylation of Meldrum’s acid appeared challenging, a different strategy was sought to access the differentially substituted substrates required. This lead us to consider a late stage formation of the cyclic diester. The alkylation of malonates is a standard
procedure in modern organic chemistry – making use of established, high-yielding methodology – and would allow easy access to mono- and disubstituted precursors of our targeted Meldrum’s acid derivatives. Ester hydrolysis followed by ketalisation would then provide the desired cascade substrates. This reasoning was confirmed by the successful synthesis of 250 (scheme 1.4.2:4). Despite delivering the desired cyclic diester, installing the ketal unit as described in scheme 1.3.1:2 only afforded modest yields; a more efficient transformation was achieved by following the procedure described by Singh and Danishefsky.115

Scheme 1.4.2:4 – Late stage ketalisation

Having established a suitable route for the synthesis of cascade substrates, we then proceeded to synthesise several bis-alkylated malonate derivatives (table 1.4.2:1). Installing both side chains prior to ketal formation then looked like the most efficient sequence, allowing us to avoid a low yielding and time consuming alkylation of Meldrum’s acid. Furthermore, we expected the gem-substitution to have a positive impact on ketalisation due to the Thorpe-Ingold effect. Unfortunately, when submitted to the previously established conditions, diacids 254 only gave traces of the expected cyclic diesters. The incomplete recovery of starting material due to partial consumption of the styryl-type double bonds suggests the formation of stable benzylic carbocations 256 as a likely explanation, incidentally scavenging the acid catalyst and preventing the ketal formation (scheme 1.4.2:5).
\[
\begin{align*}
\text{Table 1.4.2: Synthesis of bis-alkylated malonate derivatives} \\
\begin{array}{|c|c|c|}
\hline
\text{R} & \text{Yield} \\
\hline
\text{252a} & \text{H} & 61\% \\
\text{252b} & 4\text{-MeOC}_6\text{H}_4 & 34\% \\
\text{252c} & 2,4\text{-ClC}_6\text{H}_3 & 70\% \\
\hline
\end{array}
\end{align*}
\]

Scheme 1.4.2:5 – Attempted ketal formation

As the ketalisation proved impossible to perform with activated olefins already in place, the synthetic strategy was again modified to install the activating aryl group after formation of the Meldrum’s acid moiety. Cross-metathesis was therefore attempted on 250 and indeed afforded the expected product 257 in moderate yield (scheme 1.4.2:6), allowing access to the desired cyclisation substrates after an additional alkylation step. The initial conditions however were rather capricious and the product mixture rather difficult to purify, clearly requiring some optimisation. The use of a larger excess of styrene proved detrimental, as it became apparent that it was converted to trans-stilbene before any reaction with the substrate took place. Switching to trans-stilbene thus avoided homo-coupling and unnecessary catalyst turnover. Replacing the Grubbs second generation catalyst by the corresponding Hoveyda-Grubbs version resulted in the need for lower catalyst loading, and reduction of the reaction temperature from 40 °C to room temperature prevented the formation of a nearly inseparable by-product obtained at higher temperature. Finally, running the reaction under a light stream of nitrogen gave access to more consistent yields and reaction time, and permitted a further reduced catalyst loading to be used, most likely due to the removal of ethylene from the reaction mixture (table 1.4.2:2).
Under these optimised conditions, synthesis of 257 could be achieved in good yield and 259 was also accessed in moderate yield (scheme 1.4.2:7).

Scheme 1.4.2:6 – Initial cross-metathesis attempt

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>T</th>
<th>Yield</th>
<th>By-product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grubbs II (10 mol%)</td>
<td>40 °C</td>
<td>36-55%</td>
<td>Y</td>
</tr>
<tr>
<td>Hoveyda-Grubbs II (5 mol%)</td>
<td>40 °C</td>
<td>36-54%</td>
<td>Y</td>
</tr>
<tr>
<td>Hoveyda-Grubbs II (2.5 mol%)</td>
<td>rt</td>
<td>64%</td>
<td>N</td>
</tr>
</tbody>
</table>

Table 1.4.2:2 – Cross-metathesis optimisation

With optimised conditions in hand, we then set out to investigate the scope of the cyclisation cascade by preparing a variety of substrates bearing differentially activated olefin acceptors, as well as alkyne acceptors. The chain lengths were also varied to explore the construction of different ring sizes during the cascade (table 1.4.2:3).
### 1.4.3. Cyclisation cascades

Substrates 262a-h were treated with SmI$_2$–H$_2$O under optimised conditions, by adding SmI$_2$ to the reaction mixture over 2 h. Pleasingly, the cascades smoothly delivered the expected bicycles in moderate to good overall yield and typically with high diastereocontrol, usually leading to a single isolated diastereoisomer (scheme 1.4.3:1, figure 1.4.3:1).

#### Table 1.4.2: – Alkylation of mono-substituted Meldrum’s acids to give cascade substrates

<table>
<thead>
<tr>
<th>Type of cyclisation</th>
<th>260</th>
<th>262</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R$^1$</td>
<td>R$^2$</td>
</tr>
<tr>
<td>trig-trig</td>
<td></td>
<td></td>
</tr>
<tr>
<td>260a</td>
<td>H</td>
<td>Ph</td>
</tr>
<tr>
<td>260b</td>
<td>H</td>
<td>4-BrC$_6$H$_4$</td>
</tr>
<tr>
<td>260c</td>
<td>H</td>
<td>2,4-Cl$_2$C$_6$H$_3$</td>
</tr>
<tr>
<td>260d</td>
<td>H</td>
<td>2-naphthyl</td>
</tr>
<tr>
<td>260e</td>
<td>Ph</td>
<td>4-BrC$_6$H$_4$</td>
</tr>
<tr>
<td>260f</td>
<td>Ph</td>
<td>2,4-Cl$_2$C$_6$H$_3$</td>
</tr>
<tr>
<td>260g</td>
<td>Ph</td>
<td>2-naphthyl</td>
</tr>
<tr>
<td>260h</td>
<td>4-BrC$_6$H$_4$</td>
<td>4-MeOC$_6$H$_4$</td>
</tr>
<tr>
<td>260i</td>
<td>Ph</td>
<td>Ph</td>
</tr>
<tr>
<td>260j</td>
<td>Ph</td>
<td>Ph</td>
</tr>
<tr>
<td>trig-dig</td>
<td></td>
<td></td>
</tr>
<tr>
<td>260k</td>
<td>Ph</td>
<td>H</td>
</tr>
<tr>
<td>260l</td>
<td>Ph</td>
<td>Ph</td>
</tr>
<tr>
<td>260m</td>
<td>Ph</td>
<td>Ph</td>
</tr>
<tr>
<td>260n</td>
<td>2,4-Cl$_2$C$_6$H$_3$</td>
<td>Ph</td>
</tr>
<tr>
<td>260o</td>
<td>Ph</td>
<td>Ph</td>
</tr>
</tbody>
</table>

$^a$Work undertaken by B. Sautier. $^b$Work undertaken by S. E. Lyons.
Although preferential first cyclisation onto the most activated acceptor was anticipated, such high control was unexpected, underlining the extremely strong effect slight differences in activation of the olefin had on the integrity of the cascade sequence. Indeed, only 262g and 262h failed to display sufficient difference in alkene activation and led to a mixture of isomers (cf. figure 1.4.3:1). These results provided interesting mechanistic insights regarding the cyclisation cascades. The nearly complete stereocontrol obtained for
263a-f points towards the selective formation of one radical-anion from 263 over the other, providing a small but sufficient differentiation between the acceptors exists. A possible explanation is the formation of an early-stage cyclisation intermediate, thus directing the initial electron transfer. Such an explanation however would involve coordination of the most reactive olefin to samarium(II), which is not consistent with the observed outcome of the reaction when two activated olefins are used. Alternatively, a late-stage transition state would favour the formation of the most stable benzyl radical – and be consistent with the products observed – but would occur with limited control over the formation of the initial axial radical and is usually associated with endothermic reactions, which is not the case for these cyclisations. Reversible ketyl radical formation, if occurring, would be unlikely to be at the origin of the displayed selectivity as cyclisation can proceed efficiently onto either acceptor 93. The cyclisation is then proposed to occur through an anti transition state, revealing the intermediate cyclopentanone that is in turn reduced to again cyclise via a favoured anti transition structure (scheme 1.4.3:2). The formation of equatorial radical 268 is in addition favoured by the coordination between the carbonyl and samarium in the transition state.

![Scheme 1.4.3:2 – Proposed cascade cyclisation pathway](image-url)
The stereochemistry of the products and thus the order of the sequence was confirmed by X-ray crystallographic analysis of the bridged β-lactone derived from 263f (scheme 1.4.3:3).

Scheme 1.4.3:3 – X-ray crystallographic analysis of 273

The scope of the cascade was then further explored using substrates 262i-o. The use of alkynes as the second acceptor proved successful and high sequence integrity was observed, the cascade beginning with cyclisation onto the alkene. The synthesis of 5,6-bicycles was also pleasingly achieved using the standard cascade conditions, albeit with low selectivity for the cyclisation onto the second olefin acceptor (see figure 1.4.3:1). However, attempts to form 5,7-bicycles proved unsuccessful and cyclopentanol products were observed (scheme 1.4.3:4).

Scheme 1.4.3:4 – Attempted access to 5,7-bicycles

In the case of exo-trig/exo-dig cascades, the exocyclic double bond was obtained as a mixture of E and Z isomers, with greater selectivity achieved in the formation of 5,6-bicycles. We believe that the preferential formation of the E-alkene arises from the formation of the most stable vinyl radical after cyclisation. This is supported by the higher selectivity obtained in 5,6-bicycles, in which the steric clash between the Z-alkene and the
bridgehead hydroxyl substituent is far greater than when forming 5,5-bicycles due to the chair conformation of the 6-membered ring (figure 1.4.3:2).

Figure 1.4.3:2 – Proposed origin of the greater selectivity obtained for 5,6-bicycles

The stereochemistry of the 5,6-bicycle formed from the 5-exo-trig/6-exo-dig cascade was also confirmed by X-ray crystallographic analysis (figure 1.4.3:3). In all cases, the bicycles were obtained in moderate to good yields, indicating that good to excellent yields were obtained in each cyclisation event in the cascade (cf. figure 1.4.3:1).

Figure 1.4.3:3 – X-ray crystallographic analysis of 263n
Chapter 2 — Barbituric acid: SmI$_2$–H$_2$O mediated reductions and cyclisations

2.1. Introduction to barbituric acid

Barbituric acid (pyrimidine-2,4,6(1H,3H,5H)-trione, 278) was first synthesised by von Baeyer$^{116}$ in 1864 starting from uric acid 277 and the actual structure of the compound elucidated by Mulder close to ten years later.$^{117}$ The simpler synthesis of barbituric acid from malonic acid and urea was carried out by Grimaux in 1879.$^{118}$

![Barbituric acid syntheses](image)

Figure 2.1:1 – Barbituric acid syntheses

Following the discovery of the sedative properties of barbital in 1903$^{119}$ and its introduction as a pharmaceutical agent a year later, barbiturates became a major family of pharmacologically active compounds. More than 2500 biologically active derivatives have been synthesised to date, 50 of which were clinically employed including anti-convulsant, hypnotic and anti-cancer agents.$^{120,121}$ However, it was established in 1950 that barbiturates induced physical dependence,$^{122,123}$ leading to a decline in use in the 1960’s and eventually to their general replacement by benzodiazepines. Nevertheless, their use continues for specific therapeutic applications, and close to a dozen are still made use of at present.$^{124}$
Barbituric acid has also been widely used as an easily accessible building block in synthetic organic chemistry.\textsuperscript{120,125} Yet, despite over 150 years of continued interest, the mono-reduction of barbituric acids to the corresponding hemiaminals remains virtually unexplored, with a single example published by Rautio in 1979.\textsuperscript{126}

### 2.2. SmI$_2$–H$_2$O mediated reduction of barbituric acid

Following on from the successful manipulations of Meldrum’s acid, it was decided to investigate the reactivity of the closely related barbituric acid in the hope to observe a similar, selective behaviour towards reduction with SmI$_2$–H$_2$O. In order to circumvent the high solubility and polarity of barbituric acid, its 1,3-dimethyl derivative was used to investigate its susceptibility to SmI$_2$-mediated reduction.

We hypothesised that the reduction would favour one of the imide carbonyls over the urea-type carbonyl due to the lower energy of their $\pi^*$ orbital, the urea-type carbonyl being less electrophilic due to resonance from both nitrogen atoms (figure 2.2:1). We also anticipated that anomic stabilisation of the radical anion intermediate from both the oxygen and nitrogen lone pairs would favour the reduction. In addition, we were hopeful that the $n_N\rightarrow\pi^*$ delocalisation in the conformationally locked reduced system would prevent dehydration under the Lewis acidic conditions of the reaction and provide access to stable hemiaminal products.
Pleasingly, initial investigations within the group using a simple, mono-substituted barbituric acid derivative 285a indeed afforded the expected hemiaminal product (scheme 2.2:1). It was therefore decided to investigate the scope of these reductions by synthesising a range of mono- and disubstituted barbituric acids.

Scheme 2.2:1 – A preliminary result

A variety of mono-substituted substrates were consequently easily prepared via condensation reaction between 281 and carboxylic acids followed by reduction of alkylidenes 288. An additional alkylation step gave access to disubstituted barbituric acids 290 (scheme 2.2:2, table 2.2:1). A spirocyclic substrate 285o was also prepared through dialkylation and subsequent ring-closing metathesis (scheme 2.2:3)
Satisfyingly, treatment of substrates 285a-n with SmI$_2$–H$_2$O under optimised conditions$^{127}$ afforded hemiaminals 286 in good yields and diastereoselectivity. Of particular note, substrates 285a-h underwent smooth reduction despite the presence of an acidic $\alpha$ proton. A short reaction time and swift, basic workup (NaHCO$_3$) were however essential to obtain the sensitive hemiaminals 286a-h as the presence of Lewis acidic samarium salts in the reaction mixture induced dehydration to the corresponding uracil derivatives. The procedure was shown to tolerate a range of functional groups as well as the use of substrates containing a sterically hindered quaternary centre. The method was also shown to reduce alkylidene barbituric acid derivatives to their fully saturated hemiaminal counterparts 286p-q. To the best of our knowledge, this methodology constitutes the first general report of the reduction of amide-type carbonyl bonds under single electron transfer conditions, and provides an unprecedented direct access to hemiaminals from barbituric acid derivatives (table 2.2:2)$^{127}$.
The stereochemistry of the major isomer obtained was confirmed by X-ray crystallographic analysis of 286e (figure 2.2:2). A more detailed analysis of the crystal structure uncovered several unusual features. The torsion angle N\textsubscript{LP}–N\textsubscript{1}–C\textsubscript{1}–O\textsubscript{1} was found to be \(\sim 175^\circ\), indicating a significant N\textsubscript{LP}→\(\sigma^*\)C\textsubscript{1}–O\textsubscript{1} interaction in contrast with the absence of O\textsubscript{LP}→\(\sigma^*\)C\textsubscript{1}–N\textsubscript{1} overlap with an O\textsubscript{LP}–O\textsubscript{1}–C\textsubscript{1}–N\textsubscript{1} dihedral angle of \(\sim 137^\circ\). In addition, the O\textsubscript{1}–C\textsubscript{1}–C\textsubscript{2}–H\textsubscript{2} system showed a perfect antiperiplanar arrangement between the hydroxyl group and the α hydrogen atom with a torsion angle of \(\sim 180^\circ\) and the C\textsubscript{1}–C\textsubscript{2} bond length was measured to be 1.519 Å, slightly shorter than the average C\textsubscript{sp3}–C\textsubscript{sp3} bond (1.530 Å). All these parameters are consistent with the beginning of decomposition of the α-amino group.

Table 2.2:2 – SmI\textsubscript{2}–H\textsubscript{2}O mediated reduction of barbituric acid derivatives

<table>
<thead>
<tr>
<th>285</th>
<th>286</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R\textsuperscript{1}</td>
</tr>
<tr>
<td>285a</td>
<td>i-Bu</td>
</tr>
<tr>
<td>285b</td>
<td>C\textsubscript{10}H\textsubscript{21}</td>
</tr>
<tr>
<td>285c</td>
<td>i-Pr</td>
</tr>
<tr>
<td>285d</td>
<td>Ph(CH\textsubscript{2})\textsubscript{2}</td>
</tr>
<tr>
<td>285e</td>
<td>4-MeOC\textsubscript{6}H\textsubscript{4}(CH\textsubscript{2})\textsubscript{2}</td>
</tr>
<tr>
<td>285f</td>
<td>4-CF\textsubscript{3}C\textsubscript{6}H\textsubscript{4}(CH\textsubscript{2})\textsubscript{2}</td>
</tr>
<tr>
<td>285g</td>
<td>4-BrC\textsubscript{6}H\textsubscript{4}(CH\textsubscript{2})\textsubscript{2}</td>
</tr>
<tr>
<td>285h</td>
<td>PhMeCH(CH\textsubscript{2})\textsubscript{2}</td>
</tr>
<tr>
<td>285i</td>
<td>i-Bu</td>
</tr>
<tr>
<td>285j</td>
<td>C\textsubscript{10}H\textsubscript{21}</td>
</tr>
<tr>
<td>285k</td>
<td>4-MeOC\textsubscript{6}H\textsubscript{4}(CH\textsubscript{2})\textsubscript{2}</td>
</tr>
<tr>
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<td>4-CF\textsubscript{3}C\textsubscript{6}H\textsubscript{4}(CH\textsubscript{2})\textsubscript{2}</td>
</tr>
<tr>
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<td>4-BrC\textsubscript{6}H\textsubscript{4}(CH\textsubscript{2})\textsubscript{2}</td>
</tr>
<tr>
<td>285n</td>
<td>i-Pr</td>
</tr>
<tr>
<td>285o</td>
<td>-(CH\textsubscript{2})\textsubscript{2}CH=CH(CH\textsubscript{2})\textsubscript{2}</td>
</tr>
<tr>
<td>285p</td>
<td>=CHi-Pr</td>
</tr>
<tr>
<td>285q</td>
<td>=C(OH)Bn</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Work undertaken by B. Sautier. \textsuperscript{b}Work undertaken by Dr M. Szostak. \textsuperscript{c}6 eq SmI\textsubscript{2}. \textsuperscript{d}8 eq SmI\textsubscript{2}. \textsuperscript{e}Not measured. \textsuperscript{f}Yields based on 1H NMR.
alcohol moiety via elimination of the hydroxyl group to give the corresponding acylium, revealing that 286e exists under kinetic stability.127

![Image of molecule](image)

**Figure 2.2:2 – X-ray crystallographic analysis of 286e**

In analogy to the proposed reduction pathways for lactones and Meldrum’s acids, these reductions are suggested to occur via a series of electron transfers and protonations. Coordination of samarium to the imide carbonyl followed by single electron transfer gives the anomerically stabilised radical-anion 293, which upon protonation and a second electron transfer affords organosamarium(III) 295. Hemiaminal 296 is then formed by an additional proton transfer (scheme 2.2:4). The cis selectivity observed during the reduction can be explained by the formation of the equatorial organosamarium species 297.

![Scheme 2.2:4 – Proposed mechanism for the mono-reduction of barbituric acid](image)

### 2.3. SmI₂–H₂O mediated cyclisations of barbituric acid derivatives

Having established an efficient reduction pathway, it was decided to attempt to exploit the unusual radical intermediates in cyclisation reactions. To that end, a host of barbituric acid...
derivatives bearing radical acceptor containing side chains were synthesised (scheme 2.3:1, table 2.3:1).

Scheme 2.3:1 – Synthesis of cyclisation substrates

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>299a</td>
<td>i-Bu</td>
</tr>
<tr>
<td>299b</td>
<td>i-Bu</td>
</tr>
<tr>
<td>299c</td>
<td>CH₂-c-C₆H₁</td>
</tr>
<tr>
<td>299d</td>
<td>i-Bu</td>
</tr>
<tr>
<td>299e</td>
<td>(CH₂)₂CH=CH₂</td>
</tr>
<tr>
<td>299f</td>
<td>C₁₀H₂₁</td>
</tr>
<tr>
<td>299g</td>
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</tr>
<tr>
<td>299h</td>
<td>i-Bu</td>
</tr>
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</tr>
<tr>
<td>299l</td>
<td>i-Bu</td>
</tr>
<tr>
<td>299m</td>
<td>(CH₂)₂C≡CH</td>
</tr>
</tbody>
</table>

| aWork undertaken by B. Sautier. bWork undertaken by Dr M. Szostak. |

Table 2.3:1 – Cyclisation substrates
Treatment with SmI$_2$–H$_2$O pleasingly afforded bicyclic hemiaminal products 300a-e and 300j-m in good yield, showing good compatibility of the methodology with various unactivated and activated radical acceptors (table 2.3:2). Interestingly, these are the first examples of SmI$_2$–H$_2$O mediated cyclisations during which all products are formed with perfect stereocontrol around the newly formed 5-membered ring. This complete selectivity is proposed to arise from the increased half-life of the acyl-type radical intermediate due to an anomeric n$_N$$→$SOMO interaction, thus allowing the tethered acceptor to adopt the lowest energy conformation in the transition state of the cyclisation.

![Chemical structure image]

<table>
<thead>
<tr>
<th>299</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R$^1$</strong></td>
<td><strong>R$^2$</strong></td>
</tr>
<tr>
<td>299a</td>
<td>i-Bu</td>
</tr>
<tr>
<td>299b</td>
<td>i-Bu</td>
</tr>
<tr>
<td>299c</td>
<td>CH$_2$C-C$<em>6$H$</em>{11}$</td>
</tr>
<tr>
<td>299d</td>
<td>i-Bu</td>
</tr>
<tr>
<td>299e</td>
<td>(CH$_2$)$_2$CH=CH$_2$</td>
</tr>
<tr>
<td>299f</td>
<td>C$<em>{10}$H$</em>{21}$</td>
</tr>
<tr>
<td>299g</td>
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</tr>
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<td>299i</td>
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<td>i-Bu</td>
</tr>
<tr>
<td>299m</td>
<td>(CH$_2$)$_2$C=CH</td>
</tr>
</tbody>
</table>

$^a$Work undertaken by B. Sautier. $^b$Work undertaken by Dr M. Szostak. $^c$58% yield of the reduction product observed. $^d$Z:E geometry. $^e$The remaining mass balance consists of recovered starting material. – Stereochemistry assigned by analogy with the X-ray structures of 300a and 300k.

Table 2.3:2 – SmI$_2$–H$_2$O mediated cyclisation of barbituric acid derivatives
The use of a long aliphatic chain as the second substituent in 299f surprisingly resulted in a dramatic drop in yield compared to the use of shorter, bulkier side chains such as in 299a. This effect might arise from shielding of the imide carbonyls by the saturated hydrocarbon chain, preventing the approach and coordination of samarium(II). In addition, the use of an electron deficient alkene 299g or of a sterically hindered olefin 299h failed to give any cyclisation product, instead leading to starting material recovery. The absence of reduction byproducts observed for 299f-h suggests a late stage, well-defined transition state in which coordination to the radical acceptor plays an essential role in enabling the electron transfer to the imide carbonyl. Bis-activated substrates 299e and 299m provide supporting evidence for the importance of coordination, affording good yields of their respective cyclisation products despite the presence of two linear chains as substituents. Attempted 6-exo-trig cyclisation of 299i only resulted in direct reduction of the barbituric acid moiety.

The stereochemistry of both 5-exo-trig and 5-exo-dig cyclisation products were confirmed by X-ray crystallographic analysis of 300a and 300k (figure 2.3:1). In contrast with reduction product 286e, detailed analysis of the structure of 300a revealed thermodynamic stability. The C1–O1 bond was found to be 1.407 Å, shorter than the average Csp3–O bond (1.432 Å), and the C1–C2 bond to be longer than the standard Csp3–Csp3 bond (1.552 Å vs. 1.530 Å). With an OLP1–O1–C1–C2 torsion angle of ~191° and OLP2–O1–C1–N1 of ~172°, these parameters are consistent with an anomeric effect resulting from OLP1→σ*C1–C2 and OLP2→σ*C1–N1 interaction. The hemiaminal system is stabilised by the nearly non-existent NLP→σ*C1–O1 interaction, with a NLP–N1–C1–O1 dihedral angle of ~57°, which is further reduced by the delocalisation of the nitrogen lone pair into the N-acylurea conjugated system.127
The cyclisation is proposed to occur after coordination of both the imide carbonyl and the radical acceptor via generation of an acyl-type radical anion 303 and through a well-defined late stage anti transition state 304 (scheme 2.3:2).

Scheme 2.3:2 – Proposed ketyl-alkene cyclisation pathway
2.4. Mechanistic studies

Preliminary studies have been carried out in order to elucidate the mechanism of these reductions. Complete deuterium incorporation was observed when using SmI$_2$–D$_2$O as the reagent system, in agreement with the proposed series of electron transfers and protonations, and the kinetic isotope effect measured for the transformation suggests that proton transfer is not involved in the rate determining step (scheme 2.4:1).$^{127}$

![Scheme 2.4:1 – Reductions: deuterium incorporation and kinetic isotope effect](image)

It was also shown that changing the stoichiometry of SmI$_2$ and H$_2$O and the reaction time had no effect on the diastereomeric ratios obtained, suggesting that the stereochemical outcome of the reaction was not rate-dependent and suggested thermodynamic control. The essential role of water was also demonstrated by attempting the reduction with various other SmI$_2$–additive systems, resulting at best in extremely low yields of the hemiaminal. Reducing the amount of water triggered a noticeable drop in yield, culminating in complete loss of reactivity when using less than 50 equivalents.

Similarly, efficient cyclisation was only observed in the presence of the SmI$_2$–H$_2$O system and the reaction was impeded by the reduction of the amount of water used (table 2.4:1).$^{127}$
Additive eq Time Conversion Yield dr
--- --- --- --- --- ---
- - 2 h <5% <5% -
H₂O 10 2 h <5% <5% -
H₂O 200 15 min >95% 78% -
MeOH 4:1 v/v<sup>a</sup> 2 h <5% <5% -
EG 36 15 min 30% 16%<sup>b</sup> >95:5
HMPA 72 2 h >95% 25% 69:31
LiCl 24 1 h >95% <5% -

<sup>a</sup>4:1 SmI₂ 0.1 M in THF:MeOH mixture. <sup>b</sup>8% yield of the hemiaminal reduction product observed.

Table 2.4:1 – Importance of the additive for cyclisation reactions

Complete deuterium incorporation was observed during the cyclisation of 299<sub>c,j-k</sub>, and kinetic isotope effect measurements again suggested the absence of involvement of proton transfer in the rate determining step (figure 2.4:1).<sup>127</sup>

Figure 2.4:1 – Cyclisations: deuterium incorporation and kinetic isotope effect

SmI₂–D₂O treatment of 299<sub>j</sub> however showed that the terminal alkyne acted as a competing proton source for the vinylsamarium(III) formed at the end of cyclisation process, resulting in a mixture of H/D, H/H and D/D substituted exocyclic methylenes in a 2.6:1.2:1:1 ratio in 308 (figure 2.4:2).
The mixture of double bond isomers obtained for 300l was also investigated, as it suggested inversion of the vinyl radical obtained after cyclisation prior to final electron transfer and protonation. Although such a process has been suspected in the previously reported SmI₂-mediated ketyl-alkyne cyclisations of Meldrum’s acid, this hypothesis could not be confirmed. Taking advantage of the greater flexibility of conditions for the barbituric acid cyclisations, 299l was treated with different SmI₂–H₂O systems in order to modify the reaction rate and thus the half-life of the vinyl radical. These variations satisfyingly had a strong effect on the $E:Z$ ratio obtained, demonstrating a switch in selectivity depending on the water concentration (table 2.4:2).¹²⁷

These results are consistent with an anti-periplanar formation of the vinyl radical during cyclisation. As the inversion barrier for vinyl radicals is low,¹²⁹ the stereochemical outcome of the reaction is determined by the rate of the final electron transfer, giving a configurationally stable vinyl anion (scheme 2.4:2).¹³⁰ The influence of sterics on the rate of inversion of 312 is clearly shown by the cyclisation of 299k to 300k, which undergoes complete inversion to give exclusively the $E$ double bond isomer of the vinyl TMS product 300k.
Several competition experiments were carried out to show that the rate of cyclisation is governed by the electronic and steric properties of the radical acceptor (scheme 2.4:3), in agreement with previous findings on stereoselective radical cyclisations. Cyclisation onto activated, more electron rich acceptors was preferred, as well as the use of substrates bearing multiple acceptors. Interestingly, the simple reduction of barbituric acid derivatives was shown to be faster than the cyclisation onto an unactivated olefin, but slower than that onto an activated alkene. The reduction of barbituric acid derivatives was also shown to proceed more slowly than that of Meldrum’s acids, but faster than 6-membered lactones.
Reactions carried out using a 1:1 mixture of starting materials. *Work undertaken by B. Sautier. †Work undertaken by Dr M. Szostak.

Scheme 2.4:3 – Competition experiments
2.5. Reactivity of the hemiaminals

2.5.1. Nucleophilic additions to N-acyliminiums

Although hemiaminals derived from barbituric acid derivatives are well documented in the literature, their use as N-acyliminium equivalents has received little attention, with only a single example reported by Kloetzer et al.\textsuperscript{133} Given the apparent predisposition for the hemiaminals to give the corresponding N-acyliminiums (\textit{vide supra}), it was decided to investigate their use as precursors to unusual iminium electrophiles.

Iminium formation was examined using Lewis and Brønsted acids (table 2.5.1:1). BF\textsubscript{3}•OEt\textsubscript{2} was found to efficiently mediate the Sakurai-type addition of allyltrimethylsilane, cleanly affording 315 at room temperature with excellent diastereoccontrol.\textsuperscript{134}

![Diagram](image)

\textbf{Table 2.5.1:1 – Optimisation of the reaction conditions}

<table>
<thead>
<tr>
<th>Acid</th>
<th>Conversion\textsuperscript{c}</th>
<th>Yield\textsuperscript{c}</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFA</td>
<td>&gt;95%</td>
<td>31\textsuperscript{b}</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>TMSOTf</td>
<td>&gt;95%</td>
<td>87\textsuperscript{b}</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>AlMe\textsubscript{3}</td>
<td>&lt;5%</td>
<td>&lt;5\textsuperscript{a}</td>
<td>-</td>
</tr>
<tr>
<td>AlClMe\textsubscript{2}</td>
<td>&lt;5%</td>
<td>&lt;5\textsuperscript{a}</td>
<td>-</td>
</tr>
<tr>
<td>AlCl\textsubscript{3}</td>
<td>&gt;95%</td>
<td>68\textsuperscript{b}</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>TiCl\textsubscript{4}</td>
<td>&gt;95%</td>
<td>86\textsuperscript{a}</td>
<td>89:11</td>
</tr>
<tr>
<td>SnCl\textsubscript{4}</td>
<td>&gt;95%</td>
<td>81\textsuperscript{a}</td>
<td>90:10</td>
</tr>
<tr>
<td>BF\textsubscript{3}•OEt\textsubscript{2}</td>
<td>&gt;95%</td>
<td>91\textsuperscript{a}</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>BF\textsubscript{3}•OEt\textsubscript{2}</td>
<td>&gt;95%</td>
<td>81\textsuperscript{a,d}</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>BF\textsubscript{3}•OEt\textsubscript{2}</td>
<td>&gt;95%</td>
<td>&lt;5\textsuperscript{a,e}</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Work undertaken by B. Sautier. \textsuperscript{b}Work undertaken by Dr M. Szostak. \textsuperscript{c}Determined by \textsuperscript{1}H NMR. \textsuperscript{d}Reaction carried out at −78 °C. \textsuperscript{e}AllylMgBr used instead of AllylTMS.
With optimised conditions in hand, it was decided to explore the scope of these nucleophilic additions. A range of nucleophiles was successfully used including organometallics, heteroatom nucleophiles and an array of functionalised silanes, affording the target compounds in good to excellent yields and with high diastereoselectivity (table 2.5.1:2, figure 2.5.1:1).\(^{134}\)

![Nucleophilic additions into N-acyliminiums](image)

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Nucleophile</th>
</tr>
</thead>
<tbody>
<tr>
<td>317a(^{b})</td>
<td>Et(_3)SiH</td>
</tr>
<tr>
<td>317b(^{b})</td>
<td>AlMe(_3)</td>
</tr>
<tr>
<td>317c(^{b})</td>
<td>SnBu(_3)</td>
</tr>
<tr>
<td>317d(^{b})</td>
<td>OTMS</td>
</tr>
<tr>
<td>317e(^{a})</td>
<td>OMe</td>
</tr>
<tr>
<td>317f(^{a})</td>
<td>TMS</td>
</tr>
<tr>
<td>317g(^{a,c})</td>
<td>MeOH</td>
</tr>
<tr>
<td>317h(^{a})</td>
<td>Br</td>
</tr>
<tr>
<td>317i(^{a})</td>
<td>TMSN(_3)</td>
</tr>
<tr>
<td>317j(^{a})</td>
<td>Cl</td>
</tr>
<tr>
<td>317k(^{a})</td>
<td></td>
</tr>
<tr>
<td>317l(^{a})</td>
<td></td>
</tr>
<tr>
<td>317m(^{a})</td>
<td></td>
</tr>
<tr>
<td>317n(^{a})</td>
<td></td>
</tr>
<tr>
<td>317o(^{a})</td>
<td></td>
</tr>
<tr>
<td>317p(^{a})</td>
<td></td>
</tr>
<tr>
<td>317q(^{a})</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\)Work undertaken by B. Sautier. \(^{b}\)Work undertaken by Dr M. Szostak. \(^{c}\)Determined by \(^{1}\)H NMR. \(^{d}\)Carried out in CH\(_2\)Cl\(_2\) and CH\(_3\)CN. Starting material recovered.

Table 2.5.1:2 – Nucleophilic additions into N-acyliminiums
Stereochemistry assigned based on 2D NMR experiments (NOESY).

Figure 2.5.1:1 – Products of nucleophilic addition to N-acyliminiums

The use of deuterated starting material afforded the corresponding isotopically enriched hydouracils, providing a convenient solution for isotopic marking of the α-amino position (table 2.5.1:3).
Table 2.5.1:3 – Isotopic labelling

2.5.2. Further transformations

In the absence of a nucleophile, treatment of the hemiaminals containing a proton adjacent to the hemiaminal hydroxyl with BF₃•OEt₂ resulted in efficient dehydration to give uracil derivatives (scheme 2.5.2:1).

Scheme 2.5.2:1 – Dehydration to uracil derivatives

On the other hand, treatment of bicycles containing an exocyclic methylene under the previously established conditions resulted in 1,4-addition into the α,β-unsaturated N-acyliminium formed (table 2.5.2:1, figure 2.5.2:1).\textsuperscript{132}
Table 2.5.2:1 – 1,4-Additions

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>Nucleophile</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>322a</td>
<td>i-Bu</td>
<td>AllylTMS</td>
<td>89%</td>
</tr>
<tr>
<td>322b</td>
<td>(CH₂)₂CH=CH₂</td>
<td>TMSCN</td>
<td>74%</td>
</tr>
<tr>
<td>322c</td>
<td>(CH₂)₂CH=CH₂</td>
<td>TMSN₃</td>
<td>51%</td>
</tr>
<tr>
<td>322d</td>
<td>(CH₂)₂CH=CH₂</td>
<td>AllylTMS</td>
<td>82%</td>
</tr>
<tr>
<td>322e</td>
<td>(CH₂)₂CH=CH₂</td>
<td></td>
<td>81%</td>
</tr>
<tr>
<td>322f</td>
<td>(CH₂)₂CH=CH₂</td>
<td></td>
<td>66%</td>
</tr>
<tr>
<td>322g</td>
<td>(CH₂)₂CH=CH₂</td>
<td></td>
<td>94%</td>
</tr>
<tr>
<td>322h</td>
<td>(CH₂)₂CH=CH₂</td>
<td></td>
<td>76%</td>
</tr>
</tbody>
</table>
Finally, the hydrouracils obtained after nucleophilic addition were exploited in several metal-catalysed transformations, demonstrating their potential as precursors to diversely functionalised uracil derivatives (scheme 2.5.2:2).  

![Scheme 2.5.2:2 – Metal-catalysed derivatisation of hydrouracils](image-url)
Chapter 3 — Pseudolaric acid B: SmI$_2$-mediated cyclisation approach to a model substrate

3.1. Introduction to Pseudolaric acid B

The pseudolaric acids\textsuperscript{135} are a family of diterpenoids initially isolated from ‘tujingpi’ – or Cortex pseudolaricis, a traditional Chinese medicine made out of processed and dried cortex from the roots of Pseudolarix amabilis, a conifer growing in the eastern mountains of China\textsuperscript{136} which is now frequently referred to as Pseudolarix kaempferi in the recent literature.\textsuperscript{137} The first report of pseudolaric acids in the literature was made in 1957,\textsuperscript{138,139} but it was not until 1982 that their core structure was elucidated by X-ray crystallography.\textsuperscript{140} Their characteristic compact tricyclic core includes a highly unusual trans-fused perhydroazulene framework bearing a lactone and an acetoxy/hydroxy group at the ring junction, as well as four contiguous stereocentres, one of which is quaternary (C$_{10}$). Two of them – pseudolaric acids A and B – display significant biological activity.

![General skeleton of the pseudolaric acids](image1)

**Scheme 3.1:1** — General skeleton of the pseudolaric acids

![Pseudolaric acids A and B](image2)

**Scheme 3.1:2** — Pseudolaric acids A and B

Numerous studies have investigated the biological activity of pseudolaric acids A and B, demonstrating various effects including anti-microbial,\textsuperscript{141,142} anti-fertility,\textsuperscript{143-147} cytotoxicity,\textsuperscript{148-172} anti-angiogenic,\textsuperscript{173-176} and anti-cancer\textsuperscript{154,177,178} activities. In 2005, Wong \textit{et al.} identified microtubules as their cellular target.\textsuperscript{154} Microtubules are an essential cellular component giving structure to the cell and playing a crucial role in the organisation
and division of genetic material during mitosis. Interestingly, competition-binding assays with [³H]colchicine and [³H]vinblastine (two known bioactive tubulin binders) showed that pseudolaric acid B uses a different binding site than these compounds. ¹⁵⁴, ¹⁷⁶ Efforts undertaken to determine the structure-activity relationship of pseudolaric acids A and B highlighted the importance of every functional group present in these molecules, ¹⁴¹, ¹⁴², ¹⁴⁸, ¹⁷⁹-¹⁸¹ and short term studies showed that pseudolaric acid B was well tolerated in animals. ¹⁴⁴, ¹⁵⁴, ¹⁷⁶, ¹⁸⁰, ¹⁸¹

Since the determination of their core structure, ¹⁴⁰ the pseudolaric acids have attracted work from various synthetic groups, ¹⁸²-¹⁹³ eventually culminating in three total syntheses by Chiu (2006), ¹⁹⁴ Trost (2007)¹⁹⁵, ¹⁹⁶ and Yang (2011). ¹⁹⁷

3.2. Conjugate reduction of unsaturated Meldrum’s acid: a SmI₂–H₂O mediated cascade approach

3.2.1. Previous work

In previous studies in the Procter group during an approach towards the natural product stolonidiol, the feasibility of a reductive aldol cyclisation/lactone reduction cascade had been successfully demonstrated (scheme 3.2.1:1). ¹⁹⁸, ¹⁹⁹ Conjugate reduction of ³³² followed by aldol reaction gave ³³³, which upon reduction of the 6-membered lactone by the SmI₂–H₂O system gave triol ³³⁴.

![Scheme 3.2.1:1 – Cascade approach to stolonidiol](image)

Based on this approach, and building on the recent discovery by our group that SmI₂–H₂O could also be used to reduce cyclic 1,3-diesters, ⁹³, ⁹⁸ a similar cascade approach to pseudolaric acid B was envisioned. The proposed synthetic route relied on the conjugate reduction of the alkylidene Meldrum’s acid ³³⁶, followed by aldol cyclisation of the
resulting samarium enolate and subsequent chelation controlled mono-reduction of the cyclic diester to generate cyclopentanol 339 (scheme 3.2.1:2).

![Scheme 3.2.1:2 – Proposed cascade approach to pseudolaric acid B]

Model substrate 340 was therefore synthesised and treated with SmI$_2$–H$_2$O, but failed to deliver the desired cyclopentanol 343. The reaction of 340 instead afforded a mixture of 341 and 342, resulting from partial and complete reduction of the system respectively. The reaction also suffered from poor yield and mass recovery (scheme 3.2.1:3). Although 341 could arise from retro-aldol decomposition, no traces of the cyclised product could be detected. However, additional experiments using SmI$_2$–MeOH demonstrated that conjugate reduction of the alkylidene Meldrum’s acid was faster than ketone reduction, which was essential for the proposed cascade to occur.

![Scheme 3.2.1:3 – Attempted cascade sequence]

### 3.2.2. Further cascade studies

Despite these disappointing initial results, the instability of starting material 340 as well as the very poor mass recovery from the reaction prompted the investigation of a more stable,
easier to recover substrate before concluding on the feasibility of the cascade. The synthesis of 349 was therefore undertaken, in the hope that the added functionality would both improve the stability of the compound as well as its ease of purification. Gratifyingly, 4-bromobenzyl ether 349 was synthesised as a crystalline solid and purified by recrystallization, thus solving purification issues. p-Bromobenzylation of Weinreb amide 344 followed by Grignard addition gave 347, from which 349 was obtained after oxidative cleavage of the olefin and subsequent thioalkylation of Meldrum’s acid. Unfortunately, and despite an improved mass balance, no traces of 350 could be detected when 349 was subjected to the cascade conditions (scheme 3.2.1:4), instead yielding a mixture of reduced compounds.

Scheme 3.2.1:4 – Alternative cascade substrate

3.3. Conjugate reduction of γ-butyrolactones: a SmI$_2$-mediated cyclisation/reduction approach

3.3.1. Previous work

Taking into account these unsuccessful attempts to achieve the desired cyclisation from alkylidene Meldrum’s acid derivatives, a different approach to the pseudolaric acids’ core
was developed. It had been previously demonstrated within the Procter group that the treatment of γ,δ-unsaturated ketones with SmI$_2$–MeOH resulted in diastereoselective spirocyclisation (scheme 3.3.1:1). More recently, it was also shown by Hassan Harb in the group that the use of a silicon stereocontrol element provided excellent diastereocontrol in the construction of cyclobutanols and spirocyclopentanols (scheme 3.3.1:1).

Scheme 3.3.1:1 – Previous work

The complete stereocontrol observed in the formation of spirocyclopentanols such as 354 is proposed to arise from conformationally defined intermediate 356, in which selective cyclisation on the less hindered face of the enolate is enforced by the bulky silicon group. In addition, the construction of the adjacent quaternary centre is controlled by chelation of the lactone and ketone carbonyls by a bridging samarium atom (scheme 3.3.1:2).

Scheme 3.3.1:2 – Proposed origin of the stereoselectivity in spirocyclisations

Interestingly, the asymmetric synthesis of silyl lactones was also recently described by our group and could then be used in a non-racemic approach to the natural product after completion of the model study (scheme 3.3.1:3).
Scheme 3.3.1:3 – Asymmetric synthesis a silyl lactone

It was proposed that C–Si directed cyclisation could be utilised to approach the cyclopentanol core 360 of pseudolaric acid B. Spirocyclisation of 364 followed by lactone reduction would afford the densely functionalised triol 362 which could then be converted to 360 via Peterson elimination and oxidative cleavage of the resulting olefin 361 (scheme 3.3.1:4).

Scheme 3.3.1:4 – Proposed approach to the cyclopentanol core of pseudolaric acid B

Model substrate 372 was therefore synthesised to evaluate the proposed approach to the cyclopentanol core and study the subsequent formation of the 7-membered ring of the azulene framework of pseudolaric acid B (scheme 3.3.1:5). Starting from 2,3-dihydrofuran 365, dithiane formation followed by silyl protection gave 366 from which 369 was obtained after alkylation, deprotection, and Swern oxidation. 371 was then accessed through a one pot silyl conjugate addition/aldol process and converted to cyclisation substrate 372 via a mesylation/elimination sequence followed by diathiane deprotection.
Pleasingly, treatment of 372 with SmI$_2$–MeOH gave 373 as a single diastereoisomer and lactone reduction to triol 374 was found to proceed in excellent yield using the SmI$_2$–H$_2$O–Amine methodology recently introduced by our group.$^{77-79}$ Peterson elimination then proceeded in moderate yield to afford the desired cyclopentanol 375 (scheme 3.3.1:6).$^{200}$

In order to advance towards the formation of the 7-membered ring of the natural product, protection of the tertiary alcohol in 375 was essential to avoid retro-aldo ring opening upon oxidation of the primary alcohol. An initial approach featured the formation of a benzylidene acetal 376 followed by cleavage with DIBAL–H to give the benzyl protected
tertiary alcohol 377. Selective oxidative cleavage of the less hindered olefin followed by oxidation and esterification gave access to 378, from which cyclisation substrate 379 was obtained after oxidation and Wittig homologation. Unfortunately, formation of the azulene framework 380 via aldol condensation proved unfeasible under the chosen reaction conditions (scheme 3.3.1:7).

Scheme 3.3.1:7 – Initial attempt at the construction of the 7-membered ring

Aldol condensation aside, this route was also hampered by the acetal deprotection step, which afforded an inseparable mixture of the desired compound 377 together with the corresponding reduced terminal alkene and suffered from low conversion. Alternatively, bis-protection of diol 375 with TBS groups provided 381 which could successfully be converted to diester 383. Although this route was not pursued any further, mono-deprotection and oxidation of the primary alcohol followed by homologation and conversion to the ester were then expected to deliver cyclisation substrate 384 (scheme 3.3.1:8).
Scheme 3.3.1: Alternative protection strategy

3.3.2. First approach

Building on the successful synthesis of the model cyclopentanol core and despite the initial failure to complete the azulene framework, several routes starting from 381 were considered to access the bicyclic core of pseudolaric acid B (scheme 3.3.2:1).

Scheme 3.3.2:1 – Possible routes to the bicyclic core
In addition, further studies were conducted regarding the protecting group strategy for 375 in order to selectively access the mono-protected primary alcohol 391 (scheme 3.3.2:2).

Scheme 3.3.2:2 – Protecting group strategy

### 3.3.2.1. Protecting group strategy

Selective deprotection of 390 to access primary alcohol 391 is essential for the construction of the bicyclic system, as protection of the tertiary alcohol is required during the oxidation of the primary alcohol to avoid retro-aldol ring opening (*vide supra*). To that end, three different strategies were investigated (scheme 3.3.2.1:1).

Scheme 3.3.2.1:1 – Proposed protecting group strategies

Sequential protection of the diol with orthogonal protecting groups was initially investigated. Protection with two different silyl groups in one pot gave a mixture of products 396 and 397, most likely due to an unselective initial TMS protection. This lack of selectivity probably arises from the dense functionalization of the diol, although intramolecular transfer of the TMS protecting group to form the more stable tertiary silyl ether cannot be ruled out. Mono-TBS protection of 375 was however successful, providing cyclopentanol 398. Unfortunately, attempts to orthogonally protect the remaining alcohol as the pivalate ester failed (scheme 3.3.2.1:2).
An alternate strategy, the direct oxidation of silyl ethers under Swern oxidation conditions, was also studied. The propensity of TMS and TES silyl ethers to be oxidized using the standard Swern procedure has been previously reported\textsuperscript{203,204} and shown to exhibit remarkable chemoselectivity.\textsuperscript{205} The synthesis of bis-TES protected diol \textit{400} was therefore undertaken and its direct oxidation to \textit{401} attempted, pleasingly affording the desired aldehyde upon warming of the reaction mixture from $-78 \,^{\circ}C$ to $-45 \,^{\circ}C$. Aldehyde \textit{401} however proved to be rather sensitive, and unfortunately could neither be isolated nor protected (scheme 3.3.2.1:3).

Scheme 3.3.2.1:3 – Direct oxidation of the silyl ether
The conditions explored to protect crude aldehyde 401 are set out in table 3.3.2.1:1.

<table>
<thead>
<tr>
<th>Protecting group</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethylene glycol</td>
<td>TMSCl, CH₂Cl₂</td>
</tr>
<tr>
<td>ethylene glycol</td>
<td>PPTS, benzene</td>
</tr>
<tr>
<td>ethylene glycol</td>
<td>Amberlyst-15, HC(OMe)₃, CH₃CN, toluene</td>
</tr>
<tr>
<td>2,2-dimethyl-1,3-propanediol</td>
<td>Amberlyst-15, HC(OMe)₃, CH₃CN, toluene</td>
</tr>
<tr>
<td>2,2-dimethyl-1,3-propanediol</td>
<td>BF₃•OEt₂, HC(OMe)₃, CH₃CN, toluene</td>
</tr>
<tr>
<td>1,3-propanedithiol</td>
<td>BF₃•OEt₂, CH₂Cl₂</td>
</tr>
<tr>
<td>1,3-propanedithiol</td>
<td>MgBr₂•OEt₂, Et₂O</td>
</tr>
</tbody>
</table>

Table 3.3.2.1:1 – Attempted aldehyde protection

Concomitantly, work towards the selective deprotection of 405, obtained through selective dihydroxylation of 381 followed by oxidative cleavage, Pinnick oxidation and subsequent conversion to the methyl ester, was pursued. It was found that stoichiometric use of hydrofluoric acid under careful control of the reaction conditions allowed access to 406 in excellent yield with only small amounts of bis-deprotection (scheme 3.3.2.1:4, table 3.3.2.1:2).

Scheme 3.3.2.1:4 – Selective TBS deprotection
<table>
<thead>
<tr>
<th>Conditions</th>
<th>405</th>
<th>406</th>
<th>407</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsF, MeOH</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HF 0.1 M, CH3CN</td>
<td>recovered</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HF 0.3 M, CH3CN</td>
<td>58%</td>
<td>42%</td>
<td>-</td>
</tr>
<tr>
<td>HF 0.4 M, CH3CN</td>
<td>44%</td>
<td>56%</td>
<td>-</td>
</tr>
<tr>
<td>HF 0.5 M, CH3CN</td>
<td>-</td>
<td>86%</td>
<td>14%</td>
</tr>
<tr>
<td>HF 1 M, CH3CN</td>
<td>-</td>
<td>37%</td>
<td>63%</td>
</tr>
</tbody>
</table>

The fluoride source was added to a 0.1 M solution of 405.

Table 3.3.2.1:2 – Conditions screen for the selective TBS deprotection

406 was then advanced towards the desired cyclisation substrates by oxidation and subsequent homologation of the primary alcohol, affording aldehyde 385 which could then be protected as dimethyl acetal 409 when necessary (scheme 3.3.2.1:5).

Scheme 3.3.2.1:5 – Advance towards cyclisation substrates

3.3.2.2. α-Ester substitution approaches

Amongst the different routes considered to close the 7-membered ring, several required the installation of a substituent α to the ester of 405. The synthesis of α-phosphono esters has been described by Wiemer and intermediates such as 410 were therefore considered to perform the ring closure through a Horner–Wadsworth–Emmons reaction. Phosphonylation of 405 was thus attempted, as well as that of 409, unfortunately without success (scheme 3.3.2.2:1). A control using a simple commercial ester was on the other hand successful, pointing towards an issue with the actual substrates.
Similarly, $\alpha$-halogenation of 409 would provide a substrate for the ring formation via a Reformatsky reaction. $\alpha$-Bromination was first attempted by forming the TMS ketene-acetal of 409, using NBS as the electrophilic bromine source. This procedure however only resulted in the deprotection of the dimethyl acetal, affording aldehyde 385. Repeating the reaction in the absence of TMSCl using either NBS or NCS as the halogen source failed to give the desired $\alpha$-halogenated ester, and allowing the reaction mixture to warm up to room temperature after addition of the electrophile proved unsuccessful as well (table 3.3.2.1:1).

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMSCl, LDA, NBS, THF, −78 °C</td>
<td></td>
</tr>
<tr>
<td>LDA, NBS, THF, −78 °C</td>
<td></td>
</tr>
<tr>
<td>LDA, NCS, THF, −78 °C</td>
<td>X</td>
</tr>
<tr>
<td>LDA, NBS, THF, −78 °C - rt</td>
<td></td>
</tr>
<tr>
<td>LDA, NCS, THF, −78 °C - rt</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.3.1:1 – $\alpha$-Halogenation attempts
3.3.2.3. Aldol and Claisen condensation approaches

Despite the failure of the initial aldol approach (see section 3.3.1.), formation of the azulene framework via aldol or Claisen condensation was still investigated. It was well appreciated that upon treatment with base under kinetic control, substrates like 413 would preferentially form 414, from which cyclisation was unlikely, as opposed to the less hindered enolate 415 (scheme 3.3.2.3:1).

Hypothesising that reversible enolate formation conditions could result in an equilibrium between 414 and 415, 385 was treated with sodium methoxide in methanol, albeit without success. Increasing the reaction temperature to favour the formation of 416 was equally unsuccessful to access 419. The formation of a titanium enolate 417 was also attempted in the hope that coordination with the Lewis acid would help driving the reaction, but again failed to give any cyclisation product (scheme 3.3.2.3:2). In order to avoid the formation of competing enols, enolisation of 409 in presence of a Lewis acid to generate an oxonium acceptor 418 was also undertaken, to no avail (scheme 3.3.2.3:2).
In preparation for a Claisen condensation approach, the synthesis of diester 387 was attempted via Pinnick oxidation and subsequent esterification of 385 (scheme 3.3.2.3:3). This procedure however yielded a complicated mixture of products from which 387 could not be isolated, and further exploration of this route was not undertaken – the lack of literature precedent for the formation of a trans-fused 7-membered ring and the failures experienced with the aldol approach pointing towards an unfavourable outcome.

Scheme 3.3.2.3:2 – Attempted aldols

Scheme 3.3.2.3:3 – Attempted Claisen condensation approach
3.3.2.4. Ring-closing metathesis approach

The ring-closing metathesis of a similar trans-fused system has been reported by Christmann for the synthesis of englerin A\textsuperscript{209} and this strategy has been used by Yang for the synthesis of pseudolaric acid A,\textsuperscript{197} leading us to consider the synthesis of 389. It was however anticipated that the steric hindrance around the vinyl group would most likely prevent both formation of the ruthenium alkylidene and formation of the metallacyclobutane at that position, and that relay ring-closing metathesis\textsuperscript{210} would probably have to be used to form the desired metal alkylidene (scheme 3.3.2.4:1).

Conversion of the vinyl group in 381 to the corresponding ester had to be carried out before setting up either substrate for ring closing metathesis. Oxidative cleavage of the terminal olefin followed by reduction and subsequent protection of the resulting alcohol afforded 422. Direct conversion of the vinyl to ester 423 was attempted by ozonolysis but only yielded a complex mixture of products. Oxidative cleavage was observed when using ruthenium catalysed oxidative conditions, but proceeded with concomitant deprotection and oxidation of the unhindered primary alcohol, affording bis-acid 424 as the major product of the reaction, which could then be converted to the corresponding diester 425 (scheme 3.3.2.4:2). Surprisingly, simultaneous oxidation and oxidative cleavage of 421 only resulted in a complex mixture of products.
Scheme 3.3.2.4:2 – Oxidative cleavage of the vinyl group

Further elaboration towards 389 or 420 could not be undertaken due to time constraints, but would have to proceed through selective deprotection of the primary alcohol to install the first olefin – or relay chain – followed by selective conversion of the unhindered ester to the required olefin.

3.3.3. Second approach

Concurrently, another approach was being explored. It was envisioned that formation of the 7-membered ring could be effected by intramolecular nucleophilic acyl substitution, using 427 as the substrate (scheme 3.3.3:1). Of particular interest to us were the different reports made by Molander on the use SmI$_2$ to mediate such a reaction, using lactones as the acyl donor.$^{211-213}$ Lactone 427 was proposed to be accessible from cyclisation substrate 426.

Scheme 3.3.3:1 – Intramolecular nucleophilic acyl substitution approach

The synthesis of 426 followed the previously established route, using 429 as the electrophile for the dithiane alkylation. Mono-deprotection of 430 was shown to be carried
out very effectively by treatment of 430 with hydrochloric acid in ethanol, quickly and cleanly affording alcohol 431 (scheme 3.3.3:2). Oxidation followed by one pot silyl conjugate addition/aldol reaction afforded 433, which in turn gave 426 after mesylation, elimination and dithiane deprotection.

Scheme 3.3.3:2 – Cyclisation substrate synthesis

Formation of diol 436 proceeded smoothly using the established SmI$_2$-mediated cyclisation and reduction procedure, followed by Peterson elimination. In order to avoid selective deprotection issues between both primary alcohols, it was decided to attempt a direct oxidation of the bis-silyl ether of 436. Oxidation of the bis-TES ether was undertaken as described in section 3.3.2.1., successfully yielding aldehyde 437 which was then homologated to give 438 (scheme 3.3.3:3).
Removal of the remaining TES protecting group was then investigated. The silyl ether proved remarkably stable to mild deprotection conditions, withstanding even mild fluoride reagents. 438 was eventually deprotected by generating dry HCl in methanol, albeit along with concomitant deprotection of the primary alcohol, affording lactol 439 (table 3.3.3:1).

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCl(_{aq.}), THF</td>
<td>Failed</td>
</tr>
<tr>
<td>PPTS, EtOH</td>
<td>Failed</td>
</tr>
<tr>
<td>HF-Pyridine, CH(_3)CN</td>
<td>Failed</td>
</tr>
<tr>
<td>TBAF, THF</td>
<td>Decomposed</td>
</tr>
<tr>
<td>TBAF-AcOH, THF</td>
<td>Failed</td>
</tr>
<tr>
<td>AcCl, MeOH / HCl(_{aq.}) workup</td>
<td>32% yield, R = H</td>
</tr>
<tr>
<td>AcCl, MeOH / NaHCO(<em>3)(</em>{aq.}) workup</td>
<td>68% yield, R = Me</td>
</tr>
</tbody>
</table>

Table 3.3.3:1 – Silyl ether deprotection

Selective oxidation of lactol 442 using Fétizon’s reagent\(^{214,215}\) was attempted but failed to deliver the desired lactone 443. Ley oxidation\(^{216}\) was also unsuccessful, oxidizing the primary alcohol whilst leaving the lactol untouched. PCC oxidation however gave observable amounts of the bis-oxidation product 445. In an attempt to circumvent the oxidation of the primary alcohol, conversion to the bromide prior to the lactone formation was attempted. Mesylation followed by bromine displacement of the mesylate however
failed to deliver 441, as did the use of Appel’s conditions$^{217}$ – the latter resulting in hydrolysis of 440, affording 442 (scheme 3.3.3:4).

Scheme 3.3.3:4 – Attempted lactol oxidation

3.3.4. Third approach

In order to circumvent the lack of selectivity observed in the lactol oxidation, a slightly different approach was investigated, designed to avoid the simultaneous existence of the lactol and primary alcohol. It was proposed that the synthesis of 447 could be straightforwardly performed using the chemistry already established by using 446 for the formation of the cyclopentanol core. The terminal olefin would then provide a handle to install the desired halogen after oxidation of lactol 447 (scheme 3.3.4:1).

Scheme 3.3.4:1 – Modified intramolecular nucleophilic acyl substitution approach

Synthesis of 446 was performed by following the established route, using 4-bromo-1-butene for the dithiane alkylation. As noted in section 3.3.3., TBS protection of 448 allowed for quicker access to 450 thanks to a simplified and cleaner deprotection procedure (scheme 3.3.4:2). Oxidation followed by one pot silyl conjugate addition/aldol reaction afforded 452, which in turn gave 446 after mesylation, elimination and dithiane deprotection.
SmI$_2$-mediated conversion of 446 to 454 was then performed using the previously established conditions. In the absence of any additional interfering silyl group, it was decided to revert to the bis-TBS protection strategy. Despite being successful in delivering the required aldehyde, the bis-TES strategy previously used was indeed impacted by moderate yields for the transformation (see section 3.3.3.), whereas the previous experience with selective TBS deprotection compared favourably (see section 3.3.2.1.). Diol 455 was therefore converted to 456 (scheme 3.3.4:2).

Scheme 3.3.4:2 – Cyclisation substrate synthesis
Unfortunately, this choice quickly resulted in problems. Selective deprotection of 456 was affected by its very poor solubility in acetonitrile, and only mixtures of starting material, mono-deprotection and 455 could be obtained (table 3.3.4:1). Alcohol 457 could nevertheless be isolated and subjected to oxidation and homologation to give 459, from which deprotection of the remaining TBS group would give the desired lactol. Yet again, the choice of TBS protection appeared detrimental: Deprotecting 459 proved extremely difficult, as the reaction only proceeded slowly in the presence of concentrated acid at relatively high temperature, along with partial decomposition of the material (scheme 3.3.4:3, table 3.3.4:2).

Scheme 3.3.4:3 – Attempted lactol synthesis

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF 0.4 M, CH₃CN, 10 h, rt</td>
<td>traces</td>
</tr>
<tr>
<td>HF 1 M, CH₃CN, 8h, rt</td>
<td>56%</td>
</tr>
<tr>
<td>HF 1 M, CH₃CN, overnight, rt</td>
<td>37%</td>
</tr>
<tr>
<td>HF 1 M, THF, 8h, 60°C</td>
<td>53%</td>
</tr>
</tbody>
</table>

Table 3.3.4:1 – Selective deprotection
<table>
<thead>
<tr>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF 1 M, CH₂CN, rt</td>
<td>Failed</td>
</tr>
<tr>
<td>AcCl, MeOH, rt</td>
<td>Failed</td>
</tr>
<tr>
<td>CsF, THF, rt</td>
<td>Failed</td>
</tr>
<tr>
<td>HF&lt;sub&gt;conc.&lt;/sub&gt; (2 eq), CH₂CN, rt</td>
<td>Failed</td>
</tr>
<tr>
<td>HF&lt;sub&gt;conc.&lt;/sub&gt; (2 eq), CH₂CN, 60 °C</td>
<td>Mixture</td>
</tr>
<tr>
<td>HCl 6 M : THF (1:1), 75 °C</td>
<td>Mixture</td>
</tr>
</tbody>
</table>

Table 3.3.4:2 – Deprotection of the second TBS group

Although partial conversion to the lactol could be observed, 460 could not be isolated from the reaction mixture and further work could not be performed due to time constraints. Additional work, however, would have to follow the bis-TES protection strategy, as the use of TBS protecting groups clearly appears to be problematic.

3.3.5. Spirocyclisation, lactone reduction and Peterson elimination: a telescoped sequence

A pivotal sequence in our model studies towards the core of pseudolaric acid B consists in the synthesis of diols 464 via Sm<sub>2</sub>-mediated spirocyclisation, Sm<sub>2</sub>-mediated lactone reduction and Peterson elimination (scheme 3.3.5:1).

![Scheme 3.3.5:1 – Synthetic sequence towards diols 464](image)

Although the established conditions for spirocyclisation and lactone reduction reliably gave access to triol 463, the subsequent Peterson elimination was a very capricious
reaction, typically randomly affording between 30% and 70% yield. This lack of reliability at such an advanced stage in our synthesis was a great hindrance to our studies, and optimisation of our reaction conditions thus appeared essential. Various base and acid mediated Peterson elimination conditions were therefore screened, but failed to show any improvement compared to the standard conditions. Lowering the reaction temperature was also attempted but had little effect on the range of yields obtained, as did additional attention to the already stringent conditions used for the reaction. It was eventually found that consistent yields higher than 60% were obtained when no precautions were taken, carrying out the reaction in an open flask (table 3.3.5:1).

**Impact of the change of conditions**

<table>
<thead>
<tr>
<th>Negative</th>
<th>Neutral</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaH, DMF</td>
<td>KH, Et₂O</td>
<td>KH, THF</td>
</tr>
<tr>
<td>NaH, Et₂O</td>
<td>BF₃•OEt₂, Et₂O</td>
<td>NaH, THF</td>
</tr>
<tr>
<td>LiOr-Bu, THF</td>
<td>TFA, Et₂O</td>
<td>TMSCl, MeOH</td>
</tr>
<tr>
<td>NaOr-Bu, THF</td>
<td>HF, THF</td>
<td>Open vessel, “wet” solvent</td>
</tr>
</tbody>
</table>

Standard conditions: 0.01 M in THF, 2 eq KOt-Bu

Table 3.3.5:1 – Peterson elimination optimisation

In order to simplify the synthesis of diols 464, the opportunity to telescope the three steps was considered. The use of stronger coordinating additives for the lactone reduction than for the spirocyclisation suggested that the SmI₂–H₂O–Et₃N system would not be disturbed by either the samarium(III) salts formed during the spirocyclisation or the less activating alcohol additive. In addition, the compatibility of the Peterson elimination step with non-anhydrous conditions supported the possibility for it to be performed in the same pot as the lactone reduction, thus telescoping all three steps. Gratifyingly, when attempted, the telescoped sequence indeed afforded diols 464 in good overall yields, comparable to those obtained through the stepwise process (scheme 3.3.5:2).
Scheme 3.3.5:2 – Telescoped spirocyclisation, lactone reduction and Peterson elimination
Summary and future work

1. Meldrum’s acid

Cyclisation of radicals derived from the SmI₂-mediated selective mono-reduction of Meldrum’s acid derivative onto tethered alkene acceptors were further investigated by studying the impact of the ketal unit and reaction temperature on the transformation’s stereoselectivity (scheme 1:1). The selectivity observed during these cyclisations was rationalised through a proposed mechanism involving the preferential formation of an axial ketyl radical followed by ketyl-alkene cyclisation *via an anti* transition state.

Scheme 1:1 – Optimised diastereoselective radical cyclisation of a Meldrum’s acid derivative

The scope of this methodology was extended to cyclisation cascades by exploiting the second ketyl radical formed during the reduction of the cyclopentanone intermediates (scheme 1:2). The developed procedure allowed for the use of alkene and alkyne tethers to form 5,5- and 5,6-bicycles. Complete diastereoocontrol over the formation of the bicyclic skeleton was usually observed.

Scheme 1:2 – Cyclisation cascades of Meldrum’s acid derivatives
2. Barbituric acid

2.1. Reduction and cyclisation

The first general methodology for the reduction of amide-type carbonyl groups under single electron transfer conditions was developed using the SmI$_2$–H$_2$O system, providing an unprecedented direct access to hemiaminals from barbituric acid derivatives (scheme 2.1:1). Investigation of the mono-reduction of barbituric acid derivatives showed the transformation to occur with good yields and diastereoselectivity, whilst tolerating a wide range of functional groups.

Scheme 2.1:1 – Mono-reduction of barbituric acid derivatives

The intermediate acyl-type radicals were successfully exploited in radical cyclisations using tethered alkenes and alkynes as acceptors, affording bicyclic hemiaminals in good to excellent yields with perfect diastereocontrol around the newly formed 5-membered ring (scheme 2.1:2). Initial mechanistic studies were carried out and the structural features of the mono- and bicyclic hemiaminals were uncovered through analysis of X-ray crystal structures obtained for both products.

Scheme 2.1:2 – Cyclisation of barbituric acid derivatives

2.2. Nucleophilic additions into N-acyliminiums

The hemiaminals obtained after mono-reduction were exploited as N-acyliminium equivalents in reactions with nucleophiles, typically affording hydouracils in excellent yields and diastereoselectivities (scheme 2.2:1). Various nucleophiles were shown to be
compatible with the procedure, including silanes, heteroatom nucleophiles and organometallics.

![Scheme 2.2:1 - Nucleophilic additions into N-acyliminiums](image)

Vinylogous nucleophilic additions into N-acyliminiums were also demonstrated using unsaturated hemiaminals derived from the cyclisation of alkynes (scheme 2.2:2). Complete selectivity for 1,4-addition was observed, usually affording bicyclic hydouracil derivatives in good yields.

![Scheme 2.2:2 – 1,4-additions](image)

### 3. Pseudolaric acid B

#### 3.1. Summary

Following on from previous work done in an approach to pseudolaric acid B, several strategies were explored to close the seven membered ring of the natural product’s azulene core. Protecting group strategies played a key role in advancing towards the different targets, displaying a high impact on the route’s viability (figure 3.1:1). The selective deprotection strategy developed for 405 in a first approach could not be efficiently applied to 456. In a second route, successful selective oxidation of the primary TES silyl ether 466 was followed by an unselective deprotection step, failing to discriminate between the primary and tertiary silyl protected alcohols. The third synthetic approach on the other hand suffered from the unsuccessful deprotection of the tertiary alcohol in 456.
Aldol and Claisen condensation strategies to form the 7-membered ring were attempted to no avail, and efforts to access Reformatsky and Horner–Wadsworth–Emmons reaction substrates were unsuccessful (scheme 3.1:1).

The most promising lead explored, progressing towards a substrate designed for intramolecular nucleophilic acyl substitution, gave access to lactol 442 as the most advanced intermediate (scheme 3.1:2).
3.2. Future work

In order to access 427, the protecting group strategy needs to revert to the use of TES protecting groups for 455. Direct oxidation of the primary TES-protected alcohol followed by homologation and removal of the remaining TES group under mild acidic conditions would provide 469. Oxidation of a similar lactol was previously observed using PCC (see chapter 3, section 3.3.3.) and would afford lactone 470 which upon reductive cleavage of the olefin followed by conversion of the resulting alcohol to the corresponding halide would give 427. Treatment with SmI$_2$ under the conditions described by Molander$^{211-213}$ would then result in nucleophilic acyl substitution, completing the model synthesis of the azulene framework of the natural product (scheme 3.2:1).

**Scheme 3.2:1 – Proposed synthesis of the azulene framework of pseudolaric acid B**
Experimental and characterisation data

1. General experimental

All experiments were performed under an atmosphere of nitrogen, using anhydrous solvents unless stated otherwise. Tetrahydrofuran was distilled from sodium/benzophenone and stored under nitrogen or taken from a solvent purification system (SPS). Dichloromethane, triethylamine, diisopropylamine and toluene were distilled from calcium hydride and stored under nitrogen. All other dry solvents were used as bought from Sigma-Aldrich, Acros Organics and Alfa Aesar. Solvents used in conjunction with samarium diiodide were deoxygenated by bubbling with nitrogen for fifteen minutes when used. Water when used in conjunction with samarium diiodide was distilled before being deoxygenated by bubbling with nitrogen for four hours. Potassium carbonate was dried in the oven overnight prior to use.

$^{1}H$ NMR and $^{13}C$ NMR were recorded on 300, 400 and 500 MHz spectrometers, with chemical shifts values being reported in ppm relative to residual chloroform ($\delta_{H} = 7.27$ or $\delta_{C} = 77.2$), acetone ($\delta_{H} = 2.05$ or $\delta_{C} = 29.8$) or benzene ($\delta_{H} = 7.15$ or $\delta_{C} = 128.6$) as internal standards. All coupling constants ($J$) are reported in Hertz (Hz). Yields based on $^{1}H$ NMR were measured using a 0.1 M solution of nitromethane as the internal standard. Compounds were assigned based on 1D ($^{1}H, ^{13}C$, DEPT135) and 2D (COSY, HSQC) NMR experiments.

Mass spectra were obtained using positive or negative electrospray (ES±), electron ionisation (EI±) or positive chemical ionisation (APCI+) methodology. Infra-red spectra were recorded as evaporated films or neat using FT/IR spectrometers.

Column chromatography was carried out using 35-70 μ, 60 Å silica gel. Preparative thin layer chromatography was carried out on glass plates coated with silica gel GF254, 1000 μm thickness. Routine TLC analysis was carried out on aluminium sheets coated with silica gel 60 F254, 0.2 mm thickness. Plates were viewed using a 254 nm ultraviolet lamp and dipped in para-anisaldehyde or potassium permanganate.
2. Preparation of samarium(II) iodide

Samarium powder (1.2 g, 8.0 mmol, 1.2 eq), diiodoethane (1.9 g, 6.7 mmol, 1.0 eq), THF (55 mL) were added to a nitrogen flushed, oven dried round bottom flask, the flask covered with aluminium foil and the mixture stirred at room temperature for a minimum of 5 h (typically overnight). The solution was then left to settle for 1 h, titrated, and used directly.

3. Literature procedures

Meldrum’s acid derivatives were synthesised according to Zhang’s method. Knoevenagel condensations of Meldrum’s acid derivatives with aldehyde were undertaken according to Bigi’s method and subsequently reduced using standard NaBH₄ conditions. Homo-allyl bromides were synthesised according to Wong’s procedure. Sonogashira products were synthesised according to the procedure described by Floreancig. Alkyne reductions were performed with LiAlH₄ using standard condition. Conversions of alcohols to bromides were carried out using standard Appel conditions.

4. Experimental data for chapter 1: Meldrum’s acid

4.1. General procedure A – Alkylations of diethylmalonate

Diethyl 2-(but-3-en-1-yl)malonate (249)

To a stirred solution of sodium hydride (60% in oil, 2.86 g, 71.4 mmol, 1.0 eq) in THF (100 mL) at 0 °C was added diethyl malonate (11.0 mL, 72.4 mmol, 1.0 eq) and the solution stirred at room temperature for 30 minutes. Sodium iodide (5.27 g, 35.1 mmol, 0.5 eq) and 4-bromo-1-butene (8.0 mL, 78.8 mmol, 1.1 eq) were added and the solution stirred at 65 °C overnight. The reaction was quenched with H₂O (50 mL) and the aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on
silica gel, eluting with a gradient 0-5% ethyl acetate in petroleum ether (40-60 °C) gave diethyl 2-(but-3-en-1-yl)malonate 249 (11.5 g, 53.8 mmol, 75%) as a colourless oil.

\textbf{1H NMR} (400 MHz, CDCl\textsubscript{3}) $\delta$ ppm 1.26 (6 H, t, $J = 7.1$ Hz, 2 $\times$ CH\textsubscript{3})), 1.94 - 2.05 (2 H, m, CH\textsubscript{CH\textsubscript{2}}), 2.05 - 2.14 (2 H, m, CH\textsubscript{2}CH=CH\textsubscript{2}), 3.34 (1 H, t, $J = 7.3$ Hz, CH\textsubscript{CH\textsubscript{2}}), 4.19 (4 H, q, $J = 7.1$ Hz, 2 $\times$ OC\textsubscript{H\textsubscript{2}}), 4.97 - 5.08 (2 H, m, CH=CH\textsubscript{2}), 5.69 - 5.84 (1 H, m, CH=CH\textsubscript{2});

\textbf{13C NMR} (100 MHz, CDCl\textsubscript{3}) $\delta$ ppm 14.0 (2 $\times$ C\textsubscript{H\textsubscript{3}}), 27.8 (CH\textsubscript{C\textsubscript{H\textsubscript{2}}}), 31.2 (C\textsubscript{H\textsubscript{2}}C=CH), 51.1 (CH\textsubscript{HCH\textsubscript{2}}), 61.3 (2 $\times$ OCH\textsubscript{2}), 115.9 (CH=C\textsubscript{H\textsubscript{2}}), 136.8 (CH=CH\textsubscript{2}), 169.4 (2 $\times$ C=O);

Data in accordance with the literature.

\textbf{(E)-Diethyl 2-(4-phenylbut-3-enyl)malonate (251)}

As for general procedure A, reaction of diethylmalonate (0.96 mL, 6.27 mmol, 1.0 eq), sodium hydride (60% in oil, 251 mg, 6.27 mmol, 1.0 eq) and (E)-(4-bromobut-1-en-1-yl)benzene (2.00 g, 6.90 mmol, 1.1 eq) in THF (16 mL) at 65 °C gave after column chromatography (5% ethyl acetate in petroleum ether (40-60 °C)) (E)-diethyl 2-(4-phenylbut-3-enyl)malonate 251 (887.6 mg, 3.06 mmol, 48%) as a yellow oil.

\textbf{v\textsubscript{max}} (neat)/cm\textsuperscript{-1} 3025, 2981, 2938, 1727 (C=O), 1598, 1494, 1447, 1390, 1369, 1334, 1298, 1245, 1219, 1176, 1148, 1095, 1069, 1026, 966, 913, 860, 745, 694;

\textbf{1H NMR} (400 MHz, CDCl\textsubscript{3}) $\delta$ ppm 1.27 (6 H, t, $J = 7.2$ Hz, 2 $\times$ CH\textsubscript{3})), 2.10 (2 H, q, $J = 7.4$ Hz, CH\textsubscript{CH\textsubscript{2}}), 2.24 - 2.32 (2 H, m, CH\textsubscript{2}CH=CH\textsubscript{2}), 3.41 (1 H, t, $J = 7.4$ Hz, CH\textsubscript{CH\textsubscript{2}}), 4.20 (4 H, qd, $J = 7.2$, 1.5 Hz, 2 $\times$ CH\textsubscript{2}CH\textsubscript{3}), 6.17 (1 H, dt, $J = 15.8$, 7.0 Hz, CH=CH\textsubscript{Ar}), 6.41 (1 H, d, $J = 15.8$ Hz, CH=CH\textsubscript{Ar}), 7.18 - 7.24 (1 H, m, ArH), 7.28 - 7.37 (4 H, m, 4 $\times$ ArH);

\textbf{13C NMR} (100 MHz, CDCl\textsubscript{3}) $\delta$ ppm 14.1 (2 $\times$ CH\textsubscript{3}), 28.3 (CH\textsubscript{CH\textsubscript{2}}), 30.6 (CH\textsubscript{2}CH=CH\textsubscript{2}), 51.2 (CH\textsubscript{CH\textsubscript{2}}), 61.4 (2 $\times$ CH\textsubscript{2}CH\textsubscript{3}), 126.0 (2 $\times$ ArCH), 127.1 (ArCH), 128.5 (2 $\times$ ArCH), 128.6 (CH=CH\textsubscript{Ar}), 131.3 (CH=CH\textsubscript{Ar}), 137.3 (ArC\textsuperscript{q}), 169.4 (2 $\times$ C=O);

\textbf{m/z} (ES+) 271 (18%), 313 ((M + Na), 100), 314 (14), 329 (37), 381 (15). (Found: (M + Na) 313.1415. C\textsubscript{17}H\textsubscript{22}O\textsubscript{4}Na requires M, 313.1411).

Data in accordance with the literature.
4.2. General procedure B – Cross-metatheses

\[ \text{(E)-5-(Cyclohexymethyl)-2,2-dimethyl-5-(5-phenylpent-4-enyl)-1,3-dioxane-4,6-dione (229c)} \]

To a stirred solution of 5-(cyclohexymethyl)-2,2-dimethyl-5-(pent-4-enyl)-1,3-dioxane-4,6-dione 229b (254 mg, 0.82 mmol, 1.0 eq) in \( \text{CH}_2\text{Cl}_2 \) (2.0 mL), Grubbs II (5 mg, 5.89 \( \mu \text{mol}, 0.6 \text{ mol\%} \)) and styrene (209 mg, 2.01 mmol, 2.4 eq) were added and the reaction mixture stirred at 40°C overnight. The solvent was removed \( \text{in vacuo} \). Purification by column chromatography on silica gel, eluting with 50% \( \text{CH}_2\text{Cl}_2 \) in petroleum ether (40-60 °C) gave \( \text{(E)-5-(cyclohexymethyl)-2,2-dimethyl-5-(5-phenylpent-4-enyl)-1,3-dioxane-4,6-dione (229c)} \) (207 mg, 0.54 mmol, 65%) as a white solid.

mp 112-114 °C;

\( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 2924, 2846, 1772, 1736 (C=O), 1597, 1493, 1448, 1393, 1380, 1270, 1228, 1200, 1100, 1070, 1008, 971, 949, 737, 693, 613;

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 0.90 - 1.03 (2 H, m, 2 H from Cy), 1.08 - 1.24 (3 H, m, 3 H from Cy), 1.24 - 1.37 (1 H, m, CH\(_2\)CH), 1.42 - 1.53 (2 H, m, CCH\(_2\)CH\(_2\)), 1.60 - 1.71 (5 H, m, 5 H from Cy), 1.75 (6 H, s, 2 × CH\(_3\)), 1.97 (2 H, d, \( J = 5.8 \text{ Hz}, \text{CH}_2\text{CH} \)), 2.01 - 2.08 (2 H, m, CCH\(_2\)CH\(_2\)), 2.17 - 2.26 (2 H, m, CH\(_2\)CH=CH), 6.12 (1 H, dt, \( J = 15.8, 7.0 \text{ Hz}, \text{CH=CHAr} \)), 6.37 (1 H, d, \( J = 15.8 \text{ Hz}, \text{CH=CHAr} \)), 7.18 - 7.24 (1 H, m, ArH), 7.27 - 7.35 (4 H, m, 4 × ArH);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm 25.2 (CCH\(_2\)CH\(_2\)), 25.9 (CH\(_2\) from Cy), 26.0 (2 × CH\(_2\) from Cy), 29.6 (CH\(_3\)), 30.2 (CH\(_3\)), 32.7 (CH\(_2\)CH=CH), 34.0 (2 × CH\(_2\) from Cy), 35.1 (CH\(_2\)CH), 40.1 (CCH\(_2\)CH\(_2\)), 47.1 (CH\(_2\)CH), 53.2 (C\(^8\)), 105.7 (OCO), 126.0 (2 × ArCH), 127.0 (ArCH), 128.5 (2 × ArCH), 129.0 (CH=CHAr), 130.9 (CH=CHAr), 137.4 (ArC\(^8\)), 169.4 (2 × C=O);

Mass spectrometry was not informative.
(E)-5-Isobutyl-2,2-dimethyl-5-(6-phenylhex-5-enyl)-1,3-dioxane-4,6-dione (229e)

As for general procedure B, reaction of 5-(hex-5-enyl)-5-isobutyl-2,2-dimethyl-1,3-dioxane-4,6-dione 229d (155 mg, 0.55 mmol, 1.0 eq), Grubbs II (3 mg, 3.78 μmol, 0.7 mol%) and styrene (118 mg, 1.13 mmol, 2.1 eq) in CH₂Cl₂ (1.0 mL) gave after column chromatography (50% CH₂Cl₂ in petroleum ether (40-60 °C)) (E)-5-isobutyl-2,2-dimethyl-5-(6-phenylhex-5-enyl)-1,3-dioxane-4,6-dione 229e (120 mg, 0.34 mmol, 61%) as a colourless oil.

νmax (neat)/cm⁻¹ 2959, 2929, 2871, 1773, 1738 (C=O), 1495, 1456, 1392, 1379, 1309, 1261, 1202, 1141, 1068, 1003, 966, 943, 890, 834, 748, 698, 614;

¹H NMR (400 MHz, CDCl₃) δ ppm 0.92 (6 H, d, J = 6.6 Hz, 2 × CH₂CH₃), 1.31 - 1.40 (2 H, m, CCH₂CH₂), 1.42 - 1.51 (2 H, m, CCH₂CH₂CH₂), 1.60 - 1.69 (1 H, m, CH₂CH), 1.71 (3 H, s, CCH₃), 1.76 (3 H, s, CCH₃), 2.00 (2 H, d, J = 6.3 Hz, CH₃CH), 1.99 - 2.05 (2 H, m, CCH₂CH₂), 2.17 - 2.24 (2 H, m, CH₂CH=CH), 6.15 (1 H, dt, J = 15.9, 6.9 Hz, CH=CHAr), 6.36 (1 H, d, J = 15.9 Hz, CH=CHAr), 7.17 - 7.23 (1 H, m, ArH), 7.28 - 7.34 (4 H, m, 4 × ArH);

¹³C NMR (100 MHz, CDCl₃) δ ppm 23.5 (2 × CH₂CH₃), 25.2 (CCH₂CH₂), 25.7 (CH₂CH), 29.1 (CCH₂CH₂CH₂), 29.6 (CCH₃), 30.1 (CCH₃), 32.5 (CH₂CH=CH), 40.3 (CCH₂CH₂), 48.3 (CH₂CH), 53.5 (C₈), 105.7 (OCO), 125.9 (2 × ArCH), 126.9 (ArCH), 128.5 (2 ×ArCH), 130.0 (CH=CHAr), 130.4 (CH=CHAr), 137.6 (ArC₈), 169.4 (2 × C=O);

m/z (ES⁺) 279 (100%), 381 (M + Na), 98), 397 (58). (Found: (M + NH₄) 376.2495. C₂₂H₃₄O₄N requires M, 376.2482).

5-Cinnamyl-5-(cyclohexylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (231)

As for general procedure B, reaction of 5-allyl-5-(cyclohexylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 229a (300 mg, 1.07 mmol, 1.0 eq), Grubbs II (5 mg, 5.89 μmol, 0.6 mol%) and styrene (227 mg, 2.18 mmol, 2.0 eq) in CH₂Cl₂ (2.0 mL) gave after column
chromatography (50% CH$_2$Cl$_2$ in petroleum ether (40-60 °C)) 5-cinnamyl-5-(cyclohexylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 231 (280 mg, 0.79 mmol, 73%) as a white solid.

mp 121-123 °C;

$\nu_{\text{max}}$(neat)/cm$^{-1}$ 2925, 2848, 1772, 1733 (C=O), 1493, 1448, 1393, 1378, 1307, 1257, 1199, 1074, 1021, 966, 950, 745, 691, 607;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.92 - 1.05 (2 H, m, 2 H from Cy), 1.09 - 1.25 (3 H, m, 3 H from Cy), 1.26 - 1.38 (1 H, m, CH$_2$CH), 1.58 (3 H, s, CH$_3$), 1.59 - 1.70 (5 H, m, 5 H from Cy), 1.71 (3 H, s, CH$_3$), 2.03 (2 H, d, $J = 6.3$ Hz, CH$_2$CH), 2.88 (2 H, d, $J = 7.8$ Hz, CH$_2$CH=CH), 6.08 (1 H, dt, $J = 15.8$, 7.8 Hz, CH=CHAr), 6.52 (1 H, d, $J = 15.8$ Hz, CH=CHAr), 7.20 - 7.26 (1 H, m, ArH), 7.28 - 7.35 (4 H, m, 4 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 25.9 (CH$_2$ from Cy), 26.0 (2 × CH$_2$ from Cy), 29.3 (CH$_3$), 30.4 (CH$_3$), 33.9 (2 × CH$_2$ from Cy), 35.1 (CH$_2$CH), 43.0 (CH$_2$CH=CH), 47.7 (CH$_2$CH), 54.1 (C$_q$), 106.0 (OCO), 122.0 (CH=CHAr), 126.3 (2 × ArCH), 127.9 (ArCH), 128.6 (2 × ArCH), 135.8 (CH=CHAr), 136.1 (ArC$_q$), 169.2 (2 × C=O);

$m/z$ (EI+) 298 (M – C$_3$H$_6$O). (Found: (M – C$_3$H$_6$O) 298.1555. C$_{19}$H$_{22}$O$_3$ requires $M$, 298.1563).

\[
\begin{array}{c}
\text{(E)-2,2-Dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione (257)}
\end{array}
\]

As for general procedure B, reaction of 5-(but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 250 (4.02 g, 20.3 mmol, 1.0 eq), Hoveyda–Grubbs II (295 mg, 0.47 mmol, 2.3 mol%) and trans-stilbene (11.05 g, 61.3 mmol, 3.0 eq) in CH$_2$Cl$_2$ (50 mL) at room temperature under a light stream of nitrogen gave after column chromatography (20-80% CH$_2$Cl$_2$ in petroleum ether (40-60 °C)) (E)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 257 (3.54 g, 12.9 mmol, 64%) as a white solid.

mp 86-88 °C;

$\nu_{\text{max}}$(neat)/cm$^{-1}$ 3081, 3059, 3025, 2997, 2940, 2889, 1782, 1735 (C=O), 1495, 1446, 1382, 1329, 1277, 1254, 1200, 1174, 1096, 1070, 1014, 963, 870, 848, 753, 695, 630;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.70 (3 H, s, CH$_3$), 1.76 (3 H, s, CH$_3$), 2.34 (2 H, dt, $J = 7.8$, 5.7 Hz, CHCH$_2$), 2.48 (2 H, q, $J = 7.4$ Hz, CH$_2$CH=CH), 3.56 (1 H, t, $J = 5.0$ Hz,
(E)-5-(4-(4-Bromophenyl)but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (259)

As for general procedure B, reaction of diethyl 5-(but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 250 (500 mg, 2.52 mmol, 1.0 eq), Hoveyda–Grubbs II (16.4 mg, 26.2 μmol, 2.6 mol%) and 4-bromostyrene (1.0 mL, 7.65 mmol, 3.0 eq) in CH₂Cl₂ (5.0 mL) at room temperature under a light stream of nitrogen gave after column chromatography (5-15% ethyl acetate in petroleum ether (40-60 °C)) (E)-5-(4-(4-bromophenyl)but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 259 (232 mg, 0.92 mmol, 36%) as a white solid.

mp 100-102 °C;

ν max (neat)/cm⁻¹ 2997, 2924, 2893, 2877, 1781, 1734 (C=O), 1648, 1487, 1448, 1380, 1335, 1300, 1285, 1264, 1201, 1159, 1062, 1039, 1006, 978, 876, 840, 791, 710, 666, 638;

¹H NMR (400 MHz, CDCl₃) δ ppm 1.70 (3 H, d, J = 0.5 Hz, CH₃), 1.77 (3 H, s, CH₃), 2.30 - 2.37 (2 H, m, CHCH₂), 2.42 - 2.49 (2 H, m, CH₂CH=CH), 3.54 (1 H, t, J = 5.0 Hz, CH), 6.16 (1 H, dt, J = 15.9, 7.1 Hz, CH=CHAr), 6.38 (1 H, d, J = 15.9 Hz, CH=CHAr), 7.18 - 7.22 (2 H, m, 2 × ArH), 7.40 - 7.44 (2 H, m, 2 × ArH);

¹³C NMR (100 MHz, CDCl₃) δ ppm 25.8 (CHCH₂), 26.9 (CH₃), 28.3 (CH₃), 29.7 (CH₂CH=CH), 44.9 (CH), 104.9 (OCO), 120.9 (ArC), 127.6 (2 × ArCH), 129.2 (CH=CHAr), 130.8 (CH=CHAr), 131.6 (2 × ArCH), 136.1 (ArC), 165.5 (2 × C=O);

m/z (ES−) 351 ((M − H), 92%), 353 (100). (Found: (M − H) 351.0228. C₁₆H₁₆O₄Br requires M, 351.0237).
4.3. General procedure C – Alkylations of Meldrum’s acid

5-Allyl-5-(cyclohexylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (229a)

To a stirred solution of 5-(cyclohexylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (501 mg, 2.08 mmol, 1.0 eq) in DMF (5.2 mL) was added K₂CO₃ (577 mg, 4.17 mmol, 2.0 eq) and the solution stirred during 30 minutes. Allyl bromide (308 mg, 2.54 mmol, 1.2 eq) was added and the reaction stirred at room temperature for 4 days. The reaction was quenched with H₂O (5 mL) and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 50% CH₂Cl₂ in petroleum ether (40-60 °C) gave 5-allyl-5-(cyclohexylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 229a (387 mg, 1.38 mmol, 66%) as a white solid.

mp 89-91 °C;

ν max (neat)/cm⁻¹ 2923, 2849, 1764, 1731 (C=O), 1641, 1449, 1392, 1379, 1365, 1315, 1258, 1201, 1075, 1018, 1002, 951, 924, 716, 636;

¹H NMR (400 MHz, CDCl₃) δ ppm 0.90 - 1.03 (2 H, m, 2 H from Cy), 1.08 - 1.25 (3 H, m, 3 H from Cy), 1.25 - 1.36 (1 H, m, CH₂CH), 1.58 - 1.70 (5 H, m, 5 H from Cy), 1.72 (3 H, s, CCH₃), 1.74 (3 H, s, CCH₃), 1.98 (2 H, d, J = 6.1 Hz, CH₂CH), 2.72 (2 H, d, J = 7.6 Hz, CH₂CH=CH₂), 5.17 - 5.25 (2 H, m, CH=CH₂), 5.71 (1 H, ddt, J = 17.2, 9.9, 7.6 Hz, CH=CH₂);

¹³C NMR (100 MHz, CDCl₃) δ ppm 25.9 (CH₂ from Cy), 26.0 (2 × CH₂ from Cy), 29.4 (CH₃), 30.6 (CH₃), 33.9 (2 × CH₂ from Cy), 35.1 (CH₂CH), 43.8 (CH₂CH=CH₂), 47.5 (CH₂CH), 53.7 (C¼), 105.8 (OCO), 121.4 (CH=CH₂), 131.1 (CH=CH₂), 169.0 (2 × C=O);

m/z (ES+) 303 ((M + Na), 90%), 343 (100). (Found: (M + Na) 303.1560. C₁₆H₂₄O₄Na requires M, 303.1567).
5-(Cyclohexylmethyl)-2,2-dimethyl-5-(pent-4-enyl)-1,3-dioxane-4,6-dione (229b)

As for general procedure C, reaction of 5-(cyclohexylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (501 mg, 2.08 mmol, 1.0 eq), 5-bromopent-1-ene (377 mg, 2.53 mmol, 1.2 eq) and K$_2$CO$_3$ (574 g, 4.15 mmol, 2.0 eq) in DMF (5.2 mL) gave after column chromatography (50% CH$_2$Cl$_2$ in petroleum ether (40-60 °C)) 5-(cyclohexylmethyl)-2,2-dimethyl-5-(pent-4-enyl)-1,3-dioxane-4,6-dione 229b (340 mg, 1.10 mmol, 53%) as a white solid.

mp 70-72 °C;

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2921, 2850, 1769, 1731 (C=O), 1447, 1392, 1379, 1269, 1236, 1199, 1073, 988, 948, 915, 703;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.90 - 1.02 (2 H, m, 2 H from Cy), 1.05 - 1.24 (3 H, m, 3 H from Cy), 1.25 - 1.34 (1 H, m, CH$_2$CH), 1.34 - 1.45 (2 H, m, CCH$_2$CH$_2$), 1.58 - 1.71 (5 H, m, 5 H from Cy), 1.75 (6 H, s, 2 × CH$_3$), 1.95 - 2.08 (4 H, m, CH$_2$CH=CH$_2$, CCH$_2$CH$_2$), 1.96 (2 H, d, $J$ = 6.1 Hz, CH$_2$CH), 4.94 - 5.04 (2 H, m, CH=CH$_2$), 5.73 (1 H, ddt, $J$ = 16.9, 10.1, 6.8 Hz, CH=CH$_2$);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 24.7 (CCH$_2$CH$_2$), 25.9 (CH$_2$ from Cy), 26.0 (2 × CH$_2$ from Cy), 29.7 (CH$_3$), 30.2 (CH$_3$), 33.4 (CH$_2$CH=CH$_2$), 34.0 (2 × CH$_2$ from Cy), 35.1 (CH$_2$CH), 40.0 (CCH$_2$CH$_2$), 47.1 (CH$_2$CH), 53.1 (C$q$), 105.7 (OCO), 115.5 (CH=CH$_2$), 137.2 (CH=CH$_2$), 169.5 (2 × C=O);

m/z (ES+) 191 (15%), 331 ((M + Na), 30), 359 (40), 427 (100), 428 (20). (Found: (M + Na) 331.1872. C$_{18}$H$_{28}$O$_4$Na requires $M$, 331.1880).

5-(Hex-5-enyl)-5-isobutyl-2,2-dimethyl-1,3-dioxane-4,6-dione (229d)

As for general procedure C, reaction of 5-isobutyl-2,2-dimethyl-1,3-dioxane-4,6-dione (500 mg, 2.50 mmol, 1.0 eq), 6-bromohex-1-ene (472 mg, 2.89 mmol, 1.2 eq) and K$_2$CO$_3$ (691 mg, 5.00 mmol, 2.0 eq) in DMF (6.2 mL) gave after column chromatography (5%
ethyl acetate in petroleum ether (40-60 °C) 5-(hex-5-enyl)-5-isobutyl-2,2-dimethyl-1,3-dioxane-4,6-dione 229d (209 mg, 0.74 mmol, 30%) as a colourless oil.

ν\textsubscript{max} (neat)/cm\(^{-1}\) 2958, 2927, 1774, 1740 (C=O), 1461, 1437, 1391, 1378, 1259, 1202, 1068, 993, 932, 911, 701;

\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ ppm 0.92 (6 H, d, J = 6.6 Hz, 2 × CH\(_{2}\)CH\(_3\)), 1.25 - 1.34 (2 H, m, CCH\(_2\)CH\(_2\)), 1.34 - 1.42 (2 H, m, CCH\(_2\)CH\(_2\)CH\(_2\)), 1.60 - 1.71 (1 H, m, CH\(_2\)CH), 1.74 (3 H, s, CCH\(_3\)), 1.76 (3 H, s, CCH\(_3\)), 1.99 (2 H, d, J = 6.3 Hz, CH\(_2\)CH), 1.95 - 2.01 (2 H, m, CCH\(_2\)CH\(_2\)), 2.04 (2 H, q, J = 7.1 Hz, CH\(_2\)CH=CH\(_2\)), 4.92 - 5.02 (2 H, m, CH=CH\(_2\)), 5.75 (1 H, ddt, J = 17.2, 10.3, 6.8 Hz, CH=CH\(_2\));

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ ppm 23.5 (2 × CH\(_{2}\)CH\(_3\)), 25.0 (CCH\(_2\)CH\(_3\)), 25.7 (CH\(_2\)CH), 28.6 (CCH\(_2\)CH\(_2\)CH\(_2\)), 29.6 (CCH\(_3\)), 30.1 (CCH\(_3\)), 33.2 (CH\(_2\)CH=CH\(_2\)), 40.4 (CCH\(_2\)CH\(_2\)), 48.2 (CH\(_2\)CH), 53.5 (C\(_6\)), 105.5 (OCO), 114.9 (CH=CH\(_2\)), 138.0 (CH=CH\(_2\)), 169.3 (2 × C=O);

m/z (EI+) 267 (M – CH\(_3\)). (Found: (M – CH\(_3\)) 267.1582. C\(_{13}\)H\(_{23}\)O\(_4\) requires \(M\), 267.1582).

\((E)-5\)-(Cyclohexylmethyl)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione (200a)

As for general procedure C, reaction of 5-(cyclohexylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.35 g, 5.62 mmol, 1.0 eq), (E)-(4-bromobut-1-enyl)benzene (1.42 g, 6.75 mmol, 1.2 eq) and K\(_2\)CO\(_3\) (1.17 g, 8.44 mmol, 1.5 eq) in DMF (10 mL) gave after column chromatography (0-5% ethyl acetate in petroleum ether (40-60 °C)) (E)-5-(cyclohexylmethyl)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 200a (465 mg, 1.94 mmol, 81%) as a white solid.

mp 66-68 °C;

ν\textsubscript{max} (evap. film)/cm\(^{-1}\) 2925, 2851, 1774 (C=O), 1741 (C=O), 1448, 1391, 1271, 1205, 969, 744;

\(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ ppm 0.86 - 1.05 (2 H, m, CH\(_2\) from Cy), 1.09 - 1.24 (3 H, m, CH\(_2\) from Cy), 1.29 - 1.42 (1 H, m, CH), 1.61 - 1.72 (5 H, m, CH\(_2\) from Cy), 1.75 (3 H, s, CH\(_3\)), 1.77 (3 H, s, CH\(_3\)), 2.00 (2 H, d, J = 5.8 Hz, CH\(_2\)CH), 2.13 - 2.27 (4 H, m,
CH_2CH=CH, CH_2CH=CH), 6.09 (1 H, dt, J = 15.8, 6.5 Hz, CH=CHAr), 6.40 (1 H, d, J = 15.8 Hz, CH=CHAr), 7.18 - 7.26 (1 H, m, ArH), 7.28 - 7.36 (4 H, m, 4 × ArH);

**^1^H NMR** (100 MHz, CDCl_3) δ ppm 25.8 (CH_2), 26.0 (CH_2), 28.9 (CH_2CH=CH), 29.6 (CH_3), 30.1 (CH_3), 34.1 (2 × CH_2), 35.0 (CH from Cy), 39.8 (CH_2CH=CH), 47.0 (CH_2CH), 52.8 (C^q), 105.7 (OCO), 126.0 (2 × ArCH), 127.2 (ArCH), 127.7 (CH=CHAr), 128.5 (2 × ArCH), 131.5 (CH=CHAr), 137.1 (ArC^q), 169.2 (2 × C=O);

**m/z** (ES+) 291 (32%), 393 ((M + Na), 100); (Found: (M + Na), 393.2037. C_{23}H_{30}O_{4}Na requires M, 393.2036).

![Chemical structure](image)

**2,2-Dimethyl-5,5-bis((E)-4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione (239a)**

As for general procedure C, reaction of Meldrum’s acid (1.00 g, 6.94 mmol, 1.0 eq), (E)-(4-bromobut-1-enyl)benzene (3.22 g, 15.3 mmol, 2.2 eq) and K_2CO_3 (1.92 g, 13.9 mmol, 2.0 eq) in DMF (10 mL) gave after column chromatography (5-10% ethyl acetate in petroleum ether (40-60 °C)) 2,2-dimethyl-5,5-bis((E)-4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione **239a** (732 mg, 1.81 mmol, 26%) as a colourless oil.

**ν**\_max (evap. film)/cm\(^{-1}\) 2938, 1773 (C=O), 1735 (C=O), 1452, 1267, 1203, 748, 701;

**^1^H NMR** (400 MHz, CDCl_3) δ ppm 1.69 (6 H, s, 2 × CH_3), 2.14 - 2.29 (8 H, m, 2 × CH_2CH=CH, 2 × CH=CHCH=CH), 6.06 (2 H, dt, J = 15.9, 6.4 Hz, 2 × CH=CHAr), 6.38 (2 H, d, J = 15.9 Hz, 2 × CH=CHAr), 7.14 - 7.20 (2 H, m, ArH), 7.27 (8 H, s, 8 × ArH);

**^1^3^C NMR** (100 MHz, CDCl_3) δ ppm 28.9 (2 × CH_3), 29.6 (2 × CH_2CH=CH), 38.5 (2 × CH_2CH=CH), 53.6 (C^q), 105.5 (OCO), 125.9 (4 × ArCH), 127.2 (2 × ArCH), 127.5 (2 × CH=CHAr), 128.4 (4 × ArCH), 131.5 (2 × CH=CHAr), 136.9 (2 × C^q), 168.8 (2 × C=O);

Mass spectrometry was not informative.
5,5-bis((E)-4-(4-Bromophenyl)but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (239b)

As for general procedure C, reaction of Meldrum’s acid (227 mg, 1.57 mmol, 1 eq), (E)-1-bromo-4-(4-bromobut-1-enyl)benzene (1.00 g, 3.46 mmol, 2.2 eq) and K₂CO₃ (441 mg, 3.19 mmol, 2 eq) in DMF (2.0 mL) gave after column chromatography (50% CH₂Cl₂ in petroleum ether (40-60 °C)) 5,5-bis((E)-4-(4-bromophenyl)but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 239b (190 mg, 0.34 mmol, 22%) as a white solid.

mp 130-132 °C;
ν max (neat)/cm⁻¹ 3030, 2939, 2892, 2836, 2361, 1771, 1738 (C=O), 1732 (C=O), 1715, 1681, 1651, 1587, 1487, 1446, 1394, 1381, 1263, 1235, 1200, 1112, 1071, 1008, 964, 887, 833, 788;
¹H NMR (400 MHz, CDCl₃) δ ppm 1.75 (6 H, s, 2 × CH₃), 2.17 - 2.31 (8 H, m, 2 × CCH₂CH₂, 2 × CCH₂CH₂), 6.10 (2 H, dt, J = 15.9, 6.6 Hz, 2 × CH=CHAr), 6.36 (2 H, d, J = 15.9 Hz, 2 × CH=CHAr), 7.18 (4 H, d, J = 8.6 Hz, 4 × ArH), 7.42 (4 H, d, J = 8.6 Hz, 4 × ArH);
¹³C NMR (100 MHz, CDCl₃) δ ppm 29.3 (2 × CCH₂CH₂), 30.1 (2 × CH₃), 38.7 (2 × CCH₂CH₂), 54.0 (C⁶), 106.1 (OCO), 121.4 (2 × ArC⁹), 127.9 (4 × ArCH), 128.7 (2 × CH=CHAr), 130.9 (2 × CH=CHAr), 132.0 (4 × ArCH), 136.2 (2 × ArC⁴), 169.2 (2 × C=O);
m/z (EI+) 562 (M), (Found: (M – C₅H₆O) 501.9774. C₂₃H₂₀O₃⁷⁹Br₂ requires M, 501.9774).

(E)-5-(But-3-enyl)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione (260a)

As for general procedure C, reaction of (E)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 250 (503 mg, 1.83 mmol, 1.0 eq), 4-bromo-1-butene (0.3 mL, 2.96
mmol, 1.6 eq) and K$_2$CO$_3$ (508 mg, 3.68 mmol, 2.0 eq) in DMF (4.6 mL) gave after column chromatography (5% ethyl acetate in petroleum ether (40-60 °C)) (E)-5-(but-3-enyl)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 260a (395 mg, 1.20 mmol, 66%) as a colourless oil.

ν$_{\text{max}}$(neat)/cm$^{-1}$ 3077, 3065, 2998, 2937, 2873, 1772, 1732 (C=O), 1641, 1495, 1450, 1392, 1380, 1259, 1241, 1201, 1072, 1062, 1026, 991, 965, 913, 884, 753, 699, 638, 616;

$^{1}$H NMR (400 MHz, CDCl$_3$) δ ppm 1.75 (3 H, s, CH$_3$), 1.76 (3 H, s, CH$_3$), 2.06 - 2.16 (4 H, m, CH$_2$CH$_2$CH=CH$_2$, CH$_2$CH$_2$CH=CH$_2$), 2.17 - 2.29 (4 H, m, CH$_2$CH$_2$CH=CH, CH$_2$CH$_2$CH=CH), 4.99 - 5.11 (2 H, m, CH=C$_6$H$_5$), 5.68 - 5.80 (1 H, m, CH=CH$_2$), 6.10 (1 H, dt, J = 15.9, 6.4 Hz, CH=CH$_2$), 6.41 (1 H, d, J = 15.9 Hz, CH=CH$_2$), 7.19 - 7.26 (1 H, m, ArH), 7.27 - 7.35 (4 H, m, 4 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 29.1 (2 × CH$_3$), 29.6 (2 × CH$_3$), 38.3 (CH$_2$CH$_2$CH=CH$_2$), 38.6 (CH$_2$CH$_2$CH=CH$_2$), 53.8 (C$q$), 105.7 (OCO), 116.3 (CH=CH$_2$), 126.0 (2 × ArCH), 127.3 (ArCH), 127.6 (CH=CHAr), 128.5 (2 × ArCH), 131.6 (CH=CHAr), 135.9 (CH=CH$_2$), 137.0 (ArC$q$), 169.0 (2 × C=O);

m/z (ES+) 249 (88%), 309 (25), 351 ((M + Na), 100), 352 (21), 367 (53), 381 (76), 383 (32). (Found: (M + NH$_4$) 346.2011. C$_{20}$H$_{28}$O$_4$N requires M, 346.2013).

(E)-5-(4-(4-Bromophenyl)but-3-en-1-yl)-5-(but-3-en-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (260b)

As for general procedure C, reaction of 5-(but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 250 (503 mg, 2.54 mmol, 1.0 eq), (E)-1-bromo-4-(4-bromobut-1-enyl)benzene (948.0 mg, 3.27 mmol, 1.3 eq) and K$_2$CO$_3$ (701 mg, 5.07 mmol, 2.0 eq) in DMF (6.5 mL) gave after column chromatography (5% ethyl acetate in petroleum ether (40-60 °C)) (E)-5-(4-(4-bromophenyl)but-3-en-1-yl)-5-(but-3-en-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione 260b (326 mg, 0.80 mmol, 32%) as a colourless oil.

ν$_{\text{max}}$(neat)/cm$^{-1}$ 3076, 2999, 2934, 2848, 1773, 1736 (C=O), 1641, 1587, 1487, 1448, 1391, 1378, 1284, 1257, 1239, 1201, 1071, 1007, 965, 916, 881, 849, 833, 801, 714, 638;
$^{1}H$ NMR (400 MHz, CDCl$_3$) δ ppm 1.74 (3 H, s, CH$_3$), 1.76 (3 H, s, CH$_3$), 2.09 - 2.14 (4 H, m, CH$_2$CH$_2$CH=CH$_2$, CH$_2$CH=CH$_2$), 2.19 - 2.28 (4 H, m, CH$_2$CH$_2$CH=CH, CH$_2$CH=CH), 5.00 - 5.10 (2 H, m, CH=CH$_2$), 5.67 - 5.79 (1 H, m, CH=CH$_2$), 6.09 (1 H, dt, $J = 15.9, 6.3$ Hz, CH=CHAr), 6.35 (1 H, d, $J = 15.9$ Hz, CH=CHAr), 7.16 - 7.20 (2 H, m, 2 × ArH), 7.39 - 7.44 (2 H, m, 2 × ArH);

$^{13}C$ NMR (100 MHz, CDCl$_3$) δ ppm 29.0 (CH$_2$CH$_2$CH=CH), 29.6 (CH$_2$CH$_2$CH=CH$_2$), 29.7 (CH$_3$), 29.8 (CH$_3$), 38.3 (CH$_2$CH=CH), 38.3 (CH$_2$CH=CH$_2$), 53.7 (C$q$), 105.7 (OCO), 116.4 (CH=CH$_2$), 121.0 (ArC$q$), 127.6 (2 × ArCH), 128.5 (CH=CHAr), 130.5 (CH=CHAr), 131.6 (2 × ArCH), 135.9 (CH=CH$_2$), 136.0 (ArC$q$), 169.0 (2 × C=O);

Mass spectrometry was not informative.

As for general procedure C, reaction of 5-(but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (250) (499 mg, 2.52 mmol, 1.0 eq), (E)-1-(4-bromobut-1-enyl)-2,4-dichlorobenzene (847 mg, 3.03 mmol, 1.2 eq) and K$_2$CO$_3$ (700 mg, 5.07 mmol, 2.0 eq) in DMF (6.5 mL) gave after column chromatography (5% ethyl acetate in petroleum ether (40-60 °C)) (E)-5-(but-3-en-1-yl)-5-(4-(2,4-dichlorophenyl)but-3-en-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (260c) (621 mg, 1.56 mmol, 62%) as a colourless oil.

ν$_{\text{max}}$(neat)/cm$^{-1}$ 3078, 2999, 2934, 2852, 1774, 1736 (C=O), 1642, 1584, 1552, 1470, 1448, 1391, 1379, 1284, 1257, 1238, 1200, 1100, 1048, 965, 916, 881, 866, 850, 807, 756, 637;

$^{1}H$ NMR (400 MHz, CDCl$_3$) δ ppm 1.75 (3 H, s, CH$_3$), 1.77 (3 H, s, CH$_3$), 2.07 - 2.16 (4 H, m, CH$_2$CH$_2$CH=CH$_2$, CH$_2$CH=CH$_2$), 2.19 - 2.25 (2 H, m, CH$_2$CH=CHAr), 2.26 - 2.34 (2 H, m, CH$_2$CH$_2$CH=CHAr), 5.00 - 5.11 (2 H, m, CH=CH$_2$), 5.68 - 5.79 (1 H, m, CH=CHAr), 6.07 (1 H, dt, $J = 15.7, 6.7$ Hz, CH=CHAr), 6.71 (1 H, d, $J = 15.7$ Hz, CH=CHAr), 7.19 (1 H, ddd, $J = 8.6, 2.3, 0.5$ Hz, ArH), 7.35 (1 H, d, $J = 2.3$ Hz, ArH), 7.39 (1 H, d, $J = 8.6$ Hz, ArH);

$^{13}C$ NMR (100 MHz, CDCl$_3$) δ ppm 29.2 (CH$_2$CH=CH), 29.6 (CH$_2$CH=CH$_2$), 29.7 (CH$_3$), 29.8 (CH$_3$), 38.1 (CH$_2$CH$_2$CH=CH), 38.4 (CH$_2$CH$_2$CH=CH$_2$), 53.7 (C$q$), 105.8 (OCO),
116.4 (CH=CH₂), 126.8 (CH=CHAr), 127.2 (ArCH), 127.4 (ArCH), 129.3 (ArCH), 131.2 (CH=CHAr), 133.1 (ArCH), 133.3 (ArCH), 133.7 (ArCH), 135.9 (CH=CH₂), 168.9 (2 × C=O);

Mass spectrometry was not informative.

\[
\begin{align*}
\text{(E)-5-(But-3-en-1-yl)-2,2-dimethyl-5-(4-(naphthalen-2-yl)but-3-en-1-yl)-1,3-dioxane-4,6-dione (260d)}
\end{align*}
\]

As for general procedure C, reaction of 5-(but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 250 (300 mg, 1.51 mmol, 1.0 eq), (E)-2-(4-bromobut-1-enyl)naphthalene (475 mg, 1.82 mmol, 1.2 eq) and K₂CO₃ (425 mg, 3.07 mmol, 2.0 eq) in DMF (3.9 mL) gave after column chromatography (5% ethyl acetate in petroleum ether (40-60 °C)) (E)-5-(but-3-en-1-yl)-2,2-dimethyl-5-(4-(naphthalen-2-yl)but-3-en-1-yl)-1,3-dioxane-4,6-dione 260d (292 mg, 0.77 mmol, 51%) as a white solid.

\[
\begin{align*}
\text{mp} & \quad 99-101 ^\circ C; \\
\nu_{\text{max}} (\text{neat})/\text{cm}^{-1} & \quad 3073, 3059, 2995, 2978, 2941, 2836, 1773, 1732 (\text{C}=\text{O}), 1640, 1507, 1452, 1380, 1312, 1289, 1256, 1237, 1202, 1149, 1114, 1072, 1028, 962, 911, 872, 862, 807, 749, 711, 640, 619; \\
1^1\text{H NMR} & \quad (400 \text{ MHz, CDCl}_3) \delta \text{ ppm} 1.76 (3 \text{ H, s, CH}_3), 1.77 (3 \text{ H, s, CH}_3), 2.07 - 2.19 (4 \text{ H, m, CH}_2\text{CH}_2\text{CH}=\text{CH}, \text{CH}_2\text{CH}=\text{CH}_2), 2.21 - 2.28 (2 \text{ H, m, CH}_2\text{CH}_2\text{CH}=\text{CH}), 2.28 - 2.36 (2 \text{ H, m, CH}_2\text{CH}=\text{CH}), 5.00 - 5.11 (2 \text{ H, m, CH}=\text{CH}_2), 5.69 - 5.81 (1 \text{ H, m, CH}=\text{CH}_2), 6.23 (1 \text{ H, dt, J }= 15.8, 6.5 \text{ Hz, CH}=\text{CHAr}), 6.58 (1 \text{ H, d, J }= 15.8 \text{ Hz, CH}=\text{CHAr}), 7.40 - 7.49 (2 \text{ H, m, 2 × ArH}), 7.54 (1 \text{ H, dd, J }= 8.6, 1.5 \text{ Hz, ArH}), 7.66 (1 \text{ H, s, ArH}), 7.75 - 7.82 (3 \text{ H, m, 3 × ArH}); \\
13^1\text{C NMR} & \quad (100 \text{ MHz, CDCl}_3) \delta \text{ ppm} 29.2 (\text{CH}_2\text{CH}=\text{CH}), 29.7 (\text{CH}_2\text{CH}=\text{CH}_2), 29.8 (\text{CH}_3), 29.8 (\text{CH}_3), 38.4 (\text{CH}_2\text{CH}_2\text{CH}=\text{CH}), 38.6 (\text{CH}_2\text{CH}_2\text{CH}=\text{CH}), 53.8 (\text{C}^\text{q}), 105.7 (\text{OCO}), 116.3 (\text{CH}=\text{CH}_2), 123.4 (\text{ArCH}), 125.7 (\text{ArCH}), 125.8 (\text{ArCH}), 126.2 (\text{ArCH}), 127.6 (\text{CH}=\text{CHAr}), 127.9 (\text{ArCH}), 128.0 (\text{ArCH}), 128.2 (\text{ArCH}), 131.8 (\text{CH}=\text{CHAr}), 132.8 (\text{ArC}^\text{q}), 133.6 (\text{ArC}^\text{q}), 134.5 (\text{ArC}^\text{q}), 136.0 (\text{CH}=\text{CH}_2), 169.0 (2 \times \text{C}=\text{O}); \\
\text{Mass spectrometry was not informative.}
\end{align*}
\]
5-((E)-4-(4-Bromophenyl)but-3-enyl)-2,2-dimethyl-5-((E)-4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione (260e)

As for general procedure C, reaction of (E)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 257 (500 mg, 1.82 mmol, 1.0 eq), (E)-1-bromo-4-(4-bromobut-1-enyl)benzene (647 mg, 2.23 mmol, 1.2 eq) and K$_2$CO$_3$ (509 mg, 3.68 mmol, 2.0 eq) in DMF (4.6 mL) gave after column chromatography (5% ethyl acetate in petroleum ether (40-60 °C)) 5-((E)-4-(4-bromophenyl)but-3-enyl)-2,2-dimethyl-5-((E)-4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 260e (301 mg, 0.62 mmol, 34%) as a white solid.

mp 105-107 °C;

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3048, 3018, 2998, 2940, 2893, 2836, 1771, 1739 (C=O), 1489, 1447, 1392, 1328, 1267, 1255, 1233, 1199, 1117, 1103, 1074, 1046, 962, 887, 843, 793, 766, 727, 693;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.75 (3 H, s, CH$_3$), 1.76 (3 H, s, CH$_3$), 2.17 - 2.32 (8 H, m, 2 × CH$_2$CH$_2$CH=CH, 2 × CH$_2$CH=CH), 6.05 - 6.15 (2 H, m, 2 × CH=CHAr), 6.36 (1 H, d, $J = 15.6$ Hz, CH=CHAr), 6.42 (1 H, d, $J = 15.6$ Hz, CH=CHAr), 7.16 - 7.21 (2 H, m, 2 × ArH), 7.21 - 7.25 (1 H, m, ArH), 7.27 - 7.34 (4 H, m, 4 × ArH), 7.40 - 7.44 (2 H, m, 2 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 29.0 (2 × CH$_2$CH$_2$CH=CH), 29.7 (CH$_3$), 29.8 (CH$_3$), 38.4 (CH$_2$CH=CH), 38.6 (CH$_2$CH=CH), 53.7 (C$^5$), 105.7 (OCO), 121.0 (ArC$^5$), 126.0 (2 × ArCH), 127.3 (ArCH), 127.5 (CH=CHAr), 127.6 (2 × ArCH), 128.5 (CH=CHAr), 128.5 (2 × ArCH), 130.5 (CH=CHAr), 131.6 (2 × ArCH), 131.7 (CH=CHAr), 135.9 (ArC$^5$), 137.0 (ArC$^6$), 168.9 (2 × C=O);

Mass spectrometry was not informative.
As for general procedure C, reaction of (E)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 257 (499 mg, 1.82 mmol, 1.0 eq), (E)-1-(4-bromobut-1-enyl)-2,4-dichlorobenzene (622 mg, 2.22 mmol, 1.2 eq) and K$_2$CO$_3$ (505 mg, 3.66 mmol, 2.0 eq) in DMF (5.0 mL) gave after purification by column chromatography (5% ethyl acetate in petroleum ether (40-60 °C)) 5-((E)-4-(2,4-dichlorophenyl)but-3-enyl)-2,2-dimethyl-5-((E)-4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 260f (447 mg, 0.94 mmol, 52%) as a light yellow oil.

$\nu_{max}$ (neat)/cm$^{-1}$: 3083, 3061, 3026, 3000, 2932, 2852, 1773, 1736 (C=O), 1584, 1470, 1447, 1391, 1379, 1282, 1258, 1238, 1201, 1100, 1049, 965, 887, 851, 744, 693;

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 1.76 (6 H, s, 2 × CH$_3$), 2.19 - 2.37 (8 H, m, 2 × CH$_2$CH$_2$CH=CH, 2 × CH$_2$CH$_2$CH=CH), 6.04 - 6.16 (2 H, m, 2 × CH=CHAr), 6.43 (1 H, d, $J = 15.6$ Hz, CH=CHAr), 6.73 (1 H, d, $J = 15.6$ Hz, CH=CHAr), 7.19 (1 H, dd, $J = 8.3$, 1.8 Hz, ArH), 7.21 - 7.25 (1 H, m, ArH), 7.28 - 7.34 (4 H, m, 4 × ArH), 7.35 (1 H, d, $J = 2.3$ Hz, ArH), 7.39 (1 H, d, $J = 8.6$ Hz, ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm: 29.0 (CH$_2$CH$_2$CH=CH), 29.1 (CH$_2$CH$_2$CH=CH), 29.7 (CH$_3$), 29.7 (CH$_3$), 38.2 (CH$_2$CH$_2$CH=CH), 38.7 (CH$_2$CH$_2$CH=CH), 53.7 (C$^\beta$), 105.7 (OCO), 126.0 (2 × ArCH), 126.8 (CH=CHAr), 127.2 (ArCH), 127.3 (ArCH), 127.4 (CH=CHAr), 127.4 (ArCH), 128.5 (2 × ArCH), 129.3 (ArCH), 131.2 (CH=CHAr), 131.7 (CH=CHAr), 133.1 (ArC$^\beta$), 133.2 (ArC$^\beta$), 133.7 (ArC$^\beta$), 137.0 (ArC$^\beta$), 168.9 (2 × C=O);

Mass spectrometry was not informative.
2,2-Dimethyl-5-((E)-4-(naphthalen-2-yl)but-3-en-1-yl)-5-((E)-4-phenylbut-3-en-1-yl)-1,3-dioxane-4,6-dione (260g)

As for general procedure C, reaction of (E)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 257 (505 mg, 1.11 mmol, 1.0 eq), (E)-2-(4-bromobut-1-en-1-yl)naphthalene (343 mg, 1.31 mmol, 1.2 eq) and K₂CO₃ (305 mg, 2.20 mmol, 2.0 eq) in DMF (2.8 mL) gave after column chromatography (5% ethyl acetate in petroleum ether (40-60 °C)) 2,2-dimethyl-5-((E)-4-(naphthalen-2-yl)but-3-en-1-yl)-5-((E)-4-phenylbut-3-en-1-yl)-1,3-dioxane-4,6-dione 260g (245 mg, 0.54 mmol, 49%) as a white solid.

mp 93-95 °C;
ν_max (neat)/cm⁻¹ 3055, 3025, 2995, 2933, 2837, 1774, 1735 (C=O), 1597, 1507, 1493, 1447, 1389, 1291, 1258, 1231, 1202, 1114, 1074, 1030, 961, 899, 877, 863, 805, 747, 693, 618;

¹H NMR (400 MHz, CDCl₃) δ ppm 1.69 (6 H, s, 2 × CH₃), 2.12 - 2.30 (8 H, m, 4 × CH₂), 6.04 (1 H, dt, J = 15.9, 6.4 Hz, CH=CHAr), 6.16 (1 H, dt, J = 15.9, 6.5 Hz, CH=CHAr), 6.35 (1 H, d, J = 15.9 Hz, CH=CHAr), 6.51 (1 H, d, J = 15.9 Hz, CH=CHAr), 7.11 - 7.17 (1 H, m, ArH), 7.19 - 7.27 (4 H, m, 4 × ArH), 7.32 - 7.41 (2 H, m, 2 × ArH), 7.46 (1 H, dd, J = 8.6, 1.8 Hz, ArH), 7.58 (1 H, s, ArH), 7.67 - 7.74 (3 H, m, 3 × ArH);

¹³C NMR (100 MHz, CDCl₃) δ ppm 29.1 (CH₂), 29.2 (CH₂), 29.8 (2 × CH₃), 38.7 (CH₂), 38.7 (CH₂), 53.8 (C⁶), 105.8 (OCO), 123.4 (ArCH), 125.7 (ArCH), 125.8 (ArCH), 126.1 (2 × ArCH), 126.2 (ArCH), 127.4 (ArCH), 127.6 (CH=CHAr), 127.7 (ArCH), 127.9 (CH=CHAr), 128.0 (ArCH), 128.2 (ArCH), 128.6 (2 × ArCH), 131.7 (CH=CHAr), 131.8 (CH=CHAr), 132.9 (ArC⁹), 133.6 (ArC⁹), 134.5 (ArC⁹), 137.1 (ArC⁹), 169.0 (2 × C=O);
m/z (ES+) 397 (39%), 424 (24), 472 (60), 477 ((M + Na), 100), 478 (44). (Found: (M + NH₄) 472.2486. C₃₀H₃₄NO₄ requires M, 472.2482).
2,2-Dimethyl-5-((E)-4-phenylbut-3-enyl)-5-((E)-5-phenylpent-4-enyl)-1,3-dioxane-4,6-dione (260i)

As for general procedure C, reaction of (E)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 257 (314 mg, 1.14 mmol, 1.0 eq), (E)-(5-bromopent-1-enyl)benzene (309 mg, 1.37 mmol, 1.2 eq) and K₂CO₃ (320 mg, 2.32 mmol, 2.0 eq) in DMF (2.9 mL) gave after column chromatography (5% ethyl acetate in petroleum ether (40-60 °C)) 2,2-dimethyl-5-((E)-4-phenylbut-3-enyl)-5-((E)-5-phenylpent-4-enyl)-1,3-dioxane-4,6-dione 260i (228 mg, 0.54 mmol, 48%) as a white solid.

mp 111-113 °C;
νmax (neat)/cm⁻¹ 3057, 3025, 2921, 2854, 1771, 1727 (C=O), 1598, 1492, 1447, 1380, 1274, 1233, 1204, 1114, 1060, 1024, 964, 904, 850, 743, 716, 691;
¹H NMR (400 MHz, CDCl₃) δ ppm 1.47 - 1.57 (2 H, m, CH₂C₂H₂), 1.75 (3 H, s, CH₃), 1.76 (3 H, s, CH₃), 2.07 - 2.14 (2 H, m, CCH₂CH₂CH₂), 2.18 - 2.29 (6 H, m, CCH₂CH₂CH₂CH=CH, CCH₂CH₂CH=CH, CCH₂CH₂CH₂), 6.05 - 6.18 (2 H, m, 2 × CH=CHAr), 6.39 (1 H, d, J = 15.9 Hz, CH=CHR), 6.41 (1 H, d, J = 15.6 Hz, CH=CHR), 7.18 - 7.24 (2 H, m, 2 × ArH), 7.27 - 7.36 (8 H, m, 8 × ArH);
¹³C NMR (100 MHz, CDCl₃) δ ppm 25.3 (CH₂CH₂CH₂), 29.1 (CH₂CH=CH), 29.7 (CH₃), 29.8 (CH₂), 32.7 (CH₂CH=CH), 38.6 (CH₂CH₂), 38.8 (CH₂CH₂), 54.2 (Cₘ), 105.7 (OCO), 126.0 (2 × ArCH), 126.0 (2 × ArCH), 127.1 (ArCH), 127.3 (ArCH), 127.6 (CH=CHAr), 128.5 (2 × ArCH), 128.8 (CH=CHAr), 131.0 (CH=CHAr), 131.6 (CH=CHAr), 137.1 (ArCₘ), 137.3 (ArCₘ), 169.2 (2 × C=O);
m/z (ES+) 151 (18%), 183 (20), 273 (18), 339 (18), 441 ((M + Na), 100), 442 (28). (Found: (M + Na) 441.2027. C₂₇H₃₀O₄Na requires M, 441.2036).
2,2-Dimethyl-5-((E)-4-phenylbut-3-enyl)-5-((E)-6-phenylhex-5-enyl)-1,3-dioxane-4,6-dione (260j)

As for general procedure C, reaction of (E)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 257 (480 mg, 1.75 mmol, 1.0 eq), (E)-(6-bromohex-1-en-1-yl)benzene (536 mg, 2.24 mmol, 1.3 eq) and K$_2$CO$_3$ (506 mg, 3.66 mmol, 2.1 eq) in DMF (4.6 mL) gave after column chromatography (5% ethyl acetate in petroleum ether (40-60 °C)) 2,2-dimethyl-5-((E)-4-phenylbut-3-enyl)-5-((E)-6-phenylhex-5-enyl)-1,3-dioxane-4,6-dione 260j (107 mg, 0.25 mmol, 14%) as a colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3060, 3026, 2998, 2860, 1772, 1735 (C=O), 1598, 1494, 1450, 1392, 1379, 1262, 1201, 1069, 967, 884, 748, 697, 615;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.34 - 1.44 (2 H, m, CCH$_2$CH$_2$CH$_2$), 1.45 - 1.54 (2 H, m, CCH$_2$CH$_2$CH$_2$), 1.72 (3 H, s, CH$_3$), 1.73 (3 H, s, CH$_3$), 2.04 - 2.11 (2 H, m, CCH$_2$CH$_2$CH$_2$), 2.17 - 2.28 (6 H, m, CCH$_2$CH$_2$CH=CH, 2 × CH$_2$CH=CH), 6.06 - 6.21 (2 H, m, 2 × CH=CHAr), 6.37 (1 H, d, $J = 16.6$ Hz, CH=CHAr), 6.41 (1 H, d, $J = 16.6$ Hz, CH=CHAr), 7.17 - 7.26 (2 H, m, 2 × ArH), 7.28 - 7.35 (8 H, m, 8 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 25.2 (CCH$_2$CH$_2$CH$_2$), 29.0 (CCH$_2$CH$_2$CH$_2$), 29.1 (CCH$_2$CH$_2$CH=CH), 29.7 (CH$_3$), 29.8 (CH$_3$), 32.5 (CCH$_2$CH$_2$CH=CH), 38.7 (CH$_2$CH$_2$CH$_2$CH=CH), 39.2 (CCH$_2$CH$_2$CH$_2$), 54.3 (C$_9$), 105.7 (OCO), 125.9 (2 × ArCH), 126.0 (2 × ArCH), 126.9 (ArCH), 127.3 (ArCH), 127.7 (CCH$_2$CH$_2$CH=CH), 128.5 (2 × ArCH), 128.5 (2 × ArCH), 129.9 (CH$_2$CH$_2$CH$_2$CH=CH), 130.4 (CH$_2$CH$_2$CH$_2$CH=CH), 131.6 (CCH$_2$CH$_2$CH=CH), 137.1 (Ar$_C^9$), 137.6 (Ar$_C^9$), 169.2 (2 × C=O);

$\text{m/z}$ (ES+) 241 (15%), 273 (17), 413 (15), 429 (20), 471 (45), 487 ((M + Na + MeOH), 100), 488 (29), 503 (23), 524 (18). (Found: (M + NH$_4$) 450.2629. C$_{28}$H$_{36}$O$_4$N requires $M$, 450.2639).
(E)-5-(4-(2,4-Dichlorophenyl)but-3-en-1-yl)-2,2-dimethyl-5-(5-phenylpent-4-yn-1-yl)-1,3-dioxane-4,6-dione (260n)

As for general procedure C, reaction of 2,2-dimethyl-5-(5-phenylpent-4-yn-1-yl)-1,3-dioxane-4,6-dione (499 mg, 1.74 mmol, 1.0 eq), (E)-1-(4-bromobut-1-enyl)-2,4-dichlorobenzene (592 mg, 2.11 mmol, 1.2 eq) and K₂CO₃ (483 mg, 3.49 mmol, 2.0 eq) in DMF (6.0 mL) gave after column chromatography (5% ethyl acetate in petroleum ether (40-60 °C)) (E)-5-(4-(2,4-dichlorophenyl)but-3-en-1-yl)-2,2-dimethyl-5-(5-phenylpent-4-yn-1-yl)-1,3-dioxane-4,6-dione 260n (367 mg, 0.76 mmol, 43%) as a colourless oil.

ν_max (neat)/cm⁻¹ 2996, 2935, 2862, 1771, 1736 (C=O), 1467, 1391, 1379, 1279, 1262, 1198, 1101, 1051, 969, 905, 864, 850, 756, 730, 692, 648;

^1^H NMR (400 MHz, CDCl₃) δ ppm 1.64 - 1.72 (2 H, m, CH₂CH₂C≡C), 1.74 (3 H, s, CH₃), 1.77 (3 H, s, CH₃), 2.19 - 2.34 (6 H, m, 2 × CCH₂, CH₂CH=CH), 2.45 (2 H, t, J = 6.8 Hz, CH₂C=O), 6.07 (1 H, dt, J = 15.6, 6.5 Hz, CH=CHAr), 6.71 (1 H, d, J = 15.6 Hz, CH=CHAr), 7.16 - 7.20 (1 H, m, ArH), 7.27 - 7.31 (3 H, m, 3 × ArH), 7.35 (1 H, d, J = 2.3 Hz, ArH), 7.36 - 7.41 (3 H, m, 3 × ArH);

^1^C NMR (100 MHz, CDCl₃) δ ppm 19.3 (CH₂=CH₂), 24.6 (CH₂CH₂C=O), 29.2 (CH₂=CH₂), 29.7 (CH₃), 29.7 (CH₃), 37.9 (CH₂CH₂=CH₂), 38.3 (CH₂CH₂CH₂C=O), 53.8 (C=O), 81.7 (C=CHAr), 88.1 (C=CHAr), 105.7 (OCO), 123.5 (ArC=O), 126.8 (CH=CHAr), 127.2 (ArCH), 127.4 (ArCH), 127.7 (ArCH), 128.2 (2 × ArCH), 129.3 (ArCH), 131.3 (CH=CHAr), 131.5 (2 × ArCH), 133.1 (ArC=O), 133.2 (ArC=O), 133.7 (ArC=O), 168.9 (2 × C=O);

Mass spectrometry was not informative.
4.4. General procedure D – SmI₂ mediated reductions, cyclisations and cascades

![Chemical structure](image)

**rac-(1R,2S,3S)-3-Benzyl-1-(cyclohexylmethyl)-2-hydroxycyclopentanecarboxylic acid (201)**

To a stirred solution of (E)-5-(cyclohexylmethyl)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 200a (100 mg, 0.28 mmol, 1.0 eq) in THF (1.0 mL) and H₂O (6.0 mL, 336 mmol, 1200 eq) was added SmI₂ (0.1 M in THF, 22.5 mL, 2.25 mmol, 8.0 eq) dropwise using a syringe pump over 30 minutes. After decolourisation of the reaction mixture, the reaction was opened to air and water (20 mL) and tartaric acid (25 mg) were added. The aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organic phases dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) gave rac-(1R,2S,3S)-3-benzyl-1-(cyclohexylmethyl)-2-hydroxycyclopentanecarboxylic acid (82 mg, 0.260 mmol, 93%) as a white solid and as a mixture of four diastereoisomers of which 201 was the major (3:1 (others)).

**mp** 43-45 °C;

**ν**₁max (neat)/cm⁻¹ 3395, 2920, 2849, 1693 (C=O), 1445, 1209, 1062, 748, 698;

**¹H NMR** (400 MHz, CDCl₃) δ ppm 0.85 - 1.07 (2 H, m, 2 H from Cy), 1.07 - 1.42 (6 H, m, 3 H from Cy, 1 H from CCH₂CH₂, 1 H from CCH₂Cy, CH from Cy), 1.57 - 1.71 (7 H, m, 5 H from Cy, 1 H from CCH₂CH₂, 1 H from CCH₂CH₂), 1.84 - 1.93 (1 H, m, 1 H from CCH₂Cy), 2.11 - 2.18 (1 H, m, ArCH₂CH), 2.18 - 2.24 (1 H, m, 1 H from CCH₂CH₂), 2.50 (1 H, dd, J = 13.4, 9.6 Hz, 1 H from ArCH₂), 3.03 (1 H, dd, J = 13.4, 4.8 Hz, 1 H from ArCH₂), 3.84 (1 H, d, J = 8.8 Hz, CHOH), 7.17 - 7.24 (3 H, m, 3 × ArH), 7.26 - 7.33 (2 H, m, 2 × ArH);

**¹³C NMR** (100 MHz, CDCl₃) δ ppm 25.0 (C(CH₂)₂), 25.2 (CH₂ from Cy), 25.3 (CH₂ from Cy), 25.4 (CH₂ from Cy), 27.7 (CCH₂CH₂), 32.4 (CH₂ from Cy), 33.3 (CH from Cy), 34.1 (CH₂ from Cy), 37.4 (CCH₂Cy), 38.8 (ArCH₂), 44.9 (ArCH₂CH), 53.6 (Cβ), 81.6 (CHOH), 125.0 (ArCH), 127.3 (2 × ArCH), 127.9 (2 × ArCH), 139.7 (ArCβ), 182.8 (C=O);

**m/z** (ES⁺) 339 ((M + Na), 100%), 340 (18); (Found: (M + Na) 339.1934. C₂₀H₂₈O₃Na requires M, 339.1931).
2-(Cyclohexylmethyl)-2-(hydroxymethyl)pent-4-enoic acid (230a)

As for general procedure D, reaction of 5-allyl-5-(cyclohexylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 229a (50 mg, 0.18 mmol, 1.0 eq) and SmI$_2$ (0.1 M in THF, 15.0 mL, 1.50 mmol, 8.0 eq) in THF (2.5 mL) and H$_2$O (3.9 mL, 217 mmol, 1200 eq) gave after column chromatography (20% ethyl acetate in petroleum ether (40-60 °C) and 0.1% acetic acid) 2-(cyclohexylmethyl)-2-(hydroxymethyl)pent-4-enoic acid 230a (27 mg, 0.118 mmol, 66%) as a white solid.

mp 98-100 °C;

ν$_{max}$ (neat)/cm$^{-1}$ 3381 (br. OH), 2917, 2850, 2557, 1703 (C=O), 1447, 1417, 1324, 1303, 1286, 1272, 1230, 1210, 1183, 1162, 1067, 1051, 1037, 1011, 995, 962, 906, 873, 845, 830, 789, 672;

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 0.87 - 1.03 (2 H, m, 2 H from Cy), 1.06 - 1.29 (3 H, m, 3 H from Cy), 1.34 - 1.46 (1 H, m, CH from Cy), 1.53 (2 H, dd, J = 6.1, 3.3 Hz, CCH$_2$Cy), 1.58 - 1.71 (5 H, m, 5 H from Cy), 2.35 (1 H, dd, J = 14.1, 7.6 Hz, 1 H from CH$_2$CH=CH$_2$), 2.55 (1 H, dd, J = 14.1, 7.6 Hz, 1 H from CH$_2$CH=CH$_2$), 3.62 (1 H, d, J = 11.6 Hz, 1 H from CH$_2$OH), 3.80 (1 H, d, J = 11.6 Hz, 1 H from CH$_2$OH), 5.10 - 5.20 (2 H, m, CH=CH$_2$), 5.82 (1 H, ddt, J = 17.2, 10.0, 7.4 Hz, CH=CH$_2$);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 26.12 (CH$_2$ from Cy), 26.28 (CH$_2$ from Cy), 26.33 (CH$_2$ from Cy), 33.75 (CH from Cy), 34.23 (CH$_2$ from Cy), 34.49 (CH$_2$ from Cy), 38.09 (CH$_2$CH=CH$_2$), 41.12 (CCH$_2$Cy), 50.15 (C$^\text{c}$), 65.09 (CH$_2$OH), 118.87 (CH=CH$_2$), 133.43 (CH=CH$_2$), 181.48 (C=O);

2-(Cyclohexylmethyl)-2-(hydroxymethyl)hept-6-enoic acid (230b)

As for general procedure D, reaction of 5-(cyclohexylmethyl)-2,2-dimethyl-5-(pent-4-enyl)-1,3-dioxane-4,6-dione 229b (30 mg, 0.10 mmol, 1.0 eq), and SmI$_2$ (0.1 M in THF, 8.0 mL, 0.80 mmol, 8.0 eq) in THF (2.0 mL) and H$_2$O (2.1 mL, 117 mmol, 1200 eq) gave after purification by column chromatography (50% dichloromethane in petroleum ether
(40-60 °C and 1% acetic acid) 2-(cyclohexylmethyl)-2-(hydroxymethyl)hept-6-enoic acid 230b (20 mg, 78.6 μmol, 81%) as a white solid.

mp 88-90 °C;
ν max (neat)/cm⁻¹ 3376 (br. OH), 2922, 2850, 1691 (C=O), 1640, 1448, 1257, 1235, 1217, 1034, 905, 827, 663;
¹H NMR (400 MHz, CDCl₃) δ ppm 0.89 - 1.03 (2 H, m, 2 H from Cy), 1.05 - 1.30 (3 H, m, 3 H from Cy), 1.30 - 1.45 (3 H, m, 2 H from C(CH₃)₂CH₂, CH₂CH), 1.49 (1 H, dd, J = 14.4, 5.5 Hz, 1 H from CH₂CH), 1.54 - 1.77 (7 H, m, 5 H from Cy, 2 H from C(CH₃)₂CH₂), 1.58 (1 H, dd, J = 14.4, 6.6 Hz, 1 H from CH₂CH), 2.06 (2 H, q, J = 7.1 Hz, CH₂CH=CH₂), 3.65 (1 H, d, J = 11.3 Hz, 1 H from CH₂OH), 4.97 (1 H, d, J = 10.2 Hz, 1 H from CH=CH₂), 5.02 (1 H, dd, J = 17.0, 1.4 Hz, 1 H from CH=CH₂), 5.78 (1 H, ddt, J = 17.0, 10.2, 6.7 Hz, CH=CH₂);
¹³C NMR (100 MHz, CDCl₃) δ ppm 23.3 (C(CH₃)₂CH₂), 26.2 (CH₂ from Cy), 26.4 (2 × CH₂ from Cy), 33.6 (C(CH₃)₂CH₂), 33.8 (CH₂CH), 34.1 (CH₂CH=CH₂), 34.2 (CH₂ from Cy), 34.9 (CH₂ from Cy), 41.3 (CH₂CH), 50.0 (C₃), 64.7 (CH₂OH), 114.9 (CH=CH₂), 138.3 (CH=CH₂), 183.1 (C=O);
m/z (ES⁺) 277 ((M + Na), 100%). (Found: (M + Na) 277.1782. C₁₅H₂₆O₃Na requires M, 277.1774).

2-(Hydroxymethyl)-2-isobutylct-7-enoic acid (230d)

As for general procedure D, reaction of 5-(hex-5-enyl)-5-isobutyl-2,2-dimethyl-1,3-dioxane-4,6-dione 229d (31 mg, 0.11 mmol, 1.0 eq) and SmI₂ (0.1 M in THF, 8.5 mL, 0.85 mmol, 8.0 eq) in THF (2.0 mL) and H₂O (2.3 mL, 133 mmol, 1200 eq) gave after column chromatography (30-100% ethyl acetate in petroleum ether (40-60 °C)) 2-(hydroxymethyl)-2-isobutylct-7-enoic acid 230d (21 mg, 90.2 μmol, 82%) as a colourless oil.

ν max (neat)/cm⁻¹ 3376 (br. OH), 3076, 2926, 2868, 2360, 1694 (C=O), 1640, 1462, 1387, 1367, 1238, 1037, 908;
¹H NMR (400 MHz, CDCl₃) δ ppm 0.91 (6 H, d, J = 6.6 Hz, 2 × CH₃), 1.21 - 1.35 (2 H, m, C(CH₃)₂CH₂), 1.35 - 1.45 (2 H, m, C(CH₃)₂CH₂CH₂), 1.49 - 1.59 (2 H, m, CH₂CH), 1.59 - 1.65 (1 H, m, 1 H from C(CH₃)₂CH₂), 1.66 - 1.78 (2 H, m, 1 H from C(CH₃)₂CH₂, CH₂CH).
2.06 (2 H, q, \( J = 7.0 \text{ Hz} \), \( \text{CH}_2\text{CH}=\text{CH}_2 \)), 3.66 (1 H, d, \( J = 11.3 \text{ Hz} \), 1 H from \( \text{CH}_2\text{OH} \)), 3.81 (1 H, d, \( J = 11.3 \text{ Hz} \), 1 H from \( \text{CH}_2\text{OH} \)), 4.95 (1 H, dtt, \( J = 10.1, 1.8, 1.0 \text{ Hz} \), 1 H from \( \text{CH}=\text{CH}_2 \)), 5.00 (1 H, ddt, \( J = 17.2, 1.8, 1.8 \text{ Hz} \), 1 H from \( \text{CH}=\text{CH}_2 \)), 5.79 (1 H, ddt, \( J = 17.2, 10.1, 6.8 \text{ Hz} \), \( \text{CH}=\text{CH}_2 \));

\(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm 23.3 (CCH\(_2\)C\(_3\)H\(_2\)), 23.6 (CH\(_3\)C\(_3\)H), 24.3 (CH\(_3\)) 24.4 (CH\(_3\)), 29.3 (CCH\(_2\)CH\(_2\)CH\(_2\)), 33.5 (CH\(_2\)CH=CH\(_2\)), 33.7 (CCH\(_2\)CH\(_2\)), 42.6 (CH\(_2\)CH), 50.2 (C\(_q\)), 64.6 (CH\(_2\)OH), 114.5 (CH=CH\(_2\)), 138.7 (CH=CH\(_2\)), 183.1 (C=O);

\text{m/z} (\text{ES+}) 251 ((M + Na), 100%). (Found: (M + H) 229.1798. \text{C}_{13}\text{H}_{25}\text{O}_3 \text{requires} M, 229.1798).

\((E)-2-(\text{Hydroxymethyl})-2\text{-isobutyl-8-phenyloct-7-enoic acid (230e)}\)

As for general procedure D, reaction of \((E)-5\text{-isobutyl-2,2-dimethyl-5-(6-phenylhex-5-enyl)-1,3-dioxane-4,6-dione 229e (30 mg, 0.08 mmol, 1.0 eq) and SmI\(_2\) (0.1 M in THF, 7.0 mL, 0.70 mmol, 8.0 eq) in THF (2.0 mL) and H\(_2\)O (2.0 mL, 111 mmol, 1200 eq) gave after column chromatography (30-100% ethyl acetate in petroleum ether (40-60 °C)) \((E)-2\text-(hydroxymethyl)-2\text-isobutyl-8-phenyloct-7-enoic acid 230e (15 mg, 48.0 \text{μmol}, 60%) as a colourless oil.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3338 (br. OH), 3059, 3024, 2927, 2868, 1695 (C=O), 1598, 1493, 1462, 1398, 1367, 1240, 1156, 1039, 963, 911, 852, 742, 692, 641;

\(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 0.91 (6 H, d, \( J = 6.6 \text{ Hz} \), 2 × CH\(_3\)), 1.29 - 1.43 (2 H, m, CCH\(_2\)CH\(_2\)), 1.43 - 1.51 (2 H, m, CCH\(_2\)CH\(_2\)CH\(_2\)), 1.52 - 1.60 (2 H, m, CH\(_2\)CH), 1.60 - 1.68 (1 H, m, 1 H from CCH\(_2\)CH\(_2\)), 1.69 - 1.80 (2 H, m, 1 H from CCH\(_2\)CH\(_2\)CH\(_2\)), 2.24 (2 H, q, \( J = 6.8 \text{ Hz} \), CH\(_2\)CH=CH\(_2\)), 3.66 (1 H, d, \( J = 11.9 \text{ Hz} \), 1 H from CH\(_2\)OH), 3.81 (1 H, d, \( J = 11.9 \text{ Hz} \), 1 H from CH\(_2\)OH), 6.21 (1 H, dt, \( J = 15.9, 7.1 \text{ Hz} \), CH=CHAr), 6.39 (1 H, d, \( J = 15.9 \text{ Hz} \), CH=CHAr), 7.17 - 7.23 (1 H, m, ArH), 7.27 - 7.36 (4 H, m, 4 × ArH);

\(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm 23.4 (CCH\(_2\)CH\(_2\)), 23.6 (CH\(_3\)), 24.3 (CH\(_3\)), 24.4 (CH\(_2\)CH), 29.8 (CCH\(_2\)CH\(_2\)CH\(_2\)), 32.8 (CH\(_2\)CH=CH\(_2\)), 33.6 (CCH\(_2\)CH\(_2\)), 42.5 (CH\(_2\)CH), 50.2 (C\(_q\)), 64.7 (CH\(_2\)OH), 125.9 (2 × ArCH), 126.8 (ArCH), 128.5 (2 × ArCH), 130.0 (CH=CHAr), 130.6 (CH=CHAr), 137.8 (ArC\(_q\)), 183.0 (C=O);
m/z (ES+) 327 ((M + Na), 100%). (Found: (M + Na) 327.1935. C_{19}H_{28}O_{3}Na requires M, 327.1931).

\[
\text{rac-}(1S,3aR,6S,6aR)-1,6\text{-Dibenzyl-6a-hydroxyoctahydronentalene-3a-carboxylic acid (241a)}
\]

As for general procedure D, reaction of 2,2-dimethyl-5,5-bis((E)-4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 239a (100 mg, 0.25 mmol, 1.0 eq) and SmI\textsubscript{2} (0.1 M in THF, 19.8 mL, 1.98 mmol, 8.0 eq) in THF (1.0 mL) and H\textsubscript{2}O (5.4 mL, 297 mmol, 1200 eq) gave after purification by column chromatography (20% ethyl acetate in petroleum ether (40-60 °C)) rac-(1S,3aR,6S,6aR)-1,6-dibenzyl-6a-hydroxyoctahydronentalene-3a-carboxylic acid 241a (60 mg, 0.17 mmol, 69%) as a white solid.

\textbf{mp} 132-134 °C; 
\nu_{\text{max}} \text{(evap. film)/cm}^{-1} 2950, 1703, 1682, 1494, 1454, 1276, 698;

\textbf{1H NMR} (400 MHz, CDCl\textsubscript{3}) \delta ppm 1.15 - 1.40 (2 H, m, 2 H from CH\textsubscript{2}), 1.54 (1 H, dd, J = 13.1, 6.3 Hz, 1 H from CH\textsubscript{2}), 1.58 - 1.72 (2 H, m, 2 H from CH\textsubscript{2}), 1.72 - 1.81 (1 H, m, 1 H from CH\textsubscript{2}), 2.04 - 2.23 (3 H, m, 1 H from CH\textsubscript{2}, 2 × CH), 2.48 (1 H, ddd, J = 13.1, 6.1, 1.5 Hz, 1 H from CH\textsubscript{2}), 2.54 - 2.64 (2 H, m, 2 H from PhCH\textsubscript{2}), 3.14 (1 H, dd, J = 13.6, 2.5 Hz, 1 H from PhCH\textsubscript{2}), 3.34 (1 H, dd, J = 12.7, 3.2 Hz, 1 H from PhCH\textsubscript{2}), 7.20 - 7.26 (6 H, m, 6 × ArH), 7.28 - 7.36 (4 H, m, 4 × ArH);

\textbf{13C NMR} (100 MHz, CDCl\textsubscript{3}) \delta ppm 27.6 (CH\textsubscript{2}), 32.0 (CH\textsubscript{2}), 34.8 (CH\textsubscript{2}), 35.7 (PhCH\textsubscript{2}), 35.9 (CH\textsubscript{2}), 36.5 (PhCH\textsubscript{2}), 48.2 (CH), 55.4 (CH), 64.4 (C\textsuperscript{6}), 92.7 (C\textsuperscript{6}), 125.9 (ArCH), 126.0 (ArCH), 128.4 (2 × ArCH), 128.4 (2 × ArCH), 128.8 (2 × ArCH), 128.9 (2 × ArCH), 141.3 (Ar\textsuperscript{6}), 142.1 (Ar\textsuperscript{6}), 181.9 (C=O);

m/z (ES−) 349 ((M − H), 100%), 350 (13); (Found: (M − H) 349.1797. C\textsubscript{23}H\textsubscript{25}O\textsubscript{3} requires M, 349.1804).
rac-(1S,3aR,6S,6aR)-1,6-bis(4-Bromobenzyl)-6a-hydroxyoctahydropentalene-3a-carboxylic acid (241b)

As for general procedure D, reaction of 5,5-bis((E)-4-(4-bromophenyl)but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 239b (50 mg, 0.09 mmol, 1.0 eq) and SmI₂ (0.1 M in THF, 7.1 mL, 0.71 mmol, 8.0 eq) in THF (2.0 mL) and H₂O (1.9 mL, 107 mmol, 1200 eq) gave after column chromatography (20% ethyl acetate in petroleum ether (40-60 °C)) rac-(1S,3aR,6S,6aR)-1,6-bis(4-bromobenzyl)-6a-hydroxyoctahydropentalene-3a-carboxylic acid 241b (23 mg, 45.3 μmol, 54%) as a white solid.

mp 108-110 °C;

ν_max (neat)/cm⁻¹ 3040 (br. OH), 2928, 2859, 1896, 1693 (C=O), 1486, 1453, 1403, 1262, 1095, 1070, 1010, 841, 792, 741, 668;

¹H NMR (400 MHz, CDCl₃) δ ppm 1.15 - 1.25 (1 H, m, 1 H from CHCH₂CH₂), 1.26 - 1.35 (1 H, m, 1 H from CHCH₂CH₂), 1.50 - 1.65 (3 H, m, 2 H from CHCH₂CH₂, 1 H from CHCH₂CH₂), 1.65 - 1.75 (1 H, m, 1 H from CHCH₂CH₂), 1.93 - 2.03 (1 H, m, CH), 2.03 - 2.12 (1 H, m, CH), 2.12 - 2.21 (1 H, m, 1 H from CHCH₂CH₂), 2.41 - 2.51 (2 H, 1 H from CHCH₂CH₂, 1 H from ArCH₂), 2.56 (1 H, dd, J = 13.9, 11.3 Hz, 1 H from ArCH₂), 3.02 (1 H, dd, J = 13.9, 2.5 Hz, 1 H from ArCH₂), 3.24 (1 H, dd, J = 12.9, 3.0 Hz, 1 H from ArCH₂), 3.42 (4 H, dd, J = 8.3, 3.0 Hz, 4 × ArH), 7.42 (4 H, dd, J = 8.3, 2.0 Hz, 4 × ArH);

¹³C NMR (100 MHz, CDCl₃) δ ppm 27.4 (CHCH₂CH₂), 31.8 (CHCH₂CH₂), 34.8 (CHCH₂CH₂), 35.2 (ArCH₂), 35.9 (ArCH₂), 36.0 (CHCH₂CH₂), 47.9 (CH), 55.2 (CH), 64.0 (C₆), 92.1 (C₅), 119.7 (ArC₅), 119.8 (ArC₅), 130.5 (2 × ArCH), 130.6 (2 × ArCH), 131.4 (2 × ArCH), 131.5 (2 × ArCH), 140.2 (ArC₅), 140.9 (ArC₅), 180.6 (C=O);

m/z (ES⁻) 505 (63%), 506 (60), 507 (M − H), 100, 508 (55), 509 (52); (Found: (M − H) 506.9998. C₂₃H₂₃O₃⁷⁹Br₂ requires M, 506.9989).
As for general procedure D, reaction of 2,2-dimethyl-5-((E)-4-phenylbut-3-enyl)-5-((E)-6-phenylhex-5-enyl)-1,3-dioxane-4,6-dione 262j (30 mg, 69.4 μmol, 1.0 eq) and SmI$_2$ (0.1 M in THF, 5.6 mL, 0.56 mmol, 8.2 eq) in THF (1.5 mL) and H$_2$O (1.5 mL, 83 mmol, 1200 eq) gave after column chromatography (10-20% ethyl acetate in hexane with 1% acetic acid) rac-(1S,2S,3S)-3-benzyl-2-hydroxy-1-((E)-6-phenylhex-5-enyl)cyclopentanecarboxylic acid 274j (16.0 mg, 42.3 μmol, 61%) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.25 - 1.35 (2 H, m, 1H from CHCH$_2$C$\text{H}_2$, 1H from C$\text{C}$CH$_2$CH$_2$CH$_2$), 1.35 - 1.55 (4 H, m, 1H from CHCH$_2$CH$_2$, 1H from C$\text{C}$CH$_2$CH$_2$CH$_2$, C$\text{C}$CH$_2$CH$_2$CH$_2$), 1.59 - 1.68 (1 H, m, 1H from CHCH$_2$CH$_2$), 1.68 - 1.76 (1 H, m, from CHCH$_2$CH$_2$), 1.92 - 2.02 (1 H, m, 1H from C$\text{C}$CH$_2$CH$_2$), 2.11 - 2.19 (2 H, m, C$\text{C}$CH$_2$CH$_2$), 2.19 - 2.26 (2 H, m, CH$_2$CH=CH), 2.52 (1 H, dd, J = 13.4, 9.3 Hz, 1H from CHCH$_2$Ar), 3.02 (1 H, dd, J = 13.4, 5.0 Hz, 1H from CHCH$_2$Ar), 3.92 (1 H, d, J = 9.1 Hz, CH$_2$OH), 6.19 (1 H, dt, J = 15.8, 6.8 Hz, CH=CHAr), 6.37 (1 H, d, J = 15.8 Hz, CH=CHAr), 7.18 - 7.23 (4 H, m, 4 × ArH), 7.27 - 7.35 (6 H, m, 6 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 24.2 (C$\text{C}$CH$_2$CH$_2$), 26.0 (CHCH$_2$CH$_2$), 29.0 (CHCH$_2$CH$_2$), 29.8 (C$\text{C}$CH$_2$CH$_2$CH$_2$), 31.5 (C$\text{C}$CH$_2$CH$_2$CH$_2$), 32.8 (CH$_2$CH=CH), 39.8 (CHCH$_2$Ar), 46.1 (CHCH$_2$CH$_2$), 55.5 (C$^\text{C}$), 81.8 (CH$_2$OH), 125.9 (2 × ArCH), 126.0 (ArCH), 126.8 (ArCH), 128.4 (2 × ArCH), 128.5 (2 × ArCH), 128.9 (2 × ArCH), 129.9 (CH=CHAr), 130.7 (CH=CHAr), 137.8 (ArC$^\text{C}$), 140.6 (ArC$^\text{C}$), 182.3 (C=O);

As for general procedure D, reaction of (E)-5-(but-3-enyl)-2,2-dimethyl-5-(4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 262a (30 mg, 91.4 μmol, 1.0 eq) and SmI$_2$ (0.1 M in THF, 7.5 mL, 0.75 mmol, 8.3 eq, added over 2 hours) in THF (2.0 mL) and H$_2$O (2.0 mL, 111
mmol, 1200 eq) gave after column chromatography (10-20% ethyl acetate in hexane with 1% acetic acid) rac-(1S,3aS,6R,6aR)-1-benzyl-6a-hydroxy-6-methyloctahydropentalene-3a-carboxylic acid 263a (13 mg, 45.7 μmol, 50%) as an amorphous solid.

ν\textsubscript{max} (neat)/cm\textsuperscript{-1} 3432 (br. OH), 3061, 3025, 2954, 2924, 2855, 1693 (C=O), 1496, 1453, 1377, 1282, 1220, 1200, 1059, 970, 907, 868, 807, 754, 698, 667;

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ ppm 1.09 - 1.19 (1 H, m, 1 H from CHCH\textsubscript{2}CH\textsubscript{3}), 1.24 (3 H, d, J = 6.8 Hz, CH\textsubscript{3}), 1.29 - 1.39 (1 H, m, 1 H from CHCH\textsubscript{2}CH\textsubscript{2}), 1.53 (1 H, dd, J = 12.9, 6.6 Hz, 1 H from CHCH\textsubscript{2}CH\textsubscript{2}), 1.62 (1 H, dd, J = 12.2, 6.2 Hz, 1 H from CHCH\textsubscript{2}CH\textsubscript{2}), 1.66 - 1.73 (1 H, m, 1 H from CHCH\textsubscript{2}CH\textsubscript{2}), 1.73 - 1.80 (1 H, m, 1 H from CHCH\textsubscript{2}CH\textsubscript{2}), 1.92 (1 H, qd, J = 6.1, 2.8 Hz, CH), 2.01 (1 H, dt, J = 13.0, 6.4 Hz, CH), 2.29 (1 H, td, J = 12.7, 6.7 Hz, 1 H from CHCH\textsubscript{2}CH\textsubscript{2}), 2.45 (1 H, ddd, J = 13.4, 6.3, 1.3 Hz, 1 H from CHCH\textsubscript{2}CH\textsubscript{2}), 2.52 (1 H, dd, J = 13.6, 11.3 Hz, 1 H from CHCH\textsubscript{2}Ar), 3.03 (1 H, dd, J = 13.6, 2.5 Hz, 1 H from CHCH\textsubscript{2}Ar), 7.17 - 7.23 (3 H, m, 3 × ArH), 7.28 - 7.32 (2 H, m, 2 × ArH);

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ ppm 13.5 (CH\textsubscript{3}), 30.6 (CHCH\textsubscript{2}CH\textsubscript{2}), 31.8 (CHCH\textsubscript{2}CH\textsubscript{2}), 34.9 (CHCH\textsubscript{2}CH\textsubscript{2}), 36.0 (CHCH\textsubscript{2}CH\textsubscript{2}), 36.4 (CHCH\textsubscript{2}Ar), 47.3 (CH), 47.7 (CH), 64.3 (C\textsuperscript{6}), 93.0 (C\textsuperscript{4}), 125.8 (ArH), 128.3 (2 × ArH), 128.8 (2 × ArH), 142.2 (ArC\textsuperscript{8}), 181.6 (C=O);

m/z (ES\textsuperscript{−}) 273 ((M − H), 100%), 274 (19). (Found: (M − H) 273.1493. C\textsubscript{17}H\textsubscript{21}O\textsubscript{3} requires M, 273.1496).

rac-(1S,3aS,6R,6aR)-1-(4-Bromobenzyl)-6a-hydroxy-6-methyloctahydropentalene-3a-carboxylic acid (263b)

As for general procedure D, reaction of (E)-5-(4-(4-bromophenyl)but-3-en-1-yl)-5-(but-3-en-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione 262b (31 mg, 77.1 μmol, 1.0 eq) and SmI\textsubscript{2} (0.1 M in THF, 6.0 mL, 0.60 mmol, 7.8 eq, added over 2 hours) in THF (1.6 mL) and H\textsubscript{2}O (1.6 mL, 89 mmol, 1200 eq) gave after column chromatography (10-20% ethyl acetate in hexane with 1% acetic acid) rac-(1S,3aS,6R,6aR)-1-(4-bromobenzyl)-6a-hydroxy-6-methyloctahydropentalene-3a-carboxylic acid 263b (13 mg, 35.4 μmol, 46%) as a colourless oil.
\[ \nu_{\text{max}} \text{(neat)/cm}^{-1} 3416 \text{ (br. OH)}, 2953, 2873, 1694 \text{ (C=O)}, 1486, 1458, 1402, 1283, 1220, 1159, 1131, 1100, 1072, 1011, 970, 906, 842, 795, 733, 671; \]

\[^1\text{H} \text{ NMR} \] (400 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 1.12 (1 H, dd, \( J = 13.0, 6.7 \) Hz, 1 H from CH\textsubscript{2}CH\textsubscript{2}CHCH\textsubscript{2}), 1.21 (3 H, d, \( J = 6.8 \) Hz, CH\textsubscript{3}), 1.31 (1 H, dd, \( J = 12.6, 6.7 \) Hz, CH\textsubscript{2}CH\textsubscript{2}CHCH\textsubscript{3}), 1.52 - 1.55 (1 H, m, \( J = 12.6, 6.3 \) Hz, 1 H from CH\textsubscript{2}CH\textsubscript{2}CHCH\textsubscript{3}), 1.56 - 1.69 (2 H, m, CH\textsubscript{2}CH\textsubscript{2}CHAr), 1.75 (1 H, dt, \( J = 12.6, 6.3 \) Hz, 1 H from CH\textsubscript{2}CH\textsubscript{2}CHCH\textsubscript{3}), 1.80 - 1.90 (1 H, m, CH\textsubscript{2}CH\textsubscript{2}CHAr), 1.93 - 2.05 (1 H, m, CH\textsubscript{3}), 2.28 (1 H, td, \( J = 12.6, 6.7 \) Hz, 1 H from CH\textsubscript{2}CH\textsubscript{2}CHCH\textsubscript{3}), 2.40 - 2.52 (2 H, m, 1 H from CH\textsubscript{2}CH\textsubscript{2}CHCH\textsubscript{2}, 1 H from CH\textsubscript{2}Ar), 2.96 (1 H, dd, \( J = 13.9, 2.5 \) Hz, 1 H from CH\textsubscript{2}Ar), 7.06 (2 H, d, \( J = 8.3 \) Hz, 2 x ArH), 7.40 (2 H, d, \( J = 8.3 \) Hz, 2 x ArH);

\[^{13}\text{C} \text{ NMR} \] (100 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 13.5 (CH\textsubscript{3}), 30.6 (CH\textsubscript{2}CH\textsubscript{2}CHCH\textsubscript{3}), 31.7 (CH\textsubscript{2}CH\textsubscript{2}CHAr), 34.9 (CH\textsubscript{2}CH\textsubscript{2}CHCH\textsubscript{3}), 35.8 (CH\textsubscript{2}Ar), 36.0 (CH\textsubscript{2}CH\textsubscript{2}CHCH\textsubscript{2}), 47.2 (CH), 47.5 (CH), 64.3 (C\textsubscript{6}), 92.9 (C\textsubscript{6}), 119.5 (ArC\textsubscript{6}), 130.6 (2 x ArCH), 131.3 (2 x ArCH), 141.2 (ArC\textsubscript{6}), 181.5 (C=O);

\textit{m/z} (ES−) 351 ((M − H), 100%), 353 (94). (Found: (M − H) 351.0595. C\textsubscript{17}H\textsubscript{20}O\textsubscript{3}79Br requires \( M \), 351.0601).

\textit{rac-}(1S,3aS,6R,6aR)-1-(2,4-Dichlorobenzyl)-6a-hydroxy-6-methyloctahydropentalene-3a-carboxylic acid (263c)

As for general procedure D, reaction of \((E)-5-(\text{but-3-en-1-yl})-5-(4-(2,4-dichlorophenyl)but-3-en-1-yl)-2,2\text{-dimethyl-1,3-dioxane-4,6-dione} \ 262\text{c} \ (30 \text{ mg}, 75.8 \mu\text{mol}, 1.0 \text{ eq}) \) and SmI\textsubscript{2} (0.1 M in THF, 6.0 mL, 0.60 mmol, 7.9 eq, added over 2 hours) in THF (1.70 mL) and H\textsubscript{2}O (1.65 mL, 92 mmol, 1200 eq) gave after column chromatography (10-20% ethyl acetate in hexane with 1% acetic acid) \textit{rac-}(1S,3aS,6R,6aR)-1-(2,4-dichlorobenzyl)-6a-hydroxy-6-methyloctahydropentalene-3a-carboxylic acid \ 263\text{c} \ (11 \text{ mg}, 32.6 \mu\text{mol}, 43%) as a colourless oil.

\[ \nu_{\text{max}} \text{(neat)/cm}^{-1} 3428 \text{ (br. OH)}, 2953, 2873, 1691 \text{ (C=O)}, 1586, 1560, 1471, 1382, 1272, 1216, 1159, 1102, 1048, 997, 969, 940, 904, 865, 849, 820, 755, 708, 668, 645; \]

\[^1\text{H} \text{ NMR} \] (400 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 1.16 (1 H, td, \( J = 12.9, 6.1 \) Hz, 1 H from CH\textsubscript{2}CH\textsubscript{2}CHCH\textsubscript{2}), 1.23 (3 H, d, \( J = 7.1 \) Hz, CH\textsubscript{3}), 1.35 (1 H, qd, \( J = 12.7, 6.8 \) Hz, 1 H from ...
$CH_2CHCH_3$, 1.46 (1 H, dt, $J = 11.8, 5.8$ Hz, 1 H from $CH_2CHCH_2Ar$), 1.54 (1 H, dd, $J = 12.7, 6.2$ Hz, 1 H from $CH_2CH_2CHCH_3$), 1.63 (1 H, qd, $J = 12.4, 6.3$ Hz, 1 H from $CH_2CH_2CH_2Ar$), 1.76 (1 H, dt, $J = 12.7, 6.2$ Hz, 1 H from $CH_2CHCH_3$), 1.94 - 2.11 (2 H, m, 2 × CH), 2.29 (1 H, td, $J = 12.7, 6.8$ Hz, 1 H from $CH_2CH_2CHCH_3$), 2.42 - 2.50 (1 H, m, 1 H from $CH_2CH_2CHCH_2$), 2.74 (1 H, t, $J = 13.7, 11.5$ Hz, 1 H from CH$_2$Ar), 3.05 (1 H, dd, $J = 13.7, 3.7$ Hz, 1 H from CH$_2$Ar), 7.15 - 7.18 (2 H, m, 2 × ArH), 7.35 - 7.38 (1 H, m, ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 13.3 (CH$_3$), 30.6 (CH$_2$CHCH$_3$), 31.5 (CH$_2$CHCH$_2$Ar), 33.2 (CH$_2$Ar), 35.1 (CH$_2$CH$_2$CHCH$_3$), 35.7 (CH$_2$CH$_2$CHCH$_2$), 45.0 (CHCH$_2$Ar), 47.4 (CHCH$_3$), 64.3 (C$^6$), 93.2 (C$^6$), 126.8 (ArCH), 129.2 (ArCH), 132.1 (ArC$^6$), 132.2 (ArCH), 134.6 (ArC$^6$), 138.2 (ArC$^6$), 182.0 (C=O);

m/z (ES−) 341 ((M − H), 100%), 343 (76). (Found: (M − H) 341.0701. C$_{17}$H$_{19}$O$_3$Cl$_2$ requires $M$, 341.0716).

rac-(1R,3aS,6S,6aR)-6a-Hydroxy-1-methyl-6-(naphthalen-2-ylmethyl)octahydropentalene-3a-carboxylic acid (263d)

As for general procedure D, reaction of (E)-5-(but-3-en-1-yl)-2,2-dimethyl-5-(4-(naphthalen-2-yl)but-3-en-1-yl)-1,3-dioxane-4,6-dione 262d (30 mg, 78.0 μmol, 1.0 eq) and SmI$_2$ (0.1 M in THF, 6.5 mL, 0.65 mmol, 8.3 eq, added over 2 hours) in THF (1.7 mL) and H$_2$O (1.7 mL, 94 mmol, 1200 eq) gave after column chromatography (10-20% ethyl acetate in hexane with 1% acetic acid) rac-(1R,3aS,6S,6aR)-6a-hydroxy-1-methyl-6-(naphthalen-2-ylmethyl)octahydropentalene-3a-carboxylic acid 263d (11 mg, 34.2 μmol, 44%) as a colourless oil.

$\nu_{max}$ (neat)/cm$^{-1}$ 3409 (br. OH), 3050, 2953, 2873, 1691 (C=O), 1599, 1507, 1457, 1378, 1282, 1222, 1205, 1159, 1125, 1099, 1057, 995, 970, 906, 855, 819, 729, 661, 648;

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.09 - 1.20 (1 H, m, 1 H from CH$_2$CH$_2$CHCH$_2$), 1.30 (3 H, d, $J = 6.6$ Hz, CH$_3$), 1.36 (1 H, dd, $J = 12.6, 6.8$ Hz, 1 H from CH$_2$CHCH$_3$), 1.55 (1 H, dd, $J = 12.6, 6.3$ Hz, 1 H from CH$_2$CH$_2$CHCH$_3$), 1.65 - 1.73 (2 H, m, CH$_2$CHCH$_2$Ar), 1.78 (1 H, dt, $J = 12.6, 6.3$ Hz, 1 H from CH$_2$CH$_2$CHCH$_3$), 1.98 - 2.09 (2 H, m, 2 × CH), 2.31 (1 H, td, $J = 12.6, 6.8$ Hz, 1 H from CH$_2$CH$_2$CHCH$_3$), 2.42 - 2.51 (1 H, m, 1 H from
CH₂CH₂CHCH₂), 2.70 (1 H, dd, J = 13.7, 11.5 Hz, 1 H from CH₂Ar), 3.20 (1 H, dd, J = 13.7, 2.1 Hz, 1 H from CH₂Ar), 7.36 (1 H, d, J = 8.3 Hz, ArH), 7.40 - 7.49 (2 H, m, 2 × ArH), 7.63 (1 H, s, ArH), 7.75 - 7.84 (3 H, m, 3 × ArH);

¹³C NMR (100 MHz, CDCl₃) δ ppm 13.6 (CH₃), 30.6 (CH₂CH₂CHCH₂), 31.9 (CH₂CHCH₂Ar), 34.9 (CH₂CH₂CHCH₂), 36.0 (CH₂CH₂CHCH₂), 36.5 (CH₂Ar), 47.3 (CH), 47.7 (CH), 64.4 (C⁶), 93.1 (C⁶), 125.1 (ArH), 125.9 (ArH), 126.8 (ArH), 127.4 (ArH), 127.6 (ArH), 127.7 (ArH), 127.8 (ArH), 131.9 (ArC⁶), 133.6 (ArC⁶), 139.8 (ArC⁶), 181.8 (C=O);

m/z (ES+) 307 (21%), 325 (45), 342 (100), 347 ((M + Na), 76), 348 (23). (Found: (M + Na) 347.1614. C₂₁H₂₄O₃Na requires M, 347.1618).

rac-(1S,3aS,6S,6aR)-1-Benzyl-6-(4-bromobenzyl)-6a-hydroxyoctahydropentalene-3a-carboxylic acid (263e)

As for general procedure D, reaction of 5-((E)-4-(4-bromophenyl)but-3-enyl)-2,2-dimethyl-5-((E)-4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 262e (30 mg, 62.1 μmol, 1.0 eq) and SmI₂ (0.1 M in THF, 5.0 mL, 0.50 mmol, 8.1 eq, added over 2 hours) in THF (2.0 mL) and H₂O (1.34 mL, 74 mmol, 1200 eq) gave after column chromatography (10-20% ethyl acetate in hexane with 1% acetic acid) rac-(1S,3aS,6S,6aR)-1-benzyl-6-(4-bromobenzyl)-6a-hydroxyoctahydropentalene-3a-carboxylic acid 263e (17 mg, 39.1 μmol, 63%) as a white solid.

mp 77-79 °C;

νmax (neat)/cm⁻¹ 3430 (br. OH), 3026, 2952, 2931, 2854, 1695 (C=O), 1610, 1511, 1453, 1246, 1177, 1098, 1034, 836, 807, 752, 699, 667;

¹H NMR (400 MHz, CDCl₃) δ ppm 1.12 - 1.23 (1 H, m, 1 H from CH₂CH₂CH), 1.49 (1 H, dd, J = 12.6, 6.1 Hz, 1 H from CH₂CH₂CH), 1.54 - 1.78 (4 H, m, 2 × CH₂CH), 1.95 - 2.05 (1 H, m, CH), 2.07 - 2.20 (2 H, m, CH, 1 H from CH₂CH₂CH), 2.41 - 2.61 (3 H, m, 2 × 1 H from CH₂Ar, 1 H from CH₂CH₂CH), 2.99 - 3.11 (1 H, m, 1 H from CH₂Ar), 3.22 - 3.33 (1 H, m, 1 H from CH₂Ar), 7.05 - 7.11 (2 H, m, 2 × ArH), 7.18 - 7.24 (3 H, m, 3 × ArH), 7.26 - 7.32 (2 H, m, 2 × ArH), 7.37 - 7.43 (2 H, m, 2 × ArH);
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 27.6 (CH$_2$CH), 31.9 (CH$_2$CH), 34.8 (CH$_2$CH$_2$CH), 35.8 (CH$_2$Ar), 36.0 (CH$_2$Ar), 36.0 (CH$_2$CH$_2$CH), 48.0 (CH), 55.1 (CH), 64.4 (C$^q$), 92.6 (C$^q$), 126.9 (ArCH), 128.4 (2 × ArCH), 128.8 (ArCH), 130.6 (ArCH), 130.5 (ArCH), 131.4 (2 × ArCH), 140.3 (ArC$^q$), 141.0 (ArC$^q$), 141.9 (ArC$^q$), 181.5 (C=O);
m/z (ES−) 427 ((M − H), 100%), 429 (58). (Found: (M − H) 427.0907. C$_{23}$H$_{24}$O$_3$Br requires M, 427.0914).

rac-(1S,3aS,6S,6aR)-1-Benzyl-6-(2,4-dichlorobenzyl)-6a-hydroxyoctahydropentalene-3a-carboxylic acid (263f)

As for general procedure D, reaction of 5-((E)-4-(2,4-dichlorobenzyl)but-3-enyl)-2,2-dimethyl-5-((E)-4-phenylbut-3-enyl)-1,3-dioxane-4,6-dione 262f (99 mg, 0.21 mmol, 1.0 eq) and SmI$_2$ (0.1 M in THF, 17.0 mL, 1.70 mmol, 8.1 eq, added over 2 hours) in THF (4.6 mL) and H$_2$O (4.6 mL, 255 mmol, 1200 eq) gave after purification by column chromatography (10-20% ethyl acetate in hexane with 1% acetic acid) rac-(1S,3aS,6S,6aR)-1-benzyl-6-(2,4-dichlorobenzyl)-6a-hydroxyoctahydropentalene-3a-carboxylic acid 263f (46 mg, 0.11 mmol, 52%) as a white solid.

mp 164-166 °C;
ν$_{\text{max}}$ (neat)/cm$^{-1}$ 3381 (br.OH), 2933, 2865, 1774 (C=O), 1735, 1703, 1598, 1586, 1558, 1494, 1471, 1449, 1381, 1261, 1232, 1201, 1103, 1074, 1046, 1030, 962, 899, 864, 849, 806, 750, 696;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.22 (1 H, td, $J = 12.8$, 6.2 Hz, 1 H from CHCH$_2$CH$_2$), 1.35 (1 H, dq, $J = 12.6$, 6.6 Hz, 1 H from CHCH$_2$CH$_2$), 1.47 - 1.59 (2 H, m, 1 H from CHCH$_2$CH$_2$, 1 H from CHCH$_2$CH$_2$), 1.59 - 1.73 (2 H, m, 2 H from CHCH$_2$CH$_2$), 2.06 - 2.27 (3 H, m, 2 × CH, 1 H from CHCH$_2$CH$_2$), 2.49 (1 H, dd, $J = 12.9$, 5.8 Hz, 1 H from CHCH$_2$CH$_2$), 2.68 - 2.84 (2 H, m, 2 H from CHCH$_2$Ar), 3.17 (1 H, dd, $J = 13.6$, 3.5 Hz, 1 H from CHCH$_2$Ar), 3.27 (1 H, dd, $J = 12.7$, 2.9 Hz, 1 H from CHCH$_2$Ar), 7.19 (2 H, s, 2 × ArH), 7.20 - 7.26 (3 H, m, 3 × ArH), 7.28 - 7.34 (2 H, m, 2 × ArH), 7.39 (1 H, s, ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 27.6 (CHCH$_2$CH$_2$), 31.5 (CHCH$_2$CH$_2$), 33.5 (CHCH$_2$Ar), 35.0 (CHCH$_2$CH$_2$), 35.4 (CHCH$_2$Ar), 35.7 (CHCH$_2$CH$_2$), 45.3 (CH), 55.4 (CH), 64.3 (C$^q$), 92.8 (C$^q$), 126.0 (ArCH), 126.9 (ArCH), 128.4 (2 × ArCH), 128.8 (2 × ArCH), 130.6 (ArCH), 130.5 (ArCH), 131.4 (2 × ArCH), 140.3 (ArC$^q$), 141.0 (ArC$^q$), 141.9 (ArC$^q$), 181.5 (C=O);
ArCH), 129.3 (ArCH), 132.3 (ArCH, ArC\(^q\)), 134.6 (ArC\(^q\)), 138.0 (ArC\(^q\)), 141.3 (ArC\(^q\)), 181.8 (C=O);

ms (ES+) 436 (21%), 441 ((M + Na), 100), 443 (93). (Found: (M + Na) 441.0981. C\(_{23}\)H\(_{24}\)O\(_3\)Cl\(_2\)Na requires M, 441.0995).

rac-(1S,3aS,7aR)-1,7-Dibenzyl-7a-hydroxyoctahydro-1H-indene-3a-carboxylic acid (263i)

As for general procedure D, reaction of 2,2-dimethyl-5-((E)-4-phenylbut-3-enyl)-5-((E)-5-phenylpent-4-enyl)-1,3-dioxane-4,6-dione 262i (30 mg, 71.0 μmol, 1.0 eq) and SmI\(_2\) (0.1 M in THF, 5.8 mL, 0.58 mmol, 8.1 eq, added over 2 hours) in THF (2.0 mL) and H\(_2\)O (1.55 mL, 86 mmol, 1200 eq) gave after column chromatography (10-20% ethyl acetate in hexane with 1% acetic acid) rac-(1S,3aS,7aR)-1,7-dibenzyl-7a-hydroxyoctahydro-1H-indene-3a-carboxylic acid 263i (17 mg, 47.7 μmol, 67%) as a white solid and as a 1.3:1 mixture of diastereoisomers.

\textbf{mp} 68-70 °C;

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3433 (br. OH), 3061, 2939, 2869, 1688 (C=O), 1602, 1495, 1452, 1386, 1260, 1216, 1156, 1095, 1030, 751, 698;

\textbf{\(^{1}\)H NMR} (400 MHz, CDCl\(_3\)) \(\delta\) ppm 1.13 - 1.32 (1 H, m, 1 H from CH\(_2\)), 1.37 - 1.58 (6 H, m, 6 H from CH\(_2\)), 1.59 - 1.77 (7 H, m, 7 H from CH\(_2\)), 1.77 - 1.89 (2 H, m, 2 H from CH\(_2\)), 2.04 - 2.27 (5 H, m, CH (major), CH (minor), 3 H from CH\(_2\)), 2.29 - 2.46 (3 H, m, 1 H from CH\(_2\)Ar (major), 1 H from CH\(_2\)Ar (minor), 1 H from CH\(_2\)), 2.58 (1 H, dd, \(J = 13.0, 10.7\) Hz, 1 H from CH\(_2\)Ar (minor)), 2.63 - 2.73 (3 H, m, CH (major), CH (minor), 1 H from CH\(_2\)Ar (major)), 2.95 (1 H, dd, \(J = 13.0, 3.5\) Hz, 1 H from CH\(_2\)Ar (minor)), 3.12 (1 H, dd, \(J = 13.4, 2.8\) Hz, 1 H from CH\(_2\)Ar (minor)), 3.17 - 3.27 (1 H, m, 1 H from CH\(_2\)Ar (major)), 3.58 (1 H, d, \(J = 11.3\) Hz, 1 H from CH\(_2\)Ar (major)), 7.13 - 7.24 (8 H, m, 8 × ArH), 7.25 - 7.34 (12 H, m, 12 × ArH);

\textbf{\(^{13}\)C NMR} (100 MHz, CDCl\(_3\)) \(\delta\) ppm 18.3 (CH\(_2\)), 23.0 (CH\(_2\)), 24.9 (CH\(_2\)), 27.5 (CH\(_2\)), 28.1 (2 × CH\(_2\)), 28.4 (CH\(_2\)), 31.9 (CH\(_2\)), 33.1 (CH\(_2\)), 33.6 (CH\(_2\)), 33.7 (CH\(_2\)Ar (minor)), 36.3 (CH\(_2\)Ar (minor)), 37.4 (CH\(_2\)Ar (major)), 37.7 (CH\(_2\)Ar (major)), 41.9 (CH (major)), 42.7 (CH (major)), 46.9 (CH (minor)), 48.0 (CH (minor)), 54.4 (C\(^6\)), 58.7 (C\(^5\)), 83.8 (C\(^4\)), 84.9
(C\textsuperscript{6}), 125.8 (2 × ArCH), 125.9 (2 × ArCH), 125.9 (2 × ArCH), 128.2 (2 × ArCH), 128.3 (2 × ArCH), 128.4 (2 × ArCH), 128.8 (2 × ArCH), 129.1 (2 × ArCH), 129.2 (2 × ArCH), 141.3 (ArC\textsuperscript{6}), 141.6 (ArC\textsuperscript{6}), 141.8 (ArC\textsuperscript{6}), 141.9 (ArC\textsuperscript{6}), 182.0 (C=O), 182.2 (C=O);

\textbf{m/z} (ES\textsuperscript{−}) 363 ((M − H), 100%), 364 (25). (Found: (M − H) 363.1956. C\textsubscript{24}H\textsubscript{27}O\textsubscript{3} requires M, 363.1965).

\textit{rac-}(1\textit{S},3\textit{aS},7\textit{aS},\textit{E})-7-Benzylidene-1-(2,4-dichlorobenzyl)-7a-hydroxyoctahydro-1\textit{H}-indene-3a-carboxylic acid (263n)

As for general procedure D, reaction of (\textit{E})-5-(4-(2,4-dichlorophenyl)but-3-en-1-yl)-2,2-dimethyl-5-(5-phenylpent-4-en-1-yl)-1,3-dioxane-4,6-dione 262n (31 mg, 63.9 μmol, 1.0 eq) and SmI\textsubscript{2} (0.1 M in THF, 5.00 mL, 0.50 mmol, 8.0 eq, added over 2 hours) in THF (1.4 mL) and H\textsubscript{2}O (1.4 mL, 78 mmol, 1200 eq) gave after column chromatography (30% ethyl acetate in hexane and 1% acetic acid) \textit{rac-}(1\textit{S},3\textit{aS},7\textit{aS},\textit{E})-7-benzylidene-1-(2,4-dichlorobenzyl)-7a-hydroxyoctahydro-1\textit{H}-indene-3a-carboxylic acid 263n (18 mg, 42.0 μmol, 66%) as a white solid and as a 10:1 mixture of double-bond isomers.

\textbf{mp} 175-177 °C;

\textbf{v\textsubscript{max} (neat)/cm\textsuperscript{−1}} 3477 (br. OH), 3077, 3057, 3020, 2942, 2867, 1683 (C=O), 1583, 1471, 1445, 1384, 1342, 1291, 1259, 1231, 1165, 1103, 1049, 906, 866, 846, 816, 730, 699, 648;

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \textbf{δ ppm} 1.25 - 1.41 (1 H, m, 1 H from CH\textsubscript{2}CH\textsubscript{2}C=CH), 1.61 - 1.71 (1 H, m, 1 H from CH\textsubscript{2}CH\textsubscript{2}C=CH), 1.72 - 1.80 (2 H, m, 1 H from CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH=CH, 1 H from CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}C=CH), 1.80 - 1.88 (2 H, m, CH\textsubscript{2}CH\textsubscript{2}CH=CH), 2.06 - 2.16 (1 H, m, 1 H from CH\textsubscript{2}CH\textsubscript{2}C=CH), 2.17 - 2.24 (1 H, m, 1 H from CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}C=CH), 2.34 - 2.44 (1 H, m, 1 H from CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH=CH), 2.56 (1 H, dd, J = 13.3, 10.1 Hz, 1 H from CH\textsubscript{2}Ar), 2.65 - 2.76 (1 H, m, CH), 2.89 - 2.97 (1 H, m, 1 H from CH\textsubscript{2}C=CH), 3.05 (1 H, dd, J = 13.3, 3.4 Hz, 1 H from CH\textsubscript{2}Ar), 6.89 (1 H, s, C=CH), 7.10 - 7.17 (2 H, m, 2 × ArH), 7.17 - 7.25 (3 H, m, 3 × ArH), 7.31 - 7.37 (3 H, m, 3 × ArH);

\textbf{\textsuperscript{13}C NMR} (100 MHz, CDCl\textsubscript{3}) \textbf{δ ppm} 24.0 (CH\textsubscript{2}CH\textsubscript{2}C=CH), 26.8 (CH\textsubscript{2}C=CH), 27.0 (CH\textsubscript{2}CH\textsubscript{2}CH), 32.2 (CH\textsubscript{2}Ar), 34.1 (CH\textsubscript{2}CH\textsubscript{2}CH), 34.4 (CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}C=CH), 44.0 (CH), 59.5 (C\textsuperscript{6}), 84.0 (C\textsuperscript{6}), 124.5 (C=CH), 126.2 (ArCH), 126.8 (ArCH), 128.0 (2 × ArCH), 128.2 (2 × ArCH), 128.4 (2 × ArCH), 128.8 (2 × ArCH), 129.1 (2 × ArCH), 129.2 (2 × ArCH), 141.3 (ArC\textsuperscript{6}), 141.6 (ArC\textsuperscript{6}), 141.8 (ArC\textsuperscript{6}), 141.9 (ArC\textsuperscript{6}), 182.0 (C=O), 182.2 (C=O);
129.1 (2 × ArCH), 129.2 (ArCH), 132.1 (ArCH), 132.2 (C=CH), 134.5 (ArC\(^6\)), 137.9 (ArC\(^6\)), 138.0 (ArC\(^6\)), 141.1 (ArC\(^6\)), 182.3 (C=O);

\(m/z\) (ES\(−\)) 429 ((M − H), 100%), 431 (63). (Found: (M − H) 429.1019. C\(_{24}\)H\(_{23}\)O\(_3\)Cl\(_2\) requires \(M\), 429.1029).

4.5. General procedure E – Esterification/oxidation sequences

\[\textit{rac-}(1R,3S)-\text{Methyl 3-benzyl-1-(cyclohexylmethyl)-2-oxocyclopentanecarboxylate (202)}\]

To a stirred solution of the four diastereoisomers of 3-benzyl-1-(cyclohexylmethyl)-2-hydroxycyclopentanecarboxylic acid 201 (33 mg, 104 \(\mu\)mol, 1.0 eq) in MeOH (4.0 mL) and toluene (1.0 mL), was added dropwise trimethylsilyl diazomethane (2 M in hexane, 0.115 mL, 229 \(\mu\)mol, 2.2 eq) and the reaction stirred during 1 hour. The solvent was removed \textit{in vacuo} and the crude product redissolved in CH\(_2\)Cl\(_2\) (5.0 mL). Dess–Martin periodinane (65 mg, 155 \(\mu\)mol, 1.6 eq) was added and the reaction stirred during 1.5 hours then quenched with water (15 mL). The aqueous phase was extracted with CH\(_2\)Cl\(_2\) (3 × 10 mL) and the combined organic phases dried (Na\(_2\)SO\(_4\) or MgSO\(_4\)) and concentrated \textit{in vacuo}. Purification by column chromatography on silica gel, eluting with 5% ethyl acetate in hexane gave \textit{rac-}(1R,3S)-methyl 3-benzyl-1-(cyclohexylmethyl)-2-oxocyclopentanecarboxylate (30 mg, 92 \(\mu\)mol, 88%) as a colourless oil and as mixture of diastereoisomers of which 202 was the major (12:1).

\(\nu_{\text{max}}\) (evap. film)/cm\(^{-1}\) 2923, 2850, 2362, 1747 (C=O), 1721 (C=O), 1450, 1210, 912, 699;

\(^1\)H NMR (400 MHz, CDCl\(_3\)) ppm 0.97 - 1.10 (2 H, m, CH\(_2\) from Cy), 1.14 - 1.36 (2 H, m, CH\(_2\) from Cy), 1.35 - 1.49 (1 H, m, CH from Cy), 1.56 (1 H, dd, \(J = 14.1, 6.6\) Hz, 1 H from CH\(_2\)Cy), 1.61 - 1.88 (8 H, m, 6H from Cy, 1 H from CHCH\(_2\)CH\(_2\), 1 H from CHCH\(_2\)CH\(_2\)), 2.09 - 2.17 (1 H, m, 1 H from CHCH\(_2\)CH\(_2\)), 2.20 (1 H, dd, \(J = 14.1, 6.6\) Hz, 1 H from CH\(_2\)Cy), 2.51 - 2.66 (1 H, m, CHCH\(_2\)Ph), 2.67 - 2.75 (2 H, m, 1 H from CH\(_2\)Ph, 1 H from CHCH\(_2\)CH\(_2\)), 3.27 (1 H, dd, \(J = 13.5, 3.9\) Hz, 1 H from CH\(_2\)Ph), 3.74 (3 H, s, OCH\(_3\)), 7.27 (5 H, 5 Ar-H);
13C NMR (100 MHz, CDCl₃) ppm 26.1 (CH₂ from Cy), 26.2 (2 × CH₂ from Cy), 26.4 (CH₂ from Cy), 30.9 (CHCH₂CH₂), 33.5 (CH₂ from Cy), 34.1 (CH₂ from Cy), 34.8 (CH from Cy), 36.3 (CH₂Ar), 42.5 (CCH₂), 50.9 (CHCH₂Ar), 52.5 (OCH₃), 61.2 (C₈), 126.2 (ArCH), 128.3 (2 × ArCH), 129.0 (2 × ArCH), 139.4 (ArC₈), 170.9 (COOCH₃), 214.9 (C=O);

m/z (ES+) 346 (28%), 351 ((M + Na) 100), 383 (34); (Found: (M + Na) 351.1931. C₂₁H₂₈O₃Na requires M, 351.1917).

Methyl 3-benzyl-1-(cyclohexylmethyl)-2-oxocyclohexanecarboxylate (236)

As for general procedure E, reaction of the four diastereoisomers of 3-benzyl-1-(cyclohexylmethyl)-2-hydroxycyclohexanecarboxylic acid 235 (64 mg, 0.19 mmol, 1.0 eq) and trimethylsilyl diazomethane (2 M in hexane, 0.25 mL, 0.5 mmol, 2.6 eq) in MeOH (4.5 mL) and toluene (1.2 mL) followed by reaction with Dess–Martin periodinane (135 mg, 0.32 mmol, 1.6 eq) in CH₂Cl₂ (5.5 mL) gave after purification by column chromatography (5% ethyl acetate in hexane) methyl 3-benzyl-1-(cyclohexylmethyl)-2-oxocyclohexanecarboxylate 236 as a yellow oil and as a mixture of diastereoisomers, of which a single diastereoisomer was isolated (22 mg, 0.064 mmol, 33%).

νmax (neat)/cm⁻¹ 2922, 2851, 1712 (C=O), 1604, 1495, 1448, 1273, 1244, 1210, 1176, 1150, 1119, 1075, 1030, 1003, 948, 880, 827, 746, 699;

¹H NMR (400 MHz, CDCl₃) δ ppm 0.83 - 1.02 (2 H, m, 2 H from Cy), 1.08 - 1.44 (5 H, m, 3 H from Cy, CH from Cy, 1 H from CH₂), 1.48 (1 H, dd, J = 14.2, 5.2 Hz, 1 H from CCH₂Cy), 1.53 - 1.67 (6 H, m, 5 H from Cy, 1 H from CH₂), 1.68 - 1.74 (2 H, m, 2 H from CH₂), 1.85 (1 H, dd, J = 14.2, 6.1 Hz, 1 H from CCH₂Cy), 1.94 - 2.02 (1 H, m, 1 H from CH₂), 2.44 (1 H, dd, J = 14.1, 8.1 Hz, 1 H from ArCH₂), 2.56 - 2.70 (2 H, m, ArCH₂CH, 1 H from CH₂), 3.23 (1 H, dd, J = 14.1, 5.3 Hz, 1 H from ArCH₂), 3.67 (3 H, s, CH₃), 7.11 - 7.22 (3 H, m, 3 × ArH), 7.23 - 7.31 (2 H, m, 2 × ArH);

¹³C NMR (100 MHz, CDCl₃) δ ppm 22.6 (CH₂), 26.1 (CH₂ from Cy), 26.3 (CH₂ from Cy), 26.4 (CH₂ from Cy), 33.4 (CH from Cy), 34.2 (CH₂ from Cy), 34.4 (CH₂), 35.1 (CH₂ from Cy), 35.5 (ArCH₂), 37.4 (CH₂), 42.3 (CCH₂Cy), 51.5 (ArCH₂CH), 52.0 (CH₃), 60.8 (C₈), 61.2 (OCH₃), 126.2 (ArCH), 128.3 (2 × ArCH), 129.0 (2 × ArCH), 139.4 (ArC₈), 170.9 (COOCH₃), 214.9 (C=O);
125.9 (ArCH), 128.2 (2 × ArCH), 128.9 (2 × ArCH), 140.2 (ArC\textsuperscript{q}), 172.9 (C=O), 208.4 (C=O); 

\textbf{m/z} (ES+) 365 ((M + Na), 100%), 366 (23), 413 (20). (Found: (M + Na) 365.2083. C\textsubscript{22}H\textsubscript{30}O\textsubscript{3}Na requires \textit{M}, 365.2087).

### 4.6. Miscellaneous procedures

![Diagram](image)

\textbf{5-(But-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (250)}

To a stirred solution of diethyl 2-(but-3-en-1-yl)malonate 249 (11.5 g, 53.8 mmol, 1.0 eq) in MeOH (230 mL) and H\textsubscript{2}O (76 mL), NaOH (10.9 g, 272 mmol, 5.1 eq) was added and the solution stirred at 85°C overnight. The reaction was quenched with HCl (36%, 24 mL), the volume reduced to ~50 mL \textit{in vacuo}, and the aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried (Na\textsubscript{2}SO\textsubscript{4} or MgSO\textsubscript{4}) and concentrated \textit{in vacuo}. To the residue was added isopropenyl acetate (6.75 mL, 61.3 mmol, 1.1 eq) and the suspension stirred during 10 minutes. H\textsubscript{2}SO\textsubscript{4} (30 drops) was subsequently added over 30 minutes and the reaction stirred at room temperature during 3 hours. Purification by column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40-60 °C) gave 5-(but-3-enyl)-2,2-dimethyl-1,3-dioxane-4,6-dione 250 (7.54 g, 38.0 mmol, 71%) as a white solid.

\textbf{mp} 64-66 °C;

\textbf{\textit{v}}\textsubscript{max} (neat)/cm\textsuperscript{-1} 3081, 2997, 2977, 2947, 2882, 1787, 1743 (C=O), 1640, 1454, 1377, 1335, 1279, 1248, 1204, 1119, 1056, 995, 970, 935, 901, 870, 854, 698, 645;

\textbf{\textit{H}} NMR (400 MHz, CDCl\textsubscript{3}) \textit{δ} ppm 1.76 (3 H, d, \textit{J} = 0.5 Hz, CH\textsubscript{3}), 1.79 (3 H, d, \textit{J} = 0.5 Hz, CH\textsubscript{3}), 2.19 - 2.27 (2 H, m, CHCH\textsubscript{2}), 2.27 - 2.35 (2 H, m, CH\textsubscript{2}CH=CH\textsubscript{2}), 3.54 (1 H, t, \textit{J} = 5.0 Hz, CH), 5.04 - 5.13 (2 H, m, CH=CH\textsubscript{2}), 5.79 (1 H, ddt, \textit{J} = 17.1, 10.3, 6.6 Hz, CH=CH\textsubscript{2});

\textbf{\textit{C}} NMR (100 MHz, CDCl\textsubscript{3}) \textit{δ} ppm 25.2 (CHCH\textsubscript{2}), 26.7 (CH\textsubscript{3}), 28.4 (CH\textsubscript{3}), 30.6 (CH\textsubscript{2}CH=CH\textsubscript{2}), 44.9 (CH), 104.9 (OCO), 116.7 (CH=CH\textsubscript{2}), 136.7 (CH=CH\textsubscript{2}), 165.5 (2 × C=O);

\textbf{m/z} (ES−) 197 ((M − H), 100%). (Found: (M − H) 197.0811. C\textsubscript{10}H\textsubscript{13}O\textsubscript{4} requires \textit{M}, 197.0819).
 rac-(3S,3aR,4S,6aS)-3-Benzyl-4-(2,4-dichlorobenzyl)hexahydro-3a,6a-(epoxymethano)pentalen-7-one (273)

To a stirred solution of rac-(1S,3aS,6S,6aR)-1-benzyl-6-(2,4-dichlorobenzyl)-6a-hydroxyoctahydropentalene-3a-carboxylic acid 263f (23 mg, 54.9 μmol, 1.0 eq) and benzoyl chloride (7.0 μL, 60.3 μmol, 1.1 eq) in THF (1.0 mL), triethylamine (16.0 μL, 115 μmol, 2.1 eq) was added dropwise. 4-Dimethylaminopyridine (3.0 mg, 23.0 μmol, 0.4 eq) was then added and the reaction stirred at room temperature during 20 hours. The reaction was quenched with HCl (1 N, 1.0 mL), H₂O added (4.0 mL), and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 5% ethyl acetate in hexane gave rac-(3S,3aR,4S,6aS)-3-benzyl-4-(2,4-dichlorobenzyl)hexahydro-3a,6a-(epoxymethano)pentalen-7-one 273 (19 mg, 47.3 μmol, 86%) as a white solid.

mp 129-131 °C;
νmax (neat)/cm⁻¹ 3084, 3059, 3023, 2954, 2863, 1817 (C=O), 1587, 1559, 1472, 1453, 1382, 1263, 1178, 1119, 1050, 1030, 846, 819, 738, 699;

¹H NMR (400 MHz, CDCl₃) δ ppm 1.43 - 1.50 (1 H, m, 1 H from CH₂CH₂CH), 1.50 - 1.56 (1 H, m, 1 H from CH₂CH₂CH), 1.75 - 1.83 (1 H, m, 1 H from CH₂CH₂CH), 1.87 - 1.96 (1 H, m, 1 H from CH₂Ar), 1.99 - 2.09 (3 H, m, CH, 1 H from CH₂CH₂CH, 1 H from CH₂CH₂CH), 2.09 - 2.15 (2 H, m, 1 H from CH₂Ar, 1 H from CH₂CH₂CH), 2.15 - 2.22 (1 H, m, 1 H from CH₂CH₂CH), 2.33 (1 H, dt, J = 12.9, 6.4 Hz, 1 H from CH₂CH₂CH), 2.54 - 2.64 (1 H, m, CH), 2.89 (1 H, dd, J = 13.2, 9.8 Hz, 1 H from CH₂Ar), 3.06 (1 H, dd, J = 13.2, 5.5 Hz, 1 H from CH₂Ar), 6.69 - 6.74 (2 H, m, 2 × ArH), 7.15 - 7.21 (1 H, m, ArH), 7.22 - 7.26 (2 H, m, 2 × ArH), 7.28 - 7.32 (2 H, m, 2 × ArH), 7.41 (1 H, d, J = 1.5 Hz, ArH);

¹³C NMR (100 MHz, CDCl₃) δ ppm 27.2 (CH₂CH₂CH), 29.3 (CH₂CH₂CH), 32.2 (CH₂CH), 32.8 (CH₂Ar), 35.2 (CH₂Ar), 36.4 (CH₂CH), 38.9 (CH), 42.9 (CH), 75.8 (C₄), 100.2 (C₅), 126.3 (ArCH), 127.2 (ArCH), 128.5 (2 × ArCH), 128.8 (2 × ArCH), 129.4 (ArCH), 132.7 (ArCH), 133.3 (ArC₅), 134.8 (ArC₅), 136.4 (ArC₅), 139.3 (ArC₅), 174.1 (C=O);
5. Experimental data for chapter 2: barbituric acid

5.1. General procedure A – Condensations

5-(1-Hydroxy-2-(4-methoxyphenyl)ethylidene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (288e)

To a stirred solution of 1,3-dimethylbarbituric acid (1.56 g, 10.0 mmol, 1.0 eq), 2-(4-methoxyphenyl)acetic acid (1.49 g, 15.0 mmol, 1.5 eq) and 4-dimethylaminopyridine (611 mg, 5.0 mmol, 0.5 eq) in CH$_2$Cl$_2$ (10 mL) at 0 °C was added dicyclohexylcarbodiimide (2.27 g, 11.0 mmol, 1.1 eq) and the reaction stirred at room temperature overnight. The reaction mixture was filtered and the residue washed with HCl (1 N, 2 × 10 mL). Recrystallization in MeOH gave 5-(1-hydroxy-2-(4-methoxyphenyl)ethylidene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 288e (2.79 g, 9.2 mmol, 92%) as a white solid.

** mp 125-127 °C;**

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3002, 2956, 2837, 1722 (C=O), 1663 (C=O), 1551, 1489, 1445, 1347, 1300, 1246, 1179, 1028, 888, 801, 756, 673;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 3.34 (6 H, s, 2 × NCH$_3$), 3.78 (3 H, s, OCH$_3$), 4.43 (2 H, s, CH$_2$), 6.85 (2 H, d, $J = 8.6$ Hz, 2 × ArH), 7.31 (2 H, d, $J = 8.6$ Hz, 2 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 27.8 (NCH$_3$), 28.0 (NCH$_3$), 40.8 (CH$_2$), 55.1 (OCH$_3$), 95.0 (C=CO), 113.9 (2 × ArCH), 126.2 (ArC$^6$), 130.6 (2 × ArCH), 150.2 (ArC$^6$), 158.8 (C=O), 160.7 (C=O), 169.8 (C=O), 196.5 (C=CO);

$m/z$ (ES$^-$) 303 ((M − H), 100%). (Found: (M − H) 303.0984. C$_{15}$H$_{15}$N$_2$O$_5$ requires $M$, 303.0986);

Anal (Found: C, 59.19; H, 5.18; N, 9.14; C$_{15}$H$_{16}$N$_2$O$_5$ requires C, 59.21; H, 5.30; N, 9.21%).
5-(1-Hydroxy-3-methylbutylidene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (288c)

As for general procedure A, reaction of 1,3-dimethylbarbituric acid (1.56 g, 10.0 mmol, 1.0 eq), isovaleric acid (1.7 mL, 15.0 mmol, 1.5 eq), 4-dimethylaminopyridine (611 mg, 5.0 mmol, 0.5 eq) and dicyclohexylcarbodiimide (2.27 g, 11.0 mmol, 1.1 eq) in CH$_2$Cl$_2$ (10 mL) gave after crystallization of the impurities out of petroleum ether (40-60 °C) 5-(1-hydroxy-3-methylbutylidene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 288c (2.40 g, 10.0 mmol, quantitative) as an orange oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2958, 2930, 2870, 1723 (C=O), 1669, 1553, 1489, 1448, 1359, 1271, 1218, 1056, 1015, 886, 788, 755;

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.01 (6 H, d, $J = 6.6$ Hz, 2 × CHC$_3$), 2.13 - 2.26 (1 H, m, CHCH$_3$), 3.02 (2 H, d, $J = 7.1$ Hz, CH$_2$CH), 3.32 (3 H, s, NCH$_3$), 3.36 (3 H, s, NCH$_3$);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 22.6 (2 × CHC$_3$), 26.8 (CHCH$_3$), 27.8 (NCH$_3$), 28.0 (NCH$_3$), 45.0 (CH$_2$CH), 95.6 (C=CO), 150.3 (C=O), 160.9 (C=O), 169.8 (C=O), 199.2 (C=CO);

m/z (ES−) 239 ((M − H), 100%). (Found: (M − H) 239.1043. C$_{11}$H$_{15}$N$_2$O$_4$ requires $M$, 239.1037).

5-(1-Hydroxy-2-(4-(trifluoromethyl)phenyl)ethylidene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (288f)

As for general procedure A, reaction of 1,3-dimethylbarbituric acid (1.56 g, 10.0 mmol, 1.0 eq), 2-(4-trifluoromethylphenyl)acetic acid (3.06 g, 15.0 mmol, 1.5 eq), 4-dimethylaminopyridine (611 mg, 5.0 mmol, 0.5 eq) and dicyclohexylcarbodiimide (2.27 g, 11.0 mmol, 1.1 eq) in CH$_2$Cl$_2$ (10 mL) gave after recrystallization in MeOH 5-(1-hydroxy-2-(4-(trifluoromethyl)phenyl)ethylidene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 288f (2.48 g, 7.2 mmol, 72%) as a white solid.

mp 124-126 °C;
ν\text{max} (neat)/cm^{-1} 2923, 2854, 2360, 2334, 1726 (C=O), 1670 (C=O), 1558, 1493, 1452, 1324, 1166, 1124, 1067, 1016;

\textbf{^1H NMR} (400 MHz, CDCl\textsubscript{3}) δ ppm 3.34 (3 H, s, NCH\textsubscript{3}), 3.36 (3 H, s, NCH\textsubscript{3}), 4.55 (2 H, s, CH\textsubscript{2}), 7.51 (2 H, d, J = 8.1 Hz, 2 × ArH), 7.58 (2 H, d, J = 8.1 Hz, 2 × ArH);

\textbf{^13C NMR} (100 MHz, CDCl\textsubscript{3}) δ ppm 27.9 (NCH\textsubscript{3}), 28.1 (NCH\textsubscript{3}), 41.6 (CH\textsubscript{2}), 95.4 (C=CO), 124.1 (q, J\textsubscript{1} = 272.3 Hz, CF\textsubscript{3}), 125.5 (q, J\textsubscript{3} = 3.7 Hz, 2 × ArCH), 129.5 (q, J\textsubscript{2} = 32.3 Hz, ArC\textsuperscript{6}), 130.0 (2 × ArCH), 138.3 (ArC\textsuperscript{6}), 150.1 (C=O), 160.7 (C=O), 169.8 (C=O), 195.1 (C=CO);

\textit{m/z} (ES−) 341 ((M − H), 100%). (Found: (M − H) 341.0738. C\textsubscript{15}H\textsubscript{12}N\textsubscript{2}O\textsubscript{4}F\textsubscript{3} requires M, 341.0754);

\textbf{Anal} (Found: C, 52.71; H, 3.53; N, 8.17; C\textsubscript{15}H\textsubscript{13}N\textsubscript{2}O\textsubscript{4}F\textsubscript{3} requires C, 52.64; H, 3.83; N, 8.18%).

5-(2-(4-Bromophenyl)-1-hydroxyethylidene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (288g)

As for general procedure A, reaction of 1,3-dimethylbarbituric acid (1.56 g, 10.0 mmol, 1.0 eq), 2-(4-bromophenyl)acetic acid (3.23 g, 15.0 mmol, 1.5 eq), 4-dimethylaminopyridine (611 mg, 5.0 mmol, 0.5 eq) and dicyclohexylcarbodiimide (2.27 g, 11.0 mmol, 1.1 eq) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) gave after recrystallization in MeOH 5-(2-(4-bromophenyl)-1-hydroxyethylidene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 288g (3.31 g, 9.4 mmol, 94%) as a white solid.

\textbf{mp} 143-145 °C;

ν\text{max} (neat)/cm^{-1} 2956, 2923, 1715 (C=O), 1661 (C=O), 1542, 1491, 1406, 1377, 1340, 1270, 1230, 1011, 953, 884, 855, 810, 780, 752;

\textbf{^1H NMR} (400 MHz, CDCl\textsubscript{3}) δ ppm 3.33 (3 H, s, NCH\textsubscript{3}), 3.35 (3 H, s, NCH\textsubscript{3}), 4.43 (2 H, s, CH\textsubscript{2}), 7.26 (2 H, d, J = 8.3 Hz, 2 × ArH), 7.43 (2 H, d, J = 8.3 Hz, 2 × ArH);

\textbf{^13C NMR} (100 MHz, CDCl\textsubscript{3}) δ ppm 28.0 (NCH\textsubscript{3}), 28.2 (NCH\textsubscript{3}), 41.2 (CH\textsubscript{2}), 95.3 (C=CO), 121.4 (ArC\textsuperscript{6}), 131.4 (2 × ArCH), 131.7 (2 × ArCH), 133.3 (ArC\textsuperscript{6}), 150.2 (C=O), 160.8 (C=O), 169.9 (C=O), 195.5 (C=CO);

\textit{m/z} (ES−) 351 ((M − H), 100%), 353 (100). (Found: (M − H) 350.9976. C\textsubscript{14}H\textsubscript{12}N\textsubscript{2}O\textsubscript{4}Br requires M, 350.9985);
**5.2. General procedure B – NaBH₃CN reductions**

5-Isopentyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (285c)

To a stirred solution of 5-(1-hydroxy-3-methylbutyldiene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 288c (2.00 g, 8.32 mmol, 1.0 eq) in acetic acid (10 mL) was slowly added NaBH₃CN (1.57 g, 25.0 mmol, 3.0 eq) and the reaction mixture stirred at room temperature for 3 hours. H₂O (40 mL) and HCl (37%, 2.0 mL) were added and the aqueous phase extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated *in vacuo* then the residue dissolved in chloroform, filtered and concentrated *in vacuo* to give 5-isopentyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285c (1.74 g, 7.69 mmol, 92%) as a colourless oil.

ν\(_{\text{max}}\) (neat)/cm\(^{-1}\) 2954, 2868, 1673 (C=O), 1446, 1422, 1375, 1320, 1274, 1149, 1087, 994, 755;

\(^1\)H NMR (400 MHz, CDCl₃) δ ppm 0.86 (6 H, d, \(J = 6.6\) Hz, 2 × CHC\(_3\)H), 1.08 - 1.17 (2 H, m, CH₂CHCH₃), 1.46 - 1.58 (1 H, m, CHCH₃), 2.07 - 2.16 (2 H, m, C(O)CHCH₂), 3.30 (6 H, s, 2 × NCH₃), 3.48 (1 H, t, \(J = 5.3\) Hz, C(O)CH);

\(^{13}\)C NMR (100 MHz, CDCl₃) δ ppm 22.2 (2 × CHCH₃), 27.9 (CHCH₃), 28.5 (2 × NCH₃), 29.3 (C(O)CHCH₂), 34.6 (CH₂CHCH₃), 49.0 (C(O)CH), 151.6 (C=O), 168.7 (2 × C=O);

\(m/z\) (APCI+) 158 (100%), 227 ((M + H), 87), 243 (21), 315 (16). (Found: (M + H) 227.1384. C\(_{11}\)H\(_{19}\)N\(_2\)O\(_3\) requires \(M\), 227.1390).

5-(4-Methoxyphenethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (285e)

As for general procedure B, reaction of 5-(1-hydroxy-2-(4-methoxyphenyl)ethylidene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 288e (2.00 g, 6.57 mmol, 1.0 eq) and NaBH₃CN (1.24 g, 19.7 mmol, 3.0 eq) in acetic acid (10 mL) gave after extraction and
filtration 5-(4-methoxyphenethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione \textbf{285e} (1.91 g, 6.57 mmol, quantitative) as an opaque oil.

\( \nu \)\textsubscript{max} (neat)/cm\(^{-1}\) 3206 (br.), 2950, 2837, 1676 (C=O), 1511, 1446, 1421, 1378, 1286, 1245, 1181, 1098, 1034, 815, 754;

\( ^1^H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) ppm 2.47 (2 H, dt, \( J = 8.2, 6.1 \) Hz, CHCH\(_2\)), 2.61 - 2.68 (2 H, m, CH\(_2\)Ar), 3.22 (6 H, s, 2 × NCH\(_3\)), 3.46 (1 H, t, \( J = 5.4 \) Hz, CH), 3.77 (3 H, s, OCH\(_3\)), 6.80 (2 H, d, \( J = 8.7 \) Hz, 2 × ArH), 7.05 (2 H, d, \( J = 8.7 \) Hz, 2 × ArH);

\( ^13^C \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) ppm 28.4 (2 × NCH\(_3\)), 31.1 (CH\(_2\)Ar), 31.7 (CHCH\(_2\)), 47.7 (CH), 55.2 (OCH\(_3\)), 113.8 (2 × ArCH), 129.7 (2 × ArCH), 131.2 (ArC\( ^q \)), 151.3 (ArC\( ^q \)), 158.1 (C=O), 168.3 (2 × C=O);

\( m/z \) (ES+) 291 ((M + H), 100%). (Found: (M + H) 291.1348. C\(_{15}\)H\(_{19}\)N\(_2\)O\(_3\) requires \( M \), 291.1340).

1,3-Dimethyl-5-(4-(trifluoromethyl)phenethyl)pyrimidine-2,4,6(1H,3H,5H)-trione \textbf{(285f)}

As for general procedure B, reaction of 5-(1-hydroxy-2-(4-(trifluoromethyl)phenyl)ethylidene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione \textbf{288f} (2.00 g, 5.84 mmol, 1.0 eq) and NaBH\(_3\)CN (1.10 g, 17.5 mmol, 3.0 eq) in acetic acid (10 mL) gave after crystallization in the freezer overnight 1,3-dimethyl-5-(4-(trifluoromethyl)phenethyl)pyrimidine-2,4,6(1H,3H,5H)-trione \textbf{285f} (1.83 g, 5.57 mmol, 95%) as a white solid.

\( \text{mp} \) 63-65 °C;

\( \nu \)\textsubscript{max} (neat)/cm\(^{-1}\) 2953, 2864, 1674 (C=O), 1445, 1422, 1378, 1322, 1284, 1161, 1113, 1065, 1019, 833, 756, 636;

\( ^1^H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 2.47 - 2.54 (2 H, m, CHCH\(_2\)), 2.76 - 2.82 (2 H, m, CH\(_2\)Ar), 3.28 (6 H, s, 2 × NCH\(_3\)), 3.49 (1 H, t, \( J = 5.4 \) Hz, CH), 7.31 (2 H, d, \( J = 8.1 \) Hz, 2 × ArH), 7.55 (2 H, d, \( J = 8.1 \) Hz, 2 × ArH);

\( ^13^C \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm 28.6 (2 × NCH\(_3\)), 31.0 (CHCH\(_2\)), 32.0 (CH\(_2\)Ar), 47.8 (CH), 124.2 (q, \( J = 272.3 \) Hz, CF\(_3\)), 125.5 (q, \( J = 3.7 \) Hz, 2 × ArCH), 128.9 (q, \( J = 32.3 \) Hz, ArC\( ^q \)), 129.0 (2 × ArCH), 143.8 (ArC\( ^q \)), 151.3 (C=O), 168.1 (2 × C=O);
5-(4-Bromophenethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (285g)

As for general procedure B, reaction of 5-(2-(4-bromophenethyl)-1-hydroxyethylidene)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 288g (3.00 g, 8.49 mmol, 1.0 eq) and NaBH₃CN (1.60 g, 25.5 mmol, 3.0 eq) in acetic acid (10 mL) gave after extraction and filtration 5-(4-bromophenethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285g (2.67 g, 7.87 mmol, 93%) as a white solid.

\[ \text{mp 52-54 °C; } \]
\[ \nu_{\text{max}} \text{(neat)/cm}^{-1} 3402 \text{ (br.), 3226 (br.), 2948, 1674 (C=O), 1445, 1425, 1379, 1101, 1011, 817, 755, 709, 635; } \]

\[ \text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3 \delta \text{ ppm 2.42 - 2.49 (2 H, m, CHCH}_2, 2.63 - 2.70 (2 H, m, CH}_2\text{Ar), 3.25 (6 H, s, 2 × NCH}_3, 3.46 (1 H, t, J = 5.4 Hz, CH), 7.05 (2 H, d, J = 8.4 Hz, 2 × ArH), 7.39 (2 H, d, J = 8.4 Hz, 2 × ArH); } \]

\[ \text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3 \delta \text{ ppm 28.5 (2 × NCH}_3, 31.2 (CHCH}_2, 31.6 (CH}_2\text{Ar), 47.7 (CH), 120.3 (ArC}_\gamma, 130.4 (2 × ArCH), 131.5 (2 × ArCH), 138.5 (ArC}_\delta, 151.3 (\text{C=O), 168.1 (2 × C=O); } \]

\[ \text{m/z (ES–) 337 ((M – H), 98%), 339 ((M – H), 100). (Found: (M + Na) 361.0143. C}_{14}\text{H}_{15}\text{N}_2\text{O}_3\text{BrNa requires } M, 361.0158); } \]

\[ \text{Anal (Found: C, 49.53; H, 4.47; N, 8.27; Br, 23.48; C}_{14}\text{H}_{15}\text{N}_2\text{O}_3\text{Br requires C, 49.57; H, 4.46; N, 8.26; Br, 23.56%). } \]
5.3. General procedure C – Alkylations

\[ \text{5-(4-Methoxyphenethyl)-1,3,5-trimethylpyrimidine-2,4,6(1H,3H,5H)-trione (285k)} \]

To a stirred solution of 5-(4-methoxyphenethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285e (500 mg, 1.72 mmol, 1.0 eq) in acetone (2.6 mL) were added methyl iodide (1.6 mL, 17.2 mmol, 10 eq) and K₂CO₃ (475 mg, 3.44 mmol, 2.0 eq) and the reaction mixture stirred at 50 °C for 24 hours. H₂O (3.0 mL) was added, the aqueous phase extracted with ethyl acetate (3 × 3.0 mL) and the combined organic phases dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) gave 5-(4-methoxyphenethyl)-1,3,5-trimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285k (523 mg, 1.72 mmol, quantitative) as a light yellow oil.

\[ \nu_{\text{max}} \text{(neat)/cm}^{-1} \text{ 2938, 2834, 1673 (C=O), 1511, 1444, 1421, 1381, 1281, 1245, 1178, 1064, 1033, 913, 821, 749; } \]

\[ \delta_{\text{ppm}}^{1\text{H NMR}} \text{ (500 MHz, CDCl}_3\text{) 1.52 (3 H, s, CCH}_3\text{), 2.32 (1 H, d, } J = 10.2 \text{ Hz, 1 H from CCH}_2\text{), 2.33 (1 H, d, } J = 8.8 \text{ Hz, 1 H from CCH}_2\text{), 2.42 (1 H, d, } J = 8.8 \text{ Hz, 1 H from CH}_2\text{Ar), 2.43 (1 H, d, } J = 10.2 \text{ Hz, 1 H from CH}_2\text{Ar), 2.22 (6 H, s, 2 × NCH}_3\text{), 3.76 (3 H, s, OCH}_3\text{), 6.77 (2 H, d, } J = 8.6 \text{ Hz, 2 × ArH), 6.97 (2 H, d, } J = 8.6 \text{ Hz, 2 × ArH); } \]

\[ \delta_{\text{ppm}}^{13\text{C NMR}} \text{ (125 MHz, CDCl}_3\text{) 25.7 (CCH}_3\text{), 28.5 (2 × NCH}_3\text{), 30.8 (CH}_2\text{Ar), 40.3 (CCH}_2\text{), 51.0 (C}^6\text{), 55.2 (OCH}_3\text{), 113.7 (2 × ArCH), 129.4 (2 × ArCH), 131.3 (ArC}^6\text{), 150.9 (C=O), 158.1 (ArC}^6\text{), 172.0 (2 × C=O); } \]

\[ m/z \text{ (ES+) 287 (66%), 321 (60), 327 ((M + Na), 100), 337 (51). (Found: (M + NH}_4\text{) 322.1764, C}_{16}\text{H}_{24}\text{N}_3\text{O}_4 \text{ requires } M, 322.1761). } \]
1,3,5-Trimethyl-5-(4-(trifluoromethyl)phenethyl)pyrimidine-2,4,6(1H,3H,5H)-trione (285l)

As for general procedure C, reaction of 1,3-dimethyl-5-(4-(trifluoromethyl)phenethyl)pyrimidine-2,4,6(1H,3H,5H)-trione 285f (500 mg, 1.52 mmol, 1.0 eq), methyl iodide (1.4 mL, 15.2 mmol, 10 eq) and K₂CO₃ (422 mg, 3.05 mmol, 2.0 eq) in acetone (2.3 mL) gave after column chromatography (20% ethyl acetate in petroleum ether (40-60 °C)) 1,3,5-trimethyl-5-(4-(trifluoromethyl)phenethyl)pyrimidine-2,4,6(1H,3H,5H)-trione 285l (520 mg, 1.52 mmol, quantitative) as a light yellow oil.

νmax (neat)/cm⁻¹ 2941, 2862, 1676 (C=O), 1447, 1422, 1383, 1322, 1282, 1162, 1114, 1064, 1018, 914, 842, 823, 753, 632;

¹H NMR (400 MHz, CDCl₃) δ ppm 1.56 (3 H, s, CCH₃), 2.35 (1 H, d, J = 11.1 Hz, 1 H from CCH₂), 2.37 (1 H, d, J = 9.1 Hz, 1 H from CCH₂), 2.51 (1 H, d, J = 9.1 Hz, 1 H from CH₂Ar), 2.53 (1 H, d, J = 11.1 Hz, 1 H from CH₂Ar), 2.57 (6 H, s, 2 × NCH₃), 7.22 (2 H, d, J = 8.1 Hz, 2 × ArH), 7.51 (2 H, d, J = 8.1 Hz, 2 × ArH);

¹³C NMR (100 MHz, CDCl₃) δ ppm 26.1 (C₃H₇), 28.6 (2 × NCH₃), 31.5 (CH₂Ar), 39.7 (CCH₂), 51.2 (C⁹), 124.1 (q, J′ = 271.3 Hz, CF₃), 125.3 (q, J″ = 3.7 Hz, 2 × ArCH), 128.8 (2 × ArCH), 128.8 (q, J″ = 32.3 Hz, ArC⁹), 143.8 (ArC⁹), 150.8 (C=O), 171.8 (2 × C=O);
m/z (ES+) 287 (100%), 321 (81), 337 (63), 365 ((M + Na), 18), 413 (95). (Found: (M + NH₄) 360.1532. C₁₆H₂₁N₃O₃F₃ requires M, 360.1530).

5-(4-Bromophenethyl)-1,3,5-trimethylpyrimidine-2,4,6(1H,3H,5H)-trione (285m)

As for general procedure C, reaction of 5-(4-bromophenethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285g (500 mg, 1.47 mmol, 1.0 eq), methyl iodide (1.4 mL, 14.7 mmol, 10 eq) and K₂CO₃ (408 mg, 2.95 mmol, 2.0 eq) in acetone (2.2 mL) gave after column chromatography (20% ethyl acetate in petroleum ether (40-60 °C)) 5-(4-
bromophenethyl)-1,3,5-trimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285m (519 mg, 1.47 mmol, quantitative) as a light yellow oil.

νmax (neat)/cm⁻¹ 2937, 2862, 1677 (C=O), 1446, 1420, 1382, 1283, 1143, 1067, 1011, 832, 809, 754;

¹H NMR (400 MHz, CDCl₃) δ ppm 1.54 (3 H, s, CCH₃), 2.31 (1 H, d, J = 11.1 Hz, 1 H from CCH₂), 2.32 (1 H, d, J = 9.2 Hz, 1 H from CCH₂), 2.41 (1 H, d, J = 9.2 Hz, 1 H from CH₂Ar), 2.42 (1 H, d, J = 11.1 Hz, 1 H from CH₂Ar), 3.26 (6 H, s, 2 × NCH₃), 6.96 (2 H, d, J = 8.3 Hz, 2 × ArH), 7.36 (2 H, d, J = 8.3 Hz, 2 × ArH);

¹³C NMR (100 MHz, CDCl₃) δ ppm 26.0 (CCH₃), 28.6 (2 × NCH₃), 31.1 (CH₂Ar), 40.1 (CCH₂), 51.1 (C₆), 120.2 (ArC₆), 130.2 (2 × ArCH), 131.4 (2 × ArCH), 138.5 (ArC₆), 150.8 (C=O), 171.9 (2 × C=O);

m/z (EI⁺) 352 ((M), 100%). (Found: M 352.0405. C₁₅H₁₇N₂O₃⁷⁹Br requires M, 352.0417).

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5-Isopentyl-1,3,5-trimethylpyrimidine-2,4,6(1H,3H,5H)-trione (285n)

As for general procedure C, reaction of 5-isopentyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285c (240 mg, 1.00 mmol, 1.0 eq), methyl iodide (1.0 mL, 10.0 mmol, 10 eq), tetrabutylammonium bisulfate (34 mg, 0.10 mmol, 0.1 eq) and K₂CO₃ (277 mg, 2.00 mmol, 2.0 eq) in DMF (2.5 mL) at 80 °C overnight gave after column chromatography (10% ethyl acetate in petroleum ether (40-60 °C)) 5-isopentyl-1,3,5-trimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285n (86.8 mg, 0.36 mmol, 36%) as a colourless oil.

νmax (neat)/cm⁻¹ 2957, 2870, 1673 (C=O), 1445, 1418, 1381, 1359, 1313, 1279, 1190, 1098, 1061, 755;

¹H NMR (500 MHz, CDCl₃) δ ppm 0.82 (6 H, d, J = 6.6 Hz, 2 × CHCH₃), 0.88 - 0.97 (2 H, m, CH₂CH), 1.45 (1 H, dquin, J = 13.2, 6.6 Hz, CHCH₃), 1.51 (3 H, s, CCH₃), 1.92 - 1.99 (2 H, m, CCH₂), 3.30 (6 H, s, 2 × NCH₃);

¹³C NMR (125 MHz, CDCl₃) δ ppm 22.2 (2 × CHCH₃), 24.7 (CCH₃), 28.0 (CHCH₃), 28.6 (2 × NCH₃), 33.9 (CH₂CH), 38.2 (CCH₂), 51.6 (C₆), 151.2 (C=O), 172.4 (2 × C=O);

m/z (APCI⁺) 56 (100%), 57 (18), 72 (17), 74 (18), 87 (20), 88 (10), 241 ((M + H), 6). (Found: (M – CH₃) 225.1225. C₁₁H₁₇N₂O₃ requires M, 225.1243).
5,5-Di(but-3-en-1-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (299e)

As for general procedure C, reaction of 1,3-dimethylbarbituric acid (1.56 g, 10.0 mmol, 1.0 eq), 4-bromobut-1-ene (1.2 mL, 12.0 mmol, 0.6 eq), tetrabutylammonium bisulfate (34 mg, 0.10 mmol, 0.1 mol%) and K₂CO₃ (2.76 g, 20.0 mmol, 2.0 eq) in DMF (25 mL) at 80 °C overnight gave after column chromatography (10% ethyl acetate in petroleum ether (40-60 °C)) 5,5-di(but-3-en-1-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 299e (1.24 g, 4.69 mmol, 78%) as a white solid.

mp 43-45 °C;
ν max (neat)/cm⁻¹ 2955, 2928, 1672 (C=O), 1445, 1416, 1382, 1334, 1281, 1258, 1171, 1083, 1036, 999, 921, 753, 639;
¹H NMR (400 MHz, CDCl₃) δ ppm 1.85 - 1.95 (4 H, m, 2 × C₃H₂CH=CH₂), 2.07 - 2.15 (4 H, m, 2 × CCH₂), 3.28 (6 H, s, 2 × NCH₃), 4.85 - 4.93 (4 H, m, 2 × CH=CH₂), 5.55 - 5.68 (2 H, m, 2 × CH=CH₂);
¹³C NMR (100 MHz, CDCl₃) δ ppm 28.3 (2 × NCH₃), 29.8 (2 × C₂H₂CH=CH₂), 39.3 (2 × CCH₂), 55.4 (C), 115.7 (2 × CH=CH₂), 136.5 (2 × CH=CH₂), 151.0 (C=O), 171.7 (2 × C=O);
m/z (GC-MS/EI+) 264 (M). (Found: (M) 264.1461. C₁₄H₂₀N₂O₃ requires M, 264.1468);
Anal (Found: C, 63.64; H, 7.81; N, 10.67; C₁₄H₂₀N₂O₃ requires C, 63.62; H, 7.63; N, 10.60%).

5-(But-3-en-1-yl)-5-decyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (299f)

As for general procedure C, reaction of 5-decyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285b (319 mg, 1.07 mmol, 1.0 eq), 4-bromobut-1-ene (0.16 mL, 1.61 mmol, 1.5 eq) and K₂CO₃ (297 mg, 2.15 mmol, 2.0 eq) in acetone (15 mL) gave after column chromatography (10% ethyl acetate in petroleum ether (40-60 °C)) 5-(but-3-en-1-yl)-5-decyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 299f (195 mg, 0.56 mmol, 52%) as a colourless oil.
$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2924, 2854, 1679 (C=O), 1445, 1380, 1277, 1165, 1080, 993, 916, 754, 715, 638;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.86 (3 H, t, $J = 6.8$ Hz, CH$_3$CH$_2$), 0.96 - 1.07 (2 H, m, CCH$_2$CH$_2$CH$_2$), 1.14 - 1.32 (14 H, m, 7 $\times$ CH$_2$), 1.86 - 1.99 (4 H, m, CH$_2$CH=CH$_2$, CCH$_2$CH$_2$CH$_2$), 2.08 - 2.16 (2 H, m, CH$_2$CH$_2$CH$_2$), 3.30 (6 H, s, 2 $\times$ NCH$_3$), 4.84 - 4.94 (2 H, m, CH=CH$_2$), 5.55 - 5.68 (1 H, m, CH=CH$_2$);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 14.1 (CH$_2$CH$_3$), 22.6 (CH$_2$CH$_3$), 24.9 (CCH$_2$CH$_2$CH$_2$), 28.3 (2 $\times$ NCH$_3$), 29.1 (CH$_2$), 29.2 (CH$_2$), 29.4 (CH$_2$), 29.4 (CH$_2$), 30.0 (CH$_2$CH=CH$_2$), 31.8 (CH$_2$), 38.7 (CH$_2$CH$_2$CH$_2$), 40.8 (CCH$_2$CH$_2$CH$_2$), 56.1 (C$^6$), 115.6 (CH=CH$_2$), 136.7 (CH=CH$_2$), 151.1 (C=O), 172.0 (2 $\times$ C=O);

$\text{m/z}$ (GC/MS-EI+) 350.3 (M). (Found: (M) 350.2551. C$_{20}$H$_{34}$N$_2$O$_3$ requires M, 350.2564).

5-Isobutyl-1,3-dimethyl-5-((3,4,4-trifluorobut-3-en-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (299g)

As for general procedure C, reaction of 5-isobutyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285a (637 mg, 3.00 mmol, 1.0 eq), 4-bromo-1,1,2-trifluorobut-1-ene (0.50 mL, 4.50 mmol, 1.5 eq) and K$_2$CO$_3$ (829 mg, 6.00 mmol, 2.0 eq) in acetone (15 mL) gave after column chromatography (10% ethyl acetate in petroleum ether (40-60 °C)) 5-isobutyl-1,3-dimethyl-5-((3,4,4-trifluorobut-3-en-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione 299g (359 mg, 1.12 mmol, 43%) as a colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2962, 1798, 1745, 1678 (C=O), 1443, 1379, 1283, 1247, 1167, 1084, 1036, 754;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.78 (3 H, d, $J = 6.7$ Hz, CH$_3$CH$_3$), 0.78 (3 H, d, $J = 6.7$ Hz, CHCH$_3$), 1.39 - 1.53 (1 H, m, CH$CH_3$), 1.96 (2 H, d, $J = 6.6$ Hz, CH$_2$CH), 2.06 - 2.20 (2 H, m, CH$_2$CF=CF$_2$), 2.20 - 2.29 (2 H, m, CCH$_2$CH$_2$), 3.32 (3 H, d, $J = 0.8$ Hz, NCH$_3$), 3.32 (3 H, d, $J = 0.8$ Hz, NCH$_3$);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 21.6 (CH$_2$CF=CF$_2$), 23.2 (2 $\times$ CHCH$_3$), 25.4 (CHCH$_3$), 28.5 (2 $\times$ NCH$_3$), 36.0 (CCH$_2$CH$_2$), 49.2 (CH$_2$CH), 54.6 (C$^6$), 127.1 (ddd, $J = 235.3$, 52.6, 15.7 Hz, CF=CF$_2$), 150.8 (C=O), 152.9 (td, $J = 287.9$, 47.1 Hz, CF=CF$_2$), 171.2 (2 $\times$ C=O);
As for general procedure C, reaction of 5-isobutyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285a (637 mg, 3.00 mmol, 1.0 eq), 5-bromo-pent-1-ene (0.53 mL, 4.50 mmol, 1.5 eq) and K$_2$CO$_3$ (829 mg, 6.00 mmol, 2.0 eq) in acetone (15 mL) gave after column chromatography (10% ethyl acetate in petroleum ether (40-60 °C)) 5-isobutyl-1,3-dimethyl-5-(5-methylpent-3-en-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione 299h (318 mg, 1.08 mmol, 41%) as a colourless oil.

$v_{\text{max}}$ (neat)/cm$^{-1}$ 2961, 2930, 2872, 1677 (C=O), 1441, 1378, 1350, 1279, 1199, 1168, 1086, 1056, 825, 754; 

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 0.74 (6 H, d, $J = 6.7$ Hz, 2 × CH$_3$), 1.35 - 1.49 (1 H, m, CH$_3$), 1.44 (3 H, br. s, CCH$_3$), 1.59 (3 H, br. s, CCH$_3$), 1.78 - 1.88 (2 H, m, CH$_2$CH=CH), 1.94 (2 H, d, $J = 6.7$ Hz, CCH$_2$CH), 2.02 (2 H, t, $J = 7.3$ Hz, CCH$_2$CH$_2$), 3.28 (6 H, s, 2 × NCH$_3$), 4.88 (1 H, br. t, $J = 5.8$ Hz, CH=CH);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 17.4 (CCH$_3$), 23.1 (2 × CH$_3$CH), 23.9 (CH$_2$CH=CH), 25.5 (CH$_2$CH$_2$), 25.7 (CCH$_3$), 28.4 (2 × NCH$_3$), 41.2 (CCH$_2$CH$_2$), 49.1 (CCH$_2$CH), 55.0 (C), 122.0 (CH=C), 133.5 (CH=C), 151.2 (C=O), 172.1 (2 × C=O);

$m/z$ (APCI+) 295 ((M + H), 100%). (Found: (M + H) 295.2013. C$_{16}$H$_{27}$N$_2$O$_3$ requires $M$, 295.2016).

As for general procedure C, reaction of 5-isobutyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285a (637 mg, 3.00 mmol, 1.0 eq), 5-bromopent-1-ene (0.53 mL, 4.50 mmol, 1.5 eq) and K$_2$CO$_3$ (829 mg, 6.00 mmol, 2.0 eq) in acetone (15 mL) gave after column chromatography (10% ethyl acetate in petroleum ether (40-60 °C)) 5-isobutyl-1,3-dimethyl-5-(4-methylpent-3-en-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione 299i (318 mg, 1.08 mmol, 41%) as a colourless oil.

$v_{\text{max}}$ (neat)/cm$^{-1}$ 2961, 2930, 2872, 1677 (C=O), 1441, 1378, 1350, 1279, 1199, 1168, 1086, 1056, 825, 754; 

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 0.74 (6 H, d, $J = 6.7$ Hz, 2 × CH$_3$), 1.35 - 1.49 (1 H, m, CH$_3$), 1.44 (3 H, br. s, CCH$_3$), 1.59 (3 H, br. s, CCH$_3$), 1.78 - 1.88 (2 H, m, CH$_2$CH=CH), 1.94 (2 H, d, $J = 6.7$ Hz, CCH$_2$CH), 2.02 (2 H, t, $J = 7.3$ Hz, CCH$_2$CH$_2$), 3.28 (6 H, s, 2 × NCH$_3$), 4.88 (1 H, br. t, $J = 5.8$ Hz, CH=CH);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 17.4 (CCH$_3$), 23.1 (2 × CH$_3$CH), 23.9 (CH$_2$CH=CH), 25.5 (CH$_2$CH$_2$), 25.7 (CCH$_3$), 28.4 (2 × NCH$_3$), 41.2 (CCH$_2$CH$_2$), 49.1 (CCH$_2$CH), 55.0 (C), 122.0 (CH=C), 133.5 (CH=C), 151.2 (C=O), 172.1 (2 × C=O);

$m/z$ (APCI+) 295 ((M + H), 100%). (Found: (M + H) 295.2013. C$_{16}$H$_{27}$N$_2$O$_3$ requires $M$, 295.2016).
column chromatography (10% ethyl acetate in petroleum ether (40-60 °C)) 5-isobutyl-1,3-dimethyl-5-(pent-4-en-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione 299i (551 mg, 1.97 mmol, 75%) as a colourless oil.

\[ \nu_{\text{max}} \text{(neat)/cm}^{-1} \] 2960, 2929, 2869, 1677 (C=O), 1444, 1378, 1315, 1275, 1211, 1172, 1081, 995, 914, 756;

\[ ^1H \text{ NMR} \] (400 MHz, CDCl\(_3\)) \( \delta \) ppm 0.76 (6 H, d, \( J = 6.6 \) Hz, 2 \( \times \) CHCH\(_3\)), 1.04 - 1.16 (2 H, m, CCH\(_2\)CH\(_2\)), 1.39 - 1.51 (1 H, m, CHCH\(_3\)), 1.89 - 2.02 (6 H, m, CC\(_2\)CH, CCH\(_2\)CH\(_2\), CH\(_2\)CH=CH\(_2\)), 3.31 (3 H, s, NCH\(_3\)), 3.32 (3 H, s, NCH\(_3\)), 4.90 - 4.99 (2 H, m, CH=CH\(_2\)), 5.66 (1 H, ddt, \( J = 17.0, 10.2, 6.7 \) Hz, CH=CH\(_2\));

\[ ^{13}C \text{ NMR} \] (100 MHz, CDCl\(_3\)) \( \delta \) ppm 23.1 (2 \( \times \) CH\(_2\)CH\(_3\)), 24.0 (CCH\(_2\)CH\(_3\)), 25.6 (CHCH\(_3\)), 28.4 (2 \( \times \) NCH\(_3\)), 33.3 (CH\(_2\)CH=CH\(_2\)), 41.5 (CCH\(_2\)CH), 48.3 (CCH\(_2\)CH), 55.5 (C\(_6\)), 115.4 (CH=CH\(_2\)), 137.2 (CH=CH\(_2\)), 151.1 (C=O), 172.0 (2 \( \times \) C=O);

\[ m/z \] (APCI\(^+\)) 281 ((M + H), 100%). (Found: (M + H) 281.1858. C\(_{15}\)H\(_{25}\)N\(_2\)O\(_3\) requires \( M \), 281.1860).

5-(But-3-yn-1-yl)-5-isobutyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (299j)

As for general procedure C, reaction of 5-isobutyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285a (637 mg, 3.00 mmol, 1.0 eq), 4-bromobut-1-yn (0.42 mL, 4.50 mmol, 1.5 eq) and K\(_2\)CO\(_3\) (829 mg, 6.00 mmol, 2.0 eq) in acetone (15 mL) gave after column chromatography (10% ethyl acetate in petroleum ether (40-60 °C)) 5-(but-3-yn-1-yl)-5-isobutyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 299j (315 mg, 1.19 mmol, 46%) as a colourless oil.

\[ \nu_{\text{max}} \text{(neat)/cm}^{-1} \] 3275, 2960, 2872, 1676 (C=O), 1442, 1380, 1352, 1291, 1219, 1159, 1119, 1089, 1052, 755, 645;

\[ ^1H \text{ NMR} \] (400 MHz, CDCl\(_3\)) \( \delta \) ppm 0.77 (6 H, d, \( J = 6.8 \) Hz, 2 \( \times \) CHCH\(_3\)), 1.40 - 1.52 (1 H, m, CHCH\(_3\)), 1.91 (1 H, t, \( J = 2.5 \) Hz, C=CH), 1.95 (2 H, d, \( J = 6.8 \) Hz, CH\(_2\)CH), 2.11 (2 H, td, \( J = 6.3, 2.5 \) Hz, CH\(_2\)C=CH), 2.17 - 2.24 (2 H, m, CCH\(_2\)CH\(_2\)), 3.30 (6 H, s, 2 \( \times \) NCH\(_3\));

\[ ^{13}C \text{ NMR} \] (100 MHz, CDCl\(_3\)) \( \delta \) ppm 14.5 (CH\(_2\)C=CH), 23.2 (2 \( \times \) CHCH\(_3\)), 25.3 (CHCH\(_3\)), 28.5 (2 \( \times \) NCH\(_3\)), 38.8 (CCH\(_2\)CH\(_2\)), 49.3 (CH\(_3\)CH), 54.6 (C\(_6\)), 69.8 (C=CH), 81.4 (C=CH), 151.1 (C=O), 171.5 (2 \( \times \) C=O);
\( m/z \) (APCI+) 265 ((M + H), 100%). (Found: (M + H) 265.1543. C_{14}H_{21}N_{2}O_{3} requires \( M \), 265.1547).

5-Isobutyl-1,3-dimethyl-5-(4-(trimethylsilyl)but-3-yn-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (299k)

As for general procedure C, reaction of 5-isobutyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285a (637 mg, 3.00 mmol, 1.0 eq), (4-bromobut-1-ynyl)trimethylsilane (995 mg, 4.50 mmol, 1.5 eq) and K_{2}CO_{3} (829 mg, 6.00 mmol, 2.0 eq) in acetone (15 mL) gave after column chromatography (5% ethyl acetate in petroleum ether (40-60 °C)) 5-isobutyl-1,3-dimethyl-5-(4-(trimethylsilyl)but-3-yn-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione 299k (166 mg, 0.49 mmol, 19%) as a white solid.

\( \text{mp} \) 58-60 °C;
\( \nu_{\text{max}} \) (neat)/cm^{-1} 2959, 1678 (C=O), 1443, 1379, 1351, 1277, 1252, 1159, 1088, 1048, 842, 757, 700, 641;
\( ^{1}H \) NMR (500 MHz, CDCl_{3}) \( \delta \) ppm 0.11 (9 H, s, 3 × SiCH_{3}), 0.78 (6 H, d, \( J = 6.9 \) Hz, 2 × CHCH_{3}), 1.42 - 1.51 (1 H, m, CHCH_{3}), 1.96 (2 H, d, \( J = 6.9 \) Hz, CH_{2}CH), 2.11 - 2.16 (2 H, m, CH_{2}C≡C), 2.18 - 2.24 (2 H, m, CCH_{2}CH_{2}), 3.33 (6 H, s, 2 × NCH_{3});
\( ^{13}C \) NMR (125 MHz, CDCl_{3}) \( \delta \) ppm 0.0 (3 × SiCH_{3}), 15.9 (CH_{2}C≡C), 23.2 (2 × CHCH_{3}), 25.4 (CHCH_{3}), 28.6 (2 × NCH_{3}), 39.0 (CCH_{2}CH_{2}), 49.0 (CH_{2}CH), 54.7 (C^{\beta}), 86.2 (C≡CSi), 103.9 (C≡C=O), 151.1 (C=O), 171.4 (2 × C=O);
\( m/z \) (ES+) 337 ((M + H), 100%). (Found: (M + H) 337.1953. C_{17}H_{29}N_{2}O_{3}Si requires \( M \), 337.1942).

5,5-Di(but-3-yn-1-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (299m)

As for general procedure C, reaction of 1,3-dimethylbarbituric acid (1.56 g, 10.0 mmol, 1.0 eq), 4-bromobut-1-yne (1.1 mL, 12.0 mmol, 0.6 eq), tetrabutylammonium bisulfate (34
mg, 0.10 mmol, 0.1 mol%) and K$_2$CO$_3$ (2.76 g, 20.0 mmol, 2.0 eq) in DMF (25 mL) at 80 °C overnight gave after column chromatography (10% ethyl acetate in petroleum ether (40-60 °C)) 5,5-di(but-3-yn-1-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione **299m** (660 mg, 2.54 mmol, 42%) as a white solid.

**mp** 67-69 °C;

ν$_{max}$ (neat)/cm$^{-1}$ 3278, 2947, 1671 (C=O), 1440, 1382, 1348, 1284, 1127, 1062, 913, 753, 642;

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 1.93 (2 H, t, $J = 2.8$ Hz, 2 × C≡CH), 2.11 - 2.20 (4 H, m, 2 × CH$_2$C≡CH), 2.21 - 2.30 (4 H, m, 2 × CH$_2$CH$_2$C≡CH), 3.31 (6 H, s, 2 × NCH$_3$);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 14.5 (2 × CH$_2$C≡CH), 28.5 (2 × NCH$_3$), 37.9 (2 × CH$_2$CH$_2$C≡CH), 54.4 (C$^9$), 70.0 (2 × C≡CH), 81.3 (2 × C≡CH), 151.0 (C=O), 170.9 (2 × C=O);

m/z (ES+) 261 ((M + H), 100%). (Found: (M + H) 261.1229. C$_{14}$H$_{17}$O$_3$N$_2$ requires M, 261.1234);

Anal (Found: C, 64.76; H, 6.21; N, 10.69; C$_{14}$H$_{16}$N$_2$O$_3$ requires C, 64.60; H, 6.20; N, 10.76%).

### 5.4. General procedure D – Metatheses

![2,4-Dimethyl-2,4-diazaspiro[5.6]dodec-9-ene-1,3,5-trione](image)

**2,4-Dimethyl-2,4-diazaspiro[5.6]dodec-9-ene-1,3,5-trione (285o)**

To a stirred solution of 5,5-di(but-3-en-1-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione **299e** (500 mg, 1.89 mmol, 1.0 eq) in toluene (60 mL) was added Grubbs I (156 mg, 0.19 mmol, 10 mol%) and the reaction mixture stirred at 90 °C for 24 hours then concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 10% ethyl acetate in petroleum ether (40-60 °C) gave 2,4-dimethyl-2,4-diazaspiro[5.6]dodec-9-ene-1,3,5-trione **285o** (311 mg, 1.32 mmol, 70%) as a white solid.

**mp** 118-120 °C;

ν$_{max}$ (neat)/cm$^{-1}$ 3017, 2926, 2856, 1676 (C=O), 1455, 1420, 1371, 1271, 1236, 1109, 1065, 1023, 931, 756, 707, 631;

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 2.22 - 2.31 (4 H, m, 2 × CH$_2$), 2.41 - 2.51 (4 H, m, 2 × CH$_2$CH), 3.29 (6 H, s, 2 × NCH$_3$), 5.65 (2 H, t, $J = 2.6$ Hz, 2 × CH);
\( ^{13}C \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm 24.9 (2 × CH\(_2\)CH), 28.9 (2 × NCH\(_3\)), 34.6 (2 × CCH\(_2\)), 53.8 (C\(^3\)), 129.9 (2 × CH), 151.3 (C=O), 172.6 (2 × C=O); \\
m/z (GC-MS-EI+) 236.1 (M). (Found: (M) 236.1157. C\(_{12}\)H\(_{16}\)N\(_2\)O\(_3\) requires M, 236.1155); \\
Anal (Found: C, 61.22; H, 6.88; N, 11.76; C\(_{12}\)H\(_{16}\)N\(_2\)O\(_3\) requires C, 61.00; H, 6.83; N, 11.86%).

\[(E)\)-Methyl 4-((4R,5R)-5-decyl-1,3,5-trimethyl-2,6-dioxohexahydropyrimidin-4-yl)but-2-enoate (327)\]

As for general procedure D, reaction of (5R,6R)-6-allyl-5-decyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 317a (10 mg, 29.7 μmol, 1.0 eq), methyl acrylate (50 μL, 297 µmol, 10 eq) and Hoveyda–Grubbs II (1.0 mg, 1.5 μmol, 5 mol%) in CH\(_2\)Cl\(_2\) (0.5 mL) at room temperature overnight gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) \((E)\)-methyl 4-((4R,5R)-5-decyl-1,3,5-trimethyl-2,6-dioxohexahydropyrimidin-4-yl)but-2-enoate 327 (9.3 mg, 23.6 µmol, 79%) as a colourless oil.

\( \nu \) \(_{\text{max}}\) (neat)/cm\(^{-1}\) 2924, 2853, 1726 (C=O), 1710 (C=O), 1667 (C=O), 1467, 1436, 1418, 1399, 1324, 1270, 1219, 1168, 1096, 1041, 981, 855, 758, 722;

\(^1\)H NMR (400 MHz, Acetone) \( \delta \) ppm 0.86 (3 H, s, CH\(_2\)C\(_3\)H\(_3\)), 1.08 - 1.16 (1 H, m, 1 H from CCH\(_2\)CH\(_2\)), 1.19 (3 H, s, CCH\(_3\)), 1.22 - 1.33 (14 H, m, 7 × CH\(_2\)), 1.34 - 1.42 (1 H, m, 1 H from CCH\(_2\)CH\(_2\)), 1.48 (1 H, ddd, \( J = 13.4, 12.1, 4.2 \) Hz, 1 H from CCH\(_2\)), 1.59 (1 H, ddd, \( J = 13.4, 12.1, 4.8 \) Hz, 1 H from CCH\(_2\)), 2.43 (1 H, dddd, \( J = 14.2, 8.3, 6.7, 1.5 \) Hz, 1 H from CHC\(_2\)), 2.67 (1 H, dddd, \( J = 14.2, 7.3, 4.5, 1.5 \) Hz, 1 H from CHCH\(_2\)), 3.00 (3 H, s, NCH\(_3\)), 3.04 (3 H, s, NCH\(_3\)), 3.51 (1 H, dd, \( J = 6.7, 4.5 \) Hz, CH), 3.66 (3 H, s, OCH\(_3\)), 5.90 (1 H, dt, \( J = 15.6, 1.3 \) Hz, CH\(_2\)CH=CH), 6.81 (1 H, dt, \( J = 15.6, 7.8 \) Hz, CH\(_2\)CH=CH); \\
\(^{13}\)C NMR (100 MHz, Acetone) \( \delta \) ppm 14.4 (CH\(_2\)CH\(_3\)), 18.4 (CCH\(_3\)), 23.4 (CH\(_2\)), 24.5 (CCH\(_2\)CH\(_2\)), 27.7 (NCH\(_3\)), 30.1 (CH\(_2\)), 30.2 (CH\(_2\)), 30.3 (CH\(_2\)), 30.4 (CH\(_2\)), 30.6 (CH\(_2\)), 32.7 (CH\(_2\)), 33.3 (CHCH\(_2\)), 36.3 (NCH\(_3\)), 38.2 (CHCH\(_2\)), 45.7 (C\(^3\)), 51.7 (OCH\(_3\)), 62.8 (CH), 124.8 (CH\(_2\)CH=CH), 144.7 (CH\(_2\)CH=CH), 153.4 (C=O), 166.6 (C=O), 174.5 (C=O); \\
m/z (ES+) 417 ((M + Na), 100%). (Found: (M + Na) 417.2728. C\(_{22}\)H\(_{38}\)N\(_2\)O\(_4\)Na requires M, 417.2724).
5.5. General procedure E – Sonogashira reactions

5-Isobutyl-1,3-dimethyl-5-(4-phenylbut-3-yn-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (299j)

To a stirred solution of 5-(but-3-yn-1-yl)-5-isobutyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 299j (106 mg, 0.40 mmol, 1.0 eq) in THF (1.0 mL) and diisopropylamine (0.4 mL) was added iodobenzene (90 µL, 0.80 mmol, 2.0 eq) and tetrakis(triphenylphosphine)palladium(0) (9.2 mg, 8.0 µmol, 2 mol%) and the reaction mixture stirred at room temperature for 20 minutes. Copper iodide (0.8 mg, 4.0 µmol, 1 mol%) was added and the reaction stirred at 60 °C for 8 hours then filtered over a celite plug and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave 5-isobutyl-1,3-dimethyl-5-(4-phenylbut-3-yn-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione 299l (123 mg, 0.36 mmol, 91%) as a colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2959, 1676 (C=O), 1440, 1379, 1351, 1295, 1157, 1088, 1054, 916, 755, 692;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.83 (6 H, d, J = 6.6 Hz, 2 × CHCH$_3$), 1.45 - 1.57 (1 H, m, CHCH$_3$), 2.03 (2 H, d, J = 6.6 Hz, CH$_2$CH), 2.28 - 2.44 (4 H, m, CCH$_2$CH$_2$, CCH$_2$CH$_2$), 3.28 (6 H, s, 2 × NCH$_3$), 7.29 - 7.33 (3 H, m, 3 × ArH), 7.34 - 7.38 (2 H, m, 2 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 15.6 (CCH$_2$CH$_2$), 23.3 (2 × CHCH$_3$), 25.4 (CHCH$_3$), 28.6 (2 × NCH$_3$), 38.9 (CCH$_2$CH$_2$), 49.7 (CH$_2$CH), 54.8 (C$^9$), 82.4 (C=CAr), 86.8 (C=C=Ar), 122.9 (ArC$^9$), 128.1 (ArCH), 128.3 (2 × ArCH), 131.7 (2 × ArCH), 151.2 (C=O), 171.7 (2 × C=O);

$m/z$ (ES+) 341 ((M + H), 93%), 358 (100). (Found: (M + H) 341.1871. C$_{20}$H$_{25}$N$_2$O$_3$ requires M, 341.1860).
**rac-(5R,6R)-5-Isobutyl-1,3,5-trimethyl-6-(phenylethynyl)dihydropyrimidine-2,4(1H,3H)-dione (326-A)**

**rac-(5R,6S)-5-Isobutyl-1,3,5-trimethyl-6-(phenylethynyl)dihydropyrimidine-2,4(1H,3H)-dione (326-B)**

As for general procedure E, reaction of both isomers of 6-ethynyl-5-isobutyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 317I (10 mg, 42.3 µmol, 1.0 eq, 88:12 ratio), iodobenzene (10 µL, 84.6 µmol, 2.0 eq), tetrakis(triphenylphosphine)palladium(0) (1.0 mg, 0.9 µmol, 2 mol%) and copper iodide (0.1 mg, 0.4 µmol, 1 mol%) in THF (1.0 mL) and diisopropylamine (0.2 mL) gave after column chromatography (20% ethyl acetate in petroleum ether (40-60 °C)) **rac-(5R,6R)-5-isobutyl-1,3,5-trimethyl-6-(phenylethynyl)dihydropyrimidine-2,4(1H,3H)-dione** 326-A and **rac-(5R,6S)-5-isobutyl-1,3,5-trimethyl-6-(phenylethynyl)dihydropyrimidine-2,4(1H,3H)-dione** 326-B (8.5 mg, 27.2 µmol, 64%, 88:12 ratio (89:11 crude ratio)) as a colourless oil.

ν\textsubscript{max} (neat)/cm\textsuperscript{-1} 2956, 2928, 2869, 1713 (C=O), 1670 (C=O), 1465, 1443, 1414, 1392, 1285, 1174, 1090, 1070, 1037, 757, 691;

\textsuperscript{1}H NMR (400 MHz, Acetone) δ ppm 0.81 (3 H, d, J = 6.7 Hz, CHC\textsubscript{3}H\textsubscript{3}), 0.94 (3 H, d, J = 6.7 Hz, CH\textsubscript{2}CH\textsubscript{3}), 1.41 (3 H, s, CH\textsubscript{2}CH\textsubscript{3}), 1.52 (1 H, dd, J = 13.9, 4.3 Hz, 1 H from CH\textsubscript{2}CH\textsubscript{3}), 1.64 - 1.75 (1 H, m, 1 H from CH\textsubscript{2}CH\textsubscript{3}), 1.75 - 1.83 (1 H, m, CH\textsubscript{3}CH\textsubscript{3}), 3.11 (3 H, s, NCH\textsubscript{3}), 3.12 (3 H, s, NCH\textsubscript{3}), 4.31 (1 H, s, CHC≡C), 7.34 - 7.44 (5 H, m, 5 × ArH);

\textsuperscript{13}C NMR (100 MHz, Acetone) δ ppm 20.0 (CCH\textsubscript{3}), 24.2 (CH\textsubscript{2}CH\textsubscript{3}), 24.8 (CH\textsubscript{3}CH\textsubscript{3}), 25.4 (CH\textsubscript{3}CH\textsubscript{3}), 28.2 (NCH\textsubscript{3}), 35.0 (NCH\textsubscript{3}), 45.7 (CH\textsubscript{2}CH\textsubscript{3}), 46.5 (C\textsuperscript{\alpha}), 57.4 (CHC≡C), 84.7 (C≡CAr), 86.9 (C≡CAr), 122.9 (ArC\textsuperscript{\alpha}), 129.5 (2 × ArCH), 129.9 (ArCH), 132.6 (2 × ArCH), 153.9 (C=O), 174.0 (C=O);

\textbf{m/z} (ES+) 301 (47%), 335 ((M + Na), 100). (Found: (M + H) 313.1914. C\textsubscript{19}H\textsubscript{25}N\textsubscript{2}O\textsubscript{2} requires M, 313.1911).
5.6. General procedure F – SmI$_2$ mediated reductions and cyclisations

rac-(5S,6R)-6-Hydroxy-5-isopentyl-1,3-dimethylidihydropyrimidine-2,4(1H,3H)-dione (286c-A)

rac-(5S,6S)-6-Hydroxy-5-isopentyl-1,3-dimethylidihydropyrimidine-2,4(1H,3H)-dione (286c-B)

To a vigorously stirred solution of 5-isopentyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285c (23 mg, 0.10 mmol, 1.0 eq) in THF (1.0 mL) and H$_2$O (1.8 mL, 100 mmol, 1000 eq) was added SmI$_2$ (0.08 M in THF, 3.8 mL, 0.30 mmol, 3.0 eq) and the reaction mixture stirred for 10 seconds. The flask was filled with CH$_2$Cl$_2$, added to a 2:1 mixture of H$_2$O and NaHCO$_3$ aq., sat. (30 mL) and extracted with CH$_2$Cl$_2$ (2 × 30 mL). The combined organic phases were dried (Na$_2$SO$_4$ or MgSO$_4$) and concentrated in vacuo. Purification by preparative thin layer chromatography on silica gel, eluting with ethyl acetate and hexane (1:1 mixture) gave rac-(5S,6R)-6-hydroxy-5-isopentyl-1,3-dimethylidihydropyrimidine-2,4(1H,3H)-dione 286c-A and rac-(5S,6S)-6-hydroxy-5-isopentyl-1,3-dimethylidihydropyrimidine-2,4(1H,3H)-dione 286c-B (18.3 mg, 80.0 µmol, 80% ($^1$H NMR vs. internal standard), 91:9 crude dr, 94:6 purified dr) as a white solid.

**mp** 117-119 °C;

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3393 (br. OH), 2954, 2870, 1710 (C=O), 1653 (C=O), 1483, 1423, 1379, 1296, 1222, 1146, 1095, 1055, 1004, 969, 903, 762;

$^1$H NMR (500 MHz, Acetone) $\delta$ ppm 0.86 (3 H, d, $J = 2.5$ Hz, CH$_3$ (B)), 1.00 (3 H, d, $J = 6.6$ Hz, CH$_3$ (A)), 1.27 - 1.38 (4 H, m, CH$_2$CH$_3$ (A and B)), 2.61 (1 H, td, $J = 7.4$, 1.9 Hz, CHCHOH (B)), 3.05 (3 H, s, NCH$_3$ (A)), 3.06 (3 H, s, NCH$_3$ (B)), 4.88 (1 H, dd, $J = 4.7$, 1.9 Hz, CHO (B)), 5.45 (1 H, dd, $J = 5.5$, 0.8 Hz, OH (A)), 5.51 (1 H, d, $J = 4.7$ Hz, OH (B));

$^{13}$C NMR (125 MHz, Acetone) $\delta$ ppm 22.7 (CH$_3$ (B)), 22.8 (CH$_3$ (A and B)), 23.1 (CH$_3$ (A)), 24.4 (CH$_2$CH$_2$ (A and B)), 27.4 (NCH$_3$ (B)), 27.6 (NCH$_3$ (A)), 28.6
As for general procedure F, reaction of 5-(4-methoxyphenethyl)-1,3-dimethylidihydropyrimidine-2,4,6(1H,3H,5H)-trione 285e (29 mg, 0.10 mmol, 1.0 eq) and SmI\(_2\) (0.085 M in THF, 3.5 mL, 0.30 mmol, 3.0 eq) in THF (1.0 mL) and \(\text{H}_2\text{O}\) (1.8 mL, 100 mmol, 1000 eq) gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) \textit{rac}-(5S,6R)-6-hydroxy-5-(4-methoxyphenethyl)-1,3-dimethylidihydropyrimidine-2,4(1H,3H)-dione 286e (23.3 mg, 80.0 \(\mu\)mol, 80% (\(^1\)H NMR vs. internal standard), 88:12 crude dr, 88:12 purified dr) as a white solid.

\(\text{mp}\) 123-125 °C;

\(\nu_{\text{max}}\) (neat)/\(\text{cm}^{-1}\) 3373 (br. OH), 2926, 2850, 1711 (C=O), 1657 (C=O), 1510, 1484, 1424, 1296, 1244, 1178, 1120, 1033, 827, 761;

\(^1\)H NMR (500 MHz, Acetone) \(\delta\) ppm 1.77 - 1.87 (1 H, m, 1 H from CH\(_2\)CH\(_3\)), 2.24 - 2.33 (1 H, m, 1 H from CH\(_2\)CH\(_3\)), 2.70 - 2.79 (3 H, m, CH\(_2\)CH\(_2\), CH\(_2\)Ar), 3.04 (3 H, s, NCH\(_3\)), 3.06 (3 H, s, NCH\(_3\)), 3.75 (3 H, s, OCH\(_3\)), 5.05 (1 H, dd, \(J = 5.4, 3.8\) Hz, CHO\(_2\)), 5.57 (1 H, dd, \(J = 5.4, 0.9\) Hz, OH), 6.85 (2 H, d, \(J = 8.6\) Hz, 2 \(\times\) ArH), 7.16 (2 H, d, \(J = 8.6\) Hz, 2 \(\times\) ArH);

\(^{13}\)C NMR (125 MHz, Acetone) \(\delta\) ppm 27.6 (NCH\(_3\)), 28.8 (CH\(_2\)CH\(_2\)), 32.7 (CH\(_2\)Ar), 34.4 (NCH\(_3\)), 46.3 (CH\(_2\)CH\(_2\)), 55.5 (OCH\(_3\)), 80.6 (CHO\(_2\)), 114.7 (2 \(\times\) ArCH), 130.2 (2 \(\times\) ArCH), 134.8 (ArC\(^6\)), 154.1 (C=O), 159.0 (ArC\(^6\)), 171.5 (C=O);

\(m/z\) (ES+) 293 ((M + H), 100%). (Found: (M + H) 293.1501. C\(_{15}\)H\(_{21}\)N\(_2\)O\(_4\) requires \(M\), 293.1496).
As for general procedure F, reaction of 1,3-dimethyl-5-(4-(trifluoromethyl)phenethyl)pyrimidine-2,4,6(1H,3H,5H)-trione 285f (33 mg, 0.10 mmol, 1.0 eq) and SmI$_2$ (0.085 M in THF, 3.5 mL, 0.30 mmol, 3.0 eq) in THF (1.0 mL) and H$_2$O (1.8 mL, 100 mmol, 1000 eq) gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) rac-(5S,6R)-6-hydroxy-1,3-dimethyl-5-(4-(trifluoromethyl)phenethyl)dihydropyrimidine-2,4(1H,3H)-dione 286f (25.1 mg, 76.0 µmol, 76% (1H NMR vs. internal standard), 85:15 crude dr, 76:24 purified dr) as a white solid.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3391 (br. OH), 2927, 2856, 1713 (C=O), 1660 (C=O), 1485, 1423, 1325, 1163, 1120, 1066, 1017, 830, 763;

$^1$H NMR (500 MHz, Acetone) $\delta$ ppm: 1.84 - 1.93 (1 H, m, 1 H from CHCH$_2$), 2.29 - 2.39 (1 H, m, 1 H from CHCH$_2$), 2.81 - 2.85 (1 H, m, CHCH$_2$), 2.93 (2 H, t, J = 8.2 Hz, CH$_2$Ar), 3.05 (3 H, s, NCH$_3$), 3.07 (3 H, s, NCH$_3$), 5.10 (1 H, dd, J = 5.4, 3.8 Hz, CHOH), 5.61 (1 H, dd, J = 5.4, 0.6 Hz, OH), 7.50 (2 H, d, J = 7.9 Hz, 2 × ArH), 7.64 (2 H, d, J = 7.9 Hz, 2 × ArH);

$^{13}$C NMR (125 MHz, Acetone) $\delta$ ppm: 27.7 (NCH$_3$), 28.5 (CH$_2$Ar), 38.3 (CHCH$_2$), 34.4 (NCH$_3$), 46.4 (CHCH$_2$), 80.6 (CHOH), 125.6 (q, $J'$ = 272.5 Hz, CF$_3$), 126.2 (q, $J'$ = 3.6 Hz, 2 × ArCH), 128.6 (q, $J'$ = 32.7 Hz, ArC$_5$), 130.1 (2 × ArCH), 148.0 (ArC$_5$), 154.0 (C=O), 171.3 (C=O);

$\text{m/z}$ (ES+) 353 ((M + Na), 100%). (Found: (M + Na) 353.1083. C$_{15}$H$_{17}$O$_3$N$_2$F$_3$Na requires M, 353.1083).

As for general procedure F, reaction of 5-(4-bromophenethyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285g (33 mg, 0.10 mmol, 1.0 eq) and SmI$_2$ (0.085 M in THF, 3.5
mL, 0.30 mmol, 3.0 eq) in THF (1.0 mL) and H₂O (1.8 mL, 100 mmol, 1000 eq) gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) rac-(5S,6R)-5-(4-bromophenethyl)-6-hydroxy-1,3-dimethylidihydropyrimidine-2,4(1H,3H)-dione 286g (22.9 mg, 67.1 µmol, 67%, 87:13 dr (86:14 crude dr)) as a white solid.

**mp** 116-118 °C; 
ν<sub>max</sub> (neat)/cm<sup>-1</sup> 3363 (br. OH), 2962, 2851, 1710 (C=O), 1658 (C=O), 1485, 1425, 1296, 1120, 1067, 1011, 817, 762;  
<sup>1</sup>H NMR (400 MHz, Acetone) δ ppm 1.65 - 1.77 (1 H, m, 1 H from CHCH₂), 2.11 - 2.22 (1 H, m, 1 H from CHCH₂), 2.64 - 2.71 (3 H, m, CHCH₂, CH₂Ar), 2.91 (3 H, s, NCH₃), 2.93 (3 H, s, NCH₃), 4.94 (1 H, dd, J = 5.3, 3.8 Hz, CHOH), 5.43 - 5.48 (1 H, m, OH), 7.10 (2 H, d, J = 8.5 Hz, 2 × ArH), 7.33 (2 H, d, J = 8.5 Hz, 2 × ArH);  
<sup>13</sup>C NMR (100 MHz, Acetone) δ ppm 27.6 (NCH₃), 28.5 (CHCH₂), 33.0 (CH₂Ar), 34.4 (NCH₃), 46.3 (CHCH₂), 80.6 (CHOH), 120.0 (ArC<sup>q</sup>), 131.4 (2 × ArCH), 132.3 (2 × ArCH), 142.4 (ArC<sup>q</sup>), 153.9 (C=O), 171.3 (C=O);  
m/z (ES+) 287 (92%), 289 (33), 321 (100), 322 (25), 363 ((M + Na), 3), 365 ((M + Na), 3). (Found: (M + H) 341.0505. C₁₄H₁₈N₂O₃Br requires M, 341.0495).

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**rac-(5S,6R)-6-Hydroxy-5-isobutyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione** (286i)

As for general procedure F, reaction of 5-isobutyl-1,3,5-trimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285i (140 mg, 0.62 mmol, 1.0 eq) and SmI₂ (0. 11 M in THF, 11.2 mL, 1.24 mmol, 2.0 eq) in THF (1 mL) and H₂O (11.1 mL, 619 mmol, 1000 eq) gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) rac-(5S,6R)-6-hydroxy-5-isobutyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 286i (54.3 mg, 0.24 mmol, 38%, 88:12 dr (88:12 crude dr)) as a colourless oil.

ν<sub>max</sub> (neat)/cm<sup>-1</sup> 3394 (br. OH), 2956, 1711 (C=O), 1651 (C=O), 1485, 1419, 1294, 1176, 1049, 975, 913, 765, 747;  
<sup>1</sup>H NMR (500 MHz, C₆D₆) δ ppm 0.80 (3 H, s, CCH₃), 0.83 (3 H, d, J = 6.8 Hz, CHCH₃), 0.84 (3 H, d, J = 6.8 Hz, CHCH₃), 1.46 - 1.55 (1 H, m, CHCH₃), 1.72 (1 H, dd, J = 14.7, 5.5 Hz, 1 H from CH₂CH), 1.91 (1 H, dd, J = 14.7, 6.0 Hz, 1 H from CH₂CH), 2.71 (3 H, s,
NCH₃), 3.06 (1 H, d, J = 5.0 Hz, OH), 3.13 (3 H, s, NCH₃), 3.95 (1 H, d, J = 5.5 Hz, CHOH);

¹³C NMR (125 MHz, C₆D₆) δ ppm 21.0 (CCH₃), 23.4 (CHCH₃), 25.2 (CHCH₃), 25.5 (CHCH₃), 27.9 (NCH₃), 34.4 (NCH₃), 40.8 (CH₂CH), 46.8 (C⁶), 83.4 (CHOH), 153.0 (C=O), 174.2 (C=O);

m/z (ES+) 251 ((M + Na), 100%). (Found: (M + Na) 251.1361. C₁₁H₂₀N₂O₃Na requires M, 251.1367).

rac-(5S,6R)-5-Decyl-6-hydroxy-1,3,5-trimethyldihydropyrimidine-2,4(1H,3H)-dione (286j)

As for general procedure F, reaction of 5-decyl-1,3,5-trimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285j (100 mg, 0.32 mmol, 1.0 eq) and SmI₂ (0.11 M in THF, 5.9 mL, 0.64 mmol, 2.0 eq) in THF (1 mL) and H₂O (5.8 mL, 320 mmol, 1000 eq) gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) rac-(5S,6R)-5-decyl-6-hydroxy-1,3,5-trimethyldihydropyrimidine-2,4(1H,3H)-dione 286j (65.8 mg, 0.21 mmol, 66%, 92:8 dr (86:14 crude dr)) as a colourless oil.

νₘₐₓ (neat)/cm⁻¹ 3446 (br. OH), 3014, 2852, 1739, 1717 (C=O), 1652 (C=O), 1365, 1295, 1228, 1216, 1205, 1050, 898, 765;

¹¹H NMR (500 MHz, C₆D₆) δ ppm 0.97 (3 H, s, CCH₃), 1.04 (3 H, t, J = 7.0 Hz, CH₂CH₃), 1.27 - 1.48 (16 H, m, 8 × CH₂), 2.03 (1 H, td, J = 12.5, 5.0 Hz, 1 H from CH₂), 2.13 (1 H, td, J = 12.5, 4.0 Hz, 1 H from CH₂), 2.91 (3 H, s, NCH₃), 3.17 (1 H, d, J = 5.0 Hz, OH), 3.36 (3 H, s, NCH₃), 4.09 (3 H, d, J = 5.0 Hz, CHOH);

¹³C NMR (125 MHz, C₆D₆) δ ppm 14.4 (CH₂C₃), 20.7 (CCH₃), 23.1 (CH₂), 23.1 (CH₂), 27.9 (NCH₃), 29.9 (CH₂), 30.1 (CH₂), 30.2 (CH₂), 30.7 (CH₂), 32.3 (CH₂), 32.9 (CH₂), 34.6 (NCH₃), 46.2 (C⁶), 85.2 (CHOH), 153.2 (C=O), 174.5 (C=O);

m/z (ES+) 295 ((M + H), 100%). (Found: (M + H) 295.2380. C₁₇H₁₇N₂O₂ requires M, 295.2381).
As for general procedure F, reaction of 5-isopentyl-1,3,5-trimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285n (24 mg, 0.10 mmol, 1.0 eq) and SmI\(_2\) (3.6 mmol, 0.40 mmol, 4.0 eq) in THF (1.0 mL) and H\(_2\)O (0.36 mL, 20.0 mmol, 200 eq) gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) \(\text{rac-(5S,6R)-6-hydroxy-5-isopentyl-1,3,5-trimethylpyrimidine-2,4(1H,3H)-dione (285n-A)}\) and \(\text{rac-(5R,6R)-6-hydroxy-5-isopentyl-1,3,5-trimethylpyrimidine-2,4(1H,3H)-dione (285n-B)}\) (16.8 mg, 69.3 µmol, 69%, 51:49 dr (53:47 crude dr)) as a colourless oil.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3397 (br. OH), 2955, 2926, 2870, 1712 (C=O), 1655 (C=O), 1482, 1468, 1419, 1383, 1366, 1178, 1095, 1039, 945, 874, 789, 764;

\(^1\)H NMR (400 MHz, Acetone) \(\delta\) ppm 0.84 (3 H, d, \(J = 6.8 \text{ Hz}\), CH\(_3\) (B)), 0.85 (3 H, d, \(J = 6.8 \text{ Hz}\), CH\(_3\) (A)), 0.90 (3 H, d, \(J = 6.8 \text{ Hz}\), CH\(_3\)CH (B)), 1.14 (3 H, s, CH\(_3\) (A)), 1.22 (3 H, s, CH\(_3\) (B)), 1.19 - 1.26 (1 H, m, 1 H from CH\(_2\)CH (B)), 1.26 - 1.33 (2 H, m, CH\(_2\)CH (A)), 1.39 - 1.46 (1 H, m, CH\(_3\)CH (B)), 1.48 - 1.57 (3 H, m, CH\(_3\)CH (A), CCH\(_3\) (B)), 1.77 (1 H, dd, \(J = 5.9, 2.6 \text{ Hz}\), 1 H from CCH\(_2\) (A)), 1.80 (1 H, dd, \(J = 5.9, 3.1 \text{ Hz}\), 1 H from CCH\(_2\) (A)), 3.05 (6 H, s, NCH\(_3\) (A and B)), 3.06 (6 H, s, NCH\(_3\) (A and B)), 4.65 (1 H, s, CH\(_2\)OH (B)), 4.67 (1 H, s, CH\(_2\)OH (A));

\(^{13}\)C NMR (100 MHz, Acetone) \(\delta\) ppm 17.7 (CCH\(_3\) (B)), 21.1 (CCH\(_3\) (A)), 22.7 (CH\(_3\)CH (B)), 22.9 (CH\(_3\)CH (B)), 23.0 (2 × CH\(_3\)CH (A)), 27.7 (NCH\(_3\) (A and B)), 29.1 (CH\(_3\)CH (B)), 29.7 (CH\(_3\)CH (A)), 31.3 (CCH\(_2\) (A)), 32.1 (CH\(_2\)CH (A)), 33.6 (CH\(_2\)CH (B)), 34.6 (NCH\(_3\) (A)), 34.7 (NCH\(_3\) (B)), 35.3 (CCH\(_2\) (B)), 46.6 (C\(^\text{d}\) (A)), 48.0 (C\(^\text{d}\) (B)), 84.9 (CH\(_2\)OH (B)), 86.0 (CH\(_2\)OH (A)), 153.6 (C=O (A)), 153.7 (C=O (B)), 174.5 (C=O (B)), 175.6 (C=O (A));

\(m/z\) (ES\(^{-}\)) 62 (30%), 115 (28), 169 (23), 213 (15), 241 ((M – H), 38), 277 (22), 287 (100).

(Found: (M + Na) 265.1523. C\(_{12}\)H\(_{22}\)N\(_2\)O\(_3\)Na requires \(M, 265.1528\)).
5-Hydroxy-2,4-dimethyl-2,4-diazaspiro[5.6]dodec-9-ene-1,3-dione (286o)

As for general procedure F, reaction of 2,4-dimethyl-2,4-diazaspiro[5.6]dodec-9-ene-1,3,5-trione 285o (24 mg, 0.10 mmol, 1.0 eq) and SmI$_2$ (0.11 M in THF, 2.7 mL, 0.30 mmol, 3.0 eq) in THF (1.0 mL) and H$_2$O (1.8 mL, 100 mmol, 1000 eq) gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) 5-hydroxy-2,4-dimethyl-2,4-diazaspiro[5.6]dodec-9-ene-1,3-dione 286o (11.6 mg, 48.7 µmol, 55%) as a white solid.

mp 136-138 °C;
ν$_{max}$ (neat)/cm$^{-1}$ 3401 (br. OH), 3016, 2927, 2849, 1709 (C=O), 1658 (C=O), 1484, 1422, 1376, 1295, 1227, 1109, 1062, 1030, 928, 859, 763, 736;

$^1$H NMR (500 MHz, Acetone) δ ppm 1.75 (1 H, br. dd, $J = 14.3, 9.0$ Hz, 1 H from CCH$_2$), 1.84 - 1.92 (1 H, m, 1 H from CCH$_2$), 1.92 - 1.98 (1 H, m, 1 H from CCH$_2$), 2.05 - 2.13 (1 H, m, 1 H from CH$_2$CH), 2.18 - 2.29 (3 H, m, 1 H from CH$_2$CH, CH$_2$CH), 2.34 - 2.40 (1 H, m, 1 H from CCH$_2$), 3.05 (3 H, s, NCH$_3$), 3.07 (3 H, s, NCH$_3$), 4.88 (1 H, d, $J = 5.4$ Hz, CHOH), 5.58 (1 H, d, $J = 5.4$ Hz, OH), 5.59 - 5.63 (1 H, m, CH$_2$CH), 5.63 - 5.68 (1 H, m, CH$_2$CH);

$^{13}$C NMR (125 MHz, Acetone) δ ppm 14.3 (CH$_2$CH), 14.6 (CH$_2$CH), 17.9 (NCH$_3$), 19.3 (CCH$_2$), 24.9 (NCH$_3$), 24.9 (CCH$_2$), 40.7 (C$^6$), 74.7 (CHOH), 120.9 (CH$_2$CH), 122.1 (CH$_2$CH), 143.5 (C=O), 165.1 (C=O);

m/z (ES+) 239 ((M + H), 100%). (Found: (M + H) 239.1397. C$_{12}$H$_{19}$N$_2$O$_3$ requires M, 239.1390).

rac-(4aS,7S,7aR)-7a-Hydroxy-4a-isobutyl-1,3,7-trimethylhexahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (300a)

As for general procedure F, reaction of 5-(but-3-en-1-yl)-5-isobutyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (27 mg, 0.1 mmol, 1.0 eq) and SmI$_2$ (0.08 M in THF, 7.5 mL, 0.60 mmol, 6.0 eq) in THF (1.0 mL) and H$_2$O (0.36 mL, 20 mmol, 200 eq) for 15 minutes gave after preparative thin layer chromatography (ethyl acetate:hexane
(1:1)  

\[
\text{rac-}(4aS,7S,7aR)-7a\text{-hydroxy-4a-isobutyl-1,3,7-trimethylhexahydro-2H-cyclopenta}\[d]\text{pyrimidine-2,4(3H)-dione 300a}\]

(19.9 mg, 74.0 µmol, 74%) as a white solid.

\[\text{mp 112-114 °C; \quad \nu_{\text{max}} (\text{neat})/\text{cm}^{-1} 3418 (\text{br. OH}), 2957, 1704 (\text{C=O}), 1644 (\text{C=O}), 1455, 1414, 1385, 1326, 1122, 1086, 1044, 913, 754; \quad 1^H \text{NMR (400 MHz, CDCl}_3) \delta \text{ppm 0.56 (3 H, d, } J = 6.6 \text{ Hz, CCH}_3 \text{), 0.77 (3 H, d, } J = 6.6 \text{ Hz, CCH}_2\text{CHCH}_3 \text{), 1.07 - 1.16 (1 H, m, 1 H from CCH}_2\text{CHCH}_3 \text{), 1.26 (1 H, dd, } J = 12.8, 8.4 \text{ Hz, 1 H from CCH}_2\text{CHCH}_3 \text{), 1.30 - 1.41 (1 H, m, 1 H from CCH}_2\text{CH}_2 \text{), 1.44 - 1.53 (2 H, m, 1 H from CCH}_2\text{CH}_2 \text{, CCH}_2\text{CHCH}_3 \text{), 1.85 - 1.95 (1 H, m, 1 H from CCHCH}_2 \text{), 2.09 (1 H, s, OH), 2.08 - 2.17 (1 H, m, 1 H from CCHCH}_2 \text{), 2.58 - 2.66 (1 H, m, CCHCH}_3 \text{), 2.91 (3 H, s, NCH}_3 \text{), 3.02 (3 H, s, NCH}_3; \quad 1^3C \text{NMR (100 MHz, CDCl}_3) \delta \text{ppm 17.4 (CCH}_3 \text{), 23.4 (CCH}_2\text{CHCH}_3 \text{), 24.7 (CCH}_2\text{CHCH}_3 \text{, CCH}_2\text{CHCH}_3 \text{), 25.0 (CCH}_2\text{CH}_2 \text{), 28.4 (CCHCH}_3 \text{), 28.6 (NCH}_3 \text{), 29.4 (NCH}_3 \text{), 31.5 (CCH}_2\text{CHCH}_3 \text{), 42.8 (CHCH}_3 \text{), 54.9 (C})^6 \text{, 95.3 (C})^6 \text{, 152.7 (C=O), 172.8 (C=O); \quad m/z (ES+) 269 ((M + H), 100%). (Found: (M + H) 269.1864. C}_{14}\text{H}_{25}\text{N}_2\text{O}_3 \text{ requires M, 269.1860).} \]

\[
\text{rac-}(4aR,7S,7aR)-4a\text{-}(\text{But-3-en-1-yl})\text{-7a-hydroxy-1,3,7-trimethyltetrahydro-1H-cyclopenta}\[d]\text{pyrimidine-2,4(3H,4aH)-dione (300e)}
\]

As for general procedure F, reaction of 5,5-di(but-3-en-1-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 299e (26 mg, 0.10 mmol, 1.0 eq) and SmI\(_2\) (0.085 M in THF, 7.1 mL, 0.60 mmol, 6.0 eq) in THF (1.0 mL) and H\(_2\)O (0.36 mL, 20 mmol, 200 eq) for 15 minutes gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) \text{rac-}(4aR,7S,7aR)-4a\text{-}(\text{But-3-en-1-yl})\text{-7a-hydroxy-1,3,7-trimethyltetrahydro-1H-cyclopenta}\[d]\text{pyrimidine-2,4(3H,4aH)-dione (300e)} (14.6 mg, 55.0 µmol, 55%, > 95:5 dr (> 95:5 crude dr)) as a colourless oil.

\[\text{ν}_{\text{max}} (\text{neat})/\text{cm}^{-1} 3401 (\text{br. OH}), 2960, 2930, 2874, 1702 (\text{C=O}), 1649 (\text{C=O}), 1456, 1411, 1385, 1332, 1121, 1089, 1047, 913, 755, 648; \quad 1^H \text{NMR (500 MHz, Acetone) } \delta \text{ppm 0.70 (3 H, d, } J = 7.3 \text{ Hz, CHCH}_3 \text{), 1.16 (1 H, dtd, } J = 13.0, 8.5, 4.7 \text{ Hz, 1 H from CCH}_2\text{CHCH}_3 \text{), 1.64 (1 H, ddd, } J = 12.9, 9.8, 8.5 \text{ Hz, 1 H from} \]

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$\text{CH}_2\text{CH}_2\text{CHCH}_3, 1.70 - 1.83$ (2 H, m, $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), $1.84 - 1.94$ (1 H, m, 1 H from $\text{CH}_2\text{CH}=\text{CH}_2$), $1.94 - 2.08$ (2 H, m, 1 H from $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$, 1 H from $\text{CH}_2\text{CHCH}_3$), $2.38 - 2.46$ (1 H, m, $\text{CHCH}_3$), $2.57$ (1 H, ddd, $J = 12.9, 8.5, 4.1$ Hz, 1 H from $\text{CH}_2\text{CH}_2\text{CHCH}_3$), $3.02$ (3 H, s, NCH$_3$), $3.08$ (3 H, s, NCH$_3$), $4.88$ (1 H, ddt, $J = 10.4, 2.2, 1.5$ Hz, 1 H from $\text{CH}=\text{CH}_2$), $5.12$ (1 H, s, OH), $5.75$ (1 H, ddt, $J = 17.1, 10.4, 6.5$ Hz, C=CH$_2$); 

$\text{m/z}$ (ES$^+$) 249 ((M − OH), 4%). (Found: (M − OH) 249.1601. C$_{14}$H$_{21}$N$_2$O$_2$ requires $M$, 249.1598).

$\text{rac-(4aS,7aR)-7a-Hydroxy-4a-isobutyl-1,3-dimethyl-7-methylenetetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione (300j)}$

As for general procedure F, reaction of 5-(but-3-yn-1-yl)-5-isobutyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 299j (26 mg, 0.10 mmol, 1.0 eq) and SmI$_2$ (0.085 M in THF, 7.1 mL, 0.60 mmol, 6.0 eq) in THF (1.0 mL) and H$_2$O (0.36 mL, 20 mmol, 200 eq) for 15 minutes gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) $\text{rac-(4aS,7aR)-7a-hydroxy-4a-isobutyl-1,3-dimethyl-7-methylenetetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 300j}$ (16.8 mg, 63.0 µmol, 63%, > 95:5 dr (> 95:5 crude dr)) as a colourless oil.

$\nu_{\text{max}}$(neat)/cm$^{-1}$ 3376 (br. OH), 2955, 2868, 1706 (C=O), 1650 (C=O), 1460, 1416, 1386, 1325, 1110, 1070, 909, 759;

$^1\text{H NMR}$ (400 MHz, Acetone) δ ppm 0.86 (3 H, d, $J = 6.6$ Hz, CHCH$_3$), 0.90 (3 H, d, $J = 6.6$ Hz, CHCH$_3$), 1.53 (1 H, dd, $J = 14.3, 7.6$ Hz, 1 H from CH$_2$CH), 1.62 (1 H, dd, $J = 14.3, 4.5$ Hz, 1 H from CH$_2$CH), 1.66 - 1.75 (1 H, m, CH), 1.78 - 1.88 (1 H, m, 1 H from CH$_2$CH$_2$C=CH$_2$), 2.19 - 2.31 (1 H, m, 1 H from CH$_2$C=CH$_2$), 2.36 - 2.49 (2 H, m, 1 H from CH$_2$C=CH$_2$, 1 H from CH$_2$CH$_2$C=CH$_2$), 3.04 (3 H, s, NCH$_3$), 3.12 (3 H, s, NCH$_3$), 4.99 (1 H, t, $J = 2.3$ Hz, 1 H from C=CH$_2$), 5.15 (1 H, t, $J = 2.3$ Hz, 1 H from C=CH$_2$), 5.56 (1 H, s, OH);
\[ ^{13}\text{C NMR} \text{ (100 MHz, Acetone)} \delta \text{ ppm } 24.5 \text{ (CHCH}_3\text{)}, 25.2 \text{ (CHCH}_3\text{)}, 25.7 \text{ (CH)}, 26.5 \text{ (CH}_2\text{CH}=\text{CH}_2\text{)}, 28.4 \text{ (NCH}_3\text{)}, 29.7 \text{ (NCH}_3\text{)}, 30.9 \text{ (CH}_2\text{CH}_2\text{CH}=\text{CH}_2\text{)}, 41.1 \text{ (CH}_2\text{CH}), 56.5 \text{ (C}_6\text{)}, 91.6 \text{ (C}(\text{CH}_2\text{)}), 109.6 \text{ (C}=\text{CH}_2\text{)}, 151.9 \text{ (C}=\text{CH}_2\text{)}, 152.8 \text{ (C}=\text{O)}, 173.4 \text{ (C}=\text{O}); \]
\[ m/z \text{ (ES+)} 249 ((M − \text{OH}), 4\%). \text{ (Found: (M − OH) 249.1605. C}_{14}\text{H}_{21}\text{N}_2\text{O}_2 \text{ requires } M, 249.1598). \]

\[ \text{rac-}(4aS,7aS,E)-7a-\text{Hydroxy-4a-isobutyl-1,3-dimethyl-7-} \]
\[ ((\text{trimethylsilyl})\text{methylene})\text{tetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)}- \]
\[ \text{dione (300k)} \]

As for general procedure F, reaction of 5-isobutyl-1,3-dimethyl-5-(4-(trimethylsilyl)but-3-yne-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione 299k (34 mg, 0.10 mmol, 1.0 eq) and SmI\(_2\) (0.085 M in THF, 7.1 mL, 0.60 mmol, 6.0 eq) in THF (1.0 mL) and H\(_2\)O (0.36 mL, 20 mmol, 200 eq) for 15 minutes gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) rac-(4aS,7aS,E)-7a-hydroxy-4a-isobutyl-1,3-dimethyl-7-((trimethylsilyl)methylene)tetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 300k (22.2 mg, 66.0 µmol, 66%, > 95:5 dr (> 95:5 crude dr)) as a white solid.

\[ \text{mp 156-158 °C; } \]
\[ \nu_{\text{max}} \text{ (neat)/cm}^{-1} 3390 \text{ (br. OH), 2955, 1707 (C}=\text{O}, 1652 (C}=\text{O), 1462, 1414, 1385, 1324, 1249, 1103, 1063, 1024, 846, 760; } \]

\[ ^{1}\text{H NMR} \text{ (400 MHz, Acetone)} \delta \text{ ppm } 0.09 \text{ (9 H, s, } 3 \times \text{SiCH}_3\text{), 0.88 (3 H, d, } J = 6.6 \text{ Hz, CHCH}_3\text{), 0.90 (3 H, d, } J = 6.6 \text{ Hz, CHCH}_3\text{), 1.47 (1 H, dd, } J = 14.6, 7.3 \text{ Hz, 1 H from } \text{CH}_2\text{CH}, 1.60 (1 H, dd, } J = 14.6, 4.3 \text{ Hz, 1 H from } \text{CH}_2\text{CHCH}_3\text{), 1.70 - 1.80 (1 H, m, CHCH}_3\text{), 1.85 - 1.92 (1 H, m, 1 H from } \text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2\text{), 2.26 - 2.38 (2 H, m, 1 H from } \text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2\text{), 2.44 - 2.53 (1 H, m, 1 H from } \text{CH}_2\text{CH}_2\text{CH}=\text{CH}, 3.03 (3 \text{ H, s, NCH}_3\text{), 3.07 (3 H, s, NCH}_3\text{), 5.51 (1 H, s, OH), 5.72 (1 H, t, } J = 2.3 \text{ Hz, C}=\text{CH}; } \]

\[ ^{13}\text{C NMR} \text{ (100 MHz, Acetone)} \delta \text{ ppm } -0.6 \text{ ( } 3 \times \text{SiCH}_3\text{), 24.7 (CHCH}_3\text{), 25.3 (CHCH}_3\text{), 25.7 (CHCH}_3\text{), 26.8 (CH}_2\text{CH}=\text{CH}_2\text{), 28.3 (NCH}_3\text{), 29.8 (NCH}_3\text{), 30.8 (CH}_2\text{CH}_2\text{CH}=\text{CH}_2\text{), 40.8 (CH}_2\text{CH), 55.6 (C}_6\text{), 92.7 (C}_6\text{), 123.0 (C}=\text{CH), 153.0 (C}=\text{O), 159.3 (C}=\text{CH), 173.6 (C}=\text{O); } \]
\[ m/z \text{ (ES+)} 339 ((M + H), 100%). \text{ (Found: (M + H) 339.2113. C}_{17}\text{H}_{31}\text{N}_2\text{O}_2\text{Si requires } M, 339.2098). \]
rac-(4aS,7aR,E)-7-Benzylidene-7a-hydroxy-4a-isobutyl-1,3-dimethyltetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione (300I-A)

rac-(4aS,7aR,Z)-7-Benzylidene-7a-hydroxy-4a-isobutyl-1,3-dimethyltetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione (300I-B)

As for general procedure F, reaction of 5-isobutyl-1,3-dimethyl-5-(4-phenylbut-3-yn-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione 299I (27 mg, 0.08 mmol, 1.0 eq) and SmI₂ (0.085 M in THF, 5.6 mL, 0.60 mmol, 6.0 eq) in THF (1.0 mL) and H₂O (3.5 mL, 240 mmol, 2400 eq) for 15 minutes gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) rac-(4aS,7aR,E)-7-benzylidene-7a-hydroxy-4a-isobutyl-1,3-dimethyltetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 300I-A and rac-(4aS,7aR,Z)-7-benzylidene-7a-hydroxy-4a-isobutyl-1,3-dimethyltetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 300I-B (23.8 mg, 69.6 µmol, 86%, > 95:5 dr (> 95:5 crude dr), 24:76 E:Z ratio) as a white solid.

v<sub>max</sub> (neat)/cm⁻¹ 3360 (br. OH), 2955, 2869, 1653 (C=O), 1454, 1383, 1234, 1104, 1069, 1029, 756, 699;

<sup>1</sup>H NMR (500 MHz, Acetone) δ ppm 0.80 (3 H, d, J = 6.6 Hz, CHCH₃ (B)), 0.87 (3 H, d, J = 6.6 Hz, CHCH₃ (A)), 0.89 (3 H, d, J = 6.6 Hz, CHCH₃ (B)), 0.90 (3 H, d, J = 6.6 Hz, CHCH₃ (A)), 1.47 (1 H, dd, J = 14.2, 4.7 Hz, 1 H from CH₂CH (B)), 1.51 - 1.67 (4 H, m, 1 H from CH₂CH (B), CH₂CH (A), CHCH₃ (B)), 1.69 - 1.76 (1 H, m, CHCH₃ (A)), 1.80 (1 H, ddd, J = 12.0, 10.4, 7.9 Hz, 1 H from CH₂CH₂CH=CH (B)), 1.91 - 1.99 (1 H, m, 1 H from CH₂CH₂CH=CH (A)), 2.29 (3 H, s, NCH₃ (B)), 2.39 (1 H, dddd, J = 17.1, 9.8, 7.9, 1.9 Hz, 1 H from CH₂CH₂CH=CH (B)), 2.50 - 2.56 (3 H, m, 1 H from CH₂CH₂CH=CH (A and B), 1 H from CH₂CH₂CH=CH (A)), 2.60 (1 H, ddt, J = 17.1, 10.4, 2.5 Hz, 1 H from CH₂CH=CH (B)), 2.69 - 2.76 (1 H, m, 1 H from CH₂CH=CH (A)), 3.04 (3 H, s, NCH₃ (A)), 3.07 (3 H, s, NCH₃ (B)), 3.23 (3 H, s, NCH₃ (A)), 3.65 (1 H, s, OH (B)), 3.72 (1 H, s, OH (A)), 4.53 (1 H, br. s, C=CH (B)), 5.65 (1 H, t, J = 2.4 Hz, C=CH (A)), 6.04 - 7.08 (2 H, m, 2 × ArH (B)), 7.18 - 7.23 (1 H, m, ArH (B)), 7.24 - 7.31 (3 H, m, 2 × ArH (B), ArH (A)), 7.34 - 7.39 (4 H, m, 4 × ArH (A));

<sup>13</sup>C NMR (125 MHz, Acetone) δ ppm 24.4 (CHCH₃ (B)), 24.6 (CHCH₃ (A)), 25.0 (CHCH₃ (B)), 25.2 (CHCH₃ (A)), 25.6 (CHCH₃ (B)), 25.7 (CHCH₃ (A)), 26.3 (CH₂CH=CH

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Diagram A and B
(A)), 28.4 (NCH$_3$ (A)), 28.4 (NCH$_3$ (B)), 28.8 (CH$_2$CH=CH (B)), 29.5 (CH$_2$CH$_2$C=CH (B)), 29.5 (NCH$_3$ (B)), 30.0 (NCH$_3$ (A)), 31.5 (CH$_2$CH$_2$C=CH (A)), 40.3 (CH$_2$CH (B)), 40.8 (CH$_2$CH (A)), 55.9 (C$_3^d$ (A)), 58.2 (C$_3^d$ (B)), 91.1 (C$_3^d$ (B)), 93.1 (C$_3^d$ (A)), 124.6 (C=CH (A)), 127.1 (C=CH (B)), 127.5 (ArCH (B)), 128.2 (ArCH (A)), 128.9 (2 × ArCH (B)), 129.1 (2 × ArCH (B)), 129.3 (2 × ArCH (A)), 137.3 (ArC$_3^d$ (A)), 138.2 (ArC$_3^d$ (B)), 144.0 (C=CH (B)), 144.1 (C=CH (A)), 152.0 (C=O (B)), 152.9 (C=O (A)), 173.2 (C=O (B)), 173.3 (C=O (A));

m/z (ES+) 343 ((M + H), 100%). (Found: (M + H) 343.2014. C$_{20}$H$_{27}$N$_2$O$_3$ requires M, 343.2016).

rac-(4aR,7aR)-4a-(But-3-yn-1-yl)-7a-hydroxy-1,3-dimethyl-7-methylenetetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione (300m)

As for general procedure F, reaction of 5,5-di(but-3-yn-1-yl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 299m (26 mg, 0.10 mmol, 1.0 eq) and SmI$_2$ (0.11 M in THF, 5.5 mL, 0.60 mmol, 6.0 eq) in THF (1.0 mL) and H$_2$O (0.36 mL, 20 mmol, 200 eq) for 15 minutes gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) rac-(4aR,7aR)-4a-(but-3-yn-1-yl)-7a-hydroxy-1,3-dimethyl-7-methylenetetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 300m (21.8 mg, 82.0 µmol, 82%, > 95:5 dr (> 95:5 crude dr)) as a colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3298 (br. OH), 2925, 2855, 1704 (C=O), 1649 (C=O), 1459, 1415, 1385, 1334, 1220, 1136, 1054, 913, 759;

$^1$H NMR (500 MHz, Acetone) δ ppm 1.85 - 1.99 (3 H, m, CH$_2$CH$_2$C=CH, 1 H from CH$_2$CH$_2$C=CH$_2$), 2.06 - 2.12 (1 H, m, 1 H from CH$_2$CH$_2$C=CH$_2$), 2.25 - 2.32 (1 H, m, 1 H from CH$_2$C=CH), 2.33 (1 H, t, $J = 2.5$ Hz, C=CH), 2.34 - 2.43 (1 H, m, 1 H from CH$_2$C=CH$_2$), 2.45 - 2.52 (1 H, m, 1 H from CH$_2$C=CH$_2$), 2.51 - 2.59 (1 H, m, 1 H from CH$_2$C≡CH), 2.99 (3 H, s, NCH$_3$), 3.07 (3 H, s, NCH$_3$), 5.20 (1 H, t, $J = 2.4$ Hz, 1 H from C=CH$_2$), 5.37 (1 H, t, $J = 2.4$ Hz, 1 H from C=CH$_2$), 5.62 (1 H, s, OH);

$^{13}$C NMR (125 MHz, Acetone) δ ppm 15.2 (CH$_2$C=CH), 26.2 (CH$_2$C=CH$_2$), 28.2 (NCH$_3$), 29.6 (NCH$_3$), 31.3 (CH$_2$CH$_2$C=CH$_2$), 32.6 (CH$_2$CH$_2$C=CH$_2$), 54.4 (C$_3^d$), 69.8 (C=CH), 85.2 (C=CH), 92.4 (C$_3^d$), 111.8 (C=CH$_2$), 150.6 (C=CH$_2$), 152.9 (C=O), 173.0 (C=O);
\( m/z \) (ES+) 263 ((M + H), 100%). (Found: (M + H) 263.1386. \( \text{C}_{14}\text{H}_{19}\text{N}_{2}\text{O}_{3} \) requires \( M \), 263.1390).

\[
\begin{align*}
\text{A} & \quad \text{B}
\end{align*}
\]

\( \text{rac-}(5S,6R)-5\text{-Decyl-6-hydroxy}(6^{-2}\text{H})-1,3,5\text{-trimethylidihydropyrimidine-2,4}(1H,3H)\text{-dione} \ (306\text{-A}) \\
\text{rac-}(5S,6S)-5\text{-Decyl-6-hydroxy}(6^{-2}\text{H})-1,3,5\text{-trimethylidihydropyrimidine-2,4}(1H,3H)\text{-dione} \ (306\text{-B})
\]

As for general procedure F, reaction of 5-decyl-1,3,5-trimethylpyrimidine-2,4,6(1H,3H,5H)-trione 285b (31 mg, 0.10 mmol, 1.0 eq) and SmI\(_2\) (0.11 M in THF, 2.7 mL, 0.30 mmol, 3.0 eq) in THF (1.0 mL) and D\(_2\)O (1.8 mL, 100 mmol, 1000 eq) for 60 seconds gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) \( \text{rac-}(55,6R)-5\text{-decyl-6-hydroxy}(6^{-2}\text{H})-1,3,5\text{-trimethylidihydropyrimidine-2,4}(1H,3H)\text{-dione} \ 306\text{-A} \) and \( \text{rac-}(5S,6S)-5\text{-decyl-6-hydroxy}(6^{-2}\text{H})-1,3,5\text{-trimethylidihydropyrimidine-2,4}(1H,3H)\text{-dione} \ 306\text{-B} \) (16.4 mg, 57.0 µmol, 57%, > 98% \( D \), 77:23 crude dr, major isomer partially separated) as a colourless oil.

\( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 3398 (br. OH), 2924, 2854, 1711 (C=O), 1656 (C=O), 1469, 1417, 1384, 1316, 1064, 965, 847, 764;

\( ^1\text{H NMR} \) (500 MHz, Acetone) \( \delta \) ppm 0.87 (3 H, t, \( J = 6.9 \) Hz, \( \text{CH}_2\text{CH}_3 \) (B)), 0.88 (3 H, t, \( J = 6.9 \) Hz, \( \text{CH}_2\text{CH}_3 \) (A)), 1.15 (3 H, s, CCH\(_3\) (A)), 1.23 (3 H, s, CCH\(_3\) (B)), 1.22 - 1.36 (31 H, m, 1 H from CCH\(_2\)CH\(_2\) (A), 7 × CH\(_2\) (A and B), CH\(_2\) (B)), 1.36 - 1.46 (1 H, m, 1 H from CCH\(_2\)CH\(_2\) (A)), 1.42 - 1.50 (1 H, m, 1 H from CCH\(_2\) (B)), 1.50 - 1.58 (1 H, m, 1 H from CCH\(_2\) (B)), 1.70 - 1.82 (2 H, m, CCH\(_2\) (A)), 3.05 (6 H, s, NCH\(_3\) (A and B)), 3.05 (6 H, s, NCH\(_3\) (A and B)), 5.47 (1 H, s, OH (B)), 5.48 (1 H, s, OH (A));

\( ^{13}\text{C NMR} \) (125 MHz, Acetone) \( \delta \) ppm 14.4 (\( \text{CH}_2\text{CH}_3 \) (A and B)), 17.8 (CCH\(_3\) (B)), 21.1 (CCH\(_3\) (A)), 23.3 (CCH\(_2\text{CH}_2\) (A)), 23.4 (CH\(_2\) (A and B)), 24.7 (CH\(_2\) (B)), 27.7 (NCH\(_3\) (A and B)), 30.1 (CH\(_2\) (A and B)), 30.2 (CH\(_2\) (A and B)), 30.2 (CH\(_2\) (A and B)), 30.4 (CH\(_2\) (A and B)), 30.7 (CH\(_2\) (B)), 31.2 (CH\(_2\) (A)), 32.7 (CH\(_2\) (A and B)), 33.5 (CCH\(_2\) (A)), 34.6 (NCH\(_3\) (A and B)), 37.5 (CCH\(_2\) (B)), 46.6 (C\(_{\text{iii}}\) (A)), 48.0 (C\(_{\text{ii}}\) (B)), 84.8 (t, \( J = 23.6 \) Hz, CD (A and B)), 153.7 (C=O (A and B)), 174.4 (C=O (B)), 175.6 (C=O (A));

\( m/z \) (ES+) 296 ((M − OH), 90%), 336 ((M + Na), 100). (Found: (M − OH) 296.2432. \( \text{C}_{17}\text{H}_{30}\text{DN}_{2}\text{O}_{2} \) requires \( M \), 296.2443).
For the corresponding non-deuterated compound, see 286j.

\[ \text{rac-}(4aS,7aS, \ Z)-7a\text{-Hydroxy-4a-isobutyl-1,3-dimethyl-7-} (^{2}\text{H})\text{methylene})\text{tetrahydro-1H-cyclopenta}[d]\text{pyrimidine-2,4}(3H,4aH)-dione (308-A) \]

\[ \text{rac-}(4aS,7aS, \ E)-7a\text{-Hydroxy-4a-isobutyl-1,3-dimethyl-7-} (^{2}\text{H})\text{methylene})\text{tetrahydro-1H-cyclopenta}[d]\text{pyrimidine-2,4}(3H,4aH)-dione (308-B) \]

As for general procedure F, reaction of 5-(but-3-yn-1-yl)-5-isobutyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione 299j (26 mg, 0.10 mmol, 1.0 eq) and SmI\(_2\) (0.085 M in THF, 7.1 mL, 0.60 mmol, 6.0 eq) in THF (1.0 mL) and D\(_2\)O (0.36 mL, 20 mmol, 200 eq) for 15 minutes gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) \[ \text{rac-}(4aS,7aS, \ Z)-7a\text{-Hydroxy-4a-isobutyl-1,3-dimethyl-7-} (^{2}\text{H})\text{methylene})\text{tetrahydro-1H-cyclopenta}[d]\text{pyrimidine-2,4}(3H,4aH)-dione 308-A \] and \[ \text{rac-}(4aS,7aS, \ E)-7a\text{-Hydroxy-4a-isobutyl-1,3-dimethyl-7-} (^{2}\text{H})\text{methylene})\text{tetrahydro-1H-cyclopenta}[d]\text{pyrimidine-2,4}(3H,4aH)-dione 308-B \] (17.9 mg, 67.0 µmol, 67%, > 98% D, > 95:5 dr (> 95:5 crude dr)) as a colourless oil.

\[ \nu_{\text{max}} \text{(neat)/cm}^{-1} \] 3363 (br. OH), 2955, 2865, 1705 (C=O), 1647 (C=O), 1454, 1414, 1386, 1324, 1205, 1109, 1067, 1025, 974, 902, 847, 810, 757;

\[ ^{1}\text{H NMR} \] (400 MHz, Acetone) \( \delta \) ppm 0.86 (6 H, d, \( J = 6.6 \text{ Hz} \), CHC\(_3\) (A and B)), 0.89 (6 H, d, \( J = 6.6 \text{ Hz} \), CHC\(_3\) (A and B)), 1.53 (2 H, dd, \( J = 14.4, 7.6 \text{ Hz} \), 1 H from CH\(_2\)CH (A and B)), 1.62 (2 H, dd, \( J = 14.4, 4.3 \text{ Hz} \), 1 H from CH\(_2\)CH (A and B)), 1.66 - 1.74 (2 H, m, CH (A and B)), 1.78 - 1.87 (2 H, m, 1 H from CH\(_2\)CH\(_2\)C=C (A and B)), 2.19 - 2.29 (2 H, m, 1 H from CH\(_2\)C=C (A and B)), 2.36 - 2.49 (4 H, m, 1 H from CH\(_2\)CH\(_2\)C=C (A and B), 1 H from CH\(_2\)C=C (A and B)), 2.49 (6 H, s, NCH\(_3\) (A and B)), 3.04 (6 H, s, NCH\(_3\) (A and B)), 3.11 (6 H, s, NCH\(_3\) (A and B)), 4.97 (1 H, t, \( J = 2.1 \text{ Hz} \), C=CH (B)), 5.13 (1 H, t, \( J = 2.5 \text{ Hz} \), C=CH (A));

\[ ^{13}\text{C NMR} \] (100 MHz, Acetone) \( \delta \) ppm 24.5 (2 \( \times \) CHCH\(_3\) (A and B)), 25.2 (CH (A and B)), 25.7 (CH\(_2\)C=C (A and B)), 28.4 (NCH\(_3\) (A and B)), 29.7 (NCH\(_3\) (A and B)), 30.8 (CH\(_2\)CH\(_2\)C=C (A and B)), 41.0 (CH\(_2\)CH (A and B)), 56.4 (C\(_3\) (A and B)), 91.6 (C\(_3\) (A and B)), 109.1 (t, \( J = 23.6 \text{ Hz} \), C=CH (A and B)), 152.9 (C=O (A and B)), 154.3 (C=CH (A and B)), 173.4 (C=O (A and B));
m/z (ES+) 250 ((M − OH), 100%). (Found: (M − OH) 250.1665. C_{14}H_{20}DN_{2}O_{2} requires M, 250.1660).

For the corresponding non-deuterated compound, see 300j.

rac-(4aS,7aS,E)-7a-Hydroxy-4a-isobutyl-1,3-dimethyl-7-((trimethylsilyl)(^2H)methylene)tetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione (309)

As for general procedure F, reaction of 5-isobutyl-1,3-dimethyl-5-(4-(trimethylsilyl)but-3-yn-1-yl)pyrimidine-2,4,6(1H,3H,5H)-trione 299k (34 mg, 0.10 mmol, 1.0 eq) and SmI$_2$ (0.085 M in THF, 7.1 mL, 0.60 mmol, 6.0 eq) in THF (1.0 mL) and D$_2$O (0.36 mL, 20 mmol, 200 eq) for 15 minutes gave after preparative thin layer chromatography (ethyl acetate:hexane (1:1)) rac-(4aS,7aS,E)-7a-hydroxy-4a-isobutyl-1,3-dimethyl-7-((trimethylsilyl)(^2H)methylene)tetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 309 (26.5 mg, 78.1 µmol, 78%, > 98% D, > 95:5 dr (> 95:5 crude dr)) as a white solid.

mp 156-158 °C;
ν$_{max}$ (neat)/cm$^{-1}$ 3364 (br. OH), 2954, 2867, 1705 (C=O), 1648 (C=O), 1457, 1413, 1386, 1322, 1248, 1207, 1111, 1054, 999, 837, 759, 690, 649;

$^1$H NMR (400 MHz, Acetone) δ ppm 0.09 (9 H, s, 3 × SiCH$_3$), 0.87 (3 H, d, J = 6.7 Hz, CHCH$_3$), 0.90 (3 H, d, J = 6.7 Hz, CHCH$_3$), 1.47 (1 H, dd, J = 14.4, 7.3 Hz, 1 H from CH$_2$CH), 1.60 (1 H, dd, J = 14.4, 4.3 Hz, 1 H from CH$_2$CH), 1.70 - 1.81 (1 H, m, CHCH$_3$), 1.85 - 1.92 (1 H, m, 1 H from CH$_2$CH$_2$C=CD), 2.26 - 2.38 (2 H, m, 1 H from CH$_2$CH$_2$C=CD, 1 H from CH$_2$C=CD), 2.43 - 2.54 (1 H, m, 1 H from CH$_2$C=CD), 3.03 (3 H, s, NCH$_3$), 3.07 (3 H, s, NCH$_3$), 5.52 (1 H, s, OH);

$^{13}$C NMR (100 MHz, Acetone) δ ppm −0.6 (3 × SiCH$_3$), 24.7 (CHCH$_3$), 25.3 (CHCH$_3$), 25.7 (CHCH$_3$), 26.7 (CH$_2$C=CD), 28.3 (NCH$_3$), 29.8 (NCH$_3$), 30.8 (CH$_2$CH$_2$C=CD), 40.8 (CH$_2$CH), 55.6 (C$^0$), 92.6 (C$^0$), 122.6 (d, J = 20.3 Hz, C=CD), 153.0 (C=O), 159.1 (C=CD), 173.6 (C=O);

m/z (ES+) 322 (79%), 340 ((M + H), 11), 362 ((M + Na), 100). (Found: (M + H) 340.2165. C$_{17}$H$_{30}$DN$_2$O$_3$Si requires M, 340.2161).

For the corresponding non-deuterated compound, see 300k.
5.7. General procedure G – Additions into N-acyliminiums

\[
\text{rac-}(5R,6R)-6\text{-Allyl-5-isopentyl-1,3,5-trimethylidydropyrimidine-2,4}(1H,3H)\text{-dione (317b)}
\]

To a stirred solution of both isomers of 6-hydroxy-5-isopentyl-1,3,5-trimethylidydropyrimidine-2,4(1H,3H)-dione \text{285n} (10 mg, 41.3 µmol, 1.0 eq) in CH₂Cl₂ (1.0 mL) was added allyltrimethylsilane (66 µL, 0.41 mmol, 10 eq). BF₃•OEt₂ (25 µL, 0.21 mmol, 5.0 eq) was then added and the reaction mixture stirred at room temperature for 3 hours. The reaction was quenched with NH₄Cl\text{aq., sat.} (2.0 mL) and the aqueous phase extracted with CH₂Cl₂ (3 × 2.0 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated \textit{in vacuo}. Purification by preparative thin layer chromatography on silica gel, eluting with 40% ethyl acetate in petroleum ether (40-60 °C) gave \textit{rac-}(5R,6R)-6-allyl-5-isopentyl-1,3,5-trimethylidydropyrimidine-2,4(1H,3H)-dione \text{317b} (8.4 mg, 31.5 µmol, 76%, 92:8 dr (91:9 crude dr)) as a colourless oil.

\textbf{ν}\textsubscript{max} (neat)/cm\textsuperscript{-1} 2953, 2929, 2870, 1708 (C=O), 1665 (C=O), 1469, 1417, 1398, 1383, 1366, 1283, 1217, 1196, 1178, 1093, 1039, 917, 758;

\textbf{1H NMR} (400 MHz, Acetone) \textit{δ} ppm 0.84 (3 H, d, \textit{J} = 6.6 Hz, CHC₃), 0.85 (3 H, d, \textit{J} = 6.6 Hz, CHCH₃), 0.99 - 1.09 (1 H, m, 1 H from CH₂CHCH₃), 1.16 (3 H, s, CCH₃), 1.19 - 1.28 (1 H, m, 1 H from CH₂CHCH₃), 1.39 - 1.52 (2 H, m, 1 H from CCH₂, CHCH₃), 1.53 - 1.63 (1 H, m, 1 H from CCH₂), 2.17 - 2.25 (1 H, m, 1 H from CH₂CH=CH₂), 2.47 (1 H, dddt, \textit{J} = 14.2, 7.3, 4.3, 1.3 Hz, 1 H from CH₂CH=CH₂), 3.00 (3 H, s, NCH₃), 3.04 (3 H, s, NCH₃), 3.35 (1 H, dd, \textit{J} = 6.9, 4.4 Hz, CCH), 4.99 - 5.09 (2 H, m, CH=CH₂), 5.72 (1 H, dddt, \textit{J} = 17.2, 9.9, 7.4 Hz, CH=CH₂);

\textbf{13C NMR} (100 MHz, Acetone) \textit{δ} ppm 18.4 (CCH₃), 22.7 (CHCH₃), 22.9 (CHCH₃), 27.7 (NCH₃), 29.1 (CHCH₃), 33.4 (CH₂CHCH₃), 35.1 (CH₂CH=CH₂), 36.1 (CCH₂), 36.6 (NCH₃), 45.6 (C₆), 63.1 (CCH), 118.7 (CH=CH₂), 134.6 (CH=CH₂), 153.5 (C=O), 174.9 (C=O);

\textbf{m/z} (ES+) 267 ((M + H), 100%), 268 (42). (Found: (M + H) 267.2067. C₁₅H₂₇N₂O₂ requires \textit{M}, 267.2073).
5-Allyl-2,4-dimethyl-2,4-diazaspiro[5.6]dodec-9-ene-1,3-dione (317f)

As for general procedure G, reaction of 5-hydroxy-2,4-dimethyl-2,4-diazaspiro[5.6]dodec-9-ene-1,3-dione 286o (10 mg, 42.0 µmol, 1.0 eq), allyltrimethylsilane (67 µL, 0.42 mmol, 10 eq) and BF$_3$•OEt$_2$ (26 µL, 0.21 mmol, 5.0 eq) in CH$_2$Cl$_2$ (1.0 mL) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) 5-allyl-2,4-dimethyl-2,4-diazaspiro[5.6]dodec-9-ene-1,3-dione 317f (9.1 mg, 34.7 µmol, 83%) as a colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3017, 2929, 2847, 1706 (C=O), 1663 (C=O), 1475, 1436, 1416, 1398, 1373, 1282, 1219, 1135, 1093, 1052, 1028, 1001, 917, 756, 727, 632;

$^1$H NMR (400 MHz, Acetone) $\delta$ ppm 1.63 - 1.72 (1 H, m, 1 H from CCH$_2$), 1.77 - 1.94 (2 H, m, CCH$_2$), 2.10 - 2.31 (5 H, m, 1 H from CCH$_2$, CCH$_2$CH$_2$, 1 H from CCH$_2$CH$_2$, 1 H from CH$_2$CH=CH$_2$), 2.43 - 2.55 (2 H, m, 1 H from CCH$_2$CH$_2$, 1 H from CH$_2$CH=CH$_2$, 3.00 (3 H, s, NCH$_3$), 3.05 (3 H, s, NCH$_3$), 3.60 (1 H, dd, $J = 7.3, 4.3$ Hz, CH), 5.00 - 5.11 (2 H, m, CH=CH$_2$), 5.57 - 5.82 (1 H, m, CH=CH), 5.75 - 5.82 (1 H, m, CH=CH$_2$), 5.75 (1 H, ddt, $J = 17.1, 10.0, 7.4$ Hz, CH=CH$_2$);

$^{13}$C NMR (100 MHz, Acetone) $\delta$ ppm 24.4 (CCH$_2$C), 24.8 (CH$_2$CH$_2$), 27.7 (NCH$_3$), 30.8 (CCH$_2$), 34.8 (CH$_2$CH=CH$_2$), 35.0 (CCH$_2$), 36.8 (NCH$_3$), 48.3 (C$^n$), 61.5 (CH), 118.7 (CH$_2$), 130.9 (CH=CH), 132.1 (CH=CH), 134.7 (CH=CH$_2$), 153.4 (C=O), 175.6 (C=O);

$m/z$ (ES+) 263 ((M + H), 25%), 269 (22), 285 ((M + Na), 100). (Found: (M + H) 263.1753. C$_{18}$H$_{23}$N$_2$O$_2$ requires $M$, 263.1754).

rac-(5R,6R)-5-Decyl-6-methoxy-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione (317g)

As for general procedure G, reaction of both isomers of 5-decyl-6-hydroxy-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 286j (10 mg, 32.0 µmol, 1.0 eq), and HCl (2 M in Et$_2$O, 0.2 mL, 0.4 mmol, 12.5 eq) in MeOH (1.0 mL) gave rac-(5R,6R)-5-decyl-6-
methoxy-1,3,5-trimethyldihydropyrimidine-2,4(1H,3H)-dione 317g (10.3 mg, 31.7 µmol, 99% (1H NMR vs. internal standard), 71:29 dr) as a colourless oil.

νmax (neat)/cm⁻¹ 2924, 2854, 1713 (C=O), 1657 (C=O), 1487, 1467, 1421, 1380, 1293, 1184, 1070, 1040, 930, 764, 722;

1H NMR (400 MHz, Acetone) δ ppm 0.82 (3 H, t, J = 6.6 Hz, CH₂C₃H₇), 1.18 (3 H, s, CCH₃), 1.19 - 1.45 (16 H, m, 8 × CH₂), 1.45 - 1.55 (1 H, m, 1 H from CH₂), 3.00 (3 H, s, NCH₃), 3.15 (3 H, s, OCH₃), 4.59 (1 H, br. s, CH);

13C NMR (100 MHz, Acetone) δ ppm 14.3 (CH₂C₃H₇), 17.7 (CCH₃), 23.3 (CH₂), 24.6 (CH₂), 27.6 (NCH₃), 29.9 (CH₂), 30.0 (CH₂), 30.2 (CH₂), 30.6 (CH₂), 31.1 (CH₂), 32.5 (CH₂), 33.3 (CCH₂), 34.7 (NCH₃), 37.4 (OCH₃), 48.0 (Cq), 86.1 (CH), 153.6 (C=O), 174.3 (C=O);

m/z (ES+) 295 ((M – OCH₃), 100%). (Found: (M – OCH₃) 295.2392. C₁₇H₃₁N₂O₂ requires M, 295.2380).

As for general procedure G, reaction of both isomers of 5-decyl-1,3,5-trimethyldihydropyrimidine-2,6-dioxohexahydropyrimidine-4-carbonitrile 317h-A and 317h-B (10.3 mg, 32.0 µmol, quantitative, 83:17 dr (81:19 crude dr)) as a colourless oil.

νmax (neat)/cm⁻¹ 2925, 2855, 1722 (C=O), 1678 (C=O), 1465, 1415, 1390, 1355, 1289, 1181, 1070, 963, 757;

1H NMR (500 MHz, Acetone) δ ppm 0.88 (3 H, t, J = 6.9 Hz, CH₂CH₃ (A)), 1.21 - 1.36 (31 H, m, 8 × CH₂ (A), 15 H from CH₂ (B)), 1.32 (3 H,
s, CCH$_3$ (B)), 1.38 (3 H, s, CCH$_3$ (A)), 1.44 - 1.54 (1 H, m, 1 H from CH$_2$ (B)), 1.57 - 1.64 (1 H, m, 1 H from CCH$_2$ (A)), 1.64 - 1.70 (1 H, m, 1 H from CCH$_2$ (B)), 1.67 - 1.76 (1 H, m, 1 H from CCH$_2$ (A)), 2.01 - 2.08 (1 H, m, 1 H from CCH$_2$ (B)), 3.12 (3 H, s, NCH$_3$ (B)), 3.13 (3 H, s, NCH$_3$ (A)), 3.13 (3 H, s, NCH$_3$ (A)), 3.15 (3 H, s, NCH$_3$ (B)), 4.68 (1 H, s, CH (B)), 4.69 (1 H, s, CH (A));

$^{13}$C NMR (125 MHz, Acetone) δ ppm 14.4 (CH$_2$C$_3$H$_7$ (A and B)), 19.0 (CCH$_3$ (A)), 20.0 (CCH$_3$ (B)), 23.2 (CH$_2$ (B)), 23.4 (CH$_2$ (A and B)), 24.4 (CH$_3$ (A)), 28.4 (NCH$_3$ (A and B)), 29.9 (CH$_2$ (A and B)), 30.0 (CH$_2$ (A and B)), 30.2 (CH$_2$ (A and B)), 30.3 (CH$_2$ (A and B)), 30.3 (CH$_2$ (A and B)), 32.7 (CH$_2$ (A and B)), 35.0 (CCH$_2$ (B)), 35.3 (NCH$_3$ (A)), 35.3 (NCH$_3$ (B)), 36.1 (CCH$_2$ (A)), 44.7 (C$^i$ (B)), 45.3 (C$^i$ (A)), 55.5 (CH (B)), 55.9 (CH (A)), 116.4 (C≡N (B)), 116.8 (C≡N (A)), 153.3 (C=O (A)), 154.0 (C=O (B)), 172.4 (C=O (A)), 173.3 (C=O (B));

$m/z$ (ES+) 127 (44%), 128 (25), 295 (100), 296 (20), 344 ((M + Na), 46), 392 (26).

rac-(5$R$,6$R$)-6-Azido-5-decyl-1,3,5-trimethylhydropyrimidine-2,4(1$H$,3$H$)-dione (317i-A)

rac-(5$R$,6$S$)-6-Azido-5-decyl-1,3,5-trimethylhydropyrimidine-2,4(1$H$,3$H$)-dione (317i-B)

As for general procedure G, reaction of both isomers of 5-decyl-6-hydroxy-1,3,5-trimethylhydropyrimidine-2,4(1$H$,3$H$)-dione 286j (10 mg, 32.0 µmol, 1.0 eq), trimethylsilyl azide (43 µL, 0.32 mmol, 10 eq) and BF$_3$•OEt$_2$ (20 µL, 0.16 mmol, 5.0 eq) in CH$_2$Cl$_2$ (1.0 mL) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) rac-(5$R$,6$R$)-6-azido-5-decyl-1,3,5-trimethylhydropyrimidine-2,4(1$H$,3$H$)-dione 317i-A and rac-(5$R$,6$S$)-6-azido-5-decyl-1,3,5-trimethylhydropyrimidine-2,4(1$H$,3$H$)-dione 317i-B (10.8 mg, 32.0 µmol, quantitative, 76:24 dr (76:24 crude dr)) as a colourless oil.

$\nu$$_{max}$ (neat)/cm$^{-1}$ 2924, 2855, 2102 (N$_3$), 1720 (C=O), 1676 (C=O), 1466, 1420, 1379, 1295, 1237, 1072, 949, 902, 760;

$^1$H NMR (400 MHz, Acetone) δ ppm 0.88 (3 H, t, $J = 6.8$ Hz, CH$_2$CH$_3$ (A)), 0.87 (3 H, t, $J = 6.8$ Hz, CH$_2$CH$_3$ (B)), 1.24 (3 H, s, CCH$_3$ (B)), 1.27 (3 H, s, CCH$_3$ (A)), 1.15 - 1.44 (32 H, m, 8 × CH$_2$ (A and B)), 1.50 - 1.69 (3 H, m, CCH$_2$ (A), 1 H from CCH$_2$ (B)), 1.83 -
1.93 (1 H, m, 1 H from CCH₂(B)), 3.07 (6 H, s, NCH₃(A and B)), 3.21 (3 H, s, NCH₃(A)), 3.24 (3 H, s, NCH₃(B)), 5.22 (1 H, s, CH(A)), 5.25 (1 H, s, CH(B));

13C NMR (100 MHz, Acetone) δ ppm 14.4 (CH₂C₃H₃(A)), 17.9 (CCH₃(A)), 20.1 (CH₂CH₃(B)), 21.0 (CCH₃(B)), 23.1 (CH₂(B)), 23.4 (CH₂(A)), 23.4 (CH₂(B)), 24.5 (CH₂(A)), 27.9 (NCH₃(A)), 28.0 (NCH₃(B)), 29.8 (CH₂(A and B)), 30.0 (CH₂(A and B)), 30.2 (CH₂(A and B)), 30.4 (CH₂(A and B)), 30.5 (CH₂(A and B)), 30.9 (CH₂(B)), 32.7 (CH₂(A)), 33.7 (CCH₂(B)), 36.0 (NCH₃(A)), 36.2 (NCH₃(B)), 37.3 (CCH₂(A)), 46.4 (C' (B)), 47.9 (C' (A)), 80.0 (CH(B)), 81.2 (CH(A)), 153.3 (C=O (A)), 154.0 (C=O (B)), 173.1 (C=O (A)), 174.1 (C=O (B));
m/z (ES+) 295 (25%), 327 (16), 360 ((M + Na), 100), 361 (23).

5-Decyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione (317j)

As for general procedure G, reaction of both isomers of 5-decyl-6-hydroxy-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 286j (10 mg, 32.0 µmol, 1.0 eq), triethylsilane (51 µL, 0.32 mmol, 10 eq) and BF₃•OEt₂ (20 µL, 0.16 mmol, 5.0 eq) in CH₂Cl₂ (1.0 mL) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) 5-decyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 317j (9.1 mg, 30.7 µmol, 96%) as a colourless oil.

νmax (neat)/cm⁻¹ 2924, 2854, 1712 (C=O), 1673 (C=O), 1491, 1447, 1416, 1377, 1285, 1184, 1062, 757;

1H NMR (500 MHz, Acetone) δ ppm 0.87 (3 H, t, J = 6.9 Hz, CH₂C₃H₃), 1.14 (3 H, s, CCH₃), 1.22 - 1.34 (16 H, m, 8 × CH₂), 1.49 - 1.62 (2 H, m, CCH₂CH₂), 3.00 (3 H, s, NCH₃), 3.03 (3 H, s, NCH₃), 3.21 (1 H, d, J = 12.5 Hz, 1 H from NCH₂), 3.25 (1 H, d, J = 12.5 Hz, 1 H from NCH₂);

13C NMR (125 MHz, Acetone) δ ppm 14.4 (CH₂C₃H₃), 20.9 (CCH₃), 23.4 (CH₂), 24.5 (CH₂), 28.0 (NCH₃), 30.0 (CH₂), 30.1 (CH₂), 30.2 (CH₂), 30.3 (CH₂), 30.9 (CH₂), 32.7 (CH₂), 35.9 (NCH₃), 36.8 (CCH₂), 42.1 (C'), 54.0 (NCH₂), 154.3 (C=O), 175.3 (C=O);
m/z (ES+) 319 ((M + Na), 100%). (Found: (M + H) 297.2536. C₁₇H₃₃N₂O₂ requires M, 297.2537).
**rac-(5R,6R)-5-Decyl-1,3,5,6-tetramethyldihydropyrimidine-2,4(1H,3H)-dione (317k-A)**

**rac-(5R,6S)-5-Decyl-1,3,5,6-tetramethyldihydropyrimidine-2,4(1H,3H)-dione (317k-B)**

As for general procedure G, reaction of both isomers of 5-decyl-6-hydroxy-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 286j (10 mg, 32.0 µmol, 1.0 eq), trimethylaluminium (160 µL, 0.32 mmol, 10 eq, 2 M in hexane) and BF₃•OEt₂ (20 µL, 0.16 mmol, 5.0 eq) in CH₂Cl₂ (1.0 mL) gave after column chromatography (30% ethyl acetate in petroleum ether (40–60 °C)) rac-(5R,6R)-5-decyl-1,3,5,6-tetramethyldihydropyrimidine-2,4(1H,3H)-dione 317k-A and rac-(5R,6S)-5-decyl-1,3,5,6-tetramethyldihydropyrimidine-2,4(1H,3H)-dione 317k-B (7.8 mg, 25.1 µmol, 78%, 87:13 dr (86:14 crude dr)) as a colourless oil.

νmax (neat)/cm⁻¹ 2924, 2855, 1710 (C=O), 1670 (C=O), 1459, 1415, 1285, 1185, 1109, 1055, 758, 722;

^1H NMR (400 MHz, Acetone) δ ppm 0.88 (3 H, t, J = 6.8 Hz, CH₂C₃H₃ (B)), 0.87 (3 H, t, J = 6.8 Hz, CH₂C₃H₃ (A)), 1.06 (3 H, d, J = 6.6 Hz, CHCH₃ (B)), 1.07 (3 H, d, J = 6.6 Hz, CHCH₃ (A)), 1.10 (3 H, s, CCH₃ (A)), 1.11 - 1.17 (2 H, m, 1 H from CCH₂CH₂ (A and B)), 1.19 (3 H, s, CCH₃ (B)), 1.21 - 1.36 (28 H, m, 7 × CH₂ (A and B)), 1.36 - 1.42 (2 H, m, 1 H from CCH₂CH₂ (A and B)), 1.42 - 1.48 (1 H, ddd, J = 13.4, 12.2, 4.4 Hz, 1 H from CCH₂ (A)), 1.61 (1 H, ddd, J = 13.4, 12.2, 4.4 Hz, 1 H from CCH₂ (A)), 1.81 (1 H, dd, J = 13.1, 10.1 Hz, 1 H from CCH₂ (B)), 3.00 (3 H, s, NCH₃ (A)), 3.01 (3 H, s, NCH₃ (B)), 3.04 (3 H, s, NCH₃ (B)), 3.04 (3 H, s, NCH₃ (A)), 3.26 (1 H, q, J = 6.6 Hz, CH (B)), 3.27 (1 H, q, J = 6.6 Hz, CH (A));

^13C NMR (100 MHz, Acetone) δ ppm 13.8 (CH₂C₃H₃ (B)), 14.2 (CHCH₃ (A)), 14.4 (CH₂CH₃ (A and B)), 18.3 (CCH₃ (A)), 21.7 (CCH₃ (B)), 23.1 (CH₂ (B)), 23.4 (CH₂ (A)), 24.6 (CCH₂CH₂ (A and B)), 27.8 (NCH₃ (A and B)), 30.1 (CH₂ (A and B)), 30.2 (CH₂ (A and B)), 30.4 (CH₂ (A and B)), 30.4 (CH₂ (A and B)), 30.7 (CH₂ (A)), 31.1 (CH₂ (B)), 32.7 (CH₂ (A and B)), 33.7 (CCH₂ (B)), 34.6 (NCH₃ (A and B)), 37.7 (CCH₂ (A)), 46.4 (C¹ (A and B)), 58.8 (CH (B)), 59.0 (CH (A)), 153.1 (C=O (A)), 153.4 (C=O (B)), 174.7 (C=O (A)), 174.9 (C=O (B));

m/z (ES+) 333 ((M + Na), 100%). (Found: (M + Na) 333.2504. C₁₈H₃₄N₂O₂Na requires M, 333.2512).
**rac-(5R,6R)-6-Ethynyl-5-isobutyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione (317i)**

As for general procedure G, reaction of both isomers of 6-hydroxy-5-isobutyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 286i (10 mg, 43.8 µmol, 1.0 eq), ethynyltributylstannane (130 µL, 0.44 mmol, 10 eq) and BF$_3$•OEt$_2$ (27 mL, 0.22 mmol, 5.0 eq) in CH$_2$Cl$_2$ (1.0 mL) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) **rac-(5R,6R)-6-ethynyl-5-isobutyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 317i** (10.4 mg, 43.8 µmol, quantitative, 88:12 dr (81:19 crude dr)) as a colourless oil.

$v_{\text{max}}$ (neat)/cm$^{-1}$ 2956, 2925, 2871, 2852, 1714 (C=O), 1670 (C=O), 1464, 1415, 1393, 1286, 1175, 1090, 1038, 872, 761, 749, 667;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.79 (3 H, d, $J = 6.7$ Hz, CHC$_{3}$H$_3$), 0.92 (3 H, d, $J = 6.7$ Hz, CHCH$_2$), 1.34 (3 H, s, CHCH$_3$), 1.46 (1 H, dd, $J = 13.9, 4.3$ Hz, 1 H from CH$_2$CH), 1.63 - 1.70 (1 H, m, 1 H from CH$_2$CH), 1.71 - 1.80 (1 H, m, CHCH$_3$), 3.04 (1 H, s, C≡CH), 3.05 (3 H, s, NCH$_3$), 3.08 (3 H, s, NCH$_3$), 4.08 (1 H, d, $J = 2.3$ Hz, 1 H, CHC≡C);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 19.8 (C$_{3}$H$_{3}$), 24.1 (CHCH$_3$), 24.7 (CHCH$_3$), 25.3 (CHCH$_3$), 28.0 (NCH$_3$), 34.8 (NCH$_3$), 45.5 (CH$_2$CH), 46.0 (C$^0$), 56.7 (CHC≡C), 76.3 (C≡CH), 79.3 (C≡CH), 153.7 (C=O), 173.7 (C=O);

$m/z$ (ES+) 235 (73%), 259 ((M + Na), 10), 291 (100). (Found: (M + H) 237.1593. C$_{13}$H$_{21}$N$_2$O$_2$ requires $M$, 237.1598).

**rac-Methyl 2-((4S,5R)-5-isobutyl-1,3,5-trimethyl-2,6-dioxohexahydropyrimidin-4-yl)-2-methylpropanoate (317m)**

As for general procedure G, reaction of both isomers of 6-hydroxy-5-isobutyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 286i (10 mg, 43.8 µmol, 1.0 eq), 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (89 µL, 0.44 mmol, 10 eq) and BF$_3$•OEt$_2$ (27 µL, 0.22 mmol, 5.0 eq) in CH$_2$Cl$_2$ (1.0 mL) gave after column chromatography (30%
ethyl acetate in petroleum ether (40-60 °C) rac-methyl 2-\((\text{4S,5R})\)-5-isobutyl-1,3,5-trimethyl-2,6-dioxohexahydropyrimidin-4-yl)-2-methylpropanoate 317m (13.2 mg, 42.3 µmol, 96%, > 95:5 dr (> 95:5 crude dr)) as a colourless oil.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 2989, 2955, 2870, 1725 (C=O), 1708 (C=O), 1475, 1420, 1391, 1290, 1258, 1220, 1181, 1138, 1089, 1038, 981, 759, 741;

\(^1\)H NMR (400 MHz, Acetone) \(\delta\) ppm 0.74 (3 H, d, \(J = 6.7\) Hz, CH\(\text{C}_3\)), 0.92 (3 H, d, \(J = 6.7\) Hz, CH\(\text{CH}_3\)), 0.99 (3 H, s, CCH\(\text{H}_3\)), 1.06 (3 H, s, CCH\(\text{H}_3\)), 1.24 (3 H, s, CH\(\text{C}_2\text{CCH}_3\)), 1.41 - 1.46 (2 H, m, CH\(\text{H}_2\)), 1.64 - 1.76 (1 H, m, CH\(\text{CH}_3\)), 3.02 (3 H, s, NCH\(\text{3}\)), 3.18 (3 H, s, NCH\(\text{3}\)), 3.69 (3 H, s, OCH\(\text{3}\)), 3.75 (1 H, s, C\(\text{H}_2\)NCH\(\text{3}\)),

\(^{13}\)C NMR (100 MHz, Acetone) \(\delta\) ppm 17.9 (C\(\text{C}_3\)), 18.6 (C\(\text{C}_3\)), 24.1 (CH\(\text{C}_2\text{CCH}_3\)), 24.3 (CH\(\text{CH}_3\)), 25.7 (CH\(\text{CH}_3\)), 27.7 (NCH\(\text{3}\)), 28.1 (CH\(\text{C}_2\text{CCH}_3\)), 41.6 (NCH\(\text{3}\)), 45.9 (C\(\text{q}\)), 48.5 (C\(\text{q}\)), 48.9 (CH\(\text{2CH}_3\)), 52.6 (OCH\(\text{3}\)), 69.6 (CH\(\text{NCH}_3\)), 154.0 (C=O), 175.0 (C=O), 177.3 (C=O);

\(m/z\) (ES+) 301 (58%), 335 ((M + Na), 100). (Found: (M + Na) 335.1931. C\(_{16}\)H\(_{28}\)N\(_2\)O\(_4\)Na requires \(M\), 335.1947).

\(\text{rac-}(\text{5R,6R})\)-5-Decyl-1,3,5-trimethyl-6-(propa-1,2-dien-1-yl)dihydropyrimidine-2,4(1H,3H)-dione (317n)

As for general procedure G, reaction of both isomers of 5-decyl-6-hydroxy-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 286j (10 mg, 32.0 µmol, 1.0 eq), trimethyl(propargyl)silane (50 µL, .32 mmol, 10 eq) and BF\(\text{3} \cdot \text{OEt}_2\) (20 µL, 0.16 mmol, 5.0 eq) in CH\(\text{2Cl}_2\) (1.0 mL) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) \(\text{rac-}(\text{5R,6R})\)-5-decyl-1,3,5-trimethyl-6-(propa-1,2-dien-1-yl)dihydropyrimidine-2,4(1H,3H)-dione 317n (8.2 mg, 24.5 µmol, 77%, 89:11 dr (87:13 crude dr)) as a colourless oil.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 2923, 2853, 1736, 1709 (C=O), 1674 (C=O), 1466, 1416, 1396, 1381, 1287, 1230, 1186, 1096, 1075, 1061, 847, 757, 722;

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 0.88 (3 H, t, \(J = 6.6\) Hz, CH\(\text{2CH}_3\)), 1.17 (3 H, s, CCH\(\text{3}\)), 1.21 - 1.35 (14 H, m, 7 × CH\(\text{2}\)), 1.38 - 1.43 (1 H, m, 1 H from CCH\(\text{2CH}_2\)), 1.53 (1 H, ddd, \(J = 13.4, 12.1, 4.7\) Hz, 1 H from CCH\(\text{2}\)), 1.60 - 1.71 (2 H, m, 1 H from CCH\(\text{2CH}_2\),
1 H from CCH₂, 2.99 (3 H, s, NCH₃), 3.04 (3 H, s, NCH₃), 3.71 (1 H, dt, J = 7.0, 2.1 Hz, CHCH=CH₂), 4.82 - 4.94 (2 H, m, C=CH₂), 5.15 (1 H, q, J = 6.6 Hz, CHCH=C);

$^{13}$C NMR (100 MHz, CDCl₃) δ ppm 14.4 (CH₂C₃H₇), 18.7 (CCH₃), 23.4 (CH₂), 24.6 (CH₂), 27.8 (NCH₃), 28.0 (CH₂), 30.2 (CH₂), 30.3 (CH₂), 30.7 (CH₂), 32.7 (CH₂), 34.6 (NCH₃), 35.0 (CCH₂CH₂), 37.8 (CCH₂), 46.6 (C₆), 63.0 (CHCH=C), 77.7 (C=CH₂), 87.6 (CHCH=C), 153.7 (C=O), 174.0 (C=O), 209.1 (C=CH₂);

m/z (ES+) 357 ((M + Na), 100%). (Found: (M + H) 335.2690. C₂₀H₃₅N₂O₂ requires M, 335.2693).

rac-(5R,6R)-6-(But-2-yn-1-yl)-5-decyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione (317o)

As for general procedure G, reaction of both isomers of 5-decyl-6-hydroxy-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 286j (10 mg, 32.0 µmol, 1.0 eq), 3-(trimethylsilyl)-1,2-butadiene (53 µL, 0.32 mmol, 10 eq) and BF₃•OEt₂ (20 µL, 0.16 mmol, 5.0 eq) in CH₂Cl₂ (1.0 mL) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) rac-(5R,6R)-6-(but-2-yn-1-yl)-5-decyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 317o (10.7 mg, 30.7 µmol, 96%, 90:10 dr (91:9 crude dr)) as a colourless oil.

ν max (neat)/cm⁻¹ 2922, 2853, 1710 (C=O), 1665 (C≡C), 1562 (C=O), 1467, 1417, 1398, 1382, 1285, 1191, 1097, 1063, 756, 722;

$^{1}$H NMR (500 MHz, Acetone) δ ppm 0.87 (3 H, t, J = 6.9 Hz, CH₂C₃H₇), 1.11 - 1.18 (1 H, m, 1 H from CCH₂CH₂), 1.19 (3 H, s, CCH₃), 1.22 - 1.33 (14 H, m, 7 × CH₂), 1.33 - 1.41 (1 H, m, 1 H from CCH₂CH₂), 1.47 (1 H, ddd, J = 13.5, 12.0, 4.4 Hz, 1 H from CCH₂), 1.62 (1 H, ddd, J = 13.5, 12.3, 4.7 Hz, 1 H from CCH₂), 1.67 (3 H, t, J = 2.5 Hz, C≡CCH₃), 2.32 (1 H, ddq, J = 17.3, 5.1, 2.5 Hz, 1 H from CHCH₂), 2.56 (1 H, ddq, J = 17.3, 4.1, 2.5 Hz, 1 H from CHCH₂), 3.04 (3 H, s, NCH₃), 3.07 (3 H, s, NCH₃), 3.32 (1 H, dd, J = 5.1, 4.1 Hz, CH);

$^{13}$C NMR (125 MHz, Acetone) δ ppm 3.3 (C≡CCH₃), 14.4 (CH₂CH₃), 18.2 (CCH₃), 19.9 (CCH₂), 23.4 (CH₂), 24.4 (CCH₂CH₂), 27.8 (NCH₃), 30.1 (CH₂), 30.2 (CH₂), 30.3 (CH₂), 30.4 (CH₂), 30.7 (CH₂), 32.7 (CH₂), 35.7 (NCH₃), 38.9 (CHCH₂), 45.0 (C₆), 62.4 (CH), 75.0 (C≡CCH₃), 79.4 (C≡CCH₃), 153.6 (C=O), 174.3 (C=O);
\[ m/z \ (ES^+) \ 371 \ (M + Na), \ 100\%. \ \text{(Found:} \ (M + Na) \ 371.2663. \ C_{21}H_{36}N_2O_2Na \ \text{requires} \ M, \ 371.2669). \]

\[ \text{rac-} (5R,6R)-6-(2\text{-Bromoallyl})-5\text{-isobutyl}-1,3,5\text{-trimethylidihydropyrimidine-2,4}(1H,3H)\text{-dione (317p)} \]

As for general procedure G, reaction of both isomers of 6-hydroxy-5-isobutyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 286i (10 mg, 43.8 µmol, 1.0 eq), 2-bromoallyltrimethylsilane (85 µL, 0.44 mmol, 10 eq) and BF$_3$•OEt$_2$ (27 µL, 0.22 mmol, 5.0 eq) in CH$_2$Cl$_2$ (1.0 mL) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) \text{rac-} (5R,6R)-6-(2-bromoallyl)-5-isobutyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 317p (12.1 mg, 36.5 µmol, 86%, > 95:5 dr (88:12 crude dr)) as a colourless oil.

\[ \nu_{\text{max}} \ (\text{neat})/\text{cm}^{-1} \ 2956, \ 2928, \ 2866, \ 1710 (\text{C=O}), \ 1668 (\text{C=O}), \ 1631, \ 1471, \ 1418, \ 1398, \ 1284, \ 1217, \ 1178, \ 1090, \ 1037, \ 895, \ 758; \]

\[ ^1H \text{ NMR} \ (500 \text{ MHz, Acetone}) \ \delta \text{ ppm} \ 0.76 \ (3 \ H, d, J = 6.8 \text{ Hz, CHCH}_3), \ 0.93 \ (3 \ H, d, J = 6.8 \text{ Hz, CHCH}_3), \ 1.18 \ (3 \ H, s, \ CCH_3), \ 1.46 \ (1 \ H, dd, J = 14.0, 3.8 \text{ Hz, 1 H from CH}_2\text{CHCH}_3), \ 1.56 \ (1 \ H, dd, J = 14.0, 7.3 \text{ Hz, 1 H from CH}_2\text{CHCH}_3), \ 1.70 - 1.80 \ (1 \ H, m, \text{CHCH}_3), \ 2.62 \ (1 \ H, dd, J = 14.2, 9.8 \text{ Hz, 1 H from CH}_2\text{C=C}), \ 2.74 \ (1 \ H, ddd, J = 14.2, 4.0, 0.9 \text{ Hz, 1 H from CH}_2\text{C=C}), \ 3.04 \ (3 \ H, s, \text{NCH}_3), \ 3.10 \ (3 \ H, s, \text{NCH}_3), \ 3.51 \ (1 \ H, dd, J = 9.8, 4.0 \text{ Hz, CHCH}_2\text{C=C}), \ 5.55 \ (1 \ H, d, J = 1.9 \text{ Hz, 1 H from C=CCH}_2), \ 5.82 \ (1 \ H, \text{br. s, 1 H from C=CCH}_2); \]

\[ ^{13}C \text{ NMR} \ (125 \text{ MHz, Acetone}) \ \delta \text{ ppm} \ 19.0 \ (\text{CCH}_3), \ 24.0 \ (\text{CHCH}_3), \ 24.5 \ (\text{CHCH}_3), \ 25.6 \ (\text{CHCH}_3), \ 27.9 \ (\text{NCH}_3), \ 37.8 \ (\text{NCH}_3), \ 43.0 \ (\text{CH}_2\text{C=C}), \ 46.1 (\text{C}^\text{O}), \ 47.0 \ (\text{CH}_2\text{CHCH}_3), \ 63.2 \ (\text{CHCH}_2\text{C=C}), \ 121.8 \ (\text{C=CCH}_2), \ 131.4 \ (\text{C=CCH}_2), \ 153.0 \ (\text{C=O}), \ 174.5 \ (\text{C}=\text{O}); \]

\[ m/z \ (ES^+) \ 353 \ ((M + Na), \ 96\%), \ 355 \ ((M + Na), \ 100). \ \text{(Found:} \ (M + H) \ 331.1017. \ C_{14}H_{24}N_2O_2Br \ \text{requires} \ M, \ 331.1016). \]
rac-(5R,6R)-6-(2-(Chloromethyl)allyl)-5-isobutyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione (317q)

As for general procedure G, reaction of both isomers of 6-hydroxy-5-isobutyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 286i (10 mg, 43.8 µmol, 1.0 eq), 2-(chloromethyl)allyl-trimethylsilane (79 µL, 0.44 mmol, 10 eq) and BF₃•OEt₂ (27 µL, 0.22 mmol, 5.0 eq) in CH₂Cl₂ (1.0 mL) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) rac-(5R,6R)-6-(2-(chloromethyl)allyl)-5-isobutyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 317q (11.2 mg, 37.2 µmol, 85%, > 95:5 dr (> 95:5 crude dr)) as a colourless oil.

ν_max (neat)/cm⁻¹: 2955, 2926, 2873, 1707 (C=O), 1663 (C=O), 1471, 1417, 1398, 1283, 1226, 1200, 1178, 1091, 1037, 919, 759;

¹H NMR (500 MHz, Acetone) δ ppm: 0.75 (3 H, d, J = 6.5 Hz, CH₃CH₂), 0.91 (3 H, d, J = 6.5 Hz, CH₃CH₂), 1.20 (3 H, s, CCH₃), 1.42 (1 H, dd, J = 14.2, 3.8 Hz, 1 H from CH₂CHCH₃), 1.55 (1 H, dd, J = 14.2, 7.6 Hz, 1 H from CH₂CHCH₃), 1.71 - 1.79 (1 H, m, CH₂CH₃), 2.19 (1 H, ddd, J = 14.0, 10.1, 0.9 Hz, 1 H from CH₂CH₂C=C), 2.59 (1 H, ddd, J = 14.0, 4.2, 0.9 Hz, 1 H from CH₂CH₂C=C), 3.00 (3 H, s, NCH₃), 3.06 (3 H, s, NCH₃), 3.48 (1 H, dd, J = 10.1, 4.2 Hz, CH₂CH₂C=C), 4.23 (1 H, dd, J = 12.3, 0.9 Hz, 1 H from CH₂Cl), 4.30 (1 H, dd, J = 12.3, 0.9 Hz, 1 H from CH₂Cl), 5.09 (1 H, d, J = 0.9 Hz, 1 H from C=CH₂), 5.33 (1 H, d, J = 0.9 Hz, 1 H from C=CH₂);

¹³C NMR (125 MHz, Acetone) δ ppm: 19.1 (CCH₃), 24.0 (CH₂CH₃), 24.5 (CH₂CH₃), 25.7 (CH₂CH₃), 27.9 (NCH₃), 34.3 (CH₂CH₂C=C), 37.7 (NCH₃), 46.6 (C₅), 47.0 (CH₂CH₂CH₂), 48.6 (CH₂Cl), 63.4 (CH₂CH₂C=C), 119.4 (C=CH₂), 143.0 (C=CH₂), 153.1 (C=O), 174.8 (C=O);

m/z (ES+) 323 ((M + Na), 100%). (Found: (M + H) 301.1680. C₁₅H₂₆N₂O₂Cl requires M, 301.1683).
**rac-**\((5R,6R)\)-6-Allyl\((6^{2}H)\)-5-decyl-1,3,5-trimethylidihydropyrimidine-2,4\((1H,3H)\)‐dione (318a)

As for general procedure G, reaction of both isomers of 5-decyl-6-hydroxy\((6^{2}H)\)-1,3,5-trimethylidihydropyrimidine-2,4\((1H,3H)\)-dione 306 (10 mg, 31.9 µmol, 1.0 eq, > 98% D), allyltrimethylsilane (37 µL, 0.32 mmol, 10 eq) and BF₃•OEt₂ (20 µL, 0.16 mmol, 5.0 eq) in CH₂Cl₂ (1.0 mL) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) rac-\((5R,6R)\)-6-allyl\((6^{2}H)\)-5-decyl-1,3,5-trimethylidihydropyrimidine-2,4\((1H,3H)\)-dione 318a (10.8 mg, 31.9 µmol, quantitative, > 98% D, > 95:5 dr (91:9 crude dr)) as a colourless oil.

\(\nu_{\text{max}}\) (neat)/cm⁻¹ 2923, 2853, 1710 (C=O), 1669 (C=O), 1456, 1414, 1387, 1336, 1093, 1028, 917, 758;

\(^1\)H NMR (500 MHz, Acetone) δ ppm 0.87 (3 H, t, \(J = 6.9\) Hz, CH₂C₃H₃), 1.09 - 1.15 (1 H, m, 1 H from CCH₂CH₂), 1.16 (3 H, s, CCH₃), 1.21 - 1.33 (14 H, m, 7 × CH₂), 1.34 - 1.41 (1 H, m, 1 H from CCH₂CH₂), 1.46 (1 H, ddd, \(J = 13.3, 12.2, 4.4\) Hz, 1 H from CCH₂), 1.54 - 1.62 (1 H, m, 1 H from CCH₂), 2.21 (1 H, dd, \(J = 14.2, 7.4\) Hz, 1 H from CH=CH₂), 2.46 (1 H, dd, \(J = 14.2, 7.4\) Hz, 1 H from CH=CH₂), 3.00 (3 H, s, NCH₃), 3.03 (3 H, s, NCH₃), 5.01 (1 H, dt, \(J = 9.9, 1.1\) Hz, 1 H from CH=CH₂), 5.05 (1 H, dq, \(J = 17.1, 1.6\) Hz, 1 H from CH=CH₂), 5.71 (1 H, ddt, \(J = 17.1, 9.9, 7.4\) Hz, CH=CH₂);

\(^{13}\)C NMR (125 MHz, Acetone) δ ppm 14.4 (CH₂CH₃), 18.4 (CCH₃), 23.4 (CH₂), 24.5 (CCH₂CH₂), 27.6 (NCH₃), 30.1 (CH₂), 30.2 (CH₂), 30.3 (CH₂), 30.4 (CH₂), 30.7 (CH₂), 32.7 (CH₂), 34.9 (CH₂CH=CH₂), 36.5 (NCH₃), 38.4 (CCH₂), 45.6 (C⁰), 62.8 (t, \(J = 20.9\) Hz, CD), 118.7 (CH=CH₂), 134.5 (CH=CH₂), 153.5 (C=O), 174.8 (C=O);

\(m/z\) (ES+) 360 ((M + Na), 100%). (Found: (M + H) 338.2899. C₂₀H₃₆DN₂O₂ requires \(M, 338.2912\).)
5.8. General procedure H – Dehydrations

1,3-Dimethyl-5-(4-(trifluoromethyl)phenethyl)pyrimidine-2,4(1H,3H)-dione (319)
To a stirred solution of both isomers of (5S,6R)-6-hydroxy-1,3-dimethyl-5-(4-
(trifluoromethyl)phenethyl)dihydropyrimidine-2,4(1H,3H)-dione 286f (10 mg, 30.3 µmol, 1.0 eq) in CH₂Cl₂ (1.0 mL) was added BF₃•OEt₂ (19 µL, 0.15 mmol, 5.0 eq) and the reaction mixture stirred at room temperature for 3 hours. The reaction was quenched with NH₄Cl aq., sat. (2.0 mL) and the aqueous phase extracted with CH₂Cl₂ (3 × 2.0 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo to give 1,3-dimethyl-5-(4-(trifluoromethyl)phenethyl)pyrimidine-2,4(1H,3H)-dione 319 (9.0 mg, 28.8 µmol, 95%) as a colourless oil.

νmax (neat)/cm⁻¹ 2928, 2858, 1699 (C=O), 1659 (C=O), 1638, 1455, 1375, 1321, 1160, 1106, 1066, 1018, 849, 826, 780, 757, 650;
¹H NMR (500 MHz, Acetone) δ ppm 2.59 - 2.65 (2 H, m, CH₂Ar), 2.89 - 2.95 (2 H, m, CH₂CH₂Ar), 3.25 (3 H, s, NCH₃), 3.31 (3 H, s, NCH₃), 7.37 (1 H, s, C=CH), 7.45 (2 H, d, J = 7.9 Hz, 2 × ArH), 7.62 (2 H, d, J = 7.9 Hz, 2 × ArH);
¹³C NMR (125 MHz, Acetone) δ ppm 27.8 (NCH₃), 30.0 (CH₂Ar), 35.4 (CH₂CH₂Ar), 36.7 (NCH₃), 112.0 (C=CH), 125.6 (q, J₁ = 271.6 Hz, CF₃), 126.1 (q, J₂ = 3.6 Hz, 2 × ArCH), 128.6 (q, J₃ = 31.8 Hz, ArC⁹), 130.2 (2 × ArCH), 141.6 (C=CH), 147.5 (ArC⁹), 152.5 (C=O), 164.1 (C=O);
m/z (ES+) 304 (20%), 335 ((M + Na), 17), 413 (100). (Found: (M + H) 313.1155. C₁₅H₁₆N₂O₂F₃ requires M, 313.1158).

4a-(But-3-en-1-yl)-1,3,7-trimethyl-5,6-dihydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione (320)
As for general procedure H, reaction of (4aR,7S,7aR)-4a-(but-3-en-1-yl)-7a-hydroxy-1,3,7-
trimethyltetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 300e (10 mg, 37.6 µmol, 1.0 eq) and BF₃•OEt₂ (23 µL, 0.19 mmol, 5.0 eq) in CH₂Cl₂ (1.0 mL) gave after
column chromatography (20% ethyl acetate in petroleum ether (40-60 °C)) 4a-(but-3-en-1-y1)-1,3,7-trimethyl-5,6-dihydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 320 (8.2 mg, 33.0 µmol, 88%) as a colourless oil.

νmax (neat)/cm⁻¹ 2921, 2850, 1718 (C=O), 1666 (C=O), 1438, 1414, 1375, 1359, 1281, 1153, 1092, 1045, 995, 959, 911, 752; ¹H NMR (400 MHz, Acetone) δ ppm 1.54 - 1.69 (2 H, m, CH₂CH₂CH=CH₂), 1.85 (3 H, br. s, CCH₃), 1.93 - 2.04 (3 H, m, 1 H from CH₂CH₂CCH₃, CH₂CH=CH₂), 2.10 - 2.28 (2 H, m, 1 H from CH₂CH₂CCH₃, 1 H from CH₂CCH₃), 2.42 - 2.54 (1 H, m, 1 H from CH₂CCH₃), 3.07 (3 H, s, NCH₃), 3.33 (3 H, s, NCH₃), 4.88 - 4.93 (1 H, dq, J = 17.1, 1.8 Hz, 1 H from CH=CH₂), 5.00 (1 H, ddt, J = 17.1, 10.4, 6.6 Hz, CH=CH₂);

¹³C NMR (100 MHz, Acetone) δ ppm 14.6 (C C₃H₃), 28.4 (NCH₃), 29.5 (CH₂CH=CH₂), 29.9 (CH₂CH₂CCH₃), 35.2 (NCH₃), 35.5 (CH₂CCH₃), 36.7 (CH₂CH₂CH=CH₂), 57.0 (C⁰), 115.3 (CH=CH₂), 122.3 (C=CCH₃), 132.2 (C=CCH₃), 138.9 (CH=CH₂), 153.1 (C=O), 175.2 (C=O);

m/z (ES+) 271 ((M + Na), 100%). (Found: (M + H) 249.1605. C₄H₁₂N₂O₂ requires M, 249.1598).

5.9. General procedure I – 1,4-Additions

7-(But-3-en-1-y1)-4a-isobutyl-1,3-dimethyl-1,4a,5,6-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (322a)

To a stirred solution of rac-(4aS,7aR)-7a-hydroxy-4a-isobutyl-1,3-dimethyl-7-methylenetetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 300j (10 mg, 37.6 µmol, 1.0 eq) in CH₂Cl₂ (1.0 mL) was added allytrimethylsilane (60 µL, 0.38 mmol, 10 eq). BF₃•OEt₂ (24 µL, 0.19 mmol, 5.0 eq) was then added and the reaction mixture stirred at room temperature for 3 hours. The reaction was quenched with NH₄Clₐq., sat. (2.0 mL) and the aqueous phase extracted with CH₂Cl₂ (3 × 2.0 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C)
gave 7-(but-3-en-1-yl)-4a-isobutyl-1,3-dimethyl-1,4a,5,6-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione 322a (9.2 mg, 33.3 µmol, 89%) as a colourless oil. 

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2955, 2917, 2866, 2847, 1718 (C=O), 1668 (C=O), 1447, 1414, 1374, 1310, 1281, 1162, 1090, 1031, 995, 912, 754;

$^1$H NMR (500 MHz, Acetone) $\delta$ ppm 0.83 (3 H, d, $J = 6.6$ Hz, CHCH$_3$), 0.91 (3 H, d, $J = 6.6$ Hz, CHCH$_3$), 1.41 (1 H, dd, $J = 14.0$, 6.6 Hz, 1 H from CH$_2$CH), 1.51 (1 H, dd, $J = 14.0$, 5.0 Hz, 1 H from CH$_2$CH), 1.60 - 1.69 (1 H, m, CH), 2.01 (1 H, ddd, $J = 13.3$, 8.5, 1.6 Hz, 1 H from CCCH$_2$CH), 2.15 (1 H, dt, $J = 13.3$, 9.4 Hz, 1 H from CCH$_2$CH), 2.19 - 2.33 (4 H, m, CH$_2$CH=CH$_2$), 1 H from CCH$_2$CH$_2$, 1 H from CH$_2$CH$_2$CH=CH$_2$), 2.40 - 2.48 (1 H, m, 1 H from CH$_2$CH$_2$CH=CH$_2$), 2.48 - 2.55 (1 H, m, 1 H from CCH$_2$CH$_2$), 3.07 (3 H, s, NCH$_3$), 3.32 (3 H, s, NCH$_3$), 4.95 (1 H, ddt, $J = 10.2$, 2.0, 0.9 Hz, 1 H from CH=CH$_2$), 5.05 (1 H, dq, $J = 17.1$, 1.6 Hz, 1 H from CH=CH$_2$), 5.84 (1 H, ddt, $J = 17.1$, 10.2, 6.6 Hz, CH=CH$_2$);

$^{13}$C NMR (125 MHz, Acetone) $\delta$ ppm 24.5 (CHCH$_3$), 24.9 (CHCH$_3$), 25.9 (CH), 28.5 (NCH$_3$), 28.9 (CH$_2$CH$_2$CH=CH$_2$), 30.1 (CCH$_3$), 32.7 (CCH$_2$CH$_2$), 32.9 (CH$_2$CH=CH$_2$), 35.7 (NCH$_3$), 45.6 (CH$_2$CH), 57.1 (C$_4$), 115.6 (CH=CH$_2$), 125.8 (CC=C), 133.7 (CC=C), 138.9 (CH=CH$_2$), 153.2 (C=O), 175.3 (C=O);

m/z (ES+) 313 ((M + Na), 100%). (Found: (M + H) 291.2080. C$_{17}$H$_{27}$N$_2$O$_2$ requires $M$, 291.2073).

2-(4a-(But-3-yn-1-yl)-1,3-dimethyl-2,4-dioxo-2,3,4,4a,5,6-hexahydro-1H-cyclopenta[d]pyrimidin-7-yl)acetonitrile (322b)

As for general procedure I, reaction of rac-(4aR,7aR)-4a-(but-3-yn-1-yl)-7a-hydroxy-1,3-dimethyl-7-methylenetetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 300m (10 mg, 38.1 µmol, 1.0 eq), trimethylsilyl cyanide (48 µL, 0.38 µmol, 10 eq) and BF$_3$•OEt$_2$ (23 µL, 0.19 mmol, 5.0 eq) in CH$_2$Cl$_2$ (1.0 mL) gave after preparative thin layer chromatography (40% ethyl acetate in petroleum ether (40–60 °C)) 2-(4a-(but-3-yn-1-yl)-1,3-dimethyl-2,4-dioxo-2,3,4,4a,5,6-hexahydro-1H-cyclopenta[d]pyrimidin-7-yl)acetonitrile 322b (7.6 mg, 28.0 µmol, 74%) as a colourless oil.
\[ \nu_{\text{max}} \text{(neat)}/\text{cm}^{-1} \] 3284, 2921, 2852, 1719 (C=O), 1664 (C=O), 1450, 1416, 1375, 1324, 1303, 1279, 1148, 1075, 1051, 751, 645;

\[ ^1H \text{ NMR} \] (400 MHz, Acetone) \( \delta \) ppm 1.70 - 1.76 (2 H, m, \( CH_2CH_2C≡C \)), 2.00 - 2.13 (4 H, m, \( CH_2C≡C, C≡CH_2CH_2 \)), 2.24 (1 H, t, \( J = 2.6 \text{ Hz}, C≡CH \)), 2.29 - 2.38 (1 H, m, 1 H from \( C≡CH_2 \)), 2.46 - 2.59 (1 H, m, 1 H from \( C≡CH_2 \)), 2.97 (3 H, s, NCH_3), 3.29 (3 H, s, NCH_3), 3.43 - 3.62 (2 H, m, CH_2CN);

\[ ^13C \text{ NMR} \] (100 MHz, Acetone) \( \delta \) ppm 14.6 (\( C≡CH_2 \)), 17.8 (\( CH_2CN \)), 28.6 (NCH_3), 29.5 (\( C≡CH_2CH_2 \)), 33.0 (\( C≡CH_2CH_2 \)), 35.2 (NCH_3), 36.1 (\( CH_2CH_2C≡C \)), 57.2 (\( C≡CH_2 \)), 70.4 (\( C≡CH \)), 84.1 (\( C≡CH \)), 114.0 (\( C≡CH_2 \)), 117.8 (CN), 136.3 (\( C≡CH_2 \)), 152.7 (C=O), 173.9 (C=O);

\[ m/z \] (ES+) 64 (75%), 122 (100), 123 (35), 272 ((M + H), 56). (Found: (M) 271.1313. \( C_{15}H_{17}N_3O_2 \) requires \( M \), 271.1315).

4a-(But-3-yn-1-yl)-1,3-dimethyl-2,4-dioxo-2,3,4,4a,5,6-hexahydro-1H-cyclopenta[d]pyrimidine-7-carbaldehyde (322c)

As for general procedure I, reaction of rac-(4aR,7aR)-4a-(but-3-yn-1-yl)-7a-hydroxy-1,3-dimethyl-7-methylenetetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione \( 300m \) (10 mg, 38.1 \( \mu \text{mol}, 1.0 \text{ eq} \)) and BF_3·OEt_2 (23 \( \mu \text{L}, 0.19 \text{ mmol}, 5.0 \text{ eq} \)) in \( CH_2Cl_2 \) (1.0 mL) gave after preparative thin layer chromatography (40% ethyl acetate in petroleum ether (40-60 °C)) 4a-(but-3-yn-1-yl)-1,3-dimethyl-2,4-dioxo-2,3,4,4a,5,6-hexahydro-1H-cyclopenta[d]pyrimidine-7-carbaldehyde \( 322c \) (5.0 mg, 19.2 \( \mu \text{mol}, 51% \)) as a colourless oil.

\[ \nu_{\text{max}} \text{(neat)}/\text{cm}^{-1} \] 3269, 2952, 2924, 2854, 1728 (C=O), 1676 (C=O), 1600 (C=O), 1426, 1372, 1322, 1286, 1244, 1137, 1073, 1054, 962, 914, 750, 721, 644;

\[ ^1H \text{ NMR} \] (400 MHz, Acetone) \( \delta \) ppm 1.95 - 2.02 (2 H, m, \( CH_2CH_2C≡C \)), 2.06 - 2.10 (1 H, m, 1 H from \( C≡CH_2CH_2 \)), 2.13 - 2.35 (3 H, m, 1 H from \( C≡CH_2CH_2, CH_2C≡C \)), 2.39 (1 H, t, \( J = 2.8 \text{ Hz}, C≡CH \)), 2.50 (1 H, ddd, \( J = 15.8, 10.3, 7.5 \text{ Hz} \)), 1 H from \( C≡CH_2 \)), 2.62 - 2.71 (1 H, m, 1 H from \( C≡CH_2 \)), 3.17 (3 H, s, NCH_3), 3.66 (3 H, s, NCH_3), 10.16 (1 H, s, CHO);
$^{13}$C NMR (100 MHz, Acetone) δ ppm 14.9 (CH$_2$C≡C), 26.9 (C=CCH$_2$), 28.9 (NCH$_3$), 29.3 (C=CCH$_2$CH$_2$), 37.0 (CH$_2$CH$_2$C≡C), 38.2 (NCH$_3$), 58.5 (C$^6$), 70.6 (C≡CH), 83.8 (C≡CH), 122.9 (C=CCH$_2$), 151.9 (C=CCH$_2$), 152.0 (C=O), 172.5 (C=O), 187.0 (CHO);

$^{19}$F (ES+) 261 ((M + H), 100%). (Found: (M + H) 261.1235. C$_{14}$H$_{17}$N$_2$O$_3$ requires M, 261.1239).

7-(But-3-en-1-yl)-4a-(but-3-yn-1-yl)-1,3-dimethyl-1,4a,5,6-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (322d)

As for general procedure I, reaction of rac-(4aR,7aR)-4a-(but-3-yn-1-yl)-7a-hydroxy-1,3-dimethyl-7-methylenetetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 300m (10 mg, 38.1 µmol, 1.0 eq), allytrimethysilane (61 µL, 0.38 µmol, 10 eq) and BF$_3$•OEt$_2$ (23 µL, 0.19 mmol, 5.0 eq) in CH$_2$Cl$_2$ (1.0 mL) gave after preparative thin layer chromatography (40% ethyl acetate in petroleum ether (40-60 °C)) 7-(but-3-en-1-yl)-4a-(but-3-yn-1-yl)-1,3-dimethyl-1,4a,5,6-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione 322d (8.9 mg, 31.1 µmol, 82%) as a colourless oil.

ν$_{max}$ (neat)/cm$^{-1}$ 3269, 2953, 2925, 2851, 1716 (C=O), 1665 (C=O), 1450, 1415, 1374, 1281, 1142, 1073, 1050, 997, 964, 914, 751, 638;

$^1$H NMR (400 MHz, Acetone) δ ppm 1.75 - 1.83 (2 H, m, CH$_2$CH$_2$C≡C), 2.06 - 2.11 (1 H, m, 1 H from CH$_2$CH$_2$CH=CH$_2$), 2.13 - 2.21 (3 H, m, 1 H from CH$_2$CH$_2$CH=CH$_2$, CH$_2$C≡C), 2.23 - 2.33 (4 H, m, CH$_2$CH=CH$_2$, 1 H from C=CCH$_2$CH$_2$C, 1 H from C=CCH$_2$CH$_2$C), 2.36 (1 H, t, J = 2.6 Hz, C≡CH), 2.43 - 2.59 (2 H, m, 1 H from C=CCH$_2$CH$_2$C, 1 H from C=CCH$_2$CH$_2$C), 3.08 (3 H, s, NCH$_3$), 3.34 (3 H, s, NCH$_3$), 4.96 (1 H, ddt, J = 10.2, 2.0, 1.1 Hz, 1 H from CH=CH$_2$), 5.06 (1 H, dq, J = 17.1, 1.6 Hz, 1 H from CH=CH$_2$), 5.86 (1 H, ddt, J = 17.1, 10.2, 6.5 Hz, CH=CH$_2$);

$^{13}$C NMR (100 MHz, Acetone) δ ppm 14.6 (CH$_2$C≡C), 28.5 (NCH$_3$), 28.9 (C=CCH$_2$CH$_2$C), 29.6 (CH$_2$CH$_2$CH=CH$_2$), 32.8 (C=CCH$_2$CH$_2$C), 33.0 (CH$_2$CH=CH$_2$), 35.6 (NCH$_3$), 36.1 (CH$_2$CH$_2$C≡C), 56.9 (C$^6$), 70.3 (C≡CH), 84.3 (C≡CH), 115.7 (CH=CH$_2$), 126.3 (CH=CH$_2$), 132.3 (C=CCH$_2$), 138.9 (C=CCH$_2$), 152.8 (C=O), 174.7 (C=O);
m/z (ES+) 287 ((M + H), 100%), 288 (29). (Found: (M + H) 287.1754. C$_{17}$H$_{23}$N$_2$O$_2$ requires $M$, 287.1760).

Methyl 3-(4a-(but-3-yn-1-yl)-1,3-dimethyl-2,4-dioxo-2,3,4,4a,5,6-hexahydro-1H-cyclopenta[d]pyrimidin-7-yl)-2,2-dimethylpropanoate (322e)

As for general procedure I, reaction of rac-(4aR,7aR)-4a-(but-3-yn-1-yl)-7a-hydroxy-1,3-dimethyl-7-methylenetetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 300m (10 mg, 38.1 µmol, 1.0 eq), 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (77 µL, 0.38 µmol, 10 eq) and BF$_3$•OEt$_2$ (23 µL, 0.19 mmol, 5.0 eq) in CH$_2$Cl$_2$ (1.0 mL) gave after preparative thin layer chromatography (40% ethyl acetate in petroleum ether (40-60 °C)) methyl 3-(4a-(but-3-yn-1-yl)-1,3-dimethyl-2,4-dioxo-2,3,4,4a,5,6-hexahydro-1H-cyclopenta[d]pyrimidin-7-yl)-2,2-dimethylpropanoate 322e (10.7 mg, 30.9 µmol, 81%) as a colourless oil.

ν$_{\text{max}}$ (neat)/cm$^{-1}$ 3270, 2952, 2923, 2846, 1716 (C=O), 1666 (C=O), 1450, 1415, 1367, 1281, 1192, 1140, 1075, 1050, 998, 982, 959, 857, 752, 643;

$^1$H NMR (400 MHz, Acetone) δ ppm 1.17 (3 H, s, CCH$_3$), 1.23 (3 H, s, CCH$_3$), 1.79 (2 H, ddd, $J$ = 8.7, 7.2, 4.0 Hz, CH$_2$CH$_2$C=), 2.06 - 2.09 (2 H, m, CH$_2$CH$_2$C=), 2.13 - 2.21 (3 H, m, CH$_2$C=C, 1 H from CH$_2$C=C), 2.38 (1 H, t, $J$ = 2.8 Hz, C=CH), 2.33 - 2.42 (1 H, m, 1 H from CH$_2$C=C), 2.55 (1 H, d, $J$ = 14.5 Hz, 1 H from CH$_2$C=C), 2.65 (1 H, d, $J$ = 14.5 Hz, 1 H from CH$_2$C=C), 3.07 (3 H, s, NCH$_3$), 3.34 (3 H, s, NCH$_3$), 3.61 (3 H, s, OCH$_3$);

$^{13}$C NMR (100 MHz, Acetone) δ ppm 14.6 (CH$_2$C=C), 26.0 (CCH$_3$), 26.2 (CCH$_3$), 28.5 (NCH$_3$), 29.6 (CH$_2$CH$_2$C=C), 33.4 (CH$_2$C=C), 35.6 (NCH$_3$), 35.6 (CH$_2$CH$_2$C=C), 39.3 (CH$_2$C=C), 43.2 (C$^\beta$), 52.1 (OCH$_3$), 56.5 (C$^\beta$), 70.4 (C=CH), 84.1 (C=CH), 124.8 (C=CH), 134.8 (C=CH), 153.1 (C=O), 174.7 (C=O), 178.1 (C=O);

m/z (ES+) 122 (45%), 347 ((M + H), 100), 369 ((M + Na), 48). (Found: (M + Na) 369.1785. C$_{19}$H$_{26}$N$_2$O$_4$Na requires $M$, 369.1785).
4a-(But-3-yn-1-yl)-7-(buta-2,3-dien-1-yl)-1,3-dimethyl-1,4a,5,6-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (322f)

As for general procedure I, reaction of rac-(4aR,7aR)-4a-(but-3-yn-1-yl)-7a-hydroxy-1,3-dimethyl-7-methylenetetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 300m (10 mg, 38.1 µmol, 1.0 eq), trimethyl(propargyl)silane (57 µL, 0.38 µmol, 10 eq) and BF$_3$ • OEt$_2$ (23 µL, 0.19 mmol, 5.0 eq) in CH$_2$Cl$_2$ (1.0 mL) gave after preparative thin layer chromatography (40% ethyl acetate in petroleum ether (40-60 °C)) 4a-(but-3-yn-1-yl)-7-(buta-2,3-dien-1-yl)-1,3-dimethyl-1,4a,5,6-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione 322f (7.1 mg, 25.0 µmol, 66%) as a colourless oil.

\[ \nu_{\text{max}} (\text{neat})/\text{cm}^{-1} \] 3290, 2953, 2923, 2851, 1717 (C=O), 1664 (C=O), 1449, 1415, 1374, 1285, 1146, 1074, 1050, 848, 751, 638;

$^1$H NMR (400 MHz, Acetone) δ ppm 1.76 - 1.83 (2 H, m, CH$_2$CH$_2$C≡C), 2.07 - 2.12 (1 H, m, 1 H from C=CHCH$_2$), 2.12 - 2.29 (4 H, m, 1 H from C=CHCH$_2$, 1 H from C=CH$_2$CH$_2$, CH$_2$C≡C), 2.35 (1 H, t, $J = 2.8$ Hz, C≡CH), 2.52 - 2.64 (1 H, m, 1 H from C=CH$_2$CH$_2$), 2.76 - 2.90 (1 H, m, 1 H from CH$_2$CH=CH), 3.08 (3 H, s, NCH$_3$), 3.09 - 3.17 (1 H, m, 1 H from CH$_2$CH=CH), 3.35 (3 H, s, NCH$_3$), 4.77 (1 H, t, $J = 3.5$ Hz, 1 H from CH$_2$CH=CH), 4.78 (1 H, t, $J = 3.5$ Hz, 1 H from C=CH$_2$), 5.26 (1 H, quin, $J = 6.5$ Hz, CH=CH;

$^{13}$C NMR (100 MHz, Acetone) δ ppm 14.6 (CH$_2$C≡C), 28.4 (CH$_2$CH=CH), 28.5 (NCH$_3$), 29.6 (C=CH$_2$CH$_2$), 33.3 (C=CH$_2$CH$_2$), 35.3 (NCH$_3$), 36.2 (CH$_2$CH$_2$C≡C), 57.1 (C$^6$), 70.3 (C=CH), 76.3 (C=CH$_2$), 84.1 (C=CH), 88.4 (CH=CH), 124.1 (C=CH$_2$), 133.0 (C=CH$_2$), 152.8 (C=O), 174.6 (C=O), 210.1 (C=C=C);

$m/z$ (ES+) 60 (57%), 79 (25), 129 (28), 219 (26), 285 ((M + H), 100), 286 (23). (Found: (M + H) 285.1591. C$_{17}$H$_{21}$N$_2$O$_2$ requires $M$, 285.1603).
4a-(But-3-yn-1-yl)-1,3-dimethyl-7-(pent-3-yn-1-yl)-1,4a,5,6-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (322g)

As for general procedure I, reaction of rac-(4aR,7aR)-4a-(but-3-yn-1-yl)-7a-hydroxy-1,3-dimethyl-7-methylenetetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione (300m) (10 mg, 38.1 µmol, 1.0 eq), 3-(trimethylsilyl)-1,2-butadiene (63 µL, 0.38 µmol, 10 eq) and B\(_3\)OEt\(_2\) (23 µL, 0.19 mmol, 5.0 eq) in CH\(_2\)Cl\(_2\) (1.0 mL) gave after preparative thin layer chromatography (40% ethyl acetate in petroleum ether (40-60 °C)) 4a-(but-3-yn-1-yl)-1,3-dimethyl-7-(pent-3-yn-1-yl)-1,4a,5,6-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (322g) (10.2 mg, 34.2 µmol, 94%) as a colourless oil.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3279, 2950, 2918, 2851, 1716 (C=O), 1662 (C=O), 1451, 1415, 1375, 1282, 1247, 1148, 1129, 1072, 1051, 836, 752, 638;

\(^1\)H NMR (500 MHz, Acetone) \(\delta\) ppm 1.73 (3 H, t, \(J = 2.4 \text{ Hz}\), C≡CCH\(_3\)), 1.78 - 1.84 (2 H, m, CH\(_2\)CH\(_2\)C≡CH), 2.06 - 2.11 (1 H, m, 1 H from CH\(_2\)CH\(_2\)C≡CCH\(_3\)), 2.12 - 2.29 (4 H, m, CH\(_2\)CH≡CH, 1 H from CH\(_2\)CH\(_2\)C≡CCH\(_3\), 1 H from C=CCH\(_2\)CH\(_2\)C), 2.29 - 2.35 (3 H, m, 1 H from C=CCH\(_2\)CH\(_2\)C, CH\(_2\)C≡CCH\(_3\)), 2.36 (1 H, t, \(J = 2.8 \text{ Hz}\), C≡CH), 2.49 - 2.57 (1 H, m, 1 H from C=CCH\(_2\)CH\(_2\)C), 2.57 - 2.64 (1 H, m, 1 H from C=CCH\(_2\)CH\(_2\)C), 3.08 (3 H, s, NCH\(_3\)), 3.41 (3 H, s, NCH\(_3\));

\(^{13}\)C NMR (125 MHz, Acetone) \(\delta\) ppm 3.0 (C=CCH\(_3\)), 14.4 (CH\(_2\)C≡CH), 17.9 (CH\(_2\)C=CCH\(_3\)), 28.5 (C=CCH\(_2\)CH\(_2\)C), 28.5 (NCH\(_3\)), 29.6 (CH\(_2\)CH\(_2\)C=CCH\(_3\)), 32.5 (C=CCH\(_2\)CH\(_2\)C), 35.6 (NCH\(_3\)), 36.2 (CH\(_2\)CH\(_2\)C≡CH), 57.1 (C\(^4\)), 70.3 (C≡CH), 77.4 (C=CCH\(_3\)), 78.9 (C=CCH\(_3\)), 84.3 (C≡CH), 125.7 (C=CCH\(_2\)), 132.7 (C=CCH\(_2\)), 153.0 (C=O), 175.2 (C=O);

m/z (ES+) 64 (62%), 122 (77), 299 ((M + H), 100), 321 (27), 389 (62). (Found: (M + H) 299.1758. C\(_{18}\)H\(_{23}\)N\(_2\)O\(_2\) requires \(M\), 299.1754).
4a-(But-3-yn-1-yl)-7-(3-(chloromethyl)but-3-en-1-yl)-1,3-dimethyl-1,4a,5,6-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione (322h)

As for general procedure I, reaction of rac-(4aR,7aR)-4a-(but-3-yn-1-yl)-7a-hydroxy-1,3-dimethyl-7-methylenetetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione 300m (10 mg, 38.1 µmol, 1.0 eq), 2-(chloromethyl)allyltrimethylsilane (69 µL, 0.38 µmol, 10 eq) and BF₃•OEt₂ (23 µL, 0.19 mmol, 5.0 eq) in CH₂Cl₂ (1.0 mL) gave after preparative thin layer chromatography (40% ethyl acetate in petroleum ether (40-60 °C)) 4a-(but-3-yn-1-yl)-7-(3-(chloromethyl)but-3-en-1-yl)-1,3-dimethyl-1,4a,5,6-tetrahydro-2H-cyclopenta[d]pyrimidine-2,4(3H)-dione 322h (9.7 mg, 29.0 µmol, 76%) as a colourless oil.

ν max (neat)/cm⁻¹ 3291, 2950, 2925, 2851, 1715 (C=O), 1664 (C=O), 1448, 1415, 1376, 1280, 1144, 1126, 1075, 1051, 965, 909, 857, 750, 637;

¹H NMR (500 MHz, Acetone) δ ppm 1.77 - 1.83 (2 H, m, CH₂CH₂C≡C), 2.06 - 2.11 (1 H, m, 1 H from CH₂CH₂C=CH₂), 2.11 - 2.22 (3 H, m, 1 H from CH₂CH₂C=CH₂, CH₂C≡C), 2.29 - 2.35 (1 H, m, 1 H from C=CCH₂CH₂C), 2.36 (1 H, t, J = 2.7 Hz, C=CH), 2.37 - 2.48 (3 H, m, 1 H from C=CCH₂CH₂C, CH₂CH₂C=CH₂), 2.51 - 2.61 (2 H, m, 1 H from C=CCH₂CH₂C, 1 H from C=CCH₂CH₂C), 3.07 - 3.09 (3 H, m, NCH₃), 3.27 (3 H, s, NCH₃), 4.20 (2 H, br. d, J = 0.9 Hz, CH₂Cl), 5.05 (1 H, d, J = 1.3 Hz, 1 H from C=CH₂), 5.20 (1 H, br. s, 1 H from C=CH₂);

¹³C NMR (125 MHz, Acetone) δ ppm 14.6 (CH₂C≡C), 27.7 (C=CCH₂CH₂C), 28.6 (NCH₃), 29.6 (CH₂CH₂C=CH₂), 32.1 (CH₂CH₂C=CH₂), 32.8 (C=CCH₂CH₂C), 35.5 (NCH₃), 36.1 (CH₂CH₂C=C), 48.8 (CH₂Cl), 57.0 (C=CH), 70.3 (C=CH), 84.0 (C=CH), 115.3 (C=CH₂), 126.1 (C=CCH₂), 132.8 (C=CCH₂), 146.0 (C=CH₂), 153.4 (C=O), 174.2 (C=O); m/z (ES+) 79 (42%), 129 (24), 299 (19), 335 ((M + H), 100), 337 (41), 357 (M + Na).

(Found: (M + H) 335.1521. C₁₈H₂₄N₂O₂Cl requires M, 335.1526).
5.10. Miscellaneous procedures

\[ \text{rac-}(5R,6R)-5\text{-Decyl-1,3,5-trimethyl-6-}(4\text{-phenyl-1H-1,2,3-triazol-1-yl})\text{dihydropyrimidine-2,4(1H,3H)-dione (325-A)} \]

\[ \text{rac-}(5R,6S)-5\text{-Decyl-1,3,5-trimethyl-6-}(4\text{-phenyl-1H-1,2,3-triazol-1-yl})\text{dihydropyrimidine-2,4(1H,3H)-dione (325-B)} \]

To a stirred solution of both isomers of 6-azido-5-decyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 317\text{i} (10 mg, 29.6 µmol, 1.0 eq) in \( \text{H}_2\text{O} \) (0.25 mL) and \( t\text{-BuOH} \) (0.25 mL) was added phenylacetylene (3.5 µL, 32.6 µL, 1.0 eq). Sodium ascorbate (0.6 mg, 3.0 µmol, 10 mol%, in 0.1 mL \( \text{H}_2\text{O} \)) was then added, followed by copper sulfate pentahydrate (0.1 mg, 0.3 µmol, 1 mol%, in 0.1 mL \( \text{H}_2\text{O} \)) and the reaction mixture stirred at room temperature for 24 hours. The reaction was diluted with \( \text{H}_2\text{O} \) (2.0 mL) and the aqueous phase extracted with \( \text{CH}_2\text{Cl}_2 \) (3 × 2.0 mL). The combined organic phases were dried (\( \text{Na}_2\text{SO}_4 \) or \( \text{MgSO}_4 \)) and concentrated in vacuo to give \( \text{rac-}(5R,6R)-5\text{-decyl-1,3,5-trimethyl-6-}(4\text{-phenyl-1H-1,2,3-triazol-1-yl})\text{dihydropyrimidine-2,4(1H,3H)-dione (325-A)} \) and \( \text{rac-}(5R,6S)-5\text{-decyl-1,3,5-trimethyl-6-}(4\text{-phenyl-1H-1,2,3-triazol-1-yl})\text{dihydropyrimidine-2,4(1H,3H)-dione (325-B)} \) (7.7 mg, 17.5 µmol, 59%, 77:23 dr (72:28 crude dr)) as a yellow oil.

\( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 2923, 2853, 1720 (C=O), 1674 (C=O), 1481, 1467, 1419, 1395, 1299, 1273, 1159, 1073, 1036, 972, 942, 810, 764, 694;

\( \text{\textsuperscript{1}H NMR} \) (500 MHz, Acetone) \( \delta \) ppm 0.84 (3 H, t, \( J = 7.2 \text{ Hz, CH}_2\text{CH}_3 \) (B)), 0.88 (3 H, t, \( J = 6.8 \text{ Hz, CH}_2\text{CH}_3 \) (A)), 0.91 (3 H, s, CCH\(_3\) (B)), 0.93 - 1.00 (1 H, m, 1 H from \( \text{CCH}_2 \) (B)), 1.18 (3 H, s, CCH\(_3\) (A)), 1.21 - 1.36 (30 H, m, 7 × CH\(_2\) (A and B), 1 H from \( \text{CCH}_2\text{CH}_2 \) (A and B)), 1.39 - 1.45 (1 H, m, 1 H from \( \text{CCH}_2\text{CH}_2 \) (B)), 1.45 - 1.51 (1 H, m, 1 H from \( \text{CCH}_2\text{CH}_2 \) (A)), 1.76 - 1.86 (2 H, m, 1 H from \( \text{CCH}_2 \) (A and B)), 1.87 - 1.95 (1 H, m, 1 H from \( \text{CCH}_2 \) (A)), 3.05 (3 H, s, NCH\(_3\) (A)), 3.05 (3 H, s, NCH\(_3\) (B)), 3.22 (3 H, s, NCH\(_3\) (B)), 3.22 (3 H, s, NCH\(_3\) (A)), 6.01 (1 H, s, CH (A)), 6.07 (1 H, s, CH (B)), 7.31 - 7.37 (2 H, m, ArH (A and B)), 7.41 - 7.46 (4 H, m, 2 × ArH (A and B)), 7.86 - 7.90 (4 H, m, 2 × ArH (A and B)), 8.46 (1 H, s, C=CH (A)), 8.48 (1 H, s, C=CH (B));
\(^{13}\)C NMR (125 MHz, Acetone) \(\delta\) ppm: 14.4 (CH\(_2\)CH\(_3\) (A and B)), 17.5 (CCH\(_3\) (B)), 23.1 (CCH\(_2\)CH\(_2\) (B)), 23.4 (CH\(_2\) (B)), 23.4 (CH\(_2\) (A)), 24.6 (CCH\(_2\)CH\(_2\) (A)), 28.2 (NCH\(_3\) (A)), 28.3 (NCH\(_3\) (B)), 30.0 (CH\(_2\) (A and B)), 30.1 (CH\(_2\) (A and B)), 30.2 (CH\(_2\) (A and B)), 30.3 (CH\(_2\) (A and B)), 30.5 (CH\(_2\) (A and B)), 31.7 (CCH\(_3\) (A)), 32.7 (CH\(_2\) (B)), 32.7 (CH\(_2\) (A)), 33.1 (CCH\(_2\) (B)), 34.7 (NCH\(_3\) (A)), 34.8 (NCH\(_3\) (B)), 38.9 (CCH\(_2\) (A)), 46.1 (C\(\equiv\) (B)), 47.3 (C\(\equiv\) (A)), 77.2 (CH (B)), 78.0 (CH (A)), 121.5 (C=CH (B)), 121.8 (C=CH (A)), 126.5 (2 \(\times\) ArCH (A)), 126.5 (2 \(\times\) ArCH (B)), 129.1 (ArCH (A)), 129.1 (ArCH (B)), 129.8 (2 \(\times\) ArCH (A and B)), 131.6 (ArC\(\equiv\) (B)), 131.7 (ArC\(\equiv\) (A)), 147.9 (C=CH (A)), 147.9 (C=CH (B)), 153.4 (C=O (B)), 153.6 (C=O (A)), 172.7 (C=O (A)), 173.8 (C=O (B));
m/z (ES+) 295 (38%), 462 ((M + Na), 100). (Found: (M + Na) 462.2850. C\(_{25}\)H\(_{37}\)N\(_5\)O\(_2\)Na requires \(M\), 462.2839).

rac-(5R,6R)-5-Isobutyl-1,3,5-trimethyl-6-(2-phenylallyl)dihydropyrimidine-2,4(1H,3H)-dione (328)

To a stirred solution of rac-(5R,6R)-6-(2-bromoallyl)-5-isobutyl-1,3,5-trimethylidihydropyrimidine-2,4(1H,3H)-dione 317\(p\) (10 mg, 30.2 \(\mu\)mol, 1.0 eq) in toluene (0.5 mL) and H\(_2\)O (0.2 mL) was added potassium phenyltrifluoroborate (6.7 mg, 36.5 \(\mu\)mol, 1.1 eq), K\(_2\)CO\(_3\) (14 mg, 0.10 mmol, 3.0 eq) and tetrakis(triphenylphosphine)palladium(0) (1.0 mg, 0.9 \(\mu\)mol, 2 mol%) and the reaction mixture stirred at 90 °C for 3 hours. MgSO\(_4\) was added, the reaction mixture filtered through a plug of silica and the organic phase concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) gave rac-(5R,6R)-5-isobutyl-1,3,5-trimethyl-6-(2-phenylallyl)dihydropyrimidine-2,4(1H,3H)-dione 328 (7.4 mg, 22.5 \(\mu\)mol, 75%) as a colourless oil.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 2955, 2929, 2866, 1708 (C=O), 1667 (C=O), 1467, 1416, 1397, 1282, 1178, 1090, 1037, 902, 779, 758, 707;

\(^1\)H NMR (400 MHz, Acetone) \(\delta\) ppm: 0.71 (3 H, d, \(J = 6.7\) Hz, CHCH\(_3\)), 0.85 (3 H, d, \(J = 6.7\) Hz, CHCH\(_3\)), 1.26 (3 H, s, CCH\(_3\)), 1.34 (1 H, dd, \(J = 14.1, 3.8\) Hz, 1 H from CH\(_2\)CHCH\(_3\)), 1.48 (1 H, dd, \(J = 14.1, 7.6\) Hz, 1 H from CH\(_2\)CHCH\(_3\)), 1.64 - 1.77 (1 H, m, CCH\(_3\)), 2.46 (1 H, ddd, \(J = 14.1, 10.5, 0.5\) Hz, 1 H from CH\(_2\)C=CH\(_2\)), 2.77 (3 H, s,
NCH₃), 3.05 (3 H, s, NCH₃), 3.06 - 3.12 (1 H, m, 1 H from CH₂C=CH₂), 3.21 (1 H, dd, J = 10.5, 3.9 Hz, CHCH₂C=CH₂), 5.14 (1 H, br. s, 1 H from C=CH₂), 5.44 (1 H, d, J = 1.3 Hz, 1 H from C=CH₂), 7.29 - 7.35 (1 H, m, ArH), 7.36 - 7.43 (2 H, m, 2 × ArH), 7.48 - 7.54 (2 H, m, 2 × ArH);

¹³C NMR (100 MHz, Acetone) δ ppm 19.1 (C₃H₃), 24.0 (CHCH₃), 24.5 (CHCH₃), 25.6 (CHCH₃), 27.9 (NCH₃), 36.5 (CH₂C=CH₂), 37.9 (NCH₃), 46.6 (C₉), 46.9 (CH₂CHCH₃), 63.9 (CHCH₂C=CH₂), 116.8 (C=CH₂), 127.0 (2 × ArCH), 128.8 (ArCH), 129.6 (2 × ArCH), 140.7 (ArC₉), 146.0 (C=CH₂), 152.9 (C=O), 174.8 (C=O);

m/z (ES+) 351 ((M + Na), 100%). (Found: (M + H) 329.2214. C₂₀H₂₉N₂O₂ requires M, 329.2224).

6. Experimental data for chapter 3: pseudolaric acid B

6.1. General procedure A – Silyl protections


(3-(1,3-Dithian-2-yl)propoxy)tert-butyldiphenylsilane (366)
To a stirred solution of 2,3-dihydrofuran (16.2 mL, 214 mmol, 1.0 eq) in MeOH (17 mL) and CH₂Cl₂ (65 mL) at 0 °C was added BF₃•OEt₂ (8.1 mL, 64.2 mmol, 0.3 eq) dropwise and the reaction mixture stirred at room temperature for 20 minutes. Propane-1,3-dithiol (21.5 mL, 214 mmol, 1.0 eq) was then added and the reaction mixture stirred at room temperature for 2 hours. The reaction was quenched with H₂O (65 mL), diluted with CH₂Cl₂ (165 mL) and the organic phase washed with water (2 × 35 mL) and NaHCO₃ aq., sat. (45 mL). The organic phase was dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo to give crude 3-(1,3-dithian-2-yl)propan-1-ol. To a stirred solution of crude 3-(1,3-dithian-2-yl)propan-1-ol in DMF (400 mL) was added imidazole (29.2 g, 429 mmol, 2.0 eq) and TBDPSCl (61.8 g, 225 mmol, 1.05 eq) and the reaction mixture stirred at room temperature overnight. The reaction was diluted with CH₂Cl₂ (400 mL) and the organic phase washed with H₂O (3 × 600 mL) and NaHCO₃ aq., sat. (600 mL). The organic phase was dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column
chromatography on silica gel, eluting with 25% ethyl acetate in petroleum ether (40-60 °C) gave (3-(1,3-dithian-2-yl)propoxy)tert-butyldiphenylsilane 366 (84 g, 202 mmol, 94%) as a colourless oil.

\[ \nu_{\text{max}} \text{(neat)}/\text{cm}^{-1} \] 2930, 2895, 2856, 1424, 1104, 700;

\[^{1}\text{H NMR} \] (400 MHz, CDCl$_3$) \( \delta \) ppm 1.05 (9 H, s, 3 \( \times \) CH$_3$), 1.70 - 1.82 (2 H, m, OCH$_2$CH$_2$), 1.81 - 1.94 (3 H, m, CH$_2$CH, 1 H from SCH$_2$CH$_2$), 2.05 - 2.16 (1 H, m, 1 H from SCH$_2$CH$_2$), 2.72 - 2.92 (4 H, m, 2 \( \times \) SCH), 3.67 (2 H, t, \( J = 5.9 \) Hz, OCH$_2$), 4.02 (1 H, t, \( J = 6.8 \) Hz, CH), 7.34 - 7.45 (6 H, m, 6 \( \times \) ArH), 7.66 (4 H, dd, \( J = 7.8, 1.7 \) Hz, 4 \( \times \) ArH);

\[^{13}\text{C NMR} \] (100 MHz, CDCl$_3$) \( \delta \) ppm 19.4 (C$_q$), 26.2 (SCH$_2$CH$_2$), 27.0 (3 \( \times \) CH$_3$), 29.6 (CH$_2$CH), 30.6 (2 \( \times \) SCH), 32.1 (OCH$_2$CH$_2$), 47.5 (CH), 63.3 (OCH$_2$), 127.8 (4 \( \times \) ArCH), 129.7 (2 \( \times \) ArCH), 134.0 (2 \( \times \) ArC$_q$), 135.7 (4 \( \times \) ArCH);

\[ m/z \] (ES+) 205 (60%), 279 (85), 391 (100), 439 ((M + Na), 90). (Found (M + Na) 439.1562. C$_{23}$H$_{32}$OS$_2$SiNa requires \( M \), 439.1577). Data in accordance with the literature.

(3-(1,3-Dithian-2-yl)propoxy)(tert-butyl)dimethylsilane (SI-1)

As for general procedure A1, reaction of 2,3-dihydrofuran (15.1 mL, 200 mmol, 1.0 eq) and BF$_3$•OEt$_2$ (7.6 mL, 60.0 mmol, 0.3 eq) in MeOH (15 mL) and CH$_2$Cl$_2$ (60 mL), then with imidazole (20.4 g, 400 mmol, 1.5 eq) and TBSCl (33.2 g, 220 mmol, 1.1 eq, portionwise addition) in CH$_2$Cl$_2$ (300 mL) gave after filtration over a plug of silica gel (3-(1,3-dithian-2-yl)propoxy)(tert-butyl)dimethylsilane SI-1 (48 g, 164 mmol, 82%) as a colourless oil.

\[ \nu_{\text{max}} \text{(neat)}/\text{cm}^{-1} \] 2950, 2928, 2896, 2855, 1471, 1462, 1423, 1387, 1360, 1255, 1101, 1006, 967, 909, 834, 773, 717, 662;

\[^{1}\text{H NMR} \] (500 MHz, CDCl$_3$) \( \delta \) ppm 0.04 (6 H, s, 2 \( \times \) SiCH$_3$), 0.88 (9 H, s, 3 \( \times \) CCH$_3$), 1.68 - 1.75 (2 H, m, OCH$_2$CH$_2$), 1.79 - 1.84 (2 H, m, CHCH$_2$), 1.84 - 1.91 (1 H, m, 1 H from SCH$_2$CH$_2$), 2.07 - 2.14 (1 H, m, 1 H from SCH$_2$CH$_2$), 2.79 - 2.90 (4 H, m, 2 \( \times \) SCH), 3.62 (2 H, t, \( J = 6.0 \) Hz, OCH$_2$), 4.06 (1 H, t, \( J = 6.8 \) Hz, CH);

\[^{13}\text{C NMR} \] (125 MHz, CDCl$_3$) \( \delta \) ppm −5.4 (2 \( \times \) SiCH$_3$), 18.2 (C$_q$), 25.9 (3 \( \times \) CCH$_3$), 26.0 (SCH$_2$CH$_2$), 29.7 (OCH$_2$CH$_2$), 30.4 (2 \( \times \) SCH), 31.9 (CHCH$_2$), 47.4 (CH), 62.5 (OCH$_2$).
Data in accordance with the literature.²²⁴

6.1.2. General procedure A2 – Using silyl triflates

![Chemical structure]

*rac-tert*-Butyl(((1R,2S)-2-((tert-butyldimethylsilyl)oxy)-2-(pent-4-en-1-yl)-1-vinylcyclopentyl)methoxy)dimethylsilane (381)

To a stirred solution of *rac-(1S,2R)-2-(hydroxymethyl)-1-(pent-4-en-1-yl)-2-vinylcyclopentanol* 375 (404 mg, 1.09 mmol, 1.0 eq) in CH₂Cl₂ (11 mL) at 0 °C was added 2,6-lutidine (0.5 mL, 4.31 mmol, 4.0 eq), then tert-butyldimethylsilyl trifluoromethanesulfonate (743 mL, 3.24 mmol, 3.0 eq) and the reaction mixture stirred at 0 °C for 20 minutes. The reaction was quenched with NH₄Cl aq., sat. (10 mL) and the aqueous phase extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with ethyl acetate in petroleum ether (40–60 °C) (1:100 v/v) gave *rac-tert*-butyl(((1R,2S)-2-((tert-butyldimethylsilyl)oxy)-2-(pent-4-en-1-yl)-1-vinylcyclopentyl)methoxy)dimethylsilane 381 (404 mg, 0.92 mmol, 92%) as a colourless oil.

νₘₐₓ (neat)/cm⁻¹ 2955, 2929, 2884, 2860, 1472, 1255, 1093, 835, 772; ¹H NMR (400 MHz, CDCl₃) δ ppm 0.00 (3 H, s, SiCH₃), 0.00 (3 H, s, SiCH₃), 0.09 (3 H, s, SiCH₃), 0.11 (3 H, s, SiCH₃), 0.87 (9 H, s, 3 × CCH₃), 0.89 (9 H, s, 3 × CCH₃), 1.31 - 1.88 (10 H, m, 5 × CH₂), 1.98 (2 H, td, J = 7.0, 6.7 Hz, CH₂CH=CH₂), 3.58 (1 H, d, J = 9.6 Hz, 1 H from CH₂O), 3.79 (1 H, d, J = 9.6 Hz, 1 H from CH₂O), 4.89 - 5.02 (2 H, m, CH₂CH=CH₂), 4.98 - 5.16 (2 H, m, CCH=CH₂), 5.80 (1 H, ddt, J = 16.9, 10.1, 6.7 Hz, CH₂CH=CH₂), 5.92 (1 H, dd, J = 17.5, 11.0 Hz, CCH=CH₂);

¹³C NMR (100 MHz, CDCl₃) δ ppm −5.4 (SiCH₃), −5.2 (SiCH₃), −2.2 (SiCH₃), −2.0 (SiCH₃), 18.4 (CH₂), 19.0 (C⁶), 19.6 (C⁶), 24.1 (CH₂), 26.1 (3 × CCH₃), 26.2 (3 × CCH₃), 30.4 (CH₂), 34.8 (CH₂CH=CH₂), 36.8 (CH₂), 38.0 (CH₂), 58.5 (C⁶), 66.3 (CH₂O), 87.8 (C⁶), 113.7 (CCH=CH₂), 114.5 (CCH=CH₂), 139.1 (CCH=CH₂), 142.0 (CH₂CH=CH₂); m/z (ES⁺) 461 ((M + Na), 100%). (Found (M + Na) 461.3256. C₂₅H₅₀O₂Si₂Na requires M, 461.3242).
**rac-tert-Butyl(4-((1R,2R)-1-((tert-butyldimethylsilyl)oxy)-2-((tert-butyldimethylsilyl)oxy)ethyl)-2-vinylcyclopentyl)butoxy)dimethylsilane (422)**

As for general procedure A2, reaction of rac-4-((1R,2R)-1-((tert-butyldimethylsilyl)oxy)-2-((tert-butyldimethylsilyl)oxy)ethyl)-2-vinylcyclopentylbutan-1-ol 421 (50 mg, 0.11 mmol, 1.0 eq), 2,6-lutidine (53 µL, 0.45 mmol, 4.0 eq) and tert-butyldimethylsilyl trifluoromethanesulfonate (78 µL, 0.34 mmol, 3.0 eq) in CH$_2$Cl$_2$ (1.0 mL) gave after column chromatography (5% ethyl acetate in petroleum ether (40-60 °C)) rac-tert-butyl(4-((1R,2R)-1-((tert-butyldimethylsilyl)oxy)-2-((tert-butyldimethylsilyl)oxy)ethyl)-2-vinylcyclopentyl)butoxy)dimethylsilane 422 (63.0 mg, 0.11 mmol, quantitative) as a colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2952, 2930, 2885, 2857, 1638, 1387, 1358, 1252, 1095, 1005, 911, 832, 771, 666;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 0.00 (3 H, s, SiCH$_3$), 0.00 (3 H, s, SiCH$_3$), 0.05 (6 H, s, 2 × SiCH$_3$), 0.09 (3 H, s, SiCH$_3$), 0.11 (3 H, s, SiCH$_3$), 0.87 (9 H, s, 3 × CCH$_3$), 0.89 (9 H, s, 3 × CCH$_3$), 0.90 (9 H, s, 3 × CCH$_3$), 1.29 - 1.38 (1 H, m, 1 H from CH$_2$), 1.39 - 1.48 (3 H, m, 1 H from CH$_2$, CH$_2$), 1.48 - 1.56 (1 H, m, 1 H from CH$_2$), 1.57 - 1.66 (2 H, m, 2 × 1 H from CH$_2$), 1.67 - 1.77 (3 H, m, 3 × 1 H from CH$_2$), 1.77 - 1.83 (2 H, m, 2 × 1 H from CH$_2$), 3.56 - 3.63 (3 H, m, CH$_2$CH$_2$O, 1 H from CCH$_2$O), 3.76 - 3.81 (1 H, m, 1 H from CCH$_2$O), 5.02 (1 H, dd, $J = 17.6, 1.8$ Hz, 1 H from CH=CH$_2$), 5.06 (1 H, dd, $J = 11.0, 1.8$ Hz, 1 H from CH=CH$_2$), 5.92 (1 H, dd, $J = 17.6, 11.0$ Hz, CH=CH$_2$);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: −5.5 (SiCH$_3$), −5.4 (SiCH$_3$), −5.3 (2 × SiCH$_3$), −2.4 (SiCH$_3$), −2.2 (SiCH$_3$), 18.2 (C$^8$), 18.3 (C$^8$), 18.8 (C$^8$), 19.4 (CH$_2$), 21.0 (CH$_2$), 25.9 (3 × CCH$_3$), 26.0 (3 × CCH$_3$), 26.1 (3 × CCH$_3$), 30.3 (CH$_2$), 33.8 (CH$_2$), 36.7 (CH$_2$), 38.1 (CH$_2$), 58.3 (C$^8$), 63.2 (CH$_2$CH$_2$O), 66.2 (CCH$_2$O), 87.7 (C$^8$), 113.5 (CH=CH$_2$), 141.8 (CH=CH$_2$);

Mass spectrometry was not informative.
As for general procedure A2, reaction of rac-((1R,2R)-1-(but-3-en-1-yl)-2-((tert-butyldimethylsilyloxy)methyl)-2-vinylcyclopentyl)oxy)(tert-butyl)dimethylsilane (456) (83.3 mg, 0.20 mmol, 82%) as a colourless oil.

ν<sub>max</sub> (neat)/cm<sup>-1</sup> 3077, 2955, 2928, 2885, 2856, 1641, 1472, 1463, 1414, 1388, 1360, 1316, 1254, 1133, 1091, 1005, 938, 909, 833, 771, 665;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 0.01 (3 H, s, SiCH<sub>3</sub>), 0.02 (3 H, s, SiCH<sub>3</sub>), 0.12 (3 H, s, SiCH<sub>3</sub>), 0.13 (3 H, s, SiCH<sub>3</sub>), 0.88 (9 H, s, 3 × CCH<sub>3</sub>), 0.91 (9 H, s, 3 × CCH<sub>3</sub>), 1.53-1.65 (2 H, m, 1 H from CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, 1 H from CH<sub>2</sub>), 1.66 - 1.88 (6 H, m, 1 H from CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, 5 H from CH<sub>2</sub>), 2.00 - 2.13 (1 H, m, 1 H from CH<sub>2</sub>CH=CH<sub>2</sub>), 2.13 - 2.26 (1 H, m, 1 H from CH<sub>2</sub>CH=CH<sub>2</sub>), 3.61 (1 H, d, J = 9.6 Hz, 1 H from CH<sub>2</sub>O), 3.80 (1 H, d, J = 9.6 Hz, 1 H from CH<sub>2</sub>O), 4.93 (1 H, ddt, J = 10.2, 2.0, 1.2 Hz, 1 H from CH<sub>2</sub>CH=CH<sub>2</sub>), 4.99 (1 H, ddt, J = 17.1, 2.0, 2.0 Hz, 1 H from CH<sub>2</sub>CH=CH<sub>2</sub>), 5.05 (1 H, dd, J = 17.4, 1.6 Hz, 1 H from CCH=CH<sub>2</sub>), 5.09 (1 H, dd, J = 11.0, 1.6 Hz, 1 H from CCH=CH<sub>2</sub>), 5.79 (1 H, ddt, J = 17.1, 10.2, 6.5 Hz, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.94 (1 H, dd, J = 17.4, 11.0 Hz, CCH=CH<sub>2</sub>);

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ ppm −5.5 (SiCH<sub>3</sub>), −5.3 (SiCH<sub>3</sub>), −2.4 (SiCH<sub>3</sub>), −2.1 (SiCH<sub>3</sub>), 18.3 (C<sup>δ</sup>), 18.8 (C<sup>δ</sup>), 19.4 (CH<sub>2</sub>), 25.9 (3 × CCH<sub>3</sub>), 26.1 (3 × CCH<sub>3</sub>), 29.0 (CH<sub>2</sub>CH=CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 36.7 (CH<sub>2</sub>), 37.3 (CH<sub>2</sub>CH=CH<sub>2</sub>), 58.3 (C<sup>δ</sup>), 66.1 (CH<sub>2</sub>O), 87.4 (C<sup>δ</sup>), 113.7 (CCH=CH<sub>2</sub>), 113.9 (CH<sub>2</sub>CH=CH<sub>2</sub>), 139.3 (CH<sub>2</sub>CH=CH<sub>2</sub>), 141.7 (CCH=CH<sub>2</sub>);

Mass spectrometry was not informative.
6.2. General procedure B – Dithiane alkylations

(3-(2-((Pent-4-en-1-yl)-1,3-dithian-2-yl)propoxy)tert-butyldiphenylsilane (368)

To a stirred solution of (3-(1,3-dithian-2-yl)propoxy)tert-butyldiphenylsilane 366 (27.8 g, 66.8 mmol, 1.0 eq) in THF (500 mL) at −78 °C was added n-BuLi (1.6 M in hexane, 126 mL, 200 mmol, 3.0 eq) dropwise and the reaction mixture stirred at 0 °C for 90 minutes. The reaction mixture was cooled down to −78 °C and transferred by cannula into a stirred solution of 5-bromopent-1-ene (23.7 mL, 200 mmol, 3.0 eq) in THF (250 mL) at −78 °C, then stirred at room temperature overnight. The volume was reduced to ~50 mL, H₂O (50 mL) added and the aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with ethyl acetate in petroleum ether (40-60 °C) (1:30 v/v) gave (3-(2-((pent-4-en-1-yl)-1,3-dithian-2-yl)propoxy)tert-butyldiphenylsilane 368 (29.5 g, 60.9 mmol, 92%) as a white solid.

mp 85-62 °C;
νₘₐₓ (neat)/cm⁻¹ 3070, 2930, 2856, 1427, 1106, 1085, 700;
¹H NMR (300 MHz, CDCl₃) δ ppm 1.05 (3 H, s, CH₃) 1.06 (6 H, s, 2 × CH₃), 1.48 - 1.58 (2 H, m, CH₂CH₂CH=CH₂), 1.61 - 1.75 (2 H, m, OCH₂CH₂CH₂), 1.78 - 1.90 (2 H, m, CH₂CH₂CH₂CH=CH₂), 1.89 - 2.04 (4 H, m, SCH₂CH₂, OCH₂CH₂), 2.00 - 2.11 (2 H, m, CH₂CH₂CH=CH₂), 2.68 - 2.89 (4 H, m, 2 × SCH₂), 3.69 (2 H, t, J = 6.0 Hz, OCH₂), 4.92 - 5.10 (2 H, m, CH=CH₂), 5.79 (1 H, ddt, J = 16.9, 10.2, 6.6 Hz, CH=CH₂), 7.32 - 7.46 (6 H, m, 6 × ArH), 7.62 - 7.72 (4 H, m, 4 × ArH);
¹³C NMR (75 MHz, CDCl₃) δ ppm 19.2 (Cᵢ), 23.2 (CH₂CH₂CH=CH₂), 25.5 (CH₂), 26.0 (2 × SCH₂), 26.9 (3 × CH₃), 27.5 (OCH₂CH₂), 33.8 (CH₂CH=CH₂), 34.4 (CH₂), 37.8 (CH₂CH₂CH₂CH=CH₂), 53.1 (Cᵢ), 63.7 (OCH₂), 115.0 (CH=CH₂), 127.7 (4 × ArCH), 129.6 (2 × ArCH), 133.9 (2 × ArCᵢ), 135.6 (4 × ArCH), 138.3 (CH=CH₂);
m/z (ES+) 507 ((M + Na), 100%). (Found (M + NH₄) 502.2630. C₂₈H₄₄ONS₂Si requires M, 502.2628);
Anal (Found C, 69.30, H, 8.45; C₂₈H₄₀OS₂Si requires C, 69.36, H, 8.45%).
tert-Butyl(3-(2-(3-((tert-butyldimethylsilyl)oxy)propyl)-1,3-dithian-2-y)propoxy)diphenylsilane (430)

As for general procedure B, reaction of (3-(1,3-dithian-2-yl)propoxy)tert-butyldiphenylsilane 366 (586 mg, 1.41 mmol, 1.0 eq), n-BuLi (1.37 M in hexane, 3.1 mL, 4.22 mmol, 3.0 eq) and (3-bromopropoxy)(tert-butyldimethylsilane (1.0 g, 4.22 mmol, 3.0 eq) in THF (16 mL) gave after column chromatography (ethyl acetate in petroleum ether (1:30 v/v)) tert-butyl(3-(2-(3-((tert-butyldimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)propoxy)diphenylsilane 430 (672 mg, 1.14 mmol, 81%) as a light yellow oil.

ν_max (neat)/cm⁻¹ 2952, 2929, 2895, 2856, 1471, 1462, 1427, 1388, 1361, 1255, 1092, 1006, 974, 938, 835, 775, 735, 700, 687, 614;

¹H NMR (500 MHz, CDCl₃) δ ppm 0.07 (6 H, s, 2 × SiCH₃), 0.91 (9 H, s, 3 × CCH₃), 1.07 (9 H, s, 3 × CCH₃), 1.63 - 1.69 (2 H, m, OCH₂CH₂), 1.69 - 1.75 (2 H, m, OCH₂CH₂), 1.91 - 1.97 (4 H, m, CCH₂, SCH₂CH₂), 1.97 - 2.02 (2 H, m, CCH₂), 2.78 - 2.83 (4 H, m, 2 × SCH₂), 3.64 (2 H, t, J = 6.0 Hz, OCH₂), 3.69 (2 H, t, J = 6.0 Hz, OCH₂), 7.36 - 7.46 (6 H, m, 6 × ArH), 7.66 - 7.70 (4 H, m, 4 × ArH);

¹³C NMR (125 MHz, CDCl₃) δ ppm −5.3 (2 × SiCH₃), 18.3 (C⁶), 19.2 (C⁶), 25.5 (SCH₂CH₂), 25.9 (3 × CCH₃, 2 × SCH₂), 26.9 (3 × CCH₃), 27.3 (OCH₂CH₂), 27.4 (OCH₂CH₂), 34.5 (CCH₂), 34.7 (CCH₂), 52.9 (C⁶), 62.9 (OCH₂), 63.7 (OCH₂), 127.6 (4 × ArCH), 129.5 (2 × ArCH), 133.9 (2 × ArC⁶), 135.6 (4 × ArCH);

Mass spectrometry was not informative.

(3-(2-(But-3-en-1-yl)-1,3-dithian-2-yl)propoxy)(tert-butyldimethylsilane (449)

As for general procedure B, reaction of (3-(1,3-dithian-2-yl)propoxy)(tert-butyldimethylsilane SI-1 (6.4 g, 21.9 mmol, 1.0 eq), n-BuLi (1.3 M in hexane, 49 mL, 65.6 mmol, 3.0 eq) and 4-bromobut-1-ene (6.7 mL, 65.6 mmol, 3.0 eq) in THF (300 mL) gave after column chromatography (ethyl acetate in petroleum ether (1:30 v/v)) (3-(2-(but-3-en-1-yl)-1,3-dithian-2-yl)propoxy)(tert-butyldimethylsilane 449 (6.3 g, 18.1 mmol, 83%) as a light yellow oil.

ν_max (neat)/cm⁻¹ 2950, 2928, 2894, 2856, 1471, 1423, 1387, 1360, 1254, 1097, 1005, 988, 970, 909, 835, 774, 722, 661;
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 0.00 (6 H, s, 2 × SiCH$_3$), 0.84 (9 H, s, 3 × CCH$_3$), 1.55 - 1.65 (2 H, m, CH$_2$CH$_2$O), 1.84 - 1.96 (6 H, m, CH$_2$CH$_2$S, 2 × CCH$_2$), 2.11 - 2.18 (2 H, m, CH$_2$CH), 2.73 - 2.79 (4 H, m, 2 × CH$_2$S), 3.58 (2 H, t, J = 6.1 Hz, CH$_2$OSi), 4.92 (1 H, dd, J = 10.2, 1.7 Hz, 1 H from CH=CH$_2$), 5.00 (1 H, dd, J = 17.0, 1.7 Hz, 1 H from CH=CH$_2$), 5.77 (1 H, ddt, J = 17.0, 10.2, 6.6 Hz, CH=CH$_2$);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ ppm −5.3 (2 × SiCH$_3$), 18.3 (C$q$), 25.5 (C$H_2$CH$_2$S), 26.0 (3 × SiCCH$_3$), 26.0 (2 × CH$_2$S), 27.5 (CH$_2$CH$_2$O), 28.5 (CH$_2$CH), 34.5 (CCH$_2$), 37.4 (CCH$_2$), 52.8 (C$q$), 62.9 (CH$_2$OSi), 114.9 (CH=CH$_2$), 138.0 (CH=CH$_2$);

$m/z$ (ES+) 347 (21%), 348 (77), 363 ((M + H), 100), 364 (57). (Found: (M + H) 363.1844. C$_{17}$H$_{35}$O$_2$S$_2$Si requires M, 363.1843).

tert-Butyldimethyl(3-(2-methyl-1,3-dithian-2-yl)propoxy)silane (SI-2)

As for general procedure B, reaction of (3-(1,3-dithian-2-yl)propoxy)(tert-butyl)dimethylsilane SI-1 (5.0 g, 17.1 mmol, 1.0 eq), n-BuLi (1.5 M in hexane, 34 mL, 51.3 mmol, 3.0 eq) and methyl iodide (4.75 mL, 51.3 mmol, 3.0 eq) in THF (240 mL) gave after column chromatography (ethyl acetate in petroleum ether (1:30 v/v)) tert-butyldimethyl(3-(2-methyl-1,3-dithian-2-yl)propoxy)silane SI-2 (4.58 g, 14.9 mmol, 87%) as a light yellow oil.

$\nu$$_{max}$ (neat)/cm$^{-1}$ 2951, 2927, 2892, 2855, 1471, 1459, 1441, 1423, 1387, 1361, 1275, 1253, 1212, 1098, 1006, 939, 908, 833, 774, 722, 679, 661;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.05 (6 H, s, 2 × SiCH$_3$), 0.89 (9 H, s, 3 × SiCCH$_3$), 1.58 (3 H, s, CH$_3$), 1.63 - 1.74 (2 H, m, CH$_2$CH$_2$O), 1.90 - 2.02 (4 H, m, CH$_2$CH$_2$S, CCH$_2$), 2.75 - 2.91 (4 H, m, 2 × SCHR$_2$), 3.64 (2 H, t, J = 6.2 Hz, CH$_2$O);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm −5.3 (2 × SiCH$_3$), 18.2 (C$q$), 25.2 (CH$_2$CH$_2$S), 25.9 (3 × SiCCH$_3$), 26.4 (2 × SCHR$_2$), 27.7 (CH$_2$CCH$_3$), 28.0 (CH$_2$CH$_2$O), 37.6 (CCH$_2$), 48.9 (C$q$), 62.8 (CH$_2$O);

$m/z$ (ES+) 137 (41%), 160 (33), 175 (30), 210 (93), 307 ((M + H), 100). (Found: (M + H) 307.1580. C$_{14}$H$_{31}$O$^2$S$_2$Si requires M, 307.1581).
6.3. General procedure C – Silyl ether deprotections

6.3.1. General procedure C1 – HCl silyl ether deprotections

3-(2-(Pent-4-en-1-yl)-1,3-dithian-2-yl)propan-1-ol (SI-3)

Method 1
To a stirred solution of tert-butyldimethyl(3-(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)propoxy)silane (7.2 g, 19.9 mmol, 1.0 eq) in EtOH (80 mL) was added HCl (37%, 1.6 mL) and the reaction mixture stirred at room temperature for 30 minutes. The reaction was quenched with NaHCO$_3$ aq., sat. (80 mL) and the aqueous phase extracted with CH$_2$Cl$_2$ (3 × 80 mL). The combined organic phases were dried (Na$_2$SO$_4$ or MgSO$_4$) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) gave 3-(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)propan-1-ol SI-3 (3.6 g, 14.8 mmol, 74%) as a light yellow oil.

Method 2
To a stirred solution of tert-butyl(3-(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)propoxy)diphenylsilane 366 (28.6 g, 59.0 mmol, 1.0 eq) in THF (590 mL) was added TBAF (1 M in THF, 71 mL, 70.8 mmol, 1.2 eq) and the reaction mixture stirred at room temperature for 4 hours, then concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 20% ethyl acetate in hexane gave 3-(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)propan-1-ol SI-3 (13.5 g, 54.8 mmol, 93%) as a light yellow oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2362 (br. OH), 3073, 2938, 2907, 2866, 1946, 1639, 1417, 1451, 1417, 1053, 992, 907;

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 1.48 - 1.62 (2 H, m, CH$_2$CH$_2$CH=CH$_2$), 1.64 - 1.79 (2 H, m, CH$_2$CH$_2$OH), 1.82 - 2.01 (6 H, m, 3 × CH$_2$), 2.07 (2 H, m, CH$_2$CH=CH$_2$), 2.57 - 3.02 (4 H, m, 2 × SCH$_2$), 3.68 (2 H, t, $J = 6.3$ Hz, CH$_2$OH), 4.74 - 5.22 (2 H, m, CH=CH$_2$), 5.80 (1 H, ddt, $J = 16.9, 10.1, 6.6$ Hz, CH=CH$_2$);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 23.4 (CH$_2$CH$_2$CH=CH$_2$), 25.6 (CH$_2$), 26.2 (2 × SCh$_2$), 27.8 (CH$_2$CH$_2$OH), 33.9 (CH$_2$CH=CH$_2$), 34.7 (CH$_2$), 38.0 (CH$_2$), 53.1 (C$^6$), 63.1 (CH$_2$OH), 115.2 (CH=CH$_2$), 138.4 (CH=CH$_2$);

$m/z$ (ES+) 186 (100%), 269 ((M + Na), 35). (Found (M + H) 247.1181. C$_{12}$H$_{23}$OS$_2$ requires $M$, 247.1185).
3-(2-(3-((tert-Butyldiphenylsilyl)oxy)propyl)-1,3-dithian-2-yl)propan-1-ol (431)

As for general procedure C1, reaction of tert-butyl(3-(2-(3-((tert-butyldimethylsilyl)oxy)propyl)-1,3-dithian-2-yl)propoxy)diphenylsilane 430 (672 mg, 1.14 mmol, 1.0 eq) and HCl (37%, 0.1 mL) in EtOH (8.0 mL) gave after purification by column chromatography (20% ethyl acetate in petroleum ether (40-60 °C)) 3-(2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-1,3-dithian-2-yl)propan-1-ol 431 (541 mg, 1.14 mmol, quantitative) as a light yellow oil.

$\nu_{\max}$(neat)/cm$^{-1}$ 3372 (br. OH), 2950, 2930, 2896, 2856, 1472, 1427, 1389, 1361, 1274, 1254, 1110, 1087, 998, 908, 823, 734, 701, 687;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 1.07 (9 H, s, 3 × CCH$_3$), 1.66 - 1.76 (4 H, m, 2 × OCH$_2$CH$_2$), 1.93 - 1.97 (4 H, m, CCH$_2$, SCH$_2$CH$_2$), 1.98 - 2.03 (2 H, m, CCH$_2$), 2.75 - 2.87 (4 H, m, 2 × SCH$_2$), 3.67 (2 H, t, $J = 6.3$ Hz, OCH$_2$), 3.70 (2 H, t, $J = 6.1$ Hz, OCH$_2$), 7.36 - 7.46 (6 H, m, 6 × ArH), 7.65 - 7.71 (4 H, m, 4 × ArH);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ ppm 19.2 (C$q$), 25.4 (SCH$_2$C$\text{H}_2$), 26.0 (2 × SCH$_2$), 26.9 (3 × CCH$_3$), 27.4 (OCH$_2$CH$_2$), 27.5 (OCH$_2$CH$_2$), 34.5 (CCH$_2$), 34.6 (CCH$_2$), 52.8 (C$q$), 62.9 (OCH$_2$), 63.7 (OCH$_2$), 127.6 (4 × ArCH), 129.6 (2 × ArCH), 133.9 (2 × ArC$q$), 135.6 (4 × ArCH);

3-(2-(But-3-en-1-yl)-1,3-dithian-2-yl)propan-1-ol (450)

As for general procedure C1, reaction of (3-(2-(but-3-en-1-yl)-1,3-dithian-2-yl)propoxy)(tert-butyl)dimethylylsilane 449 (6.0 g, 17.3 mmol, 1.0 eq) and HCl (37%, 1.4 mL) in EtOH (70 mL) gave after purification by column chromatography (20% ethyl acetate in petroleum ether (40-60 °C)) 3-(2-(but-3-en-1-yl)-1,3-dithian-2-yl)propan-1-ol 450 (3.2 g, 13.8 mmol, 80%) as a light yellow oil.

$\nu_{\max}$(neat)/cm$^{-1}$ 3363 (br. OH), 3075, 2942, 1640, 1449, 1422, 1274, 1239, 1184, 1055, 1001, 908, 869, 795, 677;

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 1.68 - 1.78 (2 H, m, CH$_2$CH$_2$OH), 1.89 - 2.03 (6 H, m, CH$_2$CH$_2$S, 2 × CCH$_2$), 2.14 - 2.26 (2 H, m, CH$_2$CH), 2.77 - 2.86 (4 H, m, 2 × CH$_2$S), 3.68 (2 H, t, $J = 6.3$ Hz, CH$_2$OH), 4.97 (1 H, dd, $J = 10.3$, 1.6 Hz, 1 H from CH=CH$_2$), 5.05 (1
H, dd, $J = 17.0$, 1.6 Hz, 1 H from CH=CH$_2$), 5.82 (1 H, ddt, $J = 17.0$, 10.3, 6.4 Hz, CH$_2$=CH$_2$);

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 25.3 (CH$_3$CH$_2$S), 25.9 (2 × CH$_2$S), 27.4 (CH$_2$CH$_2$OH), 28.5 (CH$_2$CH), 34.5 (CCH$_2$), 37.4 (CCH$_2$), 52.7 (C$^\circ$), 62.7 (CH$_2$OH), 114.9 (CH=CH$_2$), 137.8 (CH=CH$_2$);

$m/z$ (ES+) 157 (16%), 178 (35), 215 (39), 217 (16), 255 ((M + Na), 13), 271 (100), 273 (19). (Found: (M + Na) 255.0858. C$_{11}$H$_{20}$OS$_2$Na requires $M$, 255.0848).

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3-(2-Methyl-1,3-dithian-2-yl)propan-1-ol (SI-4)

As for general procedure C1, reaction of tert-butyldimethyl(3-(2-methyl-1,3-dithian-2-yl)propoxy)silane SI-2 (4.58 g, 14.9 mmol, 1.0 eq) and HCl (37%, 1.2 mL) in EtOH (60 mL) gave after purification by column chromatography (20% ethyl acetate in petroleum ether (40-60 °C)) 3-(2-methyl-1,3-dithian-2-yl)propan-1-ol SI-4 (1.89 g, 9.83 mmol, 66%) as a light yellow oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3361 (br. OH), 2945, 2922, 1445, 1421, 1371, 1275, 1239, 1190, 1146, 1053, 1019, 906, 867, 816, 756, 722, 678, 660;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.59 (3 H, s, CH$_3$), 1.67 - 1.78 (2 H, m, CCH$_2$), 1.90 - 2.03 (4 H, m, CH$_2$CH$_2$S, CH$_2$CH$_2$O), 2.74 - 2.92 (4 H, m, 2 × SCH$_2$), 3.66 (2 H, t, $J = 6.4$ Hz, CH$_2$O);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 25.1 (CH$_2$CH$_2$S), 26.3 (2 × SCH$_2$), 27.7 (CH$_3$), 27.9 (CCH$_2$), 37.6 (CH$_2$CH$_2$O), 48.8 (C$^\circ$), 62.6 (CH$_2$O);

$m/z$ (ES+) 231 ((M + K), 100%). (Found: (M + K) 231.0264. C$_8$H$_{16}$OS$_2$K requires $M$, 231.0275).
6.3.2. General procedure C2 – HF silyl ether deprotections

rac-Methyl 4-(((1R,2R)-1-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)-2-vinylcyclopentyl)butanoate (406)

To a stirred solution of rac-4-(((1R,2R)-1-((tert-butyldimethylsilyl)oxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-2-vinylcyclopentyl)butanoate 405 (8.0 mg, 17.0 µmol, 1.0 eq) in acetonitrile (0.5 mL) was added HF (0.5 M in H2O, 34 µL, 17.0 µmol, 1.0 eq) and the reaction mixture stirred at room temperature overnight. The reaction was quenched with NaHCO3 aq., sat. (1.0 mL) and the aqueous phase extracted with CH2Cl2 (3 × 1.0 mL). The combined organic phases were dried (Na2SO4 or MgSO4) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40-60 °C) gave rac-methyl 4-(((1R,2R)-1-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)-2-vinylcyclopentyl)butanoate 406 (5.2 mg, 14.6 µmol, 86%) as a colourless oil.

νmax (neat)/cm⁻¹ 3466 (br. OH), 2954, 2929, 2885, 2856, 1741 (C=O), 1472, 1458, 1436, 1360, 1255, 1196, 1170, 1107, 1047, 1005, 915, 834, 772;

1H NMR (400 MHz, CDCl3) δ ppm 0.12 (3 H, s, SiCH3), 0.12 (3 H, s, SiCH3), 0.89 (9 H, s, 3 × CCH3), 1.45 - 1.85 (9 H, m, 9 H from CH2), 1.96 - 2.08 (1 H, m, 1 H from CH2), 2.25 (2 H, td, J = 7.3, 1.8 Hz, CH2COOCH3), 3.65 (3 H, s, OCH3), 3.67 (2 H, s, CH2O), 5.10 (1 H, dd, J = 17.6, 1.4 Hz, 1 H from CH=CH2), 5.19 (1 H, dd, J = 10.9, 1.4 Hz, 1 H from CH=CH2), 5.87 (1 H, dd, J = 17.6, 10.9 Hz, CH=CH2);

13C NMR (100 MHz, CDCl3) δ ppm −2.3 (SiCH3), −2.2 (SiCH3), 18.6 (Cq), 19.2 (CH2), 19.8 (CH2), 26.0 (3 × CCH3), 29.3 (CH2), 34.5 (CH2COOCH3), 37.1 (CH2), 37.9 (CH2), 51.4 (OCH3), 57.8 (Cq), 66.0 (CH2O), 88.1 (Cq), 115.3 (CH=CH2), 140.3 (CH=CH2), 173.7 (C=O);

m/z (ES+) 379 ((M + Na), 100%), 380 (61), 381 (21). (Found: (M + Na) 379.2269. C19H36O4SiNa requires M, 379.2276).
\( \text{rac-}((1R,2R)-2-(\text{But-3-en-1-yl})-2-((\text{tert-butyldimethylsilyl})\text{oxy})-1\text{-vinylcyclopentyl})\text{methanol (457)} \)

As for general procedure C2, reaction of \( \text{rac-}((1R,2R)-1-(\text{but-3-en-1-yl})-2-((\text{tert-butyldimethylsilyl})\text{oxy})\text{methyl})-2\text{-vinylcyclopentyl}\text{oxy})(\text{tert-butyl})\text{dimethylsilane (456)} \)

(172 mg, 0.41 mmol, 1.0 eq) and HF (1 M in \( \text{H}_2\text{O} \), 0.41 mL, 0.41 mmol, 1.0 eq) in acetonitrile (4.0 mL) for 8 hours gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) \( \text{rac-}((1R,2R)-2-(\text{but-3-en-1-yl})-2-((\text{tert-butyldimethylsilyl})\text{oxy})-1\text{-vinylcyclopentyl})\text{methanol (457)} \)

(70.0 mg, 0.23 mmol, 56%) as a colourless oil.

\( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 3424 (br. OH), 2954, 2928, 2884, 2856, 1641, 1472, 1407, 1388, 1360, 1315, 1255, 1129, 1046, 1004, 909, 833, 771, 668;

\( ^1\text{H NMR} \) (400 MHz, \( \text{CDCl}_3 \)) \( \delta \) ppm: 0.14 (3 H, s, \( \text{SiCH}_3 \)), 0.15 (3 H, s, \( \text{SiCH}_3 \)), 0.91 (9 H, s, \( 3 \times \text{CCH}_3 \)), 1.55 - 1.69 (3 H, m, \( \text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2 \), 1 H from \( \text{CH}_2 \)), 1.71 - 1.86 (4 H, m, \( \text{CH}_2 \), 2 H from \( \text{CH}_2 \)), 1.99 - 2.09 (1 H, m, 1 H from \( \text{CH}_2 \)), 2.09 - 2.28 (2 H, m, \( \text{CH}_2\text{CH}=\text{CH}_2 \)), 3.68 (1 H, d, \( J = 11.1 \text{ Hz} \), 1 H from \( \text{CH}_2\text{OH} \)), 3.72 (1 H, d, \( J = 11.1 \text{ Hz} \), 1 H from \( \text{CH}_2\text{OH} \)), 4.91 - 4.97 (1 H, m, 1 H from \( \text{CH}_2\text{CH}=\text{CH}_2 \)), 5.00 (1 H, ddt, \( J = 17.1, 1.6, 1.6 \text{ Hz} \), 1 H from \( \text{CH}_2\text{CH}=\text{CH}_2 \)), 5.13 (1 H, dd, \( J = 17.7, 1.3 \text{ Hz} \), 1 H from \( \text{CCH}=\text{CH}_2 \)), 5.21 (1 H, dd, \( J = 11.0, 1.3 \text{ Hz} \), 1 H from \( \text{CCH}=\text{CH}_2 \)), 5.77 (1 H, ddt, \( J = 17.1, 10.3, 6.6 \text{ Hz} \), \( \text{CH}_2\text{CH}=\text{CH}_2 \)), 5.89 (1 H, dd, \( J = 17.7, 11.0 \text{ Hz} \), \( \text{CCH}=\text{CH}_2 \));

\( ^{13}\text{C NMR} \) (100 MHz, \( \text{CDCl}_3 \)) \( \delta \) ppm: -2.3 (\( \text{SiCH}_3 \)), -2.1 (\( \text{SiCH}_3 \)), 18.6 (C\(^i\)), 19.2 (\( \text{CH}_2 \)), 26.0 (\( 3 \times \text{CCH}_3 \)), 28.5 (\( \text{CH}_2\text{CH}=\text{CH}_2 \)), 29.4 (\( \text{CH}_2 \)), 37.2 (\( \text{CH}_2 \)), 37.5 (\( \text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2 \)), 57.9 (C\(^i\)), 66.1 (\( \text{CH}_2\text{OH} \)), 88.2 (C\(^i\)), 114.3 (\( \text{CH}_2\text{CH}=\text{CH}_2 \)), 115.3 (\( \text{CCH}=\text{CH}_2 \)), 138.8 (\( \text{CH}_2\text{CH}=\text{CH}_2 \)), 140.5 (\( \text{CCH}=\text{CH}_2 \));

\( \text{m/z} \) (ES+) 269 (19%), 333 ((M + Na), 100), 335 (43), 365 (29).
6.4. General procedure D – Conjugate silyl-addition/aldol reactions

\[ \text{rac-}(3S,4R)-4-(\text{Dimethyl(phenyl)silyl})-3-(1\text{-hydroxy-3-(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)propyl})\text{dihydrofuran-2-one (371)} \]

To a stirred solution of chlorodimethylphenylsilane (2.25 mL, 13.5 mmol, 2.2 eq) in THF (25 mL) at 0 °C was added lithium (605 mg, 72.4 mmol, 11.8 eq) and the reaction mixture stirred at 0 °C overnight, then transferred by cannula into copper(I) cyanide (605 mg, 6.75 mmol, 1.1 eq) in THF (16 mL) at 0 °C and stirred at 0 °C for 2 hours. The reaction mixture was cooled down to −45 °C, 2(5H)-furanone (516 mg, 6.14 mmol, 1.0 eq) in THF (12 mL) at −45 °C transfered in by cannula, and the reaction mixture then stirred at −45 °C for 90 minutes. 3-(2-(Pent-4-en-1-yl)-1,3-dithian-2-yl)propanal 369 (3.0 g, 12.3 mmol, 2.0 eq) in THF (33 mL) at −45 °C was then transferred in by cannula and the reaction mixture stirred at −45 °C for 4 hours, then warmed up to room temperature. The reaction was quenched with \( \text{NH}_4\text{Cl} \), sat. (70 mL), stirred 1 hour at room temperature, then filtered through a celite plug and the aqueous phase was extracted with ethyl acetate (\( 3 \times 70 \text{ mL} \)). The combined organic phases were dried (Na$_2$SO$_4$ or MgSO$_4$) and concentrated \textit{in vacuo}. Purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) gave \textit{rac-}(3S,4R)-4-(dimethyl(phenyl)silyl)-3-(1-hydroxy-3-(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)propyl)dihydrofuran-2-one 371 (2.55 g, 5.48 mmol, 89%) as a yellow oil and as a 2.7:1 mixture of diastereoisomers.

\[ \nu_{\text{max}} \text{(neat)/cm}^{-1} : 3071 \text{ (br. OH)}, 2917, 2851, 2360, 2341, 1749 \text{ (C=O)}, 1427, 1371, 1252, 1227, 1176, 1113, 1026, 817, 753, 734, 701; \]

\textit{Major isomer}

\[ ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta \text{ ppm} \]

\[ \begin{align*}
(2 \text{ H, m, CH}_2), & \ 1.62 - 1.70 \ (1 \text{ H, m, 1 H from CH}_2), \\
1.73 - 1.86 \ (5 \text{ H, m, 5 H from CH}_2), & \ 1.89 - 1.99 \ (2 \text{ H, m, SCH}_2CH_2), \\
2.03 - 2.13 \ (3 \text{ H, m, CH}_2, \text{ CHSi}), & \ 2.49 \ (1 \text{ H, dd, } J = 11.4, 3.8 \text{ Hz, CHCHOH}), \\
2.72 - 2.87 \ (4 \text{ H, m, 2 } \times \text{SCH}_2), & \ 3.54 - 3.61 \ (1 \text{ H, m, CHOH}), \\
4.06 \ (1 \text{ H, dd, } J = 10.6, 9.1 \text{ Hz, 1 H from CH}_2O), & \ 4.37 \ (1 \text{ H, t, } J = 9.1 \text{ Hz, 1 H from CH}_2O), \\
4.97 - 5.08 \ (2 \text{ H, m, CH=CH}_2), & \ 5.81 \ (1 \text{ H, ddt, } J = 17.0, 10.3, 6.7, \text{CH=CH}_2), \\
7.33 - 7.44 \ (3 \text{ H, m, 3 } \times \text{ArH}), & \ 7.46 - 7.55 \ (2 \text{ H, m, 2 } \times \text{ArH}); 
\end{align*} \]
\[ ^{13}C \text{ NMR} \ (100 \text{ MHz, CDCl}_3 \ \delta \text{ ppm} \ -4.6 \ (\text{SiCH}_3), \ -4.3 \ (\text{SiCH}_3), \ 23.2 \ (\text{CH}_2), \ 25.4 \ (\text{SCH}_2\text{CH}_2), \ 25.6 \ (\text{CHSi}), \ 26.0 \ (2 \times \text{SCH}_2), \ 30.1 \ (\text{CH}_2), \ 33.7 \ (\text{CH}_2), \ 34.7 \ (\text{CH}_2), \ 37.9 \ (\text{CH}_2), \ 47.8 \ (\text{CHCHOH}), \ 53.0 \ (\text{C}^\circ), \ 69.2 \ (\text{CH}_2\text{O}), \ 71.8 \ (\text{CHOH}), \ 115.1 \ (\text{CH}=\text{CH}_2), \ 128.4 \ (2 \times \text{ArCH}), \ 130.0 \ (\text{ArCH}), \ 133.8 \ (2 \times \text{ArCH}), \ 135.1 \ (\text{ArC}^\circ), \ 138.3 \ (\text{CH} = \text{CH}_2), \ 178.4 \ (\text{C} = \text{O}); \]

\[ \text{m/z} \ (\text{ES}^+) \ 357 \ (70\%), \ 487 \ (\text{(M} + \text{Na}), \ 100). \ (\text{Found} \ (\text{M} + \text{Na}) \ 487.1766. \ C_{24}H_{36}O_3\text{SiS}_2\text{Na requires} \ M, \ 487.1768). \]

**rac-(3S,4R)-3-(3-(2-(But-3-en-1-yl)-1,3-dithian-2-yl)-1-hydroxypropyl)-4-(dimethyl(phenyl)silyl)dihydrofuran-2(3H)-one (452)**

As for general procedure D, reaction of chlorodimethylphenylsilane (2.5 mL, 15.2 mmol, 2.2 eq), lithium (566 mg, 81.5 mmol, 11.8 eq), copper(I) cyanide (681 mg, 7.60 mmol, 1.1 eq), 2(5H)-furanone (581 mg, 6.91 mmol, 1.0 eq) and 3-(2-(but-3-en-1-yl)-1,3-dithian-2-yl)propanal 451 (3.2 g, 13.8 mmol, 2.0 eq) in THF (86 mL) gave after column chromatography (20% ethyl acetate in petroleum ether (40-60 °C)) rac-(3S,4R)-3-(3-(2-(but-3-en-1-yl)-1,3-dithian-2-yl)-1-hydroxypropyl)-4-(dimethyl(phenyl)silyl)dihydrofuran-2(3H)-one 452 (2.62 g, 5.81 mmol, 84%) as a light yellow oil and as a 2.7:1 mixture of diastereoisomers.

\[ \nu_{\text{max}} \ (\text{neat})/\text{cm}^{-1} \ 3468 \ (\text{br. OH}), \ 3069, \ 2951, \ 2903, \ 1760 \ (\text{C} = \text{O}), \ 1640, \ 1450, \ 1427, \ 1378, \ 1253, \ 1169, \ 1113, \ 998, \ 909, \ 837, \ 820, \ 779, \ 737, \ 702, \ 650; \]

\[ ^1H \text{ NMR} \ (400 MHz, CDCl}_3 \ \delta \text{ ppm} \ 0.39 \ (3 \text{ H, s, SiCH}_3 \ (\text{minor})), \ 0.40 \ (3 \text{ H, s, SiCH}_3 \ (\text{minor})), \ 0.41 \ (3 \text{ H, s, SiCH}_3 \ (\text{major})), \ 0.42 \ (3 \text{ H, s, SiCH}_3 \ (\text{major})), \ 1.64 - 1.71 \ (2 \text{ H, m, 1 H from CH}_2\text{CH}_2\text{CHOH (major and minor)}), \ 1.75 - 1.81 \ (4 \text{ H, m, 1 H from CH}_2\text{CH}_2\text{CHOH (major and minor)}), \ 1.86 - 1.91 \ (4 \text{ H, m, CH}_2\text{CH}_2\text{CH} = \text{CH}_2 \ (\text{major and minor})), \ 1.92 - 1.98 \ (4 \text{ H, m, SCH}_2\text{CH}_2 \ (\text{major and minor})), \ 1.99 - 2.14 \ (4 \text{ H, m, 1 H from CH}_2\text{CH}_2\text{CHOH (major and minor)}), \ 2.14 - 2.25 \ (4 \text{ H, m, CH}_2\text{CH} = \text{CH}_2 \ (\text{major and minor})), \ 2.48 \ (1 \text{ H, dd, J} = 11.2, \ 3.6 \text{ Hz, CHCHOH (major)}), \ 2.64 \ (1 \text{ H, dd, J} = 10.4, \ 3.8 \text{ Hz, CHCHOH (minor)}), \ 2.73 - 2.85 \ (8 \text{ H, m, 2 x SCH}_2 \ (\text{major and minor})), \ 3.58 \ (1 \text{ H, dt, J} = 8.6, \ 4.1 \text{ Hz, CHOH (major)}), \ 3.71 - 3.77 \ (1 \text{ H, m, CHOH (minor)}), \ 4.06 \ (1 \text{ H, dd, J} = 10.6, \ 9.0 \text{ Hz, 1 H from CH}_2\text{OH (major)}), \ 4.10 \ (1 \text{ H, t, J} = 9.2 \text{ Hz, 1 H from CH}_2\text{OH (minor)}), \ 4.37 \ (1 \text{ H, t, J} = 9.1 \text{ Hz, 1 H from}}

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\[ \text{CH}_2\text{OH (major)), 4.41 (1 H, t, } J = 9.2 \text{ Hz, 1 H from } \text{CH}_2\text{OH (minor)), 4.95 - 5.02 (2 H, m, 1 H from CH=CH}_2\text{ (major and minor)), 5.03 - 5.10 (2 H, m, 1 H from CH=CH}_2\text{ (major and minor)), 5.74 - 5.90 (2 H, m, CH=CH}_2\text{ (major and minor)), 7.36 - 7.43 (6 H, m, 3 × ArH (major and minor)), 7.47 - 7.53 (4 H, m, 2 × ArH (major and minor));} \]

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta \text{ ppm −5.1 (SiCH}_3\text{ (minor)), −4.7 (SiCH}_3\text{ (major)), −4.6 (SiCH (minor)), −4.4 (SiCH}_3\text{ (major)), 24.2 (CHSi (minor)), 25.2 (SCH}_2\text{CH}_2\text{ (major and minor)), 25.5 (CHSi (major)), 28.4 (CH}_2\text{CH}=\text{CH}_2\text{ (major and minor)), 29.8 (CH}_2\text{CH}_2\text{CHOH (major and minor)), 34.7 (CH}_2\text{CHOH (major)), 34.7 (CH}_2\text{CHOH (minor)), 37.6 (CH}_2\text{CH}_2\text{CH}=\text{CH}_2\text{ (major and minor)), 47.7 (CHCHOH (major)), 47.8 (CHCHOH (minor)), 52.7 (C}_1\text{ (major)), 52.7 (C}_1\text{ (minor)), 69.2 (CH}_2\text{O (major)), 69.7 (CH}_2\text{O (minor)), 71.1 (CHOH (minor)), 71.7 (CHOH (major)), 114.9 (CH=CH}_2\text{ (major and minor)), 128.3 (2 × ArCH (major and minor)), 129.9 (ArCH (major)), 130.0 (ArCH (minor)), 133.6 (2 × ArCH (minor)), 133.7 (2 × ArCH (major)), 135.1 (ArC}_1\text{ (major and minor)), 137.8 (CH=CH}_2\text{ (major and minor)), 178.3 (C=O (major)), 179.8 (C=O (minor));} \]

\[ \text{m/z (ES+)} 343 (100%), 344 (28), 383 (28), 468 ((M + NH}_4\text{)), 474 (32), 490 (53), 491 (18). (Found: (M + Na) 473.1606. C}_{23}\text{H}_{34}\text{O}_3\text{S}_2\text{SiNa requires } M, 473.1611. \]

\[ \text{rac- (3S,4R)}\text{-3-(1-Hydroxy-3-(2-methyl-1,3-dithian-2-yl)-propyl)-4-dimethyl(phenyl)silyl-dihydro-furan-2-one (SI-5)} \]

As for general procedure D, reaction of chlorodimethylphenylsilane (2.2 mL, 13.1 mmol, 2.2 eq), lithium (490 mg, 70.7 mmol, 11.8 eq), copper(I) cyanide (593 mg, 6.55 mmol, 1.1 eq), 2(5)-furanone (500 mg, 5.95 mmol, 1.0 eq) and 3-(2-methyl-1,3-dithian-2-yl)propionaldehyde (3.39 g, 17.9 mmol, 3.0 eq) gave after column chromatography (30 % ethyl acetate in petroleum ether (40-60 °C)) rac- (3S,4R)-3-(1-hydroxy-3-(2-methyl-1,3-dithian-2-yl)-propyl)-4-dimethyl(phenyl)silyl-dihydro-furan-2-one SI-5 (1.93 g, 4.70 mmol, 79%) as a colourless oil and as a 1.6:1 mixture of diastereoisomers.

\[ \nu_{_{\text{max}}} \text{(neat)/cm}^{-1} 3453 \text{ (br. OH), 2922, 1748 (C=O), 1426, 1377, 1252, 1168, 1112, 1057, 998, 906, 818, 778, 735, 101, 649;} \]

Major isomer
$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 0.42 (3 H, s, SiCH$_3$), 0.42 (3 H, s, SiCH$_3$), 1.53 (3 H, s, CCH$_3$), 1.55 - 1.60 (1 H, m, 1 H from CH$_2$), 1.65 - 1.72 (1 H, m, 1 H from CH$_2$), 1.78 - 1.86 (1 H, m, 1 H from CH$_2$), 1.90 - 2.03 (2 H, m, SCH$_2$CH$_2$), 2.08 - 2.16 (2 H, m, CHSi, 1 H from CH$_2$), 2.50 (1 H, dd, $J = 11.2$, 3.9 Hz, C$_3$HCHOH), 2.71 - 2.91 (4 H, m, 2 $\times$ SCH$_2$), 3.55 - 3.64 (1 H, m, C$_2$H$_2$O), 4.07 (1 H, dd, $J = 10.6$, 9.1 Hz, 1 H from CH$_2$O), 4.38 (1 H, t, $J = 9.1$ Hz, 1 H from CH$_2$O), 7.30 - 7.56 (5 H, m, 5 $\times$ ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm −4.7 (SiCH$_3$), −4.4 (SiCH$_3$), 25.1 (SCH$_2$CH$_2$), 25.5 (CHSi), 26.4 (2 $\times$ SCHR), 27.8 (CCH$_3$), 30.4 (CH$_2$), 37.7 (CH$_2$), 47.8 (CHCHOH), 48.7 (C$_3$), 69.2 (CH$_2$O), 71.7 (CHOH), 128.4 (2 $\times$ ArCH), 130.0 (ArCH), 133.8 (2 $\times$ ArCH), 135.4 (ArC$_3$), 177.9 (C=O);

$m/z$ (ES+) 119 (38%), 151 (45), 433 ((M + Na) 100). (Found (M + Na) 433.1309. C$_{20}$H$_{30}$O$_3$S$_2$SiNa requires $M$, 433.1309).

6.5. General procedure E – Mesylation/elimination sequences

![Chemical structure](image)

4-(Dimethyl(phenyl)silyl)-3-(3-(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)propylidene)dihydrofuran-2-one (372)

To a stirred solution of rac-(3S,4R)-4-(dimethyl(phenyl)silyl)-3-(1-hydroxy-3-(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)propyl)dihydrofuran-2-one 371 (906 mg, 1.95 mmol, 1.0 eq) and triethylamine (1.1 mL, 7.80 mmol, 4.0 eq) in CH$_2$Cl$_2$ (20 mL) at 0 °C was added methanesulfonyl chloride (302 µL, 3.90 mmol, 2.0 eq) dropwise and the reaction mixture stirred at 0 °C for 5 minutes. DBU (1.7 mL, 11.7 mmol, 6.0 eq) was then added and the reaction mixture stirred at room temperature for 2 hours. The reaction was quenched with NH$_4$Cl$_{aq}$, sat. (20 mL), the aqueous phase extracted with CH$_2$Cl$_2$ (3 $\times$ 20 mL) and the combined organic phases dried (Na$_2$SO$_4$ or MgSO$_4$) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 10% ethyl acetate in petroleum ether (40-60 °C) gave 4-(dimethyl(phenyl)silyl)-3-(3-(2-(pent-4-en-1-yl)-1,3-dithian-2-yl)propylidene)dihydrofuran-2-one 372 (635 mg, 1.42 mmol, 73%) as a light yellow oil and as a 2.7:1 mixture of double-bond isomers.
$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3006, 2941, 2853, 2340, 2320, 1650 (C=O), 1451, 1433, 1262, 1093, 1022, 805, 737;

Major isomer

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.36 (3 H, s, SiCH$_3$), 0.36 (3 H, s, SiCH$_3$), 1.44 - 1.63 (2 H, m, CH$_2$CH$_2$CH=CH$_2$), 1.65 - 1.75 (1 H, m, 1 H from CH$_2$CH$_2$CH$_2$CH=CH$_2$), 1.81 - 1.89 (3 H, m, 1 H from CH$_2$CH$_2$CH$_2$CH=CH$_2$, CH$_2$CH$_2$CH=C), 2.14 - 2.20 (2 H, m, SCH$_2$CH$_2$), 2.07 (2 H, q, $J = 6.7$ Hz, CH$_2$CH=CH$_2$), 2.61 - 2.67 (1 H, m, CHSi), 2.69 - 2.93 (6 H, m, 2 × SCH$_2$, CH$_2$CH=C), 4.21 (1 H, dd, $J = 8.8$, 4.0 Hz, 1 H from CH$_2$O), 4.41 (1 H, t, $J = 8.8$ Hz, 1 H from CH$_2$O), 5.82 (1 H, ddt, $J = 16.9$, 10.2, 6.7 Hz, CH=$\text{CH}_2$), 7.34 - 7.53 (5 H, m, 5 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm −5.5 (SiCH$_3$), −5.3 (SiCH$_3$), 23.0 (CH$_2$CH=C), 23.2 (CH$_2$CH$_2$CH=CH$_2$), 25.6 (SCH$_2$CH$_2$), 26.2 (2 × SCH$_2$), 30.4 (CHSi), 33.9 (CH$_2$CH=CH$_2$), 37.4 (CH$_2$CH$_2$CH=C), 37.8 (CH$_2$CH$_2$CH$_2$CH=CH$_2$), 53.0 (C$_q$), 67.2 (CH$_2$O), 115.1 (CH=CH$_2$), 126.6 (C=CH), 128.3 (2 × ArCH), 130.1 (ArCH), 134.1 (2 × ArCH), 138.5 (CH=CH$_2$), 139.6 (C=CH), 170.4 (C=O); ArC$_q$ not observed.

Minor isomer

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.37 (3 H, s, SiCH$_3$), 0.38 (3 H, s, SiCH$_3$), 1.44 - 1.63 (2 H, m, CH$_2$CH$_2$CH=CH$_2$), 1.65 - 1.75 (1 H, m, 1 H from CH$_2$CH$_2$CH$_2$CH=CH$_2$), 1.80 - 1.89 (3 H, m, 1 H from CH$_2$CH$_2$CH$_2$CH=CH$_2$, CH$_2$CH$_2$CH=C), 1.89 - 2.02 (2 H, m, SCH$_2$CH$_2$), 2.07 (2 H, dt, $J = 6.9$, 6.8 Hz, CH$_2$CH=CH$_2$), 2.69 - 2.93 (7 H, m, CHSi, 2 × SCH$_2$, CH$_2$CH=C), 4.28 - 4.40 (2 H, m, CH$_2$O), 4.93 - 5.10 (2 H, m, CH=CH$_2$), 5.82 (1 H, ddt, $J = 16.9$, 10.2, 6.8 Hz, CH=$\text{CH}_2$), 6.51 (1 H, ddd, $J = 8.4$, 5.4, 2.2 Hz, C=CH), 7.34 - 7.53 (5 H, m, 5 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm −5.1 (SiCH$_3$), −4.5 (SiCH$_3$), 23.4 (CH$_2$CH=C), 23.4 (CH$_2$CH$_2$CH=CH$_2$), 25.7 (SCH$_2$CH$_2$), 26.2 (2 × SCH$_2$), 28.9 (CHSi), 33.8 (CH$_2$CH=CH$_2$), 37.0 (CH$_2$CH$_2$CH=C), 38.0 (CH$_2$CH$_2$CH$_2$CH=CH$_2$), 52.9 (C$_q$), 67.7 (CH$_2$O), 115.1 (CH=CH$_2$), 128.4 (2 × ArCH), 130.2 (ArCH), 131.4 (C=CH), 134.0 (2 × ArCH), 135.9 (C=CH), 138.3 (CH=CH$_2$), 173.3 (C=O); ArC$_q$ not observed.

Mass spectrometry was not informative.
4-(Dimethyl(phenyl)silyl)-3-[3-(2-methyl-1,3-dithian-2-yl)propylidene]-dihydrofuran-2-one (SI-6)

As for general procedure E, reaction of rac-(3S,4R)-3-(1-hydroxy-3-(2-methyl-1,3-dithian-2-yl)propyl)-4-(dimethyl(phenyl)silyl)dihydro-furan-2-one SI-5 (1.44 g, 3.51 mmol, 1.0 eq), triethylamine (2.0 mL, 14.0 mmol, 4.0 eq), methanesulfonyl chloride (543 µL, 7.0 mmol, 2.0 eq) and DBU (3.1 mL, 21.0 mmol, 6.0 eq) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) 4-(dimethyl(phenyl)silyl)-3-[3-(2-methyl-1,3-dithian-2-yl)propylidene]-dihydrofuran-2-one SI-6 (818 mg, 2.08 mmol, 59%) as a colourless oil and as a 1.6:1 mixture of double bonds isomers.

ν\text{max}\ (\text{neat})/\text{cm}^{-1} 2953, 2903, 1747 (C=O), 1661, 1426, 1181, 1112, 1022;

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 0.37 (3 H, s, SiCH$_3$ (major)), 0.37 (3 H, s, SiCH$_3$ (major)), 0.38 (3 H, s, SiCH$_3$ (minor)), 0.39 (3 H, s, SiCH$_3$ (minor)), 1.45 (3 H, s, CCH$_3$ (minor)), 1.60 (3 H, s, CCH$_3$ (major)), 1.82 - 2.11 (8 H, m, CH$_2$CH$_2$CH=C (major and minor), SCH$_2$CH$_2$ (major and minor)), 2.63 - 2.69 (1 H, m, CHSi (major)), 2.69 - 2.97 (13 H, m, 2 × SCH$_2$ (major and minor), CHSi (minor), CH$_2$CH=C (major and minor), 4.22 (1 H, dd, $J = 8.8, 4.0$ Hz, 1 H from CH$_2$O (major)), 4.30 - 4.39 (2 H, m, CH$_3$O (minor)), 4.42 (1 H, t, $J = 8.8$ Hz, 1 H from CH$_2$O (major)), 5.77 (1 H, td, $J = 7.9, 2.3$ Hz, C=CH (major)), 6.50 - 6.56 (1 H, m, C=CH (minor)), 7.33 - 7.45 (6 H, m, 3 × ArH (major and minor)), 7.45 - 7.54 (4 H, m, 2 × ArH (major and minor));

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm −5.6 (SiCH$_3$ (major)), −5.4 (SiCH$_3$ (major)), −5.1 (SiCH$_3$ (minor)), −4.7 (SiCH$_3$ (minor)), 23.4 (CH$_2$ (major)), 25.1 (CH$_2$ (minor)), 25.2 (CCH$_3$ (minor)), 25.9 (CCH$_3$ (major)), 26.5 (4 × CH$_2$), 27.5 (CH$_2$), 27.7 (CH$_2$), 28.8 (CHSi (minor)), 30.2 (CHSi (major)), 39.9 (CH$_2$ (minor)), 40.4 (CH$_2$ (major)), 48.6 (C$q^1$ (minor)), 48.7 (C$q^1$ (major)), 67.1 (CH$_2$O (major)), 67.6 (CH$_2$O (minor)), 126.6 (C=CH (major and minor), 128.2 (2 × ArCH (major)), 128.3 (2 × ArCH (minor)), 129.9 (ArCH (major), 130.1 (ArCH (minor)), 133.9 (2 × ArCH (minor)), 134.0 (2 × ArCH (major)), 135.1 (ArC$q^1$), 135.4 (ArC$q^1$), 135.8 (C=CH (minor)), 139.5 (C=CH (major)), 170.3 (C=O), 171.8 (C=O);

$\text{m/z}$ (ES+) 415 ((M + Na), 100%). (Found (M + Na) 415.1178. C$_{20}$H$_{28}$O$_2$S$_2$SiNa requires $M$, 415.1192).
6.6. General procedure F – Dithiane deprotections

![Chemical Structure](image)

4-(Dimethyl(phenyl)silyl)-3-(4-oxonon-8-en-1-ylidene)dihydrofuran-2-one (372)

To a stirred solution of 4-(dimethyl(phenyl)silyl)-3-(3-(2-(pent-4-en-1-yl)-1,3-dithiane-2-yl)propyldiene)dihydrofuran-2-one 371 (635 mg, 1.42 mmol, 1.0 eq) in acetonitrile (136 mL) and H2O (34 mL) at 0 °C was added silver nitrate (2.4 g, 14.2 mmol, 10 eq) and N-chlorosuccinimide (1.1 mg, 8.53 mmol, 6.0 eq) and the reaction mixture stirred at 0 °C for 2 hours. The reaction was quenched with NaHSO3 aq., sat. (63 mL) then carefully added to NaHCO3 aq., sat. (189 mL) and extracted with diethyl ether (3 × 200 mL). The combined organic phases were dried (Na2SO4 or MgSO4) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 10% ethyl acetate in petroleum ether (40-60 °C) gave 4-(dimethyl(phenyl)silyl)-3-(4-oxonon-8-en-1-ylidene)dihydrofuran-2-one 372 (381 mg, 1.07 mmol, 75%) as a light pink oil as a 2.7:1 mixture of double-bond isomers.

νmax (neat)/cm⁻¹ 3071, 2654, 2926, 2852, 2360, 2341, 1749 (C=O), 1712 (C=O), 1427, 1372, 1251, 1153, 1112, 1026, 819, 701;

Major isomer

1H NMR (400 MHz, CDCl3) δ ppm 0.27 (3 H, s, SiCH3), 0.28 (3 H, s, SiCH3), 1.53 - 1.65 (2 H, m, CH2CH2CH=CH2), 1.91 - 2.04 (2 H, m, CH2CH=CH2), 2.33 (2 H, t, J = 7.5 Hz, CH2CH2CH2CH=CH2), 2.40 (2 H, q, J = 7.2 Hz, CH2CH2CH=CH=CH2), 2.57 (1 H, ddd, J = 8.8, 4.0, 2.0 Hz, CHSi), 2.68 - 2.82 (1 H, m, 1 H from CH2CH=CH2), 2.83 - 2.97 (1 H, m, 1 H from CH2CH=CH=CH2), 4.14 (1 H, dd, J = 8.8, 4.0 Hz, 1 H from CH2O), 4.33 (1 H, t, J = 8.8 Hz, 1 H from CH2O), 4.87 - 5.00 (2 H, m, CH=CH), 5.62 - 5.77 (2 H, m, C=CH, CH=CH2), 7.26 - 7.47 (5 H, m, 5 × ArH);

13C NMR (100 MHz, CDCl3) δ ppm −5.6 (SiCH3), −5.5 (SiCH3), 19.9 (CH2CH=CH2), 22.8 (CH2CH2CH=CH2), 30.2 (CHSi), 33.1 (CH2CH=CH2), 41.6 (CH2CH2CH2CH=CH2), 42.2 (CH2CH2CH2CH=C), 67.2 (CH2O), 115.3 (CH=CH2), 126.8 (C=CH), 128.1 (2 × ArCH), 129.9 (ArCH), 133.9 (2 × ArCH), 138.0 (C=CH), 139.0 (CH=CH2), 170.5 (C=O), 209.9 (C=O); ArCα not observed.
Minor isomer

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 0.29 (3 H, s, SiCH$_3$), 0.31 (3 H, s, SiCH$_3$), 1.53 - 1.65 (2 H, m, CH$_2$CH$_2$CH=CH$_2$), 1.73 - 1.84 (1 H, m, 1 H from CH$_2$CH=CH), 1.91 - 2.04 (2 H, m, CH$_2$CH=CH$_2$), 2.05 - 2.17 (1 H, m, 1 H from CH$_2$CH=CH), 2.12 - 2.24 (1 H, m, 1 H from CH$_2$CH$_2$CH$_2$CH=CH$_2$), 2.26 (2 H, t, $J$ = 7.5 Hz, CH$_2$CH$_2$CH=CH$_2$), 2.27 - 2.39 (1 H, m, 1 H from CH$_2$CH$_2$CH$_2$CH=CH$_2$), 2.76 - 2.83 (1 H, m, CHSi), 4.22 - 4.34 (2 H, m, CH$_2$O), 4.87 - 5.00 (1 H, ddd, $J$ = 8.6, 6.3, 2.2 Hz, C=CH), 6.32 (1 H, ddd, $J$ = 8.6, 6.3, 2.2 Hz, C=CH), 7.26 - 7.47 (5 H, m, 5 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm −5.1 (SiCH$_3$), −4.9 (SiCH$_3$), 22.6 (CH$_2$CH$_2$CH=CH$_2$), 24.1 (CH$_2$CH=CH), 28.8 (CHSi), 33.0 (CH$_2$CH=CH$_2$), 41.0 (CH$_2$CH$_2$CH$_2$CH=CH$_2$), 41.9 (CH$_2$CH$_2$CH=CH), 67.7 (CH$_2$O), 115.4 (CH=CH$_2$), 128.2 (2 × ArCH), 130.0 (ArCH), 134.0 (2 × ArCH), 134.7 (C=CH), 135.1 (C=CH), 137.8 (CH=CH$_2$) 171.9 (C=O), 208.9 (C=O); ArCq not observed.

m/z (ES+) 220 (15%), 379 ((M + Na), 100). (Found (M + Na) 379.1704. C$_{21}$H$_{28}$O$_3$SiNa requires M, 379.1700).

4-(Dimethyl(phenyl)silyl)-3-(4-oxooct-7-en-1-ylidene)dihydrofuran-2(3H)-one (446)

As for general procedure F, reaction of 3-(3-(2-(but-3-en-1-yl)-1,3-dithian-2-yl)propylidene)-4-(dimethyl(phenyl)silyl)dihydrofuran-2(3H)-one (1.37 g, 3.16 mmol, 1.0 eq), silver nitrate (5.4 g, 31.6 mmol, 10 eq) and N-chlorosuccinimide (2.5 g, 18.9 mmol, 6.0 eq) in acetonitrile (320 mL) and H$_2$O (80 mL) gave after column chromatography (10% ethyl acetate in petroleum ether (40-60 °C)) 4-(dimethyl(phenyl)silyl)-3-(4-oxooct-7-en-1-ylidene)dihydrofuran-2(3H)-one 446 (837 mg, 2.44 mmol, 77%) as a light pink oil and as a 2.7:1 mixture of double-bond isomers.

$\nu$$_{max}$ (neat)/cm$^{-1}$ 3066, 2956, 2901, 1749 (C=O), 1712 (C=O), 1658, 1488, 1427, 1373, 1252, 1153, 1112, 1024, 997, 951, 914, 818, 778, 735, 701;

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 0.34 (3 H, s, SiCH$_3$ (major)), 0.34 (3 H, s, SiCH$_3$ (major)), 0.35 (3 H, s, SiCH$_3$ (minor)), 0.37 (3 H, s, SiCH$_3$ (minor)), 2.19 - 2.26 (1 H, m, $J$ = 2.3 Hz, 1 H from CH$_2$CH$_2$CH=CH (minor)), 2.26 - 2.34 (4 H, m, CH$_2$CH$_2$CH=CH (major and minor)), 2.39 - 2.44 (1 H, m, 1 H from CH$_2$CH$_2$CH=CH (minor)), 2.44 - 2.53 (8 H, m, CH$_2$CH=CH$_2$ (major and minor), CH$_2$CH=C (major and minor)), 2.62 - 2.67 (1 H, m,
CHSi (major)), 2.80 (1 H, dqd, J = 14.6, 7.2, 1.5 Hz, 1 H from CH₂CH₂CH=C (major)), 2.85 - 2.90 (1 H, m, CHSi (minor)), 2.92 - 3.04 (1 H, m, 1 H from CH₂CH₂CH=C (major)), 4.20 (1 H, dd, J = 8.8, 4.0 Hz, 1 H from CH₂O (major)), 4.29 - 4.45 (3 H, m, 1 H from CH₂O (major), CH₂O (minor)), 4.95 - 4.99 (2 H, m, 1 H from CH=CH₂ (major and minor)), 4.99 - 5.06 (2 H, m, 1 H from CH=CH₂ (major and minor)), 5.67 - 5.89 (3 H, m, CH=CH₂ (major and minor)), 6.38 (1 H, ddd, J = 8.6, 6.4, 2.1 Hz, C=CH (minor)), 7.33 - 7.42 (6 H, m, 3 × ArH (major and minor)), 7.44 - 7.52 (4 H, m, 2 × ArH (major and minor));

¹³C NMR (100 MHz, CDCl₃) δ ppm −5.8 (SiCH₃ (major)), −5.7 (SiCH₃ (major)), −5.2 (SiCH₃ (minor)), −5.1 (SiCH₃ (minor)), 21.6 (CH₂CH₂CH=C (major)), 27.5 (CH₂CH₂CH=CH₂ (minor)), 27.6 (CH₂CH₂CH=CH₂ (major)), 28.6 (CHSi (minor)), 29.9 (CHSi (major)), 40.8 (CH₂CH₂CH=C (minor)), 41.3 (CH₂CH=CH₂ (minor)), 41.6 (CH₂CH=C (major)), 42.0 (CH₂CH=CH₂ (major and minor)), 67.0 (CH₂O (major)), 67.5 (CH₂O (minor)), 115.1 (CH=CH₂ (major)), 115.2 (CH=CH₂ (minor)), 128.0 (2 × ArCH (major)), 128.0 (2 × ArCH (minor)), 129.7 (ArCH (major)), 129.8 (ArCH (minor)), 133.5 (ArC (major and minor)), 133.8 (2 × ArCH (major and minor)), 134.5 (C=CH (minor)), 134.9 (C=CH (major)), 135.2 (C=CH (minor)), 136.7 (CH=CH₂ (minor)), 136.9 (CH=CH₂ (major)), 138.8 (C=CH (major)), 170.3 (C=O (major)), 171.7 (C=O (minor)), 208.1 (C=O (minor)), 208.9 (C=O (major));

m/z (ES+) 343 ((M + H), 23%), 365 ((M + Na), 100). (Found: (M + H) 343.1736. C₂₀H₂₇O₃Si requires M, 343.1724).

As for general procedure F, reaction of 4-(dimethyl(phenyl)silyl)-3-(4-oxopentylidene)dihydrofuran-2(3H)-one SI-6 (984 mg, 2.51 mmol, 1.0 eq), silver nitrate (4.3 g, 25.1 mmol, 10 eq) and N-chlorosuccinimide (2.0 g, 15.0 mmol, 6.0 eq) in acetonitrile (256 mL) and H₂O (64 mL) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) 4-(dimethyl(phenyl)silyl)-3-(4-oxopentylidene)dihydrofuran-2(3H)-one 353 (220 mg, 0.73 mmol, 29%) as a colourless oil and as a 1.6:1 mixture of double-bond isomers.
$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3048, 2957, 2904, 1750 (C=O), 1714 (C=O), 1663, 1426, 1369, 1254, 1160, 1110, 1022, 951, 821, 781, 737, 703;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 0.34 (3 H, s, SiCH$_3$ (major)), 0.35 (3 H, s, SiCH$_3$ (major)), 0.36 (3 H, s, SiCH$_3$ (minor)), 0.38 (3 H, s, SiCH$_3$ (minor)), 1.82 - 1.90 (1 H, m, 1 H from C=CHCH$_2$ (minor)), 2.06 (3 H, s, CH$_3$C(O) (minor)), 2.12 (3 H, s, CH$_3$C(O) (major)), 2.13 - 2.20 (1 H, m, 1 H from C=CHCH$_2$ (minor)), 2.22 - 2.29 (1 H, m, 1 H from CH$_2$C(O) (minor)), 2.37 - 2.46 (1 H, m, 1 H from CH$_2$C(O) (minor)), 2.49 (2 H, dt, $J = 9.5$, 7.1 Hz, CH$_2$C(O) (major)), 2.62 - 2.68 (1 H, m, CHSi (major)), 2.75 - 2.84 (1 H, m, 1 H from C=CHCH$_2$ (major)), 2.86 (1 H, dd, $J = 6.3$, 0.6 Hz, CHSi (minor)), 2.94 - 3.03 (1 H, m, 1 H from C=CHCH$_2$ (major)), 4.21 (1 H, dd, $J = 8.8$, 4.1 Hz, 1 H from CH$_2$O (major)), 4.31 - 4.38 (2 H, m, CH$_2$O (minor)), 4.40 (1 H, t, $J = 8.8$ Hz, 1 H from CH$_2$O (major)), 5.78 (1 H, td, $J = 7.9$, 2.2 Hz, C=CH (major)), 6.39 (1 H, ddd, $J = 8.6$, 6.5, 2.2 Hz, C=CH (minor)), 7.35 - 7.42 (6 H, m, 3 × ArH (major), 3 × ArH (minor)), 7.45 - 7.47 (2 H, m, 2 × ArH (major)), 7.48 - 7.51 (2 H, m, 2 × ArH (minor));

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ ppm −5.7 (SiCH$_3$ (major)), −5.6 (SiCH$_3$ (major)), −5.1 (SiCH$_3$ (minor)), −5.1 (SiCH$_3$ (minor)), 21.7 (C=CHCH$_2$ (major)), 24.0 (C=CHCH$_2$ (minor)), 28.7 (CHSi (minor)), 29.5 (CH$_3$C(O) (major)), 29.8 (CH$_3$C(O) (minor)), 30.0 (CHSi (major)), 41.7 (CH$_2$C(O) (minor)), 42.9 (CH$_2$C(O) (major)), 67.0 (CH$_2$O (major)), 67.6 (CH$_2$O (minor)), 126.8 (C=CH (minor)), 128.0 (2 × ArCH (major)), 128.1 (2 × ArCH (minor)), 128.8 (C=CH (major)), 129.8 (ArCH (major)), 129.9 (ArCH (minor)), 133.8 (2 × ArCH (major)), 133.9 (2 × ArCH (minor)), 134.5 (C=CH (minor)), 135.0 (ArC$_q$ (minor)), 135.3 (ArC$_q$ (major)), 138.7 (C=CH (major)), 170.3 (OC=O (minor)), 171.7 (OC=O (major)), 206.6 (CH$_3$C=O (minor)), 207.7 (CH$_3$C=O (major));

$\text{m/z}$ (ES+) 106 (79%), 110 (75), 122 (52), 143 (33), 147 (33), 161 (33), 184 (31), 257 (85), 278 (52), 288 (100), 325 ([M + Na], 34), 335 (34). (Found: (M + H) 303.1412. C$_{17}$H$_{23}$O$_3$Si requires $M$, 303.1411).
6.7. General procedure G – SmI₂-mediated spirocyclisations

\begin{center}
\begin{minipage}{0.8\textwidth}
\includegraphics[width=1\textwidth]{image}
\end{minipage}
\end{center}


To a stirred solution of SmI₂ (0.096 M in THF, 2.2 mL, 0.21 mmol, 2.5 eq) and MeOH (327 µL, 8.08 mmol, 96 eq) at 0 °C was added 4-(dimethyl(phenyl)silyl)-3-(4-oxonon-8-en-1-ylidene)dihydrofuran-2-one 372 (30 mg, 84.1 µmol, 1.0 eq) in THF (1.0 mL) and the reaction mixture stirred at 0 °C for 5 minutes. The reaction was quenched with air (bubbling), tartaric acid (25 mg) and H₂O (3.0 mL) added, and the aqueous phase extracted with ethyl acetate (3 × 3.0 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated \textit{in vacuo}. Purification by column chromatography on silica gel, eluting with 10% ethyl acetate in petroleum ether (40-60 ºC) gave \textit{rac-}(4\textit{R},5\textit{S},6\textit{S})-4-(Dimethyl(phenyl)silyl)-6-hydroxy-6-(pent-4-en-1-yl)-2-oxaspiro[4.4]nonan-1-one 373 (29 mg, 80.9 µmol, 96%) as a light yellow oil.

\textbf{ν\textsubscript{max} (neat)/cm\textsuperscript{-1}} 3442 (br. OH), 3064, 2946, 2914, 2863, 1739 (C=O), 1427, 1372, 1261, 1191, 1111, 1029, 910, 832, 817, 736, 703;

\textbf{1H NMR} (400 MHz, CDCl₃) δ ppm 0.39 (3 H, s, SiCH₃), 0.47 (3 H, s, SiCH₃), 1.31 - 1.48 (5 H, m, CH₂CH₂CH=CH₂, 3 H from CH₂), 1.48 - 1.55 (1 H, m, 1 H from CH₂), 1.74 - 1.84 (2 H, m, CH₂), 1.85 - 1.97 (1 H, m, 1 H from CH₂), 2.00 - 2.08 (3 H, m, CHSi, CH₂CH=CH₂), 2.13 (1 H, ddd, J = 13.3, 10.8, 5.7 Hz, 1 H from CH₂), 3.74 (1 H, s, OH), 4.14 (1 H, dd, J = 9.0, 8.3 Hz, 1 H from CH₂O), 4.31 (1 H, t, J = 8.3 Hz, 1 H from CH₂O), 4.90 - 5.11 (2 H, m, CH=CH₂), 5.78 (1 H, ddt, J = 16.9, 10.2, 6.7 Hz, CH=CH₂), 7.32 - 7.46 (3 H, m, 3 × ArH), 7.47 - 7.52 (2 H, m, 2 × ArH);

\textbf{13C NMR} (100 MHz, CDCl₃) δ ppm −3.0 (SiCH₃), −2.7 (SiCH₃), 20.9 (CH₂), 23.3 (CH₂), 30.8 (CHSi), 31.8 (CH₂), 34.3 (CH₂CH=CH₂), 35.7 (CH₂), 36.4 (CH₂), 58.1 (C²), 68.3 (CH₂O), 85.7 (C³), 115.0 (CH=CH₂), 128.4 (2 × ArCH), 130.0 (ArCH), 133.7 (2 × ArCH), 136.6 (ArC²), 138.7 (CH=CH₂), 183.3 (C=O);

\textbf{m/z} (ES+) 381 ((M + Na), 100%). (Found (M + Na) 381.1850. C₂₁H₃₀O₃SiNa requires \textit{M}, 381.1857).
\[ \text{rac}-\text{(4S,5S,6R)-6-}\left(\text{3-}\left(\text{tert-butyldiphenylsilyl}\right)\text{oxy}\right)\text{propyl}-4-\left(\text{dimethyl(phenyl)silyl}\right)\text{-6-hydroxy-2-oxaspiro[4.4]nonan-1-one (434)} \]

As for general procedure G, reaction of \(3\)-\(\left(\text{7-}\left(\text{tert-butyldiphenylsilyl}\right)\text{oxy}\right)\text{-4-oxoheptylidene}\)-\(4\)-\(\left(\text{dimethyl(phenyl)silyl}\right)\text{dihydrofuran-2(3H)-one (426)} \) with \(\text{SmI}_2\) (0.11 M in THF, 58 mL, 6.41 mmol, 2.5 eq) and \(\text{MeOH}\) (10.9 mL, 246 mmol, 96 eq) gave after column chromatography (20% ethyl acetate in petroleum ether (40-60 °C)) \(\text{rac}-\text{(4S,5S,6R)-6-}\left(\text{3-}\left(\text{tert-butyldiphenylsilyl}\right)\text{oxy}\right)\text{propyl}-4-\left(\text{dimethyl(phenyl)silyl}\right)\text{-6-hydroxy-2-oxaspiro[4.4]nonan-1-one (434)} \) (1.44 g, 2.45 mmol, 96%) as a light yellow oil.

\[ \nu_{\text{max}} \text{ (neat)/cm}^{-1} \quad 3438 \text{ (br. OH)}, \quad 3070, \quad 2953, \quad 2929, \quad 2857, \quad 1763 \text{ (C=O)}, \quad 1427, \quad 1374, \quad 1253, \quad 1173, \quad 1110, \quad 1028, \quad 998, \quad 909, \quad 821; \]

\[ ^1\text{H NMR} \text{ (400 MHz, CDCl}_3\text{)} \delta \text{ ppm} \quad 0.40 \text{ (3 H, s, SiCH}_3\text{)}, \quad 0.46 \text{ (3 H, s, SiCH}_3\text{), 1.08} \text{ (9 H, s, 3 } \times \text{ CCH}_3\text{), 1.32 - 1.41} \text{ (1 H, m, 1 H from CH}_2\text{), 1.45 - 1.53} \text{ (1 H, m, 1 H from CH}_2\text{), 1.54 - 1.63} \text{ (3 H, m, CH}_2\text{CH}_2\text{OSi, 1 H from CH}_2\text{CH}_2\text{CH}_2\text{OSi), 1.65 - 1.74} \text{ (1 H, m, 1 H from CH}_2\text{CH}_2\text{CH}_2\text{OSi), 1.74 - 1.88} \text{ (2 H, m, 2 H from CH}_2\text{), 1.88 - 2.00} \text{ (1 H, m, 1 H from CH}_2\text{), 2.04} \text{ (1 H, t, } J = 7.7 \text{ Hz, CHSi), 2.15} \text{ (1 H, ddd, } J = 13.2, 10.7, 6.0 \text{ Hz, 1 H from CH}_2\text{), 3.68} \text{ (2 H, t, } J = 5.7 \text{ Hz, CH}_2\text{OSi), 4.14} \text{ (1 H, dd, } J = 9.1, 7.6 \text{ Hz, 1 H from CHCH}_2\text{O), 4.32} \text{ (1 H, t, } J = 8.7 \text{ Hz, 1 H from CHCH}_2\text{O), 7.32 - 7.50} \text{ (11 H, m, 11 } \times \text{ ArH), 7.64 - 7.71} \text{ (4 H, m, 4 } \times \text{ ArH);} \]

\[ ^{13}\text{C NMR} \text{ (100 MHz, CDCl}_3\text{)} \delta \text{ ppm} \quad -3.1 \text{ (SiCH}_3\text{), -3.0} \text{ (SiCH}_3\text{), 19.2} \text{ (C}^\text{CH}_2\text{), 20.6} \text{ (CH}_2\text{), 26.9} \text{ (3 } \times \text{ CCH}_3\text{), 27.1} \text{ (CH}_2\text{CH}_2\text{CH}_2\text{OSi), 30.3} \text{ (CHS}_2\text{), 31.7} \text{ (CH}_2\text{), 32.5} \text{ (CH}_2\text{CH}_2\text{OSi), 36.1} \text{ (CH}_2\text{), 58.0} \text{ (C}^\text{OSi), 64.3} \text{ (CH}_2\text{OSi), 68.0} \text{ (CHCH}_2\text{O), 85.4} \text{ (C}^\text{O), 127.6} \text{ (4 } \times \text{ ArCH), 128.2} \text{ (2 } \times \text{ ArCH), 129.6} \text{ (2 } \times \text{ ArCH), 129.7} \text{ (ArCH), 133.5} \text{ (2 } \times \text{ ArCH), 133.8} \text{ (ArC}^\text{O), 133.8} \text{ (ArC}^\text{O), 135.5} \text{ (4 } \times \text{ ArCH), 136.6} \text{ (ArC}^\text{O), 182.9} \text{ (C=O);} \]

\[ m/z \text{ (ES+) 130} \text{ (29%), 491 (25), 587} \text{ ((M + H), 89), 628} \text{ (100).} \]
As for general procedure G, reaction of 4-(dimethyl(phenyl)silyl)-3-(4-oxooct-7-en-1-ylidene)dihydrofuran-2(3H)-one 446 (837 mg, 2.44 mmol, 1.0 eq, in 3.0 mL THF) with SmI$_2$ (0.1 M in THF, 61 mL, 6.11 mmol, 2.5 eq) and MeOH (9.5 mL, 235 mmol, 96 eq) gave after column chromatography (20% ethyl acetate in petroleum ether (40-60 °C)) rac-(4S,5S,6R)-6-(but-3-en-1-yl)-4-(dimethyl(phenyl)silyl)-6-hydroxy-2-oxaspiro[4.4]nonan-1-one 453 (725 mg, 2.10 mmol, 86%) as a light yellow oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3446 (br. OH), 3070, 2954, 2909, 1762 (C=O), 1738, 1428, 1373, 1253, 1171, 1111, 1028, 997, 912, 832, 815, 779, 735, 701, 652;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.39 (3 H, s, SiCH$_3$), 0.47 (3 H, s, SiCH$_3$), 1.30 - 1.40 (1 H, m, 1 H from CH$_2$CH$_2$CH), 1.41 - 1.47 (1 H, m, 1 H from CH$_2$), 1.51 - 1.57 (2 H, m, CH$_2$), 1.75 - 1.85 (2 H, m, 1 H from CH$_2$, 1 H from CH$_2$CH=CH$_2$), 1.88 - 1.96 (1 H, m, 1 H from CH$_2$CH$_2$CH), 2.05 - 2.09 (2 H, m, 1 H from CH$_2$, CHSi), 2.11 - 2.18 (1 H, m, 1 H from CH$_2$CH=CH$_2$), 2.19 - 2.25 (1 H, m, 1 H from CH$_2$), 4.16 (1 H, dd, $J$ = 9.1, 7.9 Hz, 1 H from CH$_2$O), 4.34 (1 H, t, $J$ = 9.1 Hz, 1 H from CH$_2$O), 4.96 (1 H, dd, $J$ = 10.2, 1.8 Hz, 1 H from CH=CH$_2$), 5.02 (1 H, dd, $J$ = 17.0, 1.8 Hz, 1 H from CH=CH$_2$), 5.80 (1 H, ddt, $J$ = 17.0, 10.2, 6.6 Hz, CH=CH$_2$), 7.38 - 7.42 (3 H, m, 3 × ArH), 7.48 - 7.53 (2 H, m, 2 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm −3.3 (SiCH$_3$), −3.0 (SiCH$_3$), 20.6 (CH$_2$CH$_2$CH), 28.3 (CH$_2$), 30.4 (CHSi), 31.5 (CH$_2$CH=CH$_2$), 35.2 (CH$_2$), 35.8 (CH$_2$), 58.0 (C$^6$), 68.0 (CH$_2$O), 85.4 (C$^6$), 114.5 (CH=CH$_2$), 128.2 (2 × ArCH), 129.7 (ArCH), 133.5 (2 × ArCH), 136.4 (ArC$^6$), 138.6 (CH=CH$_2$), 182.8 (C=O);

$m/z$ (ES+) 367 ((M + Na), 100%). (Found: (M + Na) 367.1714. C$_{20}$H$_{28}$O$_3$SiNa requires $M$, 367.1700).
As for general procedure G, reaction of 4-(dimethyl(phenyl)silyl)-3-(4-oxopentylidene)dihydrofuran-2-one 353 (30.2 mg, 0.10 mmol, 1.0 eq) with SmI$_2$ (0.11 M in THF, 2.3 mL, 0.25 mmol, 2.5 eq) and MeOH (389 µL, 9.6 mmol, 96 eq) gave after column chromatography (20% ethyl acetate in petroleum ether (40-60 °C)) rac-(4R,5S,6S)-4-(dimethyl(phenyl)silyl)-6-hydroxy-6-methyl-2-oxaspiro[4.4]nonan-1-one 354 (26.8 mg, 88.0 µmol, 88%) as a white solid.

$\text{mp } 71-74 ^\circ\text{C}$;

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3436 (br. OH), 3276, 3068, 2360, 1747 (C=O), 1661, 1427, 1375, 1250, 1181, 1113, 1021, 833, 818;

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 0.39 (3 H, s, SiCH$_3$), 0.45 (3 H, s, SiCH$_3$), 1.26 (3 H, s, CCH$_3$), 1.32 - 1.44 (1 H, m, 1 H from CH$_2$), 1.57 - 1.65 (1 H, m, 1 H from CH$_2$), 1.75 (1 H, ddd, $J = 13.6$, 10.3, 5.0 Hz, 1 H from CH$_2$), 1.87 - 2.02 (2 H, m, 2 × 1 H from CH$_2$), 2.05 - 2.15 (2 H, m, 1 H from CH$_2$, CHSi), 4.16 (1 H, dd, $J = 8.8$, 6.1 Hz, 1 H from CH$_2$O), 4.39 (1 H, t, $J = 8.8$ Hz, 1 H from CH$_2$O), 7.33 - 7.45 (3 H, m, 3 × ArH), 7.45 - 7.55 (2 H, m, 2 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm −4.2 (SiCH$_3$), −4.0 (SiCH$_3$), 19.1 (CH$_2$), 23.0 (CCH$_3$), 28.7 (CHSi), 30.4 (CH$_2$), 37.7 (CH$_2$), 57.4 (C$q$), 66.9 (CH$_2$O), 82.4 (C$q$), 127.2 (2 × ArCH), 128.7 (ArCH), 132.6 (2 × ArCH), 135.7 (ArC$q$), 181.0 (C=O);

$m/z$ (ES+) 327 ((M + Na), 100%). (Found (M + Na) 327.1402. C$_{17}$H$_{24}$O$_3$SiNa requires $M$, 327.1387).
6.8. General procedure H – SmI$_2$-mediated lactone reductions

rac-(1S,2R)-2-((R)-1-(Dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)-1-(pent-4-en-1-yl)cyclopentanol (374)

To a stirred solution of SmI$_2$ (0.086 M in THF, 65 mL, 5.58 mmol, 8.0 eq), triethylamine (2.3 mL, 16.7 mmol, 24 eq) and H$_2$O (300 µL, 16.7 mmol, 24 eq) was added rac-(4R,5S,6S)-4-(dimethyl(phenyl)silyl)-6-hydroxy-6-(pent-4-en-1-yl)-2-oxaspiro[4.4]nonan-1-one 373 (200 mg, 0.56 mmol, 1.0 eq, in 2.0 mL THF) and the reaction stirred at room temperature for 10 minutes. The reaction was quenched with air (bubbling), tartaric acid (150 mg) and H$_2$O (70 mL) added, and the aqueous phase extracted with ethyl acetate ($3 \times 70$ mL). The combined organic phases were dried (Na$_2$SO$_4$ or MgSO$_4$) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 30% ethyl acetate in hexane gave rac-(1S,2R)-2-((R)-1-(dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)-1-(pent-4-en-1-yl)cyclopentanol 374 (192 mg, 0.51 mmol, 91%) as a light yellow oil.

$\nu_{\text{max}}$(neat)/cm$^{-1}$ 3289 (br. OH), 2953, 2878, 1427, 1250, 1109, 1049, 910, 834, 818, 700;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.45 (3 H, s, SiCH$_3$), 0.47 (3 H, s, SiCH$_3$), 1.15 (2 H, dd, $J = 8.9, 6.8$ Hz, CH$_2$), 1.19 - 1.31 (1 H, m, 1 H from CH$_2$), 1.28 - 1.50 (2 H, m, 1 H from CH$_2$, 1 H from CH$_2$CH$_2$CH=CH$_2$), 1.48 - 1.63 (3 H, m, 1 H from CH$_2$CH$_2$CH=CH$_2$, CH$_2$), 1.65 (1 H, dd, $J = 5.7, 1.6$ Hz, CHSi), 1.74 - 1.88 (1 H, m, 1 H from CH$_2$), 1.98 (1 H, ddd, $J = 13.4, 9.5, 2.3$ Hz, 1 H from CH$_2$), 2.02 - 2.16 (2 H, m, CH$_2$CH=CH$_2$), 3.61 (1 H, d, $J = 12.5$ Hz, 1 H from CCH$_2$OH), 3.84 (1 H, dd, $J = 10.8, 5.6$ Hz, 1 H from CHCH$_2$OH), 3.96 (1 H, dd, $J = 12.5, 1.6$ Hz, 1 H from CCH$_2$OH), 4.46 (1 H, dd, $J = 10.8, 1.3$ Hz, 1 H from CHCH$_2$OH), 4.92 - 5.08 (2 H, m, CH=CH$_2$), 5.83 (1 H, ddt, $J = 16.9, 10.2, 6.6$ Hz, CH=CH$_2$), 7.31 - 7.38 (3 H, m, 3 × ArH), 7.55 - 7.62 (2 H, m, 2 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 0.1 (SiCH$_3$), 0.4 (SiCH$_3$), 18.1 (CH$_2$), 22.7 (CH$_2$), 34.1 (CH$_2$), 34.5 (CH$_2$), 34.5 (CH$_2$), 34.8 (CH$_2$), 36.4 (CHSi), 51.5 (C$^\alpha$), 61.7 (CHCH$_2$OH), 68.5 (CCH$_2$OH), 87.7 (C$^\beta$), 114.8 (CH=CH$_2$), 128.0 (2 × ArCH), 129.0 (ArCH), 134.0 (2 × ArCH), 138.9 (CH=CH$_2$), 140.3 (ArC$^\alpha$);

$m/z$ (ES+) 385 ((M + Na), 100%). (Found (M + Na) 385.2169. C$_{21}$H$_{34}$O$_3$SiNa requires $M$, 385.2170).
rac-(1R,2R)-1-(3-((tert-Butyldiphenylsilyl)oxy)propyl)-2-((S)-1-(dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)cyclopentanol (435)

As for general procedure H, reaction of rac-(1R,2R)-1-(3-((tert-Butyldiphenylsilyl)oxy)propyl)-2-((S)-1-(dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)cyclopentanol 434 (1.44 g, 2.46 mmol, 1.0 eq, in 3.0 mL THF) with SmI₂ (0.11 M in THF, 179 mL, 19.7 mmol, 8.0 eq), triethylamine (8.2 mL, 59.1 mmol, 24 eq) and H₂O (1.1 mL, 59.1 mmol, 24 eq) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) rac-(1R,2R)-1-(3-((tert-Butyldiphenylsilyl)oxy)propyl)-2-((S)-1-(dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)cyclopentanol 435 (546 mg, 0.92 mmol, 38%) as a light yellow oil.

ν_{max} (neat)/cm⁻¹ 3290 (br. OH), 3069, 2956, 2928, 2856, 1472, 1427, 1250, 1110, 1047, 1008, 821, 735, 700, 614;

H NMR (400 MHz, CDCl₃) δ ppm 0.46 (3 H, s, SiCH₃), 0.50 (3 H, s, SiCH₃), 1.05 (9 H, s, 3 × C(CH₃)), 1.12 - 1.18 (1 H, m, 1 H from CH₂), 1.21 - 1.35 (3 H, m, CH₂, 1 H from CH₂), 1.42 - 1.92 (6 H, m, CHSi, 5 H from CH₂), 1.95 - 2.04 (1 H, m, 1 H from CH₂), 3.58 (1 H, d, J = 12.4 Hz, 1 H from C(CH₃)₂OH), 3.63 - 3.73 (2 H, m, CH₂CH₂OSi), 3.81 (1 H, dd, J = 11.3, 5.6 Hz, 1 H from CHCH₂OH), 4.04 (1 H, dd, J = 12.4, 1.6 Hz, 1 H from C(CH₃)₂OH), 4.52 (1 H, dd, J = 11.3, 0.5 Hz, 1 H from CHCH₂OH), 7.32 - 7.46 (9 H, m, 9 × ArH), 7.58 - 7.62 (1 H, m, ArH), 7.63 - 7.70 (5 H, m, 5 × ArH);

C NMR (100 MHz, CDCl₃) δ ppm 0.0 (Si(CH₃)), 0.2 (Si(CH₃)), 18.1 (CH₂), 19.1 (C₆), 26.4 (CH₂), 26.8 (3 × C(CH₃)), 29.7 (CH₂), 32.8 (CH₂), 34.5 (CH₂), 37.0 (CHSi), 51.5 (C₆), 61.2 (CHCH₂OH), 64.9 (CH₂CH₂OSi), 68.4 (C(CH₂)OH), 87.3 (C₆), 127.6 (2 × ArCH), 127.7 (4 × ArCH), 128.7 (ArCH), 129.8 (ArCH), 132.1 (2 × ArCH), 133.1 (ArC₆), 133.8 (ArC₆), 133.9 (ArC₆), 135.6 (4 × ArCH);

m/z (ES+) 60 (20%), 147 (100), 613 ((M + Na), 25).
**rac-(1R,2R)-1-(But-3-en-1-yl)-2-((S)-1-(dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)cyclopentanol (454)**

As for general procedure H, reaction of rac-(4S,5S,6R)-6-(but-3-en-1-yl)-4-(dimethyl(phenyl)silyl)-6-hydroxy-2-oxaspiro[4.4]nonan-1-one 453 (725 mg, 2.10 mmol, 1.0 eq, in 3.0 mL THF) with SmI$_2$ (0.11 M in THF, 153 mL, 16.8 mmol, 8.0 eq), triethylamine (7.0 mL, 50.5 mmol, 24 eq) and H$_2$O (0.9 mL, 50.5 mmol, 24 eq) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) rac-(1R,2R)-1-(but-3-en-1-yl)-2-((S)-1-(dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)cyclopentanol 454 (369 mg, 1.06 mmol, 50%) as a light yellow oil.

$\nu_{\text{max}}$(neat)/cm$^{-1}$ 3273 (br. OH), 3069, 2953, 2882, 1640, 1427, 1316, 1248, 1217, 1109, 1052, 1019, 957, 908, 816, 755, 732, 701, 646;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 0.45 (3 H, s, SiCH$_3$), 0.48 (3 H, s, SiCH$_3$), 1.11 - 1.20 (2 H, m, CH$_2$), 1.24 - 1.43 (2 H, m, 1 H from CH$_2$CH$_2$CH, 1 H from CH$_2$), 1.48 - 1.62 (1 H, m, 1 H from CH$_2$), 1.67 (1 H, d, $J$ = 5.4 Hz, CHSi), 1.69 - 1.76 (1 H, m, 1 H from CH$_2$CH$_2$CH), 1.76 - 1.87 (1 H, m, 1 H from CH$_2$), 1.95 - 2.04 (1 H, m, 1 H from CH$_2$), 2.07 - 2.18 (1 H, m, 1 H from CH$_2$CH=CH$_2$), 2.19 - 2.30 (1 H, m, 1 H from CH$_2$CH=CH$_2$), 3.61 (1 H, d, $J$ = 12.4 Hz, 1 H from CCH$_2$OH), 3.82 (1 H, dd, $J$ = 10.5, 5.4 Hz, 1 H from CCH$_2$OH), 3.95 (1 H, dd, $J$ = 12.4, 1.3 Hz, 1 H from CCH$_2$OH), 4.43 (1 H, d, $J$ = 10.5 Hz, 1 H from CCH$_2$OH), 4.99 (1 H, ddt, $J$ = 10.1, 1.7, 1.0 Hz, 1 H from CH=CH$_2$), 5.08 (1 H, dd, $J$ = 17.0, 1.7 Hz, 1 H from CH=CH$_2$), 5.88 (1 H, ddt, $J$ = 17.0, 10.1, 6.7 Hz, CH=CH$_2$), 7.32 - 7.39 (3 H, m, 3 × ArH), 7.56 - 7.62 (2 H, m, 2 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm −0.2 (SiCH$_3$), 0.1 (SiCH$_3$), 17.8 (CH$_2$), 27.8 (CH$_2$CH=CH$_2$), 33.7 (CH$_2$), 34.2 (CH$_2$), 34.4 (CH$_2$CH$_2$CH), 36.0 (CHSi), 51.3 (C$^6$), 61.0 (CHCH$_2$OH), 68.0 (CCH$_2$OH), 87.3 (C$^6$), 114.6 (CH=CH$_2$), 127.7 (2 × ArCH), 128.7 (ArCH), 133.8 (2 × ArCH), 139.3 (CH=CH$_2$), 140.1 (ArC$^6$);

$m/z$ (ES+) 371 ((M + Na), 100%), 372 (31). (Found: (M + Na) 371.2016. C$_{20}$H$_{32}$O$_3$SiNa requires $M$, 371.2013).
6.9. General procedure I – Peterson eliminations

\[ \text{rac-}(1S,2R)-2-(\text{Hydroxymethyl})-1-(\text{pent-4-en-1-yl})-2-vinylcyclopentanol (375) \]

To a stirred solution of \textit{rac}-\((1S,2R)-2-(\text{hydroxymethyl})-2-((R)-1-(\text{dimethyl(phenyl)silyl})-2-hydroxyethyl)-1-(pent-4-en-1-yl)cyclopentanol 374\) (50 mg, 0.14 mmol, 1.0 eq) in THF (10 mL) at 0 °C was added potassium \textit{tert}-butoxide (31 mg, 0.28 mmol, 2.0 eq) and the reaction mixture stirred at 0 °C for 20 minutes. The reaction was quenched with \(\text{NH}_4\text{Cl}_{\text{aq.}}\), sat. (10 mL) and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried (Na\(_2\text{SO}_4\) or MgSO\(_4\)) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40-60 °C) gave \textit{rac}-\((1S,2R)-2-(\text{hydroxymethyl})-1-(\text{pent-4-en-1-yl})-2-vinylcyclopentanol 375\) (20.2 mg, 96.0 µmol, 70%) as a colourless oil.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3011 (br. OH), 3080, 2945, 2876, 1639, 1454, 1440, 1415, 1055, 1002, 908; \(\text{\(1^H\)} \text{NMR}\) (400 MHz, CDCl\(_3\) \(\delta\) ppm 1.24 - 1.39 (2 H, m, 1H from \(CH_2CH_2CH=CH_2\), 1H from \(CH_2\)), 1.44 - 1.79 (7 H, m, 1 H from \(CH_2CH_2CH=CH_2\), 3 × \(CH_2\)), 1.89 - 2.01 (2 H, m, \(CH_2CH=CH_2\)), 2.01 - 2.12 (1 H, m, 1 H from \(CH_2\)), 2.17 - 2.46 (1 H, br. s, \(OH\)), 2.58 - 2.90 (1 H, br. s, \(OH\)), 3.56 (1 H, d, \(J = 11.3\) Hz, 1 H from \(CH_2OH\)), 3.76 (1 H, d, \(J = 11.3\) Hz, 1 H from \(CH_2OH\)), 4.81 - 4.94 (2 H, m, \(CH_2CH=CH_2\)), 4.97 (1 H, dd, \(J = 12.7\), 1.2 Hz, 1 H from \(CH_2OH\)), 5.01 (1 H, dd, \(J = 15.3\), 1.2 Hz, 1 H from \(CH_2=CH_2\)), 5.61 - 5.78 (2 H, m, \(CCH=CH_2\), \(CH_2CH=CH_2\));

\(\text{\(13^C\)} \text{NMR}\) (100 MHz, CDCl\(_3\) \(\delta\) ppm 19.5 (\(CH_2\)), 23.6 (\(CH_2\)), 29.7 (\(CH_2\)), 34.4 (\(CH_2\)), 36.1 (\(CH_2\)), 37.3 (\(CH_2\)), 55.3 (\(CH_3\)), 66.0 (\(CH_2OH\)), 86.6 (\(CH_3\)), 114.2 (\(CH_2CH=CH_2\)), 114.8 (\(CCH=CH_2\)), 138.8 (\(CCH=CH_2\)), 140.8 (\(CH_2CH=CH_2\)).

\(m/z\) (ES+) 233 ((M + Na), 73%), 443 (2M + Na), 100). (Found (M + Na) 233.1505. \(C_{13}H_{22}O_2Na\) requires \(M\), 233.1512).
As for general procedure I, reaction of rac-(1R,2R)-1-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2-(hydroxymethyl)-2-vinylcyclopentanol 435 (48 mg, 81.2 µmol, 1.0 eq) and potassium tert-butoxide (18 mg, 0.16 mmol, 2.0 eq) in THF (5.9 mL) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) rac-(1R,2R)-1-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2-(hydroxymethyl)-2-vinylcyclopentanol 436 (25.1 mg, 57.2 µmol, 70%) as a colourless oil.

ν max (neat)/cm⁻¹: 3354 (br. OH), 3068, 2955, 2930, 2857, 1755, 1731, 1472, 1428, 1389, 1256, 1110, 1053, 1006, 917, 823, 739, 701, 613;

1H NMR (400 MHz, CDCl₃) δ ppm: 1.06 (9 H, s, 3 × CH₃), 1.59 - 1.90 (9 H, m, 9 H from CH₂), 2.13 - 2.24 (1 H, m, 1 H from CH₂), 2.82 (2 H, br. s., 2 × OH), 3.70 (1 H, d, J = 11.3 Hz, 1 H from CH₂OH), 3.62 - 3.77 (2 H, m, CH₂OSi), 3.84 (1 H, d, J = 11.3 Hz, 1 H from CH₂OH), 5.06 (1 H, dd, J = 17.7, 1.3 Hz, 1 H from CH=CH₂), 5.11 (1 H, dd, J = 11.0, 1.3 Hz, 1 H from CH=CH₂), 5.84 (1 H, dd, J = 17.7, 11.0 Hz, CH=CH₂), 7.36 - 7.46 (6 H, m, 6 × ArH), 7.65 - 7.71 (4 H, m, 4 × ArH);

13C NMR (100 MHz, CDCl₃) δ ppm: 19.1 (C⁸), 19.3 (CH₂), 26.8 (3 × CH₃), 27.3 (CH₂), 29.5 (CH₂), 33.7 (CH₂), 36.9 (CH₂), 54.8 (C⁸), 64.9 (CH₂OSi), 66.2 (CH₂OH), 86.0 (C⁸), 113.7 (CH=CH₂), 127.7 (4 × ArCH), 129.8 (2 × ArCH), 133.2 (ArC⁹), 133.2 (ArC⁸), 135.6 (4 × ArCH), 141.1 (CH=CH₂);

m/z (ES+) 461 ((M + Na), 100%), 462 (30). (Found: (M + Na) 461.2487. C₂₇H₃₈O₃SiNa requires M, 461.2483).

rac-(1R,2R)-1-(But-3-en-1-yl)-2-(hydroxymethyl)-2-vinylcyclopentanol 455

As for general procedure I, reaction of rac-(1R,2R)-1-(but-3-en-1-yl)-2-((S)-1-(dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)cyclopentanol 454 (222 mg, 0.64 mmol, 1.0 eq) and potassium tert-butoxide (143 mg, 1.27 mmol, 2.0 eq) in THF (45 mL) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C))
rac-(1R,2R)-1-(but-3-en-1-yl)-2-(hydroxymethyl)-2-vinylcyclopentanol 455 (69.6 mg, 0.35 mmol, 56%) as a light yellow oil.

ν\textsubscript{max} (neat)/cm\textsuperscript{-1} 3309 (br. OH), 3082, 2946, 2875, 1639, 1446, 1418, 1313, 1228, 1113, 1052, 1001, 911;

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 1.52 (1 H, ddd, \(J = 13.9, 11.0, 5.0\) Hz, 1 H from CH\textsubscript{2}CH\textsubscript{2}CH=CH\textsubscript{2}), 1.65 - 1.78 (5 H, m, 1 H from CH\textsubscript{2}CH\textsubscript{2}CH=CH\textsubscript{2}, CH\textsubscript{2}, 2 H from CH\textsubscript{2}), 1.79 - 1.87 (1 H, m, 1 H from CH\textsubscript{2}), 2.05 - 2.19 (2 H, m, 1 H from CH\textsubscript{2}, 1 H from CH\textsubscript{2}CH=CH\textsubscript{2}), 2.23 - 2.33 (1 H, m, 1 H from CH\textsubscript{2}CH=CH\textsubscript{2}), 3.66 (1 H, d, \(J = 11.3\) Hz, 1 H from CH\textsubscript{2}OH), 3.86 (1 H, d, \(J = 11.3\) Hz, 1 H from CH\textsubscript{2}OH), 4.94 - 4.98 (1 H, m, 1 H from CH\textsubscript{2}CH=CH\textsubscript{2}), 5.05 (1 H, dd, \(J = 17.0, 1.7\) Hz, 1 H from CH\textsubscript{2}CH=CH\textsubscript{2}), 5.05 (1 H, dd, \(J = 17.7, 1.1\) Hz, 1 H from CCH=CH\textsubscript{2}), 5.79 (1 H, dd, \(J = 17.7, 11.0\) Hz, CCH=CH\textsubscript{2}), 5.86 (1 H, ddt, \(J = 17.0, 10.2, 6.6\) Hz, CH\textsubscript{2}CH=CH\textsubscript{2});

\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) ppm 19.3 (CH\textsubscript{2}), 28.7 (CH\textsubscript{2}CH=CH\textsubscript{2}), 29.5 (CH\textsubscript{2}), 35.6 (CH\textsubscript{2}CH\textsubscript{2}CH=CH\textsubscript{2}), 36.8 (CH\textsubscript{2}), 55.0 (C\textsuperscript{\textit{a}}), 65.7 (CH\textsubscript{2}OH), 86.4 (C\textsuperscript{\textit{a}}), 114.0 (CH\textsubscript{2}CH=CH\textsubscript{2}), 114.5 (CCH=CH\textsubscript{2}), 139.3 (CCH=CH\textsubscript{2}), 140.5 (CH\textsubscript{2}CH=CH\textsubscript{2});

m/z (ES+) 119 (50%), 161 (85), 219 ((M + Na), 100). (Found: (M + Na) 219.1364. C\textsubscript{12}H\textsubscript{20}O\textsubscript{2}Na requires \(M\) 219.1356).

6.10. General procedure J – Telescoped spirocyclisation/lactone reductions

\textbf{rac-(1S,2R)-2-((R)-1-(Dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)-1-(pent-4-en-1-yl)cyclopentanol (374)}

To a stirred solution of SmI\textsubscript{2} (0.11 M in THF, 45 mL, 5.07 mmol, 2.5 eq) and MeOH (7.9 mL, 195 mmol, 96 eq) at 0 °C was added 4-(dimethyl(phenyl)silyl)-3-(4-oxonon-8-en-1-ylidene)dihydrofuran-2-one 372 (723 mg, 2.03 mmol, 1.0 eq) in THF (3.0 mL) and the reaction mixture stirred at 0 °C for 5 minutes. The reaction mixture was then transferred by cannula into a stirred solution of SmI\textsubscript{2} (0.11 M in THF, 144 mL, 16.2 mmol, 8.0 eq), triethylamine (6.8 mL, 48.7 mmol, 24 eq) and H\textsubscript{2}O (876 µL, 48.7 mmol, 24 eq) and stirred at room temperature for 10 minutes. The reaction was quenched with air (bubbling),
tartaric acid (600 mg) and H₂O (200 mL) added, and the aqueous phase extracted with ethyl acetate (3 × 200 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40-60 °C) gave rac-(1S,2R)-2-((R)-1-(dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)-1-(pent-4-en-1-yl)cyclopentanol 374 (703 mg, 1.94 mmol, 96%) as a light yellow oil.

Data given earlier.

rac-(1R,2R)-1-(3-((tert-Butyldiphenylsilyl)oxy)propyl)-2-((S)-1-(dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)cyclopentanol (435)

As for general procedure J, reaction of 3-((tert-butyldiphenylsilyl)oxy)-4-oxoheptylidene)-4-(dimethyl(phenyl)silyldihydrofuran-2(3H)-one 426 (161 mg, 0.28 mmol, 1.0 eq) with SmI₂ (0.11 M in THF, 6.3 mL, 0.69 mmol, 2.5 eq) and MeOH (1.1 mL, 26.4 mmol, 96 eq), then with SmI₂ (0.11 M in THF, 20 mL, 2.20 mmol, 8.0 eq), triethylamine (921 µL, 6.60 mmol, 24 eq) and H₂O (109 µL, 6.60 mmol, 24 eq) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) rac-(1R,2R)-1-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2-((S)-1-(dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)cyclopentanol 435 (123 mg, 0.21 mmol, 74%) as a light yellow oil.

Data given earlier.

rac-(1R,2R)-1-(But-3-en-1-yl)-2-((S)-1-(dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)cyclopentanol (454)

As for general procedure J, reaction of 4-(dimethyl(phenyl)silyl)-3-(4-oxooct-7-en-1-ylidene)dihydrofuran-2(3H)-one 446 (1.2 g, 3.50 mmol, 1.0 eq) with SmI₂ (0.11 M in THF, 80 mL, 8.75 mmol, 2.5 eq) and MeOH (13.6 mL, 336 mmol, 96 eq), then with SmI₂ (0.11 M in THF, 255 mL, 28.0 mmol, 8.0 eq), triethylamine (11.7 mL, 84.0 mmol, 24 eq) and H₂O (1.5 mL, 84.0 mmol, 24 eq) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) rac-(1R,2R)-1-(but-3-en-1-yl)-2-((S)-1-
(dimethyl(phenyl)silyl)-2-hydroxyethyl)-2-(hydroxymethyl)cyclopentanol 454 (1.06 g, 3.04 mmol, 87%) as a light yellow oil. Data given earlier.

\[
\text{OH} \quad \text{OH} \\
\text{PhMe}_2\text{Si} \quad \text{OH}
\]

\textit{rac-}(1\text{S},2\text{R})-2-((\text{R})-1-(\text{Dimethyl(phenyl)silyl})-2-hydroxyethyl)-2-(hydroxymethyl)-1-methylcyclopentan-1-ol (SI-7)

As for general procedure J, reaction of 4-(dimethyl(phenyl)silyl)-3-(4-oxopentylidene)dihydrofuran-2(3\text{H})-one 354 (30.2 mg, 0.10 mmol, 1.0 eq) with SmI\(_2\) (0.11 M in THF, 2.3 mL, 0.25 mmol, 2.5 eq) and MeOH (388 \(\mu\)L, 9.6 mmol, 96 eq), then with SmI\(_2\) (0.11 M in THF, 7.3 mL, 0.80 mmol, 8.0 eq), triethylamine (334 \(\mu\)L, 2.4 mmol, 24 eq) and H\(_2\)O (43 \(\mu\)L, 2.4 mmol, 24 eq) gave after column chromatography (30% ethyl acetate in petroleum ether (40-60 °C)) \textit{rac-}(1\text{S},2\text{R})-2-((\text{R})-1-(\text{dimethyl(phenyl)silyl})-2-hydroxyethyl)-2-(hydroxymethyl)-1-methylcyclopentan-1-ol SI-7 (22.0 g, 71.3 \(\mu\)mol, 71%) as a light yellow oil.

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\) 3284 (br. OH), 2957, 2876, 1427, 1372, 1304, 1248, 1145, 1110, 1054, 961, 912, 816, 777, 733, 699, 645;

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) ppm 0.46 (3 H, s, SiCH\(_3\)), 0.47 (3 H, s, SiCH\(_3\)), 1.20 (3 H, s, CCH\(_3\)), 1.17 - 1.23 (2 H, m, CH\(_2\)), 1.39 - 1.48 (1 H, m, 1 H from CH\(_2\)), 1.51 - 1.59 (1 H, m, 1 H from CH\(_2\)), 1.61 (1 H, br. d, \(J = 5.4\) Hz, CHSi), 1.72 (1 H, ddd, \(J = 12.8, 9.9, 2.5\) Hz, 1 H from CH\(_2\)), 2.02 - 2.11 (1 H, m, 1 H from CH\(_2\)), 3.63 (1 H, d, \(J = 12.5\) Hz, 1 H from CCH\(_2\)OH), 3.85 (1 H, dd, \(J = 10.8, 5.5\) Hz, 1 H from CHCH\(_2\)OH), 3.94 (1 H, dd, \(J = 12.5, 1.7\) Hz, 1 H from CCH\(_2\)OH), 4.51 (1 H, dd, \(J = 10.8, 0.9\) Hz, 1 H from CHCH\(_2\)OH), 7.33 - 7.38 (3 H, m, 3 × ArH), 7.56 - 7.61 (2 H, m, 2 × ArH);

\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) ppm -0.2 (SiCH\(_3\)), 0.2 (SiCH\(_3\)), 17.8 (CH\(_2\)), 25.3 (CCH\(_3\)), 34.8 (CH\(_2\)), 37.0 (CHSi), 39.6 (CH\(_2\)), 50.6 (C\(^8\)), 61.4 (CHCH\(_2\)OH), 67.8 (CCH\(_2\)OH), 85.8 (C\(^8\)), 127.8 (2 × ArCH), 128.8 (ArCH), 133.9 (2 × ArCH), 140.1 (ArC\(^8\));

m/z (ES+) 89 (32%), 121 (100), 331 ((M + Na), 40).
6.11. General procedure K – Telescopied spirocyclisation/lactone reduction/Peterson eliminations

\[
\text{rac-}(1R,2R)-1-\text{(But}-3\text{-en-1-yl)}-2-(\text{hydroxymethyl})-2\text{-vinylcyclopentanol (455)}
\]

To a stirred solution of \(\text{SmI}_2\) (0.11 M in THF, 4.5 mL, 0.50 mmol, 2.5 eq) and MeOH (778 \(\mu\)L, 19.6 mmol, 96 eq) at 0 °C was added 4-(dimethyl(phenyl)silyl)-3-(4-oxooct-7-en-1-ylidene)dihydrofuran-2(3\(H\))-one 446 (68.5 mg, 0.20 mmol, 1.0 eq) and the reaction mixture stirred at 0 °C for 5 minutes. The reaction mixture was then transferred by cannula into a stirred solution of \(\text{SmI}_2\) (0.11 M in THF, 14.5 mL, 1.60 mmol, 8.0 eq), triethylamine (670 \(\mu\)L, 4.80 mmol, 24 eq) and H\(_2\)O (86 \(\mu\)L, 4.80 mmol, 24 eq) and stirred at room temperature for 10 minutes. The flask was then opened, the reaction quenched with air (bubbling), potassium tert-butoxide (898 mg, 8.00 mmol, 40 eq) added over 20 minutes and the reaction mixture stirred at room temperature for 20 minutes. The reaction was quenched with NH\(_4\)Cl\(_{aq.}\), sat. (20 mL) and the aqueous phase extracted with ethyl acetate (3 \(\times\) 20 mL). The combined organic phases were dried (Na\(_2\)SO\(_4\) or MgSO\(_4\)) and concentrated \textit{in vacuo}. Purification by column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40-60 °C) gave \(\text{rac-}(1R,2R)-1\text{-}(\text{but}\text{-3\text{-en-1-yl})-2-}
\text{(hydroxymethyl)-2-vinylcyclopentanol 455 (26.2 mg, 0.13 mmol, 67\%) as a light yellow oil.\[\text{OH} \quad \text{OH}
\]

Data given earlier.

\[
\text{rac-}(1S,2R)-2-(\text{Hydroxymethyl})-1\text{-methyl-2-vinylcyclopentan-1-ol (465)}
\]

As for general procedure K, reaction of 4-(dimethyl(phenyl)silyl)-3-(4-oxopentylidene)dihydrofuran-2(3\(H\))-one 354 (30.2 mg, 0.10 mmol, 1.0 eq) with \(\text{SmI}_2\) (0.11 M in THF, 2.3 mL, 0.25 mmol, 2.5 eq) and MeOH (388 \(\mu\)L, 9.6 mmol, 96 eq), then with \(\text{SmI}_2\) (0.11 M in THF, 7.3 mL, 0.80 mmol, 8.0 eq), triethylamine (334 \(\mu\)L, 2.4 mmol, 24 eq) and H\(_2\)O (43 \(\mu\)L, 2.4 mmol, 24 eq), then with potassium tert-butoxide (449 mg, 4.00 mmol, 40 eq) gave after column chromatography (30% ethyl acetate in petroleum ether.
(40-60 °C) rac-(1S,2R)-2-(hydroxymethyl)-1-methyl-2-vinylcyclopentan-1-ol 465 (23.6 mg, 0.15 mmol, 76%) as a colourless oil.

ν_max (neat)/cm⁻¹ 3322 (br. OH), 2961, 2877, 1454, 1427, 1407, 1374, 1303, 1254, 1215, 1111, 1048, 1026, 961, 913, 833, 817, 736, 700, 657;

¹H NMR (400 MHz, CDCl₃) δ ppm 1.26 (3 H, s, CH₃), 1.62 - 1.87 (5 H, m, 5 H from CH₂), 1.98 - 2.08 (1 H, m, 1 H from CH₂), 3.71 (1 H, d, J = 11.3 Hz, 1 H from CH₂OH), 3.78 (1 H, d, J = 11.3 Hz, 1 H from CH₂OH), 5.10 (1 H, dd, J = 17.6, 1.3 Hz, 1 H from CH=CH₂), 5.14 (1 H, dd, J = 11.0, 1.3 Hz, 1 H from CH=CH₂), 5.86 (1 H, dd, J = 17.6, 11.0 Hz, CH=CH₂);

¹³C NMR (100 MHz, CDCl₃) δ ppm 19.1 (CH₂), 24.3 (CH₃), 29.2 (CH₂), 39.8 (CH₂), 54.3 (C₉), 66.1 (CH₂OH), 84.1 (C₉), 114.2 (CH=CH₂), 140.6 (CH=CH₂);


rac-Methyl 4-((1R,2S)-1-((tert-butyldimethylsilyl)oxy)-2-formyl-2-vinylcyclopentyl)butanoate (408)

To a stirred solution of methyl rac-4-((1R,2R)-1-((tert-butyldimethylsilyl)oxy)-2-(hydroxymethyl)-2-vinylcyclopentyl)butanoate 406 (93 mg, 0.26 mmol, 1.0 eq) in CH₂Cl₂ (8.0 mL) was added DMP (166 mg, 0.39 mmol, 1.5 eq) and the reaction mixture stirred at room temperature for 1 hour. H₂O (10 mL) was then added and the aqueous phase extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave rac-methyl 4-((1R,2S)-1-((tert-butyldimethylsilyl)oxy)-2-formyl-2-vinylcyclopentyl)butanoate 408 (91 mg, 0.26 mmol, 98%) as a colourless oil.

ν_max (neat)/cm⁻¹ 2953, 2929, 2882, 2856, 1740 (C=O), 1721 (C=O), 1472, 1463, 1436, 1360, 1255, 1199, 1168, 1136, 1104, 1045, 1002, 920, 882, 834, 773, 676;

¹H NMR (500 MHz, CDCl₃) δ ppm 0.11 (3 H, s, SiCH₃), 0.12 (3 H, s, SiCH₃), 0.87 (9 H, s, 3 × CCH₃), 1.55 - 1.63 (1 H, m, 1 H from CH₂), 1.65 - 1.93 (8 H, m, 8 H from CH₂), 2.28 (2 H, t, J = 6.6 Hz, CH₂COOCH₃), 2.36 - 2.44 (1 H, m, 1 H from CH₂), 3.66 (3 H, s,
OCH₃), 5.11 (1 H, dd, J = 17.7, 0.9 Hz, 1 H from CH=CH₂), 5.27 (1 H, dd, J = 11.0, 0.9 Hz, 1 H from CH=CH₂), 6.08 (1 H, dd, J = 17.7, 11.0 Hz, CH=CH₂), 9.82 (1 H, s, HC=O);

¹³C NMR (125 MHz, CDCl₃) δ ppm −2.5 (SiCH₃), −2.4 (SiCH₃), 18.6 (Cₙ), 19.8 (CH₂), 20.5 (CH₂), 25.9 (3 × CCH₃), 28.5 (CH₂), 34.3 (CH₂COOCH₃), 37.4 (CH₂), 37.8 (CH₂), 51.5 (OCH₃), 66.8 (Cₙ), 90.2 (Cₙ), 116.6 (CH=CH₂), 135.8 (CH=CH₂), 173.5 (C=O), 204.1 (HC=O);

m/z (ES⁺) 263 (27%), 377 ((M + Na), 100). (Found: (M + Na) 377.2121. C₁₉H₃₄O₄SiNa requires M, 377.2119).

rac-(1S,2R)-2-(But-3-en-1-yl)-2-((tert-butyldimethylsilyl)oxy)-1-vinylcyclopentanecarbaldehyde (458)

As for general procedure L, reaction of rac-((1R,2R)-2-(but-3-en-1-yl)-2-((tert-butyldimethylsilyl)oxy)-1-vinylcyclopentyl)methanol 457 (92.1 mg, 0.30 mmol, 1.0 eq) and DMP (189 mg, 0.44 mmol, 2.0 eq) in CH₂Cl₂ (6.0 eq) gave after concentration in vacuo, trituration of the residue in hexane, filtration and concentration in vacuo rac-(1S,2R)-2-(but-3-en-1-yl)-2-((tert-butyldimethylsilyl)oxy)-1-vinylcyclopentanecarbaldehyde 458 (88.8 mg, 0.29 mmol, 97%) as a colourless oil.

νmax (neat)/cm⁻¹ 2954, 2929, 2880, 2856, 1719 (C=O), 1641, 1472, 1463, 1415, 1388, 1360, 1313, 1255, 1132, 1079, 1051, 995, 913, 834, 772, 676;

¹H NMR (300 MHz, CDCl₃) δ ppm 0.12 (3 H, s, SiCH₃), 0.14 (3 H, s, SiCH₃), 0.89 (9 H, s, 3 × CCH₃), 1.58 - 1.85 (6 H, m, 2 × CH₂, 2 H from CH₂), 1.85 - 1.98 (1 H, m, 1 H from CH₂), 2.03 - 2.27 (2 H, m, CH₂CH=CH₂), 2.34 - 2.49 (1 H, m, 1 H from CH₂), 4.90 - 5.06 (2 H, m, CH₂CH=CH₂), 5.12 (1 H, d, J = 17.6 Hz, 1 H from CCH=CH₂), 5.28 (1 H, d, J = 11.0 Hz, 1 H from CCH=CH₂), 5.77 (1 H, ddt, J = 17.0, 10.4, 6.4 Hz, CH₂CH=CH₂), 6.08 (1 H, dd, J = 17.6, 11.0 Hz, CCH=CH₂), 9.84 (1 H, s, CHO);

¹³C NMR (75 MHz, CDCl₃) δ ppm −2.5 (SiCH₃), −2.4 (SiCH₃), 18.6 (Cₙ), 20.6 (CH₂), 25.9 (3 × CCH₃), 28.5 (CH₂CH=CH₂), 28.6 (CH₂), 37.0 (CH₂), 38.0 (CH₂), 66.8 (Cₙ), 90.4 (Cₙ), 114.5 (CH₂CH=CH₂), 116.6 (CCH=CH₂), 135.9 (CCH=CH₂), 138.1 (CH₂CH=CH₂), 204.3 (CHO);

m/z (ES⁺) 331 ((M + Na), 50%), 413 (100).
6.13. General procedure M – Homologations of aldehydes

To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (164 mg, 0.48 mmol, 4.0 eq) in THF (3.0 mL) at −78 °C was added KHMDS (0.5 M in THF, 0.96 mL, 0.48 mmol, 4.0 eq) and the reaction mixture stirred at −78 °C for 30 minutes. rac-(1S,2R)-2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2-((triethylsilyl)oxy)-1-vinylcyclopentanecarbaldehyde 437 (66 mg, 0.12 mmol, 1.0 eq) in THF (0.5 mL) was added dropwise and the reaction mixture left to warm up to room temperature overnight. The reaction was quenched with HCl (1 N, 5.0 mL) and stirred at room temperature for 24 hours, then the aqueous phase extracted with ethyl acetate (3 × 5.0 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave rac-(1S,2R)-2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2-((triethylsilyl)oxy)-1-vinylcyclopentanecarbaldehyde 438 (41.1 mg, 71.0 µmol, 59%) as a light yellow oil.

νₘₐₓ (neat)/cm⁻¹ 3069, 2955, 2873, 1720 (C=O), 1472, 1428, 1386, 1237, 1190, 1110, 1087, 1006, 918, 823, 738, 721, 701, 613;

¹H NMR (400 MHz, CDCl₃) δ ppm 0.62 (2 H, q, J = 7.9 Hz, SiCH₂), 0.63 (4 H, q, J = 7.9 Hz, 2 × SiCH₂), 0.95 (3 H, t, J = 7.9 Hz, CH₃CH₂), 0.96 (6 H, t, J = 7.9 Hz, 2 × CH₂CH₃), 1.07 (9 H, s, 3 × CCH₃), 1.55 - 1.88 (8 H, m, 8 H from CH₃), 1.96 - 2.03 (2 H, m, 2 H from CH₂), 2.56 (1 H, dd, J = 15.4, 3.0 Hz, 1 H from CH₂CHO), 2.68 (1 H, dd, J = 15.4, 3.0 Hz, 1 H from CH₂CHO), 3.60 - 3.66 (2 H, m, CH₂O), 5.06 (1 H, dd, J = 17.5, 0.9 Hz, 1 H from CH=CH₂), 5.11 (1 H, dd, J = 11.0, 0.9 Hz, 1 H from CH=CH₂), 5.85 (1 H, dd, J = 17.5, 11.0 Hz, CH=CH₂), 7.37 - 7.45 (6 H, m, 6 × ArH), 7.65 - 7.70 (4 H, m, 4 × ArCH), 9.67 (1 H, t, J = 3.0 Hz, HC=O);

¹³C NMR (100 MHz, CDCl₃) δ ppm 6.6 (2 × SiCH₂), 6.8 (SiCH₂), 7.3 (2 × CH₂CH₃), 7.3 (CH₂CH₃), 19.2 (C₆), 19.9 (CH₂), 26.8 (3 × CCH₃), 27.8 (CH₂), 33.2 (CH₂), 33.9 (CH₂), 36.9 (CH₂), 48.0 (CH₂CHO), 55.1 (C₆), 64.4 (CH₂O), 87.5 (C₆), 114.1 (CH=CH₂), 127.6 (4 × ArCH), 129.5 (2 × ArCH), 133.9 (2 × ArC₆), 135.6 (4 × ArCH), 141.5 (CH=CH₂), 204.3 (C=O);
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\[ m/z \text{ (ES+)} \ 279 \ (54\%), \ 301 \ (56), \ 579 \ (44), \ 587 \ ((M + Na), \ 84), \ 588 \ (100). \text{ (Found: (M + Na) 587.3342. C}_{34}H_{52}O_{3}Si_{2}Na \text{ requires } M, \ 587.3348).} \]

\[
\begin{array}{c}
\text{OTBS} \\
\text{O}
\end{array}
\]

\[ \text{rac-2-}((1S,2R)-2-(\text{But-3-en-1-yl})-2-((\text{tert-butylmethyldimethylsilyl})oxy)-1-vinylcyclopentyl)acetaldehyde (459) \]

As for general procedure M, reaction of \[ \text{rac-(1S,2R)-2-(but-3-en-1-yl})-2-((\text{tert-butylmethyldimethylsilyl})oxy)-1-vinylcyclopentanecarbaldehyde 458 \] (162 mg, 0.53 mmol, 1.0 eq), \[(\text{methoxymethyl})\text{triphenylphosphonium chloride (721 mg, 2.10 mmol, 4.0 eq) and LiHMDS (1 M in THF, 2.1 mL, 2.10 mmol, 4.0 eq) in THF (11 mL) gave rac-2-((1S,2R)-2-(but-3-en-1-yl})-2-((\text{tert-butylmethyldimethylsilyl})oxy)-1-vinylcyclopentyl)acetaldehyde 459 (113 mg, 0.35 mmol, 66\%) as a colourless oil.} \]

\[ \text{^1H NMR (400 MHz, CDCl}_3\text{)} \delta \text{ppm 0.14 (3 H, s, SiCH}_3\text{), 0.15 (3 H, s, SiCH}_3\text{), 0.92 (9 H, s, 3 \times \text{CCH}_3\text{), 1.57 - 1.66 (2 H, m, CH}_2\text{CH}_2\text{CH=CH}_2\text{), 1.68 - 1.88 (2 H, m, CH}_2\text{), 1.76 - 1.81 (2 H, m, CH}_2\text{), 1.90 - 2.07 (2 H, m, CH}_2\text{), 2.09 - 2.26 (2 H, m, CH}_2\text{CH=CH}_2\text{), 2.63 (1 H, dd, } J = 15.4, 3.4 \text{ Hz, 1 H from CH}_2\text{CHO), 2.73 (1 H, dd, } J = 15.4, 2.7 \text{ Hz, 1 H from CH}_2\text{CHO), 4.92 - 4.97 (1 H, m, 1 H from CH}_2\text{CH=CH}_2\text{), 5.00 (1 H, ddt, } J = 17.1, 1.6, 1.6 \text{ Hz, 1 H from CH}_2\text{CH=CH}_2\text{), 5.09 (1 H, dd, } J = 17.6, 0.9 \text{ Hz, 1 H from CCH=CH}_2\text{), 5.16 (1 H, dd, } J = 11.0, 0.9 \text{ Hz, 1 H from CCH=CH}_2\text{), 5.76 (1 H, ddt, } J = 17.1, 10.3, 6.6 \text{ Hz, CH}_2\text{CH=CH}_2\text{), 5.88 (1 H, dd, } J = 17.6, 11.0 \text{ Hz, CCH=CH}_2\text{), 9.64 (1 H, dd, } J = 3.4, 2.7 \text{ Hz, CHO);} \]

\[ \text{^13C NMR (100 MHz, CDCl}_3\text{)} \delta \text{ppm } -2.5 \text{ (SiCH}_3\text{), -2.3 (SiCH}_3\text{), 18.8 (CH}^6\text{), 19.8 (CH}_2\text{, 26.1 (3 \times \text{CCH}_3\text{), 28.7 (CH}_2\text{CH=CH}_2\text{), 32.9 (CH}_2\text{), 36.2 (CH}_2\text{), 36.6 (CH}_2\text{CH}_2\text{CH=CH}_2\text{), 48.1 (CH}_2\text{CHO), 54.8 (CH}^6\text{), 87.5 (CH}^6\text{), 114.3 (CH}_2\text{CH=CH}_2\text{), 114.7 (CCH=CH}_2\text{), 138.7 (CH}_2\text{CH=CH}_2\text{), 141.1 (CCH=CH}_2\text{), 204.5 (CHO);} \]
6.14. Miscellaneous procedures

\[
\begin{align*}
\text{Br} & \quad \text{O} & \quad \text{C} \\
& \quad \text{O} & \quad \text{N} \\
\end{align*}
\]

4-(4-Bromobenzyloxy)-N-methoxy-N-methylbutanamide (346)

To a stirred suspension of NaH (60% in oil, 338 mg, 8.45 mmol, 1.2 eq) in THF (10 mL) at 0 °C was added 4-hydroxy-N-methoxy-N-methylbutanamide 344 (1.01 g, 6.86 mmol, 1.0 eq) dropwise. 4-Bromobenzyl bromide (2.08 g, 8.33 mmol, 1.2 eq) was then added and the reaction mixture stirred at room temperature overnight. The reaction was quenched with NH₄Cl aq., sat. (10 mL) and the aqueous phase extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with a gradient 20-100% ethyl acetate in petroleum ether (40-60 °C) gave 4-(4-bromobenzyloxy)-N-methoxy-N-methylbutanamide 346 (1.48 g, 4.67 mmol, 68%) as a colourless liquid.

\[
\nu_{\text{max}} \text{(neat)/cm}^{-1} 3489 \text{ (br.)}, 2935, 2860, 1771, 1734, 1656 (\text{C=O}), 1592, 1486, 1460, 1441, 1414, 1385, 1362, 1176, 1094, 1069, 998, 802;
\]

\[
^1\text{H NMR} \text{ (400 MHz, CDCl}_3) \delta \text{ ppm } 1.92 - 2.00 (2 \text{ H, m, OCH}_2\text{C}_2\text{H}_2), 2.55 (2 \text{ H, t, } \text{J} = 7.3 \text{ Hz, C(O)CH}_2), 3.18 (3 \text{ H, s, NCH}_3), 3.54 (2 \text{ H, t, } \text{J} = 6.2 \text{ Hz, OCH}_2\text{CH}_2), 3.68 (3 \text{ H, s, OCH}_3), 4.46 (2 \text{ H, s, CH}_2\text{Ar}), 7.20 - 7.24 (2 \text{ H, m, 2 × ArH}), 7.45 - 7.49 (2 \text{ H, m, 2 × ArH});
\]

\[
^{13}\text{C NMR} \text{ (100 MHz, CDCl}_3) \delta \text{ ppm } 24.6 (\text{OCH}_2\text{CH}_2), 28.4 (\text{C(O)CH}_2), 32.2 (\text{NCH}_3), 61.2 (\text{OCH}_3), 69.7 (\text{OCH}_2\text{CH}_2), 72.0 (\text{CH}_2\text{Ar}), 121.3 (\text{ArC}^\text{b}), 129.2 (2 \times \text{ArCH}), 131.4 (2 \times \text{ArCH}), 137.6 (\text{ArC}^\text{b}), 174.2 (\text{C=O});
\]

\[
\text{m/z} \text{ (ES+)} 316 (20%), 318 (23), 338 ((\text{M + Na}, 100), 340 (94). \text{ (Found: (M + H)} 316.0554, \text{ C}_{13}\text{H}_{19}\text{NO}_3^{79}\text{Br requires } M, 316.0543).
\]

1-(4-Bromobenzyloxy)oct-7-en-4-one (347)

To a stirred suspension of magnesium (1.41 g, 4.45 mmol, 3.3 eq) in THF (25 mL) was added 4-bromobut-1-ene (1.80 g, 13.3 mmol, 3.0 eq) dropwise. The reaction mixture was stirred at room temperature during 1 hour and then added to 4-(4-bromobenzyloxy)-N-methoxy-N-methylbutanamide 346 (1.41 g, 4.45 mmol, 1.0 eq) in THF (25 mL) at 0 °C. The reaction mixture was stirred for 30 minutes at 0 °C and then 1 hour at room
temperature. The reaction was quenched with HCl (1 N, 10 mL) and the aqueous phase extracted with diethylether (3 × 20 mL). The combined organic phases were dried (Na$_2$SO$_4$ or MgSO$_4$) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 10% ethyl acetate in petroleum ether (40-60 °C) gave 1-(4-bromobenzyloxy)oct-7-en-4-one 347 (1.13 g, 3.62 mmol, 81%) as a colourless liquid.

v$_{\text{max}}$ (neat)/cm$^{-1}$ 3338 (br.), 3077, 2929, 2861, 1710 (C=O), 1641, 1592, 1487, 1439, 1407, 1360, 1272, 1203, 1092, 1069, 1010, 912, 795, 759, 629;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.85 - 1.94 (2 H, m, OCH$_2$C$_2$H$_2$), 2.27 - 2.36 (2 H, m, CH$_2$CH=CH$_2$), 2.52 (4 H, q, $J$ = 7.2 Hz, CH$_2$C(O)CH$_2$, CH$_2$C(O)CH$_2$), 3.47 (2 H, t, $J$ = 6.2 Hz, OCH$_2$CH$_2$), 4.43 (2 H, s, OCH$_2$Ar), 4.95 - 5.06 (2 H, m, CH=CH$_2$), 5.80 (1 H, ddt, $J$ = 17.0, 10.3, 6.4 Hz, CH=CH$_2$), 7.18 - 7.22 (2 H, m, 2 × ArH), 7.45 - 7.50 (2 H, m, 2 × ArH);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 23.7 (OCH$_2$C$_2$H$_2$), 27.7 (CH$_2$CH=CH$_2$), 39.3 (CH$_2$C(O)CH$_2$), 41.8 (CH$_2$C(O)CH$_2$), 69.4 (OCH$_2$CH$_2$), 72.1 (OCH$_2$Ar), 115.2 (CH=CH$_2$), 129.2 (2 × ArCH), 131.5 (2 × ArCH), 137.1 (CH=CH$_2$), 209.8 (C=O);

m/z (ES+) 333 ((M + Na), 100%), 335 (97). (Found: (M + H) 311.0652. C$_{15}$H$_{20}$O$_2$Br requires $M$, 311.0641).

7-(4-Bromobenzyloxy)-4-oxoheptanal (348)

To a stirred suspension of 1-(4-bromobenzyloxy)oct-7-en-4-one 347 (603 mg, 1.94 mmol, 1.0 eq) in THF (12 mL) and H$_2$O (2.4 mL) was added NaIO$_4$ (910 mg, 4.25 mmol, 2.2 eq) and OsO$_4$ (5 mg, 0.02 mmol, 1 mol%) and the reaction mixture was stirred for 6 hours at room temperature. The reaction was quenched with NH$_4$Cl$_{\text{aq, sat.}}$ (10 mL) and the aqueous phase extracted with ethyl acetate (3 × 20 mL). The combined organic phases were then dried (Na$_2$SO$_4$ or MgSO$_4$) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether (40-60 °C) gave 7-(4-bromobenzyloxy)-4-oxoheptanal 348 (333 mg, 1.06 mmol, 55%) as a yellow liquid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 1.87 - 1.96 (2 H, m, OCH$_2$CH$_2$), 2.60 (2 H, t, $J$ = 7.2 Hz, OCH$_2$CH$_2$CH$_2$), 2.69 - 2.78 (4 H, m, CH$_2$CH$_2$CHO, CH$_2$CHO), 3.48 (2 H, t, $J$ = 6.1 Hz, OCH$_2$CH$_2$), 4.40 - 4.46 (2 H, m, OCH$_2$Ar), 7.17 - 7.24 (2 H, m, 2 × ArH), 7.45 - 7.50 (2 H, m, 2 × ArH), 9.80 (1 H, s, CHO);
\[ ^{13}C \text{ NMR} \ (100 \text{ MHz, CDCl}_3) \ \delta \text{ ppm} \ 23.9 \ (\text{OCH}_2\text{CH}_2), \ 34.7 \ (\text{CH}_2\text{CHO}), \ 37.5 \ (\text{CH}_2\text{CHO}), \ 39.3 \ (\text{OCH}_2\text{CH}_2\text{CH}_2), \ 69.4 \ (\text{OCH}_2\text{CH}_2), \ 72.1 \ (\text{OCH}_2\text{Ar}), \ 121.4 \ (\text{ArC}\^\text{\textcircled{o}}), \ 129.3 \ (2 \times \text{ArCH}), \ 131.5 \ (2 \times \text{ArCH}), \ 137.3 \ (\text{ArC}\^\text{\textcircled{o}}), \ 200.5 \ (\text{CHO}), \ 208.3 \ (\text{C=O}); \]

\[ \text{m/z} \ (\text{ES}+) \ 367 \ ((\text{M} + \text{CH}_4\text{NaO}), \ 100%), \ 369 \ (98). \] (Found: (M + Na) 335.0253. C\textsubscript{14}H\textsubscript{17}O\textsubscript{3}BrNa requires \text{M}, 335.0254).

5-(7-(4-Bromobenzzyloxy)-4-oxoheptylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (349)

To a stirred solution of Meldrum’s acid (146 mg, 1.03 mmol, 1.0 eq), 7-(4-bromobenzzyloxy)-4-oxoheptanal 348 (333 mg, 1.06 mmol, 1.0 eq) and thiophenol (118 mg, 1.07 mmol, 1.1 eq) in acetonitrile (3.0 mL) at 0 °C was added piperidine (9.0 mg, 0.11 mmol, 0.1 eq) and AcOH (6.0 mg, 0.11 mmol, 0.1 eq). The ice bath was allowed to melt and the reaction stirred at room temperature overnight. The reaction was quenched with aqueous citric acid (10% solution, 3.0 mL) and the aqueous phase extracted with ethyl acetate (3 × 5.0 mL). The combined organic phases were washed with NH\textsubscript{4}Cl\text{aq}, sat. (10 mL). The solvent was removed \textit{in vacuo} at room temperature and the crude product redissolved in acetonitrile (2.0 mL). Aqueous KOH (2 M, 7.0 mL) was added and the mixture stirred 5 minutes. Aqueous K\textsubscript{3}Fe(CN)\textsubscript{6} (7.0 mL, 1.1 eq) was added dropwise at 0 °C and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic phases were then added to HCl (10%, 14 mL) at 0 °C and the aqueous phase extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried (Na\textsubscript{2}SO\textsubscript{4} or MgSO\textsubscript{4}) and concentrated \textit{in vacuo}. The crude oil was dissolved in hexane and stirred at 0 °C for 2 hours. The precipitate was then filtered and dried \textit{in vacuo} to give 5-(7-(4-bromobenzzyloxy)-4-oxoheptylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione 349 (270 mg, 0.62 mmol, 60%) as a white solid.

mp 84-86 °C;

\[ \text{v}_{\text{max}} \ (\text{neat})/\text{cm}^{-1} \ 2947, \ 2927, \ 2872, \ 1784, \ 1745 \ (\text{C=O}), \ 1704 \ (\text{C=O}), \ 1581, \ 1481, \ 1438, \ 1388, \ 1330, \ 1306, \ 1270, \ 1203, \ 1177, \ 1118, \ 1092, \ 1065, \ 1041, \ 1011, \ 985, \ 877, \ 802, \ 749, \ 735, \ 693, \ 637; \]

\[ ^{1}H \text{ NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta \text{ ppm} \ 1.76 \ (6 \text{ H, s, } 2 \times \text{CH}_3), \ 1.86 - 1.94 \ (2 \text{ H, m, OCH}_2\text{CH}_2), \ 2.55 \ (2 \text{ H, t, } J = 7.1 \text{ Hz, OCH}_2\text{CH}_2\text{CH}_2), \ 2.76 \ (2 \text{ H, t, } J = 6.7 \text{ Hz, CHCH}_2\text{CH}_2), \ 3.11 \ (2 \text{ H, q, } J = 6.8 \text{ Hz, CHCH}_2), \ 3.45 - 3.49 \ (2 \text{ H, m, OCH}_2\text{CH}_2), \ 4.43 \ (2
H, s, CH₂Ar), 7.18 - 7.21 (2 H, m, 2 × ArH), 7.46 - 7.50 (2 H, m, 2 × ArH), 7.82 (1 H, t, J = 7.3 Hz, CH);

**¹³C NMR** (100 MHz, CDCl₃) δ ppm 23.9 (OCH₂CH₂), 25.3 (CH₂CH₂), 27.7 (2 × CH₃), 39.3 (OCH₂CH₂CH₂), 40.4 (CH₃CH₂CH₂), 69.3 (OCH₂CH₂), 72.1 (CH₂Ar), 105.1 (OCO), 118.5 (ArC₆), 125.6 (C₆), 129.1 (2 × ArCH), 129.3 (ArC₆), 129.4 (2 × ArCH), 131.5 (CH), 167.0 (2 × C=O), 208.2 (C=O);
m/z (ES+) 144 (57%), 145 (52), 173 (24), 228 (40), 369 (20), 381 (23), 383 (27), 435 (17), 437 (89), 439 (64), 456 (27), 461 ((M + Na), 100), 463 (87), 464 (15), 479 (25), 493 (44), 495 (88), 497 (44). (Found: (M + Na) 461.0567. C₂₀H₂₃O₆⁷Na requires M, 461.0570).

rac-5-((1R,2R)-1-((tert-Butyldimethylsilyl)oxy)-2-((tert-butyldimethylsilyl)oxy)methyl)-2-vinylcyclopentyl)pentane-1,2-diol (SI-8)

To a stirred solution of rac-tert-butyll((1R,2S)-2-((tert-butylidemethylsilyl)oxy)-2-(pent-4-en-1-yl)-1-vinylcyclopentyl)methoxy)dimethylsilane 381 (404 mg, 0.92 mmol, 1.0 eq) in acetone (70 mL) and H₂O (14 mL) was added osmium tetroxide (2.5 %w in t-BuOH, 0.94 mL, 92.1 µmol, 0.1 eq) and N-methyl morpholine oxide (324 mg, 2.76 mmol, 3.0 eq) and the reaction mixture stirred at room temperature overnight. The reaction was quenched with Na₂S₂O₃ aq., sat. (21 mL) and the aqueous phase extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated *in vacuo*. Purification by column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether gave rac-5-((1R,2R)-1-((tert-butyldimethylsilyl)oxy)-2-((tert-butyldimethylsilyl)oxy)methyl)-2-vinylcyclopentyl)pentane-1,2-diol SI-8 (407 mg, 0.86 mmol, 94%) as a colourless oil.

νₘₚₑₓₙ (neat)/cm⁻¹ 3372 (br. OH), 2953, 2929, 2885, 2856, 1471, 1463, 1254, 1093, 1005, 910, 835, 773, 666;

**¹H NMR** (400 MHz, CDCl₃) δ ppm 0.01 (3 H, s, SiCH₃), 0.01 (3 H, s, SiCH₃), 0.10 (3 H, s, SiCH₃), 0.12 (3 H, s, SiCH₃), 0.87 (9 H, s, 3 × CCH₃), 0.90 (9 H, s, 3 × CCH₃), 1.31 - 1.87 (12 H, m, 6 × CH₂), 3.43 (1 H, ddd, J = 11.0, 7.6, 1.5 Hz, 1 H from CH₂OH), 3.58 (1 H, dd, J = 9.6, 1.3 Hz, 1 H from CH₂OSi), 3.66 (1 H, ddd, J = 11.0, 3.0, 0.8 Hz, 1 H from CH₂OH), 3.68 - 3.75 (1 H, m, CHOH), 3.78 (1 H, d, J = 9.6 Hz, 1 H from CH₂OSi), 4.99 - 5.11 (2 H, m, CH=CH₂), 5.93 (1 H, ddd, J = 17.5, 11.0, 1.5 Hz, CH=CH₂);
\[^{13}\text{C NMR}\ (100\ \text{MHz, CDCl}_3)\ \delta\ \text{ppm}\ -5.5\ (\text{SiCH}_3),\ -5.3\ (\text{SiCH}_3),\ -2.4\ (\text{SiCH}_3),\ -2.1\ (\text{SiCH}_3),\ 18.3\ (\text{SiC}^6),\ 18.8\ (\text{SiC}^6),\ 19.4\ (\text{CH}_2),\ 20.5\ (\text{CH}_2),\ 25.6\ (\text{CCH}_3),\ 25.8\ (\text{CCH}_3),\ 25.9\ (2\ \times\ \text{CCH}_3),\ 26.0\ (2\ \times\ \text{CCH}_3),\ 30.1\ (\text{CH}_2),\ 34.1\ (\text{CH}_2),\ 36.5\ (\text{CH}_2),\ 38.3\ (\text{CH}_2),\ 58.2\ (\text{C}^6),\ 66.1\ (\text{CH}_2\text{OSi}),\ 66.8\ (\text{CH}_2\text{OH}),\ 72.1\ (\text{CHOH}),\ 87.5\ (\text{C}^6),\ 113.6\ (\text{CH}═\text{CH}_2),\ 141.8\ (\text{CH}═\text{CH}_2);\]

\[^{13}\text{C NMR}\ (100\ \text{MHz, CDCl}_3)\ \delta\ \text{ppm}\ -5.5\ (\text{SiCH}_3),\ -5.3\ (\text{SiCH}_3),\ -2.4\ (\text{SiCH}_3),\ -2.1\ (\text{SiCH}_3),\ 18.3\ (\text{SiC}^6),\ 18.8\ (\text{SiC}^6),\ 19.4\ (\text{CH}_2),\ 20.5\ (\text{CH}_2),\ 25.6\ (\text{CCH}_3),\ 25.8\ (\text{CCH}_3),\ 25.9\ (2\ \times\ \text{CCH}_3),\ 26.0\ (2\ \times\ \text{CCH}_3),\ 30.1\ (\text{CH}_2),\ 34.1\ (\text{CH}_2),\ 36.5\ (\text{CH}_2),\ 38.3\ (\text{CH}_2),\ 58.2\ (\text{C}^6),\ 66.1\ (\text{CH}_2\text{OSi}),\ 66.8\ (\text{CH}_2\text{OH}),\ 72.1\ (\text{CHOH}),\ 87.5\ (\text{C}^6),\ 113.6\ (\text{CH}═\text{CH}_2),\ 141.8\ (\text{CH}═\text{CH}_2);\]

\[m/z\ (\text{ES}−)\ 439\ ((M − H), 100\%),\ 440\ (37),\ 507\ (60).\ \text{(Found:}\ (M − H)\ 439.3050.\ \text{C}_{24}\text{H}_{47}\text{O}_3\text{Si}_2\text{Na requires}\ M,\ 439.3069).\]
To a stirred solution of rac-4-((1R,2R)-1-((tert-butylidimethylsilyl)oxy)-2-((tert-butylidimethylsilyl)oxy)methyl)-2-vinylcyclopentyl)butanoic acid 404 in acetonitrile (2.5 mL), t-BuOH (2.5 mL) and 2-methyl-2-buten (2.5 mL) was added NaClO₂ (224 mg, 2.47 mmol, 10 eq) and Na₂HPO₄·H₂O (463 mg, 2.97 mmol, 12 eq) in H₂O (2.5 mL) dropwise and the reaction mixture stirred at room temperature overnight. The reaction was diluted with H₂O (5.0 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40-60 °C) gave rac-4-((1R,2R)-1-((tert-butylidimethylsilyl)oxy)-2-((tert-butylidimethylsilyl)oxy)methyl)-2-vinylcyclopentyl)butanoic acid 404 (113 mg, 0.25 mmol, quantitative) as a colourless oil.

νmax (neat)/cm⁻¹ 3079 (br. OH), 2956, 2929, 2878, 2857, 1712 (C=O), 1470, 1458, 1413, 1386, 1359, 1255, 1090, 1060, 1003, 911, 833, 770, 668;

¹H NMR (400 MHz, CDCl₃) δ ppm 0.00 (3 H, s, SiCH₃), 0.01 (3 H, s, SiCH₃), 0.11 (3 H, s, SiCH₃), 0.12 (3 H, s, SiCH₃), 0.87 (9 H, s, 3 × CH₃), 0.90 (9 H, s, 3 × CH₃), 1.47 - 1.86 (10 H, m, 5 × CH₂), 2.29 (2 H, t, J = 6.8 Hz, CH₂COOH), 3.57 (1 H, d, J = 9.6 Hz, 1 H from CH₂OSi), 3.79 (1 H, d, J = 9.6 Hz, 1 H from CH₂OSi), 5.00 - 5.11 (2 H, m, CH=CH₂), 5.93 (1 H, dd, J = 17.5, 11.0 Hz, CH=CH₂);

¹³C NMR (100 MHz, CDCl₃) δ ppm −5.5 (SiCH₃), −5.4 (SiCH₃), −2.4 (SiCH₃), −2.2 (SiCH₃), 18.2 (C⁹), 18.8 (C⁹), 19.4 (CH₂), 20.1 (CH₂), 25.9 (3 × CCH₃), 26.0 (3 × CCH₃), 30.0 (CH₂), 34.6 (CH₂COOH), 36.5 (CH₂), 37.7 (CH₂), 58.2 (C⁹), 66.0 (CH₂OSi), 87.3 (C⁹), 113.8 (CH=CH₂), 141.5 (CH=CH₂), 178.7 (C=O);

m/z (ES⁺) 195 (16%), 209 (33), 235 (20), 288 (23), 479 ((M + Na), 100), 481 (35). (Found: (M + Na) 479.2982. C₂₄H₄₈O₄Si₂Na requires M, 479.2984).
**rac-Methyl 4-((1R,2R)-1-(((tert-butyldimethylsilyl)oxy)methyl)-2-vinylcyclopentyl)butanoate (405)**

To a stirred solution of **rac-4-((1R,2R)-1-(((tert-butyldimethylsilyl)oxy)methyl)-2-vinylcyclopentyl)butanoic acid 404** (134 mg, 0.29 mmol, 1.0 eq) in MeOH (3.0 mL) at 0 °C was added trimethylsilyldiazomethane (2 M in hexane, 0.29 mL, 0.58 mmol, 2.0 eq) dropwise and the reaction mixture stirred at room temperature for 1 hour, then concentrated *in vacuo*. Purification by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave **rac-methyl 4-((1R,2R)-1-(((tert-butyldimethylsilyl)oxy)methyl)-2-vinylcyclopentyl)butanoate 405** (122 mg, 0.26 mmol, 88%) as a colourless oil.

**νmax (neat)/cm⁻¹** 2953, 2982, 2885, 2856, 1743 (C=O), 1476, 1458, 1360, 1253, 1169, 1091, 1064, 1005, 911, 833, 771, 667;

**¹H NMR** (400 MHz, CDCl₃) δ ppm 0.00 (3 H, s, SiCH₃), 0.01 (3 H, s, SiCH₃), 0.11 (3 H, s, SiCH₃), 0.12 (3 H, s, SiCH₃), 0.87 (9 H, s, 3 × CCH₃), 0.90 (9 H, s, 3 × CCH₃), 1.46 - 1.88 (10 H, m, 5 × CH₂), 2.22 - 2.28 (2 H, m, CH₂COOCH₃), 3.57 (1 H, d, J = 9.6 Hz, 1 H from CH₂O), 3.67 (3 H, s, OCH₃), 3.79 (1 H, d, J = 9.6 Hz, 1 H from CH₂O), 4.99 - 5.11 (2 H, m, CH=CH₂), 5.93 (1 H, dd, J = 17.5, 11.0 Hz, CH=CH₂);

**¹³C NMR** (100 MHz, CDCl₃) δ ppm −5.5 (SiCH₃), −5.4 (SiCH₃), −2.4 (SiCH₃), −2.2 (SiCH₃), 18.2 (Cᵣ), 18.8 (Cᵣ), 19.4 (CH₂), 20.3 (CH₂), 25.9 (3 × CCH₃), 26.0 (3 × CCH₃), 30.1 (CH₂), 34.8 (CH₂COOCH₃), 36.5 (CH₂), 37.8 (CH₂), 51.4 (OCH₃), 58.2 (Cᵣ), 66.0 (CH₂O), 87.3 (Cᵣ), 113.7 (CH=CH₂), 141.6 (CH=CH₂), 174.0 (C=O);

**m/z** (ES⁺) 493 ((M + Na), 100%), 495 (16). (Found: (M + Na) 493.3149. C₂₅H₅₀O₄Si₂Na requires M, 493.3140).

**rac-4-((1R,2R)-1-(((tert-Butyldimethylsilyl)oxy)methyl)-2-vinylcyclopentyl)butan-1-ol (421)**

To a stirred solution of **rac-4-((1R,2R)-1-(((tert-butyldimethylsilyl)oxy)methyl)-2-vinylcyclopentyl)butanal (350 mg, 0.79 mmol, 1.0 eq) in**
MeOH (8.0 mL) at 0 °C was added sodium borohydride (60 mg, 1.59 mmol, 2.0 eq) and the reaction mixture stirred at 0 °C for 15 minutes. The reaction was quenched with H$_2$O (10 mL) and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried (Na$_2$SO$_4$ or MgSO$_4$) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with a gradient 10-20% ethyl acetate in petroleum ether (40-60 °C) gave rac-4-(((1R,2R)-1-((tert-butyldimethylsilyl)oxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-2-vinylcyclopentyl)butan-1-ol 421 (262 mg, 0.59 mmol, 74%) as a colourless oil.

$\nu_{\text{max}}$ (neat)/cm$^{-1}$ 3327 (br. OH), 2953, 2931, 2886, 2858, 1467, 1253, 1070, 1006, 911, 835, 772, 667;

$^1$H NMR (500 MHz, CDCl$_3$) δ ppm 0.01 (3 H, s, SiCH$_3$), 0.01 (3 H, s, SiCH$_3$), 0.10 (3 H, s, SiCH$_3$), 0.11 (3 H, s, SiCH$_3$), 0.87 (9 H, s, 3 × C$_C$H$_3$), 0.87 (9 H, s, 3 × C$_C$H$_3$), 1.30 - 1.86 (12 H, m, 6 × CH$_2$), 3.59 (1 H, d, $J = 9.6$ Hz, 1 H from CH$_2$OSi), 3.63 (2 H, t, $J = 6.5$ Hz, CH$_2$OH), 3.79 (1 H, d, $J = 9.6$ Hz, 1 H from CH$_2$OSi), 5.03 (1 H, dd, $J = 17.6, 1.5$ Hz, 1 H from CH=CH$_2$), 5.08 (1 H, dd, $J = 11.0, 1.5$ Hz, 1 H from CH=CH$_2$), 5.93 (1 H, dd, $J = 17.6, 11.0$ Hz, CH=CH$_2$);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ ppm −5.5 (SiCH$_3$), −5.3 (SiCH$_3$), −2.4 (SiCH$_3$), −2.1 (SiCH$_3$), 18.2 (C$^6$), 18.8 (C$^6$), 19.4 (CH$_2$), 20.7 (CH$_2$), 25.9 (3 × C$_C$H$_3$), 26.1 (3 × C$_C$H$_3$), 30.2 (CH$_2$), 33.7 (CH$_2$CH$_2$OH), 36.6 (CH$_2$), 39.1 (CH$_2$), 58.3 (C$^6$), 62.9 (CH$_2$OH), 66.1 (CH$_2$OSi), 87.6 (C$^6$), 113.6 (CH=CH$_2$), 141.8 (CH=CH$_2$);

m/z (ES+) 311 (91%), 312 (100), 460 (30), 465 ((M + Na), 86), 466 (61). (Found: (M + Na) 465.3187. C$_{24}$H$_{50}$O$_3$Si$_2$Na requires $M$, 465.3191).

![TBDPSO](image)

rac-(1S,2R)-2-(3-((tert-Butyldiphenylsilyl)oxy)propyl)-2-((triethylsilyl)oxy)-1-vinylcyclopentane-carbaldehyde (437)

To a stirred solution of oxalyl chloride (22 µL, 0.26 mmol, 1.5 eq) in CH$_2$Cl$_2$ (1.7 mL) at −78 °C was added DMSO (37 µL, 0.51 mmol, 3.0 eq) dropwise and the reaction mixture stirred at −78 °C for 30 minutes. rac-tert-Butyldiphenyl(3-((1R,2R)-1-((triethylsilyl)oxy)-2-(((triethylsilyl)oxy)methyl)-2-vinylcyclopentyl)propoxy)silane (114 mg, 0.17 mmol, 1.0 eq) in CH$_2$Cl$_2$ (0.5 mL) was added dropwise at −78 °C and the reaction mixture stirred at −78 °C for 20 minutes, then at −45 °C for 20 minutes. Triethylamine (72 µL, 0.51 mmol,
3.0 eq) was added dropwise at −78 °C and the reaction mixture stirred at room temperature for 1 hour. H₂O (2.0 mL) was added and the aqueous phase extracted with CH₂Cl₂ (2.0 mL). The combined organic phases were then dried (Na₂SO₄ or MgSO₄) and concentrated in vacuo. Purification by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether (40-60 °C) gave rac-(1S,2R)-2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2-((triethylsilyl)oxy)-1-vinylcyclopentane carbaldehyde 437 (66 mg, 0.12 mmol, 70%) as a light yellow oil.

ν max (neat)/cm⁻¹ 3068, 2954, 2875, 2731, 1719 (C=O), 1472, 1458, 1428, 1389, 1313, 1237, 1106, 1089, 1003, 920, 823, 734, 725, 700, 613; 

¹H NMR (400 MHz, CDCl₃) δ ppm 0.54 (2 H, q, J = 7.9 Hz, SiCH₂), 0.63 (4 H, q, J = 7.9 Hz, 2 × SiCH₂), 0.95 (3 H, t, J = 7.9 Hz, CH₂CH₃), 0.96 (6 H, t, J = 7.9 Hz, 2 × CH₂CH₃), 1.07 (9 H, s, 3 × CCH₃), 1.56 - 1.99 (9 H, m, 9 H from CH₂), 2.37 - 2.50 (1 H, m, 1 H from CH₂), 3.59 - 3.70 (2 H, m, CH₂O), 5.11 (1 H, dd, J = 17.7, 1.0 Hz, 1 H from CH=CH₂), 5.25 (1 H, dd, J = 11.0, 1.0 Hz, 1 H from CH=CH₂), 6.08 (1 H, dd, J = 17.7, 11.0 Hz, CH=CH₂), 7.36 - 7.47 (6 H, m, 6 × ArH), 7.64 - 7.72 (4 H, m, 4 × ArH), 9.82 (1 H, s, HC=O);

¹³C NMR (100 MHz, CDCl₃) δ ppm 6.4 (SiCH₂), 6.5 (2 × SiCH₂), 6.8 (CH₂CH₃), 7.1 (2 × CH₂CH₃), 19.2 (C⁰), 20.8 (CH₂), 26.8 (3 × CCH₃), 27.6 (CH₂), 28.7 (CH₂), 34.6 (CH₂), 38.8 (CH₂), 64.1 (CH₂O), 66.6 (C⁰), 90.4 (C⁰), 116.2 (CH=CH₂), 127.6 (4 × ArCH), 129.5 (2 × ArCH), 133.8 (ArC⁰), 133.8 (ArC⁰), 135.6 (4 × ArCH), 136.3 (CH=CH₂), 204.5 (C=O);

m/z (ES+) 454 (20%), 568 (100), 569 (73), 573 ((M + Na), 69), 574 (66), 597 (50), 598 (29), 611 (23). (Found: (M + Na) 573.3198. C₃₃H₅₀O₃Si₂Na requires M, 573.3191).

rac-3-((3aS,6aR)-2-Methoxy-3a-vinylhexahydro-2H-cyclopenta[b]furan-6a-yl)propan-1-ol (440)

To a stirred solution of rac-2-((1S,2R)-2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-2-((triethylsilyl)oxy)-1-vinylcyclopentyl) acetaldehyde 438 (65 mg, 0.11 mmol, 1.0 eq) in MeOH (1.1 mL) was added acetyl chloride (40 µL, 0.56 mmol, 5.0 eq) dropwise and the reaction mixture stirred at room temperature overnight. The reaction was quenched with NaHCO₃ aq. sat. (2.0 mL) and the aqueous phase extracted with CH₂Cl₂ (3 × 2.0 mL). The
combined organic phases were dried (Na₂SO₄ or MgSO₄) and concentrated in *vacuo*. Purification by column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether (40-60 °C) gave *rac*-3-((3aS,6aR)-2-methoxy-3a-vinylhexahydro-2H-cyclopenta[b]furan-6a-yl)propan-1-ol **440** (17.3 mg, 76.4 µmol, 68%) as a colourless oil and as a single diastereoisomer.

ν<sub>max</sub> (neat)/cm<sup>-1</sup> 3455 (br. OH), 3082, 2948, 2872, 1636, 1441, 1376, 1321, 1287, 1243, 1200, 1126, 1100, 1051, 1004, 959, 911, 807, 762, 674;

<sup>1</sup>H NMR (500 MHz, CDCl₃) δ ppm 1.50 - 1.85 (9 H, m, 9 H from CH₂), 1.90 - 1.96 (1 H, m, 1 H from CH₂), 1.99 (1 H, dd, J = 13.5, 4.8 Hz, 1 H from CH₂CH), 2.38 (1 H, dd, J = 13.5, 0.6 Hz, 1 H from CH₂CH), 3.49 (3 H, s, CH₃), 3.64 - 3.70 (1 H, m, 1 H from CH₂OH), 3.83 - 3.89 (1 H, m, 1 H from CH₂OH), 5.05 (1 H, dd, J = 10.7, 0.9 Hz, 1 H from CH=CH₂), 5.13 (1 H, dd, J = 17.3, 0.9 Hz, 1 H from CH=CH₂), 5.44 (1 H, d, J = 4.8 Hz, CH), 6.07 (1 H, dd, J = 17.3, 10.7 Hz, CH=CH₂);

<sup>13</sup>C NMR (125 MHz, CDCl₃) δ ppm 22.3 (CH₂), 27.7 (CH₂), 33.5 (CH₂), 40.5 (CH₂), 42.3 (CH₂), 48.5 (CH₂CH), 50.8 (CH₃), 56.9 (C<sup>q</sup>), 62.7 (CH₂OH), 99.5 (C<sup>q</sup>), 100.6 (CH), 112.3 (CH=CH₂), 142.4 (CH=CH₂);

m/z (ES+) 101 (19%), 145 (27), 195 (20), 249 ((M + Na), 100), 250 (21). (Found: (M + Na) 249.1452. C₁₃H₂₂O₃Na requires M, 249.1462).

### 7. X-ray crystal structures

X-ray crystal structure of *rac*-((1R,2S,3S)-3-benzyl-1-(cyclohexylmethyl)-2-hydroxycyclopentanecarboxylic acid (201)
### Crystal data

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### Data collection

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### Refinement

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X-ray crystal structure of \textit{rac-}(3S,3aR,4S,6aS)-3-benzyl-4-(2,4-
dichlorobenzyl)hexahydro-3a,6a-(epoxymethano)pentalen-7-one (273)

\textit{Crystal data}

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X-ray crystal structure of rac-(1S,3aS,7aS,E)-7-benzylidene-1-(2,4-dichlorobenzyl)-7a-hydroxyoctahydro-1H-indene-3a-carboxylic acid (263n)

**Crystal data**

- Chemical formula: C_{24}H_{24}Cl_{2}O_{3}
- $M_r$: 431.33
- Crystal system, space group: Triclinic, $P \bar{1}$
- Temperature (K): 100
- $a$, $b$, $c$ (Å): 11.3127 (12), 11.5028 (12), 17.0515 (18)
- $\alpha$, $\beta$, $\gamma$ (°): 76.160 (2), 74.987 (2), 81.589 (2)
- $V$ (Å$^3$): 2072.5 (4)
- $Z$: 4
- Radiation type: Mo Kα
- $\mu$ (mm$^{-1}$): 0.34
- Crystal size (mm): 0.31 × 0.25 × 0.24

**Data collection**

- Diffractometer: CCD area detector diffractometer
- Absorption correction: –
- No. of measured, independent and observed [$I > 2\sigma(I)$] reflections: 18048, 9412, 8084
- $R_{int}$: 0.032
- $(\sin \theta/\lambda)_{\text{max}}$ (Å$^{-1}$): 0.665

**Refinement**

- $R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, $S$: 0.044, 0.107, 1.05
- No. of reflections: 9412
- No. of parameters: 527
X-ray crystal structure of rac-(5S,6R)-6-hydroxy-5-(4-methoxyphenethyl)-1,3-dimethylidihydropyrimidine-2,4(1H,3H)-dione (286e)

Crystal data
Chemical formula C_{15}H_{20}N_{2}O_{4}
Mr 292.33
Crystal system, space group Monoclinic, $P2_1/c$
Temperature (K) 100
$a$, $b$, $c$ (Å) 9.9234 (8), 11.5741 (8), 25.7812 (19)
$\beta$ (°) 92.474 (5)
$V$ (Å$^3$) 2958.3 (4)
$Z$ 8
Radiation type Cu $K\alpha$
$\mu$ (mm$^{-1}$) 0.79
Crystal size (mm) 0.22 × 0.19 × 0.06

Data collection
Diffractometer Bruker APEX-II CCD diffractometer
Absorption correction Multi-scan SADABS
$T_{\text{min}}$, $T_{\text{max}}$ 0.623, 0.954
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections 11362, 5181, 4254

Refinement
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, $S$ 0.055, 0.149, 1.03
No. of reflections 5181
No. of parameters 387
No. of restraints 0
H-atom treatment H-atom parameters constrained
$\Delta \rho_{\text{max}}, \Delta \rho_{\text{min}}$ (e Å$^{-3}$) 0.32, -0.37

X-ray crystal structure of rac-(4aS,7aS,E)-7a-hydroxy-4a-isobutyl-1,3-dimethyl-7-((trimethylsilyl)methylene)tetrahydro-1H-cyclopenta[d]pyrimidine-2,4(3H,4aH)-dione (300k)

Crystal data

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</tr>
<tr>
<td>Crystal system, space group</td>
<td>Monoclinic, $P2_1/c$</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>100</td>
</tr>
<tr>
<td>$a$, $b$, $c$ (Å)</td>
<td>24.0386 (14), 17.4493 (11), 18.3975 (13)</td>
</tr>
<tr>
<td>$\alpha$, $\beta$, $\gamma$ (°)</td>
<td>90, 90, 90</td>
</tr>
<tr>
<td>$V$ (Å$^3$)</td>
<td>7717.0 (9)</td>
</tr>
<tr>
<td>$Z$</td>
<td>16</td>
</tr>
<tr>
<td>Radiation type</td>
<td>Cu $K\alpha$</td>
</tr>
<tr>
<td>$\mu$ (mm$^{-1}$)</td>
<td>1.20</td>
</tr>
<tr>
<td>Crystal size (mm)</td>
<td>$0.18 \times 0.13 \times 0.07$</td>
</tr>
</tbody>
</table>
**Data collection**

Diffractometer

- Bruker APEX-II CCD diffractometer

Absorption correction

- Multi-scan SADABS

$T_{\text{min}}$, $T_{\text{max}}$

- 0.629, 0.921

No. of measured, independent and observed [$I > 2\sigma(I)$] reflections

- 13438, 13438, 7400

$R_{\text{int}}$

- 0.0000

$(\sin \theta/\lambda)_{\text{max}}$ (Å$^{-1}$)

- 0.609

**Refinement**

$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, $S$

- 0.091, 0.278, 0.98

No. of reflections

- 13438

No. of parameters

- 862

No. of restraints

- 0

H-atom treatment

- H-atom parameters constrained

$\Delta \rho_{\text{max}}$, $\Delta \rho_{\text{min}}$ (e Å$^{-3}$)

- 0.55, -0.62
References


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(178) Ling, V. Cancer 1992, 69, 2603.


