1-Bromo-1-lithioethene as a building block for organic synthesis

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by

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LIST OF ABBREVIATIONS AND DEFINITIONS

<table>
<thead>
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<th>Definition</th>
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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2’-azobisisobutyronitrile</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>boc</td>
<td>tert-butyloxy carbonyl</td>
</tr>
<tr>
<td>br</td>
<td>broad (spectral)</td>
</tr>
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<td>9-BBN</td>
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</tr>
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<td>δ</td>
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</tr>
<tr>
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</tr>
<tr>
<td>DEAD</td>
<td>diethyldiazo dicarboxylate</td>
</tr>
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<td>DIBAH</td>
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</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>ds</td>
<td>diastereoselectivity</td>
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<td>ee</td>
<td>enantiomeric excess</td>
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<td>MEM</td>
<td>CH$_2$OCH$_2$CH$_2$OCH$_2$- protecting group</td>
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<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
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</table>
ppm  parts per million
i-Pr  isopropyl
q  quartet
Rf  retention factor
rt  room temperature
RTD  resistance temperature detector (a coil from platinum wire which resistance is strongly and reproducibly dependent on temperature)
s  singlet
SCF  self consistent field
SEM  Me₃SiCH₂CH₂OCH₂- protecting group
t  triplet
TBAF  tetrabutylammonium fluoride
TFA  trifluoroacetyl
THF  tetrahydrofuran
THP  tetrahydropyran
Ts  tosyl
TS  transition state
Chapter 1. Introduction

1.1. Why 1-bromo-1-lithioethene?

One of the most widely used ways to provide a site of reactivity in organic molecules is to induce a partial charge on a carbon atom by introducing an electropositive (e.g. metal) or electronegative (e.g. halogen) element (Fig. 1).

Fig. 1 Ways to induce a partial charge on a carbon atom

This technique allows for the creation of a reaction center within the molecule which subsequently allows the use of this molecule as a building block to synthesize complex target structures. However, in most cases, a simple building block with only one reaction center can only be only used to introduce a side (capping) substituent to the molecule being built. It is obvious that the more different reacting centers a building block has, the more versatile and flexible it becomes. There is also another trend: smaller building blocks can potentially be used for the synthesis of a wider variety of target molecules. In other words, it seems attractive to introduce as many potential reaction centers as possible in the smallest molecule. But what would happen if two different kinds of substituents were attached to the same carbon (as in the molecule 1, Fig. 2)? Nature has shown that the intuitive answer “the effect of an electropositive element would cancel or at least weaken the effect of an electronegative element” is not correct. Besides the very strong
propensity to fragment to metal halide and carbene, much of the known chemistry of such compounds takes advantage of both potential reaction centers.\(^1\)

**Fig. 2. Reactivity of dichloromethyllithium (1)**

For example, chloromethyllithium and dichloromethyllithium (1) were successfully used as two-reaction-center building blocks in the relatively recent synthesis of *serricornin* – a pheromone of the cigarette beetle.\(^2\)

However, there are some limitations in the usage of the building blocks described above besides the formation of carbenes. When \(\alpha\)-haloalkyllithium 2 reacted with aldehydes or ketones (the most common electrophiles), the \(\beta\)-halo alcohol 3 obtained are often insufficiently reactive toward common nucleophiles to be further functionalized. Also, 3 is not a very good substrate for many other transformations, including Pd\(^{0}\) catalyzed C-C bond formation (Scheme 1). Transition metal catalyzed cross coupling is best achieved starting from alkenyl, alkynyl or allyl halides for two reasons: (i) the initial
formation of a metal – olefin $\pi$ complex which leads to a metal insertion product and greatly accelerates the overall reaction is only possible when alkenyl, alkynyl or allyl halide is used, and, more importantly, (ii) the metal insertion product obtained formed from Pd$^{0}$ insertion into alkyl halides is often very unstable due to metal hydride $\beta$-elimination. This latter reaction is typically so fast that no coupled products can be obtained from alkyl halides$^3$. (Recently some advances were made in the area of cross coupling of alkyl halides. However, special catalysts must be used to achieve such coupling while conditions proposed do not seem general enough$^4$)

Scheme 1. Potential synthetic utility of 1-halo-1-lithioalkanes

$$\text{Cl} - \text{C} - \text{Li} \quad + \quad \text{O} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \quad \text{Cl} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \quad \text{Nu} \quad \text{Nu}^- \quad \text{OH} \quad \text{OH}$$

difficult transformation

In addition, alkoxide derivatives of $\beta$-halo alcohols 3 are prone to epoxide formation. In some cases this secondary reaction is so fast that the isolation of the corresponding $\beta$-halo alcohol becomes difficult (e.g., Scheme 2).$^5$ Frequently, the further elaboration of such epoxides is difficult because of regioselectivity issues.

Scheme 2. Epoxide formation during the reaction of 1-bromo-1-lithioethane with an aldehyde
This type of chemical behavior seriously decreases the synthetic value of α-halo-α-lithioalkanes (such as 2) as building blocks in organic synthesis. However, if the halo atom in 2 was attached to an $sp^2$ hybridized carbon instead of an $sp^3$ hybridized carbon, many possibilities would be opened up for subsequent utilization of this halide atom including Ni$^{(0)}$-catalyzed, Pd$^{(0)}$-catalyzed and Nozaki-Kishi coupling. Undesirable epoxide formation (Scheme 2) also would be greatly suppressed due to the lack of reactivity of vinyl halides toward nucleophilic substitution. (It is important to note that only Cl, Br or I halo atoms would be useful in such building blocks. Fluorine substituents are usually not reactive enough to permit further elaboration through such coupling processes. Hence, 1-fluoro-1-lithioalkenes and their equivalents will not be considered herein.)

The simplest type of substrate which possesses all the required features to behave as a small, highly functionalized building block for organic synthesis is a 1-halo-1-lithioethene. Such compounds contain only two carbon atoms but, at the same time, have three potential reaction centers: a nucleophilic C-Li bond, an electrophilic C-Hal bond and a carbon – carbon double bond.

1.2. Published precedents of 1-halo-1-lithioalkene syntheses

1-Chloro-1-lithioethene (4) was synthesized by Köbrich in 1965 by direct deprotonation of chloroethene with $n$-BuLi at –110 to –108 °C (Scheme 3). The unstable 4 was trapped in situ with carbon dioxide in excellent yield. To achieve the required
temperature, a methylcyclohexane / liquid nitrogen cooling bath was used.

Scheme 3. Generation of 1-chloro-1-lithioethene (4)

\[
\begin{align*}
\text{Cl} & \quad n\text{-BuLi} \quad \text{THF:ether:pentane} \quad \text{4 : 1 : 1} \quad -110^\circ\text{C} \\
\text{Cl} & \quad \text{Li} \quad \text{Cl} \quad \text{4} \quad -110^\circ\text{C} \quad 99\%
\end{align*}
\]

Surprisingly, very few subsequent groups have further explored the synthetic utility of 4 (see below). The presence of the double bond in such building blocks makes compounds of general structure 5 susceptible to undesired Fritsch-Buttenberg-Wiechell rearrangement,\(^{12}\) which destroys much of the useful functionality in affording an internal alkyne (Scheme 4).

Scheme 4. An example of Fritsch-Buttenberg-Wiechell rearrangement

\[
\begin{align*}
\text{5} & \quad \text{-LiHal} \\
\text{6} & \quad \text{5}
\end{align*}
\]

It is known that, generally, 1-halo-1-lithioethenes exhibit carbanionic - type reactivity at temperatures below \(-90^\circ\text{C}\) while, above this temperature, carbenoid behavior becomes dominant.\(^{13}\) Also, the stability of these compounds was greatly enhanced when \(1^R\) (a substituent trans to the halogen) was a carbon atom,\(^{1,14}\) allowing the generation and use of such \((E)\)-1-halo-1-lithioalkenes at \(-80\) to \(-40^\circ\text{C}\) (Fig. 3). Because of this trend, the most information available in this area is concerned with compounds 5
with at least $^1R$ (or both $^1R$ and $^2R$) being carbon-based substituents.

Fig. 3. An example of different stabilities of monosubstituted 1-chloro-1-lithioethenes

\[
\begin{align*}
\text{Ph} & \quad \text{Li} \quad \text{Cl} \\
\quad & \quad -60 \degree C \quad - \text{LiCl} \\
\quad & \quad \text{Ph} \quad \text{Li} \quad \text{Cl} \\
\quad & \quad -110 \degree C \quad - \text{LiCl}
\end{align*}
\]

Carbanionic-type behavior of substituted 1-halo-1-lithioalkenes is well documented in the literature. The reactivity of these compounds is reported to be similar to simple organolithiums with the exception of their reaction with protected $\alpha$-hydroxy-aldehydes.

Scheme 5. Anti- diastereoselectivity of 1-bromo-1-alkenyllithium addition to MEM-protected lactaldehyde

While simple organolithiums and organomagnesiums react with these electrophiles providing syn- products, as predicted by Cram’s cyclic model, 1-bromo-1-lithioalkenes form anti- adducts as predicted by the Felkin-Anh model. While high levels of diastereoselectivity (10:1 to 100:1) are typical for carbonyl addition reactions
that proceed via the chelated mode of addition (Cram’s model), the non-chelated mode (Felkin-Anh model) rarely gives diastereomeric ratios better than 1:5.\textsuperscript{15} In contrast, 1-bromo-1-lithioalkenes often provide very high diastereomeric ratio of adducts via the non-chelated mode. For example, 1-bromo-2,2-dimethyl-1-lithioethene reacted with MEM-protected lactaldehyde with the formation of the corresponding anti-adduct resulting from Felkin-Anh control in a 92:8 diastereomeric ratio\textsuperscript{18} (Scheme 5)!

Scheme 6. Some selective reactions of 1,1-disubstituted versus 1,1,2-trisubstituted double bonds

Although much less is known about 1-halo-1-lithioethenes (5, $^1$R and $^2$R = H), such molecules have considerably more potential than other 1-halo-1-lithioalkenes 5 ($^1$R and $^2$R $\neq$ H) as building blocks for organic synthesis. If one is introducing several reaction centers into a molecule, these centers must have different reactivities to allow for selective reactions later in the sequence. In the case of 5 ($^1$R and $^2$R = H), product alkenes
having one end of the double bond crowded while the other is easily accessible allows for high regioselectivity in subsequent transformations (Scheme 6). The same transformations would be quite difficult to perform selectively for tri- or tetra-substituted alkenes.

In spite of their potential utility, there is very little known about unsubstituted 1-halo-1-lithioethenes, especially about their chemical behavior. Apart from the original Köbrich report\(^\text{11}\) (where only one reaction of 1-chloro-1-lithioethene (4) with CO\(_2\) was described), there is only one more publication where a 1-halo-1-lithioethene was prepared separately and then reacted with an electrophile (Scheme 7).\(^\text{19}\)

**Scheme 7. Reported preparation and trapping of 1-iodo-1-lithioethene**

![Scheme 7](image)

The amount of electrophile used (5 eq!) along with low yields (10 – 40%; in addition it was not reported if these were isolated or \(^1\)H NMR yields and no details were provided) does not render the method attractive for preparative synthesis.

**Scheme 8. Generation and trapping of 4 in the presence of a zirconium electrophile**

![Scheme 8](image)

Interestingly, the trapping with benzophenone, which is a non-enolizable ketone,
seems to be the single reported precedent of a reaction of 1-halo-1-lithioethenes with a carbonyl compound.

In two other cases, 1-chloro- and 1-bromo-1-lithioethenes were generated already in the presence of an electrophile. This means that the electrophile used must be unreactive toward the strong base needed to generate the 1-halo-1-lithioethene, which severely limits the synthetic utility of the corresponding organometallic reagent. 1-Chloro-1-lithioethene (4) was generated in this way in the presence of a zirconium-based electrophile (Scheme 8). However, in these reactions, the stability of the intermediate 4 could not be estimated directly because of the nature of the trapping reaction and high reaction temperature. It is unclear if ethenyl carbene was formed first and then inserted into the carbon-zirconium bond, or if the reaction went through an “ate” complex (Scheme 9).

In the second example 1-bromo-1-lithioethene (7) was generated in the presence of Me₃SiCl which allowed for formation of 60% of the expected silylated product along with 7% of ethynyltrimethylsilane (Scheme 10).
Scheme 10. The single reported case of 1-bromo-1-lithioethene formation and trapping with Me$_3$SiCl

Again, this single reaction was possible only because Me$_3$SiCl is not reactive toward LDA below dry ice temperature. Base-sensitive electrophiles (such as enolizable carbonyl compounds) and other electrophiles reactive toward LDA are not compatible with this protocol.

Table 1. Available literature data for preparation and chemical behavior of 1-halo-1-lithioethenes

<table>
<thead>
<tr>
<th>entry</th>
<th>organometallic reagent obtained</th>
<th>electrophile used</th>
<th>ref.</th>
<th>yield %</th>
<th>Was the electrophile already present during the organometallic preparation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-chloro-1-lithioethene (4)</td>
<td>CO$_2$</td>
<td>11</td>
<td>100</td>
<td>no</td>
</tr>
<tr>
<td>2</td>
<td>1-iodo-1-lithioethene</td>
<td>I$_2$</td>
<td>19</td>
<td>25</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>1-iodo-1-lithioethene</td>
<td>Me$_3$SiCl</td>
<td>19</td>
<td>20</td>
<td>no</td>
</tr>
<tr>
<td>4</td>
<td>1-iodo-1-lithioethene</td>
<td>Bu$_3$SnCl</td>
<td>19</td>
<td>40</td>
<td>no</td>
</tr>
<tr>
<td>5</td>
<td>1-iodo-1-lithioethene</td>
<td>Ph$_2$C=O</td>
<td>19</td>
<td>10</td>
<td>no</td>
</tr>
<tr>
<td>6</td>
<td>1-chloro-1-lithioethene (4)</td>
<td>C$<em>{10}$H$</em>{21}$ZrCp$_2$Cl</td>
<td>20</td>
<td>38 (GC)</td>
<td>yes</td>
</tr>
<tr>
<td>7</td>
<td>1-chloro-1-lithioethene (4)</td>
<td>C$<em>{10}$H$</em>{19}$ZrCp$_2$Cl</td>
<td>20</td>
<td>55 (GC)</td>
<td>yes</td>
</tr>
<tr>
<td>8</td>
<td>1-bromo-1-lithioethene (7)</td>
<td>Me$_3$SiCl</td>
<td>21</td>
<td>60 (GC)</td>
<td>yes</td>
</tr>
</tbody>
</table>

The four references cited above represent all literature information available for 1-halo-1-lithioethenes (halo is Cl, Br or I here). In addition, only a very limited range of electrophiles were tested while yields seem quite unpredictable (Table 1).
In our opinion there are several reasons that have limited the development of 1-halo-1-lithioethenes as widespread preparative reagents to this point:

- At the time when 1-chloro-1-lithioethene (4) was initially reported (1965) there were no well developed tools to efficiently use alkenyl chlorides in organic synthesis. So the products that could be obtained from 4 did not seem synthetically interesting.

- The low temperature and the complex experimental procedure required for the synthesis of 1-halo-1-lithioethenes, in addition to the unpredictable yields reported, did not encourage chemists to use such reagents on a routine basis.

- The wrong early presumption that bromo- and iodoethenes would undergo halogen-metal exchange instead of deprotonation\(^1\) precluded use of these substances for the direct synthesis of 1-bromo- and 1-iodo-1-lithioethenes for a long time.

We decided to focus on the preparation of 1-bromo-1-lithioethene (7) and then examine the scope and limitations of this building block for organic synthesis. The bromo substituent was selected because of several practical considerations (Table 2).

**Table 2. Comparison of various 1-halo-1-lithioethenes from a practical standpoint**

<table>
<thead>
<tr>
<th>organometallic precursor</th>
<th>required</th>
<th>commercial availability of the precursor</th>
<th>physical property of the precursor</th>
<th>further usage of the products obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-chloro-1-lithioethene (4)</td>
<td>chloroethene(^a)</td>
<td>regulated substance $437 per 227g</td>
<td>gas, bp (-13) (^\circ)C; requires special technique to handle</td>
<td>difficult, C-Cl bond is often not reactive enough</td>
</tr>
<tr>
<td>1-bromo-1-lithioethene (7)</td>
<td>bromoethene(^a,b)</td>
<td>$84 per 900g</td>
<td>gas, bp +16 (^\circ)C; 35% solution in THF can be handled with common syringe techniques</td>
<td>easy</td>
</tr>
<tr>
<td>1-iodo-1-lithioethene</td>
<td>iodoethene</td>
<td>not available</td>
<td>unstable liquid</td>
<td>very easy</td>
</tr>
</tbody>
</table>

\(^a\) Aldrich. \(^b\) Fisher – Acros.
Because of the intrinsic instability of 1-halo-1-lithioethenes, their preparation must be followed with a suitable “trapping” step. This second step should occur much faster than the decomposition of the reagent. Because it is easier to displace lithium than the halogen atom in 1-halo-1-lithioethenes, the best choice for such a secondary reaction would be an electrophilic trapping.

Carbonyl compounds are the most frequently used electrophiles in reactions with various more traditional organolithiums in mainstream organic chemistry. If such electrophilic trapping were performed with 7, α-bromoallylic alcohols (8) would be obtained (Scheme 11). These adducts are potentially useful products for further elaboration, since they have very densely packed orthogonal functionality that should allow for chemoselective reactions at the alcohol, C-Br bond or alkene.

**Scheme 11. Potential synthesis of α-bromoallylic alcohols 8**

In addition, potential products derived from the interception of 7 with non-carbonyl-based electrophiles (e.g. iodine, silicon and tin based electrophiles, etc) are themselves attractive building blocks which could be widely used in organic synthesis.
1.3. Preparation and synthetic applications of \( \alpha \)-bromoallylic alcohols 8 resulting from electrophilic trapping of 1-bromo-1-lithioethene (7) with carbonyl compounds

Synthetic applications of 8 (\(^1 R = H \)) include various Pd(0)-catalyzed coupling reactions such as Sonogahira coupling\(^{22,23,24,25,26} \) Stille coupling,\(^{27} \) Suzuki coupling,\(^{28,29} \) and Heck reaction.\(^{30} \) Some examples are presented in Scheme 12.

**Scheme 12. Examples of Pd(0) catalyzed reactions of \( \alpha \)-bromoallylic alcohols**

Interestingly, \( \alpha \)-bromoallylic alcohols can undergo Pd(0) catalyzed coupling reactions without protection of the OH group. An example of a “reversed case” when the bromine atom in 8 is first replaced with a tin atom was published recently (Scheme 13).\(^{31} \) In the latter case, the usual reaction conditions of Stille coupling failed to provide synthetically
useful yields of products due to steric congestion while the cuprous chloride accelerated modification allowed for good yields of the coupled product (Scheme 13).

**Scheme 13. CuCl-catalyzed Stille coupling of an alkenylstannane derived from an α-bromoallylic alcohol**

Another reported reaction of α-bromoallylic alcohols (8) is methyldebromination with Me₄CoLi₂ which allows easily substitution of the bromine atom in 8 with a methyl (and quite possible any primary alkyl) group while tolerating a wide variety of other functional groups, including the free α-hydroxy group.

**Scheme 14. Substitution of the bromine atom in 8 for a methyl group**

A suitably substituted α-bromoallylic alcohol (8) was used in the synthesis of Calcitriol (a compound related to vitamin D₃). A key step in construction of the Calcitrol core was a radical cyclization which utilized the bromine substituent in 8.
(Scheme 15).

**Scheme 15. Application of 8 in Calcitriol core synthesis**

The vinylic radical formed after the abstraction of the bromine atom underwent a smooth 6-exo-trig reaction allowing for an excellent yield of the delicate Calcitriol fragment.

**Scheme 16. Synthetic transformations of 8 with retention of the bromine substituent**

An example of a synthetic transformation of an α-bromoallylic alcohol (8) where the bromine substituent remained intact through several steps to allow the formation of a
bromodienoic alcohol (Scheme 16). This report clearly demonstrates that 8 are quite stable molecules which could allow a great deal of flexibility in their use as synthetic building blocks.

In another example, an α-bromoallylic alcohol (8) was used as an intermediate to efficiently construct a substituted furan ring. Later, similar chemistry was used to synthesize a key precursor to the skeleton of the natural product Kallolide (Scheme 17). The “bond A” of the reactant was constructed by Sonogashira coupling of an appropriately substituted α-bromoallylic alcohol with a corresponding alkyne (Scheme 12).

Scheme 17. Usage of 8 in the synthesis of Kallolide B skeleton

Substituted indoles are also accessible from α-bromoallylic alcohols (8) by using an intramolecular radical cyclization after substitution of the hydroxy group in 8 by an amino group under Mitsunobu conditions. The remarkable feature of this chemistry is the generation of a radical center in a substituted arylamine without a need for organotin compounds. An example of 2,3-dimethylindole synthesis by using this approach is presented in Scheme 18. Some tricyclic indoles also were obtained by using this methodology.
α-Bromoallylic alcohols (8) were also used for elaboration of synthetic intermediates for Prins – pinacol cyclization. Tetrahydropyrans available via Prins – pinacol cyclization are present as structural features in a variety of biologically active natural products such as polyether antibiotics, marine toxins, and pheromones.

Scheme 18. Indole synthesis via α-bromoallylic alcohols (8)

Scheme 19. An example of diastereoselective tetrahydropyran synthesis from 8
It is interesting that the bromine atom in 8 could undergo lithium-halogen exchange with a two-fold excess of \( t\-\text{BuLi} \) and then be further converted to the corresponding cuprate (Scheme 19).\(^{36}\) Thus, a variety of organocuprate additions could be potentially used to conveniently utilize the bromine atom in 8 (and therefore in 1-bromo-1-lithioethene), so complementing the Pd, Ni and Cr-catalyzed C-C bond forming reactions discussed earlier.

The preparation of 8 (\( ^1\text{R} = \text{H} \)) has usually been achieved by 1,2-addition of alkynyllithium,\(^{22}\) Grignard\(^{38}\) or enolate\(^{25,34}\) nucleophiles to 2-bromoacrolein. This approach is intrinsically limited to secondary \( \alpha \)-bromoallylic alcohols (8, \( ^1\text{R} = \text{H} \)). Often modest yields of the 1,2-adducts were observed during these transformations. In addition, 2-bromoacrolein is not commercially available, so extra synthetic work is required to prepare this precursor.\(^{39}\) \( \alpha \)-Bromoallylic alcohols (8) also were obtained by an HBr addition to terminal alkyn-3-ols\(^{22,31,32}\)

**Scheme 20. Synthesis of \( \alpha \)-bromoallylic alcohols via HBr addition to terminal alkynes**

![Scheme 20](image)

The harsh reaction conditions required for this transformation (bubbling HBr gas through a reaction mixture at rt) limits the scope of this chemistry to simple substrates which are resistant to strongly acidic media. In an example above\(^{23}\) (Scheme 20), a protecting group (which is not even particularly acid sensitive!) must be introduced after
the α-bromoallylic alcohol formation, which in turn, led to the necessity to differentiate a primary hydroxy group versus a secondary allylic OH group in the next step.

Bromination / dehydrobromination of α,β-unsaturated ketones followed by Luche reduction was explored to access certain types of secondary α-bromoallylic alcohols with good yields (Scheme 21). Again, the usage of elemental bromine limits the scope of usable precursors to compounds containing only those functional groups which are stable to bromine.

There are some additional isolated reports where a Luche reduction of 3-bromo-3-buten-2-one or an ene reaction of 2-bromoacrolein were used to construct secondary α-bromoallylic alcohols (8, 1R = H).

Scheme 21. Synthesis of 8 by bromination/dehydrobromination sequence

Prior to our work in this area, there were no reported general approaches to tertiary α-bromoallylic alcohols (8, 1R and 2R ≠ H). To the best of our knowledge, the Ag⁺-mediated opening of the corresponding gem-dibromocyclopropane in the presence of acetic acid or an alcohol were the only reported approaches to 8 (1R and 2R ≠ H). However, this methodology leads to moderate overall yields and often mixtures of products were obtained. Typical examples of this type of chemistry are presented in Scheme 22.
Scheme 22. Preparation of tertiary α-bromoallylic alcohols via opening gem-dibromocyclopropanes

In summary, very little information about the preparation and trapping of 1-halo-1-lithioethenes is available to date. In addition, only a single example where a carbonyl compound was trapped with a 1-halo-1-lithioethene (in 10% yield) was published. From the other side, α-bromoallylic alcohols proved to be useful substrates for further elaboration and were used in some natural products syntheses. All existing synthetic approaches to α-bromoallylic alcohols are multistep synthetic sequences, often involving the usage of harsh conditions (HBr gas, elemental bromine, Ag⁺ catalysis) which significantly decreases their applicability to sensitive substrates. In contrast, the proposed 1-bromo-1-lithioethene building block 7 potentially allows a one step approach to α-bromoallylic alcohols starting from an immense variety of carbonyl compounds. Given
the very low temperature used for these kind of reactions, there is a great chance that the 1-bromo-1-lithioethene building block would be compatible with many functional groups present in the starting carbonyl compound, thus obviating the necessity for complicated protection / deprotection strategies.

We thought that careful study of formation and further reactions of 1-bromo-1-lithioethene (7) would allow it broad usage as a building block in organic synthesis.
Chapter 2. Synthesis and structure of 1-bromo-1-lithioetene (7)

2.1. Cryogenic reactor design

After ca the 1950s, when iron core NMR spectrometers and other sophisticated tools became more and more common in an average organic laboratory, the amount of reported experimental details in journal articles started to decrease (compare 1940 and 1970 articles in *J. Am. Chem. Soc.* or *J. Org. Chem*.). There are many compounds reported in journals such as *Tetrahedron Lett.* just once without any experimental procedures published elsewhere. The mention of the mysterious “standard workup” is frequently observed in current synthetic publications. Almost every third article (!) mentions so called –78°C reaction temperature but, in reality, the reaction was just cooled with a dry ice bath without monitoring of the actual reaction temperature. According to our experience, the actual internal temperature of such reaction mixtures may vary widely (–72 to –60 °C typically and up to –45 °C in extreme cases) depending on the reaction exothermicity, rate of addition of reagents, flask size, stirring efficiency and the reaction medium viscosity. The internal temperature is often not monitored, in large part because, for many reactions, the short-term temperature fluctuations are not detrimental.

However, this lack of attention to experimental details is probably the primary reason for erratic yields in reactions involving 1-halo-1-lithioethenes. Therefore, as we set out to develop 1-bromo-1-lithioethene (7) as a synthetically useful reagent, one major challenge was to reveal the source of those yield variations. The synthesis of 1-chloro-1-
lithioethene (4) by the deprotonation of chloroethene at \(-110 \, ^\circ\text{C}\)\textsuperscript{11} was selected as a model reaction for this purpose, since this kind of chemistry was very efficient in the hands of Kobrich. Because the reaction of 1-halo-1-lithioethene with carbonyl compounds was of primary interest, we decided to use acetone (instead of the originally used carbon dioxide) as a trapping reagent for 1-chloro-1-lithioethene (Scheme 23).

**Scheme 23. Model reaction chosen for cryogenic reactor optimization**

\[
\text{Cl} = \text{Cl} + \text{n-BuLi} \xrightarrow{\text{THF:ether:pentane}} \text{Cl Li} \xrightarrow{-110 \, ^\circ\text{C}} \text{Cl OH}
\]

The desired temperature could only be obtained if liquid nitrogen was used as a cooling agent. (Commercial cooling devices only provide access to temperatures down to \(-90 \, ^\circ\text{C}\)). However, after the first attempt it became obvious that usual simple low temperature techniques failed to provide the necessary temperature control within the reaction flask. It seemed likely that this was due to the formation of a solid coolant crust (Fig. 4) when ether, pentane or methylcyclohexane were used along with liquid nitrogen as coolants.

This undesirable effect became especially pronounced at temperatures below \(-90 \, ^\circ\text{C}\). The crust prevented the convection of the liquid coolant, introduced dangerous stresses and made careful temperature control in the reaction flask impossible.
Fig. 4. Formation of a solidified coolant crust below –90 °C in a conventional cooling bath setup

A more sophisticated setup, which included a heat exchanger tube (to keep separately the liquid nitrogen and the liquid coolant) and mechanical stirring within the cooling bath (Fig. 5), solved the crust formation problem. However, the observed yields of α-chloroallylic alcohol (9) were still irreproducible (10-50% isolated yield of the desired adduct).

Moreover, the usage of a syringe pump was necessary because a conventional addition funnel could not reliably provide the required slow addition rate on a small scale. The rate of n-BuLi addition was important because even momentary overheating of the reaction mixture above –105 °C started the exothermic formation of carbene 6 (Scheme 4, \(^1R = ^2R = H\)) which, in turn, led to further uncontrollable temperature rise and complete decomposition of 1-chloro-1-lithioethene (4).

The erratic yields of 9 were attributed to unpredictable heat transfer between drops of n-BuLi solution (which were almost at rt) and the viscous cold reaction mixture, which could trigger local exothermic formation of carbene 6 from the initially formed 1-chloro-
1-lithioethene (4).

**Fig. 5. Initial low-temperature setup with a heat exchanger tube**

It should be noted that the viscosity of the reaction mixture could not be dramatically reduced. The major cause of high viscosity of the reaction medium is THF for which the melting point (-108 °C) is above the desired reaction temperature. According to Kobrich’s results\(^1\) as well our own observations, THF is a necessary component of the reaction mixture during the deprotonation step leading to the formation of 4. The reaction between chloroethene (as well as bromoethene) and \(n\)-BuLi slowed down significantly when the concentration of THF dropped below 50% (vol.) and no reaction at all could be observed at –110 °C without THF.

It probably was possible to arrange the conventional reactor in such a way that the
\( n\text{-BuLi} \) solution would cool first on a reaction vessel wall and only then reach the reaction mixture. However, the usage of a syringe pump still would be necessary. We noticed that prolonged addition (\textit{ca} 2 h) of \( n\text{-BuLi} \) required a new, well fitting, heavily greased glass syringe. (Plastic syringes do not provide smooth enough addition when filled with \( n\text{-BuLi} \)). In addition, the commercial 2M \( n\text{-BuLi} \) solution in pentane tended to release some gaseous material upon prolonged standing at rt (presumably butane) which uncontrollably increased the effective addition rate.

Overall, the conventional experimental setup did not prove to be reliable for the synthesis of 1-chloro-1-lithioethene (4). Obviously, the synthesis of the less stable 1-bromo-1-lithioethene (7) would be even more difficult. We thought, if possible, that the addition of a \textit{precooled} \( n\text{-BuLi} \) solution to the reaction mixture might increase the reliability of these syntheses. However, there is no convenient way to do such an addition at the required low temperature. All conventional approaches include an intermediate link such as a cannula, a stopcock or other connector/valve, which is kept almost at rt or, rarely, at the low temperature.

An interesting reactor was reported for a low temperature synthesis of 3-iodoindole\textsuperscript{43} (Fig. 6, on the left). Obviously, such an arrangement could not be adopted for a \(-110 \, ^{\circ}\text{C} \) reaction protocol because of the freezing crust problem (see Fig. 4) and the necessity to use vacuum jacketed coolant vessels. Another reactor, which was reported by Hoffman et al\textsuperscript{44} is much more suitable for the task (Fig. 6, on the right). Interestingly, we became aware that this design had been used for low temperature chemistry only after our article had appeared in \textit{J. Org. Chem.} (ASAP articles, 11/14/05) and Hoffman himself had
contacted us with the reference.

Fig. 6. Previously reported low temperature reactors

Even more interestingly, this exact 2-chamber cell was made independently by me, prior to the Hoffman report, in ca 1991 (at Lviv Polytechnic Institute, Ukraine). Indeed, it was possible to operate it at low temperatures but the main drawback was the stirring efficiency. It was (and it is) notoriously difficult to use magnetic stirring through an outer Dewar flask, especially when the reaction mixture becomes viscous. In addition, the design reported does not readily allow for the measurement of the internal reaction temperature.

Instead of repeating the known partial solutions, to this low temperature control problem, we decided to develop our own experimental approach. It seemed reasonable to
get rid of the intermediate connector or valve to simplify the reactor and allow all parts of it to be cooled in the same cooling bath. After two completely unsuccessful attempts we came up with the fruitful idea presented below (Fig. 7).

**Fig. 7. Low temperature reactor designed by us for preparation of 1-halo-1-lithioethenes**

All parts of the reactor are submerged into a cooling bath so that the reagent being added is never warmed up along the way. The actual addition is forced by increasing the argon pressure in the side tube. A simple argon flow regulator made from a piece of a capillary tube obtained from a broken mercury thermometer and a glass stopcock (described in detail in the experimental section) allowed simple and reliable regulation of
the addition rate over a prolonged period (5 to 30 min).

**Scheme 24. Synthesis of 1-bromo-1-lithioethene and trapping with acetone**

An attempt to generate 1-chloro-1-lithioethene (4) in the designed reactor followed by trapping with acetone resulted in an 80% isolated yield of 9 (Scheme 23). This constitutes the first example of trapping 4 with a carbonyl compound.

At this point we decided to switch to the generation of 1-bromo-1-lithioethene (7), still using acetone as the trapping electrophile. To avoid possible side reactions, a low temperature quench by acetic acid (an 8% solution of acetic acid in ether remains liquid at –110 – 105 °C) was used. The reaction afforded pure α-bromoallylic alcohol 10 (Scheme 24) in about 45 to 50% isolated yield. Although the yield was modest, it was reproducible from run to run. Notably, no traces of halogen metal-exchange (i.e. formation of allylic alcohol 12 from an intermediate vinyllithium) were observed during this transformation, in contrast with early assumptions about rates of deprotonation versus halogen-metal exchange for bromoalkenes.¹
Attempts to adjust the reaction temperature (-110 to –130 °C), n-BuLi addition rate or reagent ratio did not change the isolated yield of 10. As was stated above, no byproducts could be observed on GC analysis of the crude reaction mixture (the mixture was subjected to a bulb to bulb distillation with a receiver cooled in a dry ice bath to remove lithium salts prior to GC analysis) but n-BuLi was completely consumed. We treated the aqueous extract from the reaction mixture with nitric acid / silver nitrate to determine the bromide ion concentration. The amount of silver bromide found corresponded to 0.20 – 0.25 eq of bromide ion.

**Scheme 25. Material balance of 1-bromo-1-lithioethene (7) decomposition**

This bromide ion must originate from the decomposition of 1-bromo-1-lithioethene (7). From the material balance of the reaction, one can deduce that each mole of 1-bromo-1-lithioethene consumed 1 mole of n-BuLi during formation. Therefore, after its decomposition, 1 mole LiBr and 1 mole of acetylene would be released. Acetylene in turn would consume one more mole of n-BuLi (or 1-bromo-1-lithioethene) to form lithium acetylide. In other words, 0.20 – 0.25 eq of bromide ion found in the reaction mixture
means that 0.40 – 0.50 eq of n-BuLi were effectively destroyed by thermal decomposition (Scheme 25).

We assumed that lithium acetylide was not sufficiently nucleophilic to react with acetone at –110 °C. This would explain the absence of the expected byproduct, propargylic alcohol 11 (Scheme 24). The weak dependence of the yield of 7 with variation of all the reaction parameters was quite strange. It seemed as if some decomposition occurred at the beginning of the n-BuLi addition but, as byproducts (LiBr and acetylene) were building up in the reaction mixture, the decomposition rate of 1-bromo-1-lithioethene (7) was progressively decreasing. Thus, we decided to intentionally add those byproducts before the addition of n-BuLi.

We anticipated that lithium acetylide should not have any effect on 1-bromo-1-lithioethene (7). In contrast, it has been previously observed that lithium halides sometimes increase the stability of some 1-halo-1-lithiated compounds.13 Since 0.20 – 0.25 eq of lithium bromide was typically formed in our previous reaction runs we decided to intentionally add 0.20 eq LiBr to the reaction mixture prior to n-BuLi addition. (It is important to note that LiBr is soluble in the reaction medium even at –125 °C). To our delight, this modification afforded 80% of α-bromoallylic alcohol 10 (>99% pure by GC) after a vacuum distillation. This precedent was a key indication that 1-bromo-1-lithioethene (7) could be a synthetically useful reagent.

Before examining various other electrophiles, we decided to intentionally change some reaction parameters to reveal the “area of stability” of 1-bromo-1-lithioethene (7). We noticed that, in all successful runs, 7 was formed as a white solid suspended in the
reaction mixture. If the reaction mixture temperature was raised (even temporarily) above –108 to -105 °C, the cloudy white slurry promptly became a clear colorless solution and uncontrollable exothermic decomposition of 7 to acetylene and lithium bromide was triggered. Albeit not dangerous experimentally (the temperature only rose up to –90 °C in the worst case), this decomposition was completed in 1 to 2 min; this could not be slowed down by addition of liquid nitrogen. In contrast, the solid form of 7 could be safely kept at –115 to –120 °C for several hours without noticeable acetylene formation.

Fig. 8. Formation of a cold spot within the low temperature reactor
preparation of 1-bromo-1-lithioethene (7) was accidentally revealed when a “reverse addition” reactor was used for the synthesis of 7. That reactor was supposed to allow the addition of preformed 1-bromo-1-lithioethene to an electrophile and employed the same principle as the reactor shown in Fig. 7. Because of the increased complexity of the reactor and the confined space within the Dewar vessel, the cavity where 1-bromo-1-lithium (7) was prepared was placed far away from the heat exchanger. Even though the inner temperature within the cavity was appropriate (−112-118 °C) for some reason the white slurry of 7 was only occasionally formed. The dissolved form of 7 was much less stable, thus only poor yields of 1-bromo-1-lithioethene (7) adducts were frequently obtained. To further explore these unexpected observations, we carefully measured the temperature gradients in the apparatus which has afforded highly reproducible results (Fig. 7). We observed that the viscosity of methylcyclohexane (which always was used in conjunction with liquid nitrogen as the external coolant, mp -127 °C) significantly increased when the coolant temperature dropped below -110 °C. This caused a temperature difference of ca 15 °C along the height of the reactor which did not change appreciably with more efficient coolant stirring. After a short time, the frozen coolant formed a bridge between the bottom of the heat exchanger and the flask wall (Fig. 8). (This condition could be detected by attempting to move slightly the outer Dewar flask.) This, in turn, caused the region of the flask wall in contact with the frozen coolant to cool temporarily below -127 °C. This cold spot reproducibly caused the “crystallization” of 7. Because the average temperature in the reaction flask was usually about −115 to -120 °C during this process, the main bulk of the solvent did not freeze.
It is interesting that methylcyclohexane (mp –126 °C), which was initially used by Kobrich, happened to have almost perfect temperature – viscosity properties to allow a convenient synthesis of 7. When pentane (mp –130 °C) was used as a coolant only a 1 to 3 °C temperature gradient along the height of the reactor was observed and, instead of formation of the frozen coolant bridge, the bulk freezing of the reaction mixture was often observed.

The basic design of the reactor shown in Fig. 7 could be used on different scales. For example, we have made and tested a 30 mL main flask volume reactor (which allowed us to work with 1 – 3 mmol of 7) as well as 250 mL reactor (for 15 – 35 mmol of 7). A standard Dewar flask (120 mm inner diameter, 190 mm inside depth, 1.9 L volume) which required about 1 to 1.3L of methylcyclohexane was used for all experiments. Typical methylcyclohexane loss was about 5 to 10 vol % per synthesis. Water, which was condensed from the atmosphere, did not pose a significant problem and could be easily separated from the coolant after warming.

2.2. Optimization of the preparation of 1-bromo-1-lithioethene (7)

The next important parameter after the reaction temperature was the solvent mixture composition. Ether and ether – pentane mixtures did not provide any deprotonation product on treatment of bromoethene with n-BuLi and only the addition of unreacted n-BuLi to the subsequently added electrophile was observed. In various runs, successful results were observed when using THF:ether:pentane mixtures in ratios from 2:1:1 to 4:1:1. Further decreasing of the THF content led to incomplete deprotonation of
bromoethene while increasing THF content caused complete freezing of the reaction mixture.

We have also attempted to exploit the fact that the solid form of 7 seemed to be much more stable than the dissolved form. Changing from THF (mp -108 °C) to THP (mp -45 °C) and/or from n-pentane (-130 °C) to n-heptane (-91 °C) was expected to cause crystallization of 7 at higher temperatures. Unfortunately only minute amounts of 7 were detected at -100 °C while no traces of 7 formation were observed at -95 °C and above by GC and 1H NMR analysis after trapping with benzaldehyde. In addition, complete spontaneous freezing of the reaction mixture frequently was observed in these cases.

**Scheme 26. Optimization of the deprotonation time for the synthesis of 7**

\[
\begin{array}{ccc}
\text{Br} & \text{1. } n\text{-BuLi in 15 min.} & \text{iodine} \\
& \text{2. delay at -115 °C} & \text{Br} \\
& & \text{Li} \\
\text{7} & \text{Br} & \text{13} \\
& & + n\text{-Bu–I} \\
\end{array}
\]

<table>
<thead>
<tr>
<th>delay</th>
<th>ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>70</td>
</tr>
<tr>
<td>15 min</td>
<td>90</td>
</tr>
<tr>
<td>90 min</td>
<td>98</td>
</tr>
</tbody>
</table>

Reaction time happened to be a critical parameter as well. The designed reactor (Fig. 7) allowed us to shorten the addition time of n-BuLi to 15 min, providing that the initial temperature of the reaction mixture was about –115 °C. However, after frozen coolant bridge formation and crystallization of 7, at least 40 min (or, better, 90 min) of stirring at -115 to –120 °C was required to complete the deprotonation. For example, prompt addition of an electrophile (iodine) just 5 min after n-BuLi addition afforded 30% of iodobutane along with the desired product 13 (Scheme 26). After completion of the
formation of 1-bromo-1-lithioethene (7), the time needed for the subsequent reaction with an electrophile seemed to be less important. Good overall results were observed when this parameter varied from 15 min to 2 h.

Absolute concentrations and reagent ratios proved to be less important than the parameters discussed before. The overall concentration of the solution was dictated by use of 2M n-BuLi in pentane; all the rest of the solvents were calculated so that the pentane from n-BuLi provided the needed 2:1:1 to 4:1:1 THF:ether:pentane ratio. The bromoethene : n-BuLi ratio was not critical (1.1 : 1 to 2:1) while the amount of LiBr used clearly had an optimum at about 0.2 eq (based on the amount of n-BuLi used). Lower loading of LiBr decreased the yield of the trapped product while using more than 0.5 eq of LiBr significantly slowed down the rate of bromoethene deprotonation.

Scheme 27. Reactivity of bromoethene to n-BuLi versus t-BuLi

The last variable tested was the base used for bromoethene deprotonation. We were interested to know if a stronger base still would cause clean reaction. Interestingly, when bromoethene was treated with t-butyllithium under the same conditions as those employed above for n-BuLi, a 7:3 mixture of H\textsubscript{2}C=CHLi and 1-bromo-1-lithioethene (7) was obtained and further characterized by electrophilic trapping with
chlorotrimethylsilane (Scheme 27).

2.3. Computational evaluation of deprotonation versus halogen-metal exchange reactions of bromoethene

In an attempt to rationalize the different reactivity of bromoethene toward \(n\)-BuLi and \(t\)-BuLi, liquid phase \textit{ab initio} HF6-31G*/SM5.42R calculations\textsuperscript{45} were undertaken. To define the computational task, it was assumed that the base used (\(n\)-BuLi or \(t\)-BuLi) first underwent partial dissociation induced by THF. This assumption is partially supported by the observation that bromoethene was essentially unreactive toward \(n\)-BuLi at \(-110\) °C in pentane solution. In addition, it was observed that the presence of more than 0.5 eq of LiBr in the reaction mixture significantly decreased the rate of the reaction between bromoethene and \(n\)-BuLi. This was consistent with the participation of a relatively free carbanion in the deprotonation step. This assumption prompted us to computationally examine direct reactions between appropriate alkyl anions and bromoethene (Scheme 28).

Scheme 28. Halogen-metal exchange versus deprotonation pathways for bromoethene

To minimize complications resulting from the conformational freedom of \(n\)-butyl
anion, methyl anion was used as a surrogate nucleophile/base.

No transition states could be observed in gas phase HF6-31G* calculations for all model reactions (deprotonation and halogen-metal exchange with methyl and tert-butyl anions).

Fig. 9. Energy diagram for reaction of bromoethene with tert-butyl anion in THF

The energy of the system was monotonously decreasing without revealing any stationary points. HF6-31G*/SM5.42 type calculations tend to converge very slowly and, worse yet, SCF subcalculation tends to oscillate because only numeric methods are used for derivatives computations. In contrast, HF6-31G*/SM5.42R calculations should give
almost the same energies while optimized geometries differ very little. However, the difference between these two methods is profound: the latter one does not optimize geometries; it just calculates the free energy of solvation of a given solute, hence it works very fast.

**Fig. 10. Energy diagram for reaction of bromoethene with methyl anion in THF**

It should be noted that there were no initial optimized geometries for solutes to start with in the case being discussed because of a lack of stationary points in the reaction pathways. So an alternative approach had to be used. The four reactions of interest were
traced along the single reaction coordinate which was fixed during each run while all other variables were optimized. The corresponding bond lengths (indicated with arrows on Scheme 28) were selected as reaction coordinates. Corresponding zero point energies were added to each calculated point. The number of imaginary vibrational frequencies was 0 in regions close to starting materials and products while it was 1 for intermediate points.

The computational results obtained for the reaction of bromoethene with tert-butyllithium anion suggest the formation of an unstable complex between reactants at about 2.8 \( \text{Å} \) distance for the halogen-metal exchange pathway (C---Br) (Fig. 9). This might be rationalized as the solvation of the “hard” tert-butyl anion with a polarizable bromine atom.

Even though calculated TS energy barriers are the same (~ 5 kcal/mol) for both halogen-metal exchange and deprotonation reactions involving \( t \)-butyl anion, the existence of the abovementioned complex might slightly increase the effective reaction rate of halogen-metal exchange through a “prearranging” of the reactants with resulting favorable influence on the entropic factor. Overall, the predicted reaction outcome was in reasonable agreement with the experimentally observed 7:3 ratio of products derived from halogen-metal exchange and deprotonation (Scheme 27).

The calculated trends for the reactions of bromoethene with methyl anion were quite different from the previous case. First, an unstable reactant complex could be observed during the deprotonation of bromoethene (\( \text{H}_3\text{C} \cdots \text{H} \) at about 2.3 to 2.1 \( \text{Å} \)) (Fig. 10). Calculated TS energy barriers for the two competing pathways were quite different (~10
kcal/mol for deprotonation versus ~16 kcal/mol for halogen-metal exchange) which was
in excellent agreement with the experimentally observed results (see Scheme 27).

Furthermore, the experimentally observed rates for reaction of tert-butyllithium with
bromoethene (almost instantly completed, 5 kcal/mol TS barrier) and for n-butyllithium
with bromoethene (~70% completion after 5 min, ~98% after 90 min, 10 kcal/mol TS
barrier) seem to be in a reasonable agreement with computations.

2.4. Possible solid state structure of 1-bromo-1-lithioethene (7)

Another interesting question was about the structure of 7 itself. Was the observed
solid phase a polymer or just a crystalline phase? According to previously reported\textsuperscript{19}
calculations, the structure of 1-iodo-1-lithioethane should favor the monomeric structure
over the cyclic dimer structure by about 7 kcal/mol at the MP2/DZV(d) level of theory
(Scheme 29). These calculations employed H\textsubscript{2}O as a coordinating ligand on lithium,
which is clearly not equivalent to solvating THF ligands that would be expected in
reality.

Scheme 29. Calculated dimer/monomer equilibrium for 1-iodo-1-lithioethene

In a very recent (2005) publication,\textsuperscript{46} which appeared after our preliminary results in
this area had been published, DFT calculations were undertaken to address the dimer to monomer equilibrium of 7 solvated with THF molecules at the B3LYP/6-311+G(2df, 2pd) level of theory. However, again a cyclic dimer was analyzed while the monomer was solvated only with two THF molecules, which led to a bridged structure for the monomeric 7. These results indicated a slight preference for the cyclic dimer of 7 (Scheme 30).

**Scheme 30. Calculated dimer/monomer equilibrium for 7 solvated with THF**

![Diagram](image)

In our experience, it was not a good practice to optimize the geometry of an organolithium with only three ligands attached to the lithium atom. Given the significant positive charge on the lithium, the bromine atom which belongs to 1-bromo-1-lithioethene will play the role of the fourth ligand in this case and optimized geometries will tend to be quite distorted.

**Fig. 11. X-ray crystal structure of substituted 1-chloro-1-lithioethene and its precursor**

![Image](image)
Indeed, the reported geometries\textsuperscript{46} of solvated 7 show that the optimized C=C-Li angle was $176^\circ$ and the Li-Br distance was 2.55Å. These were the result of bromine to lithium attraction because of the lack of the fourth ligand for lithium. On the contrary, the reported crystal structure\textsuperscript{48} of 2,2-disubstituted 1-chloro-1-lithioethene (the only compound of this type for which an X-ray crystal structure has been solved) exhibited a $137^\circ$ C=C-Li angle, while the lithium was not bound to the chlorine atom (Fig. 11).

Scheme 31. Calculated energies of dissociation of solvated linear dimers of 7

We wanted to explore if a linear dimer of 7 would be more stable than the corresponding monomer. To further test this hypothesis, liquid phase \textit{ab initio} HF6-31G*/SM5.42R calculations\textsuperscript{45} were undertaken. Since only ground state structures were being considered, the balance between the level of theory used and maximum complexity of the structure being studied was shifted toward the latter.

Given the enormous amount of time\textsuperscript{49} required even for a single geometry optimization of structures such as 16 (Scheme 31), no attempts were made to locate
global minima.

A traditional computational strategy was employed, whereby the starting geometries of solvated dimers 16 and 19 were optimized until local minima were found (no imaginary vibrations after the corresponding Hessian calculations). The same procedures were then applied to their monomeric fragments. Finally, the energetics of the dissociation reactions were evaluated (Scheme 31).

Fig. 12. Optimized geometry of dimer 16

In accordance with reported calculations for the 1-iodo-1-lithioethene dimer,19 current calculations support the notion that 1-bromo-1-lithioethene dimers might be less energetically favorable than their monomers. This is somewhat contradicts the very recent calculations of Pratt,46 however, the major reason for this controversy is the wrong coordination number (3) chosen for lithium in the latter case (Scheme 30) which led to a
situation when the bromine atom from 7 was used for intramolecular lithium chelation. Meanwhile, a computational experiment at the HF6-31G* level showed that the addition of a third molecule of THF to the monomer of 7 chelated with two THF molecules released 0.32 kcal/mol of energy, rendering the monomer again more energetically preferable (by \(ca 0.32-0.05=0.27\) kcal/mol,) than the dimer (compare Scheme 30 and Scheme 32).

Scheme 32. Intramolecular chelation of Li vs intermolecular chelation of Li in 7

\[
\begin{align*}
\text{Br} & \quad \text{Li} \\
\text{Li} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
& \quad \text{Br}
\end{align*}
\]

\(-0.32\) kcal/mol

17

In addition, the optimized geometry at the \(=\text{C(Br)}-\text{Li}\) site seemed more realistic for the case when the bromine atom which belongs to 7 was not chelated to Li. This could be most clearly seen from the calculated dimer of 7 which is shown in Fig. 12. The dimer part with a non-chelated bromine atom (left end of the molecule in Fig. 12) is closer to the usual \(sp^2\) carbon geometry while the chelation of bromine brings more carbenoid character to 7 (right end of the molecule in Fig. 12). The chelation of bromine with lithium in 7 elongates the C-Br bond in 7 (up to \(ca 0.9\)\(\text{Å}\)) while it shortens the Li-Br distance by \(ca 0.8\)\(\text{Å}\), thus rendering 7 as a carbene – LiBr complex.

This means that if the bromine-chelated (e.g. polymeric, cyclic or linear) model was representing the actual structure of 7, halogen exchange between added LiBr and the
bromine atom originating from bromoethene should occur quite easily. However, in a
direct experiment when the generation of 7 was performed in the presence of 0.3 eq of
LiI (instead of the usual LiBr), the trapping with benzaldehyde did not produce any
noticeable amounts of then-to-be-expected expected α-iodoallylic alcohol (Scheme 33).
Instead, only the α-bromoallylic alcohol 20 was observed in the crude reaction mixture
by 1H NMR analysis. A modification of this experiment (7 was generated as usual with
LiBr but 1 eq of LiI was added before the reaction with benzaldehyde) also did not
provide any product with incorporated iodine. (The expected 1-iodo-1-lithioethene was
known to be detectable under the conditions used and is sufficiently reactive toward a
carbonyl group to afford α-iodoallylic alcohol products, at least in the reaction with
benzophenone.)19

Scheme 33. The synthesis of 7 in the presence of LiI

Table 3 presents a summary of calculated data for various 1-bromo-1-lithioethene
monomers and dimers. A single related crystal structure determined by low temperature
X-ray crystallography (14, Fig. 11) was included for comparison.

Interestingly, the calculated complex 18 (Scheme 34) seemed to have the lowest
energy between all other calculated molecules. In addition, its geometry was the closest
to the known crystal structure of substituted 1-chloro-1-lithioethene 14.
Based on available literature data\textsuperscript{18}, our computational results, the sharp phase transitions observed for 7 and the absence of halogen exchange with LiI, we presume that 7 most probably exists as a regular monomeric crystalline solid rather than a polymer. The low viscosity of the 1-bromo-1-lithioethene (7) slurry at -112 °C might also support this conclusion.

**Scheme 34. Calculated energetics for the formation of 18**

Table 3. Calculated geometry data for 7 dimers and monomers

<table>
<thead>
<tr>
<th>structure</th>
<th>C\textsubscript{1}-Hal bond elongation, Å</th>
<th>C\textsubscript{2}-C\textsubscript{1}-Hal angle, degrees</th>
<th>C\textsubscript{2}-C\textsubscript{1}-Li, angle, degrees</th>
<th>Li-Br distance, Å</th>
<th>source of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 (reference)</td>
<td>0.12</td>
<td>112.6</td>
<td>137.1</td>
<td>n/a (Li-Cl)</td>
<td>X-Ray</td>
</tr>
<tr>
<td>18 (monomer)</td>
<td>0.31</td>
<td>107</td>
<td>148</td>
<td>3.45</td>
<td>Computation</td>
</tr>
<tr>
<td>17 (monomer)</td>
<td>0.32</td>
<td>108</td>
<td>170</td>
<td>2.84</td>
<td>Computation</td>
</tr>
<tr>
<td>16 (dimer)</td>
<td>1.00</td>
<td>104</td>
<td>154</td>
<td>2.52</td>
<td>Computation</td>
</tr>
<tr>
<td>19 (dimer)</td>
<td>1.18</td>
<td>98</td>
<td>158</td>
<td>2.60</td>
<td>Computation</td>
</tr>
<tr>
<td>7 + 2THF</td>
<td>0.32</td>
<td>56</td>
<td>176</td>
<td>2.55</td>
<td>Computation\textsuperscript{46}</td>
</tr>
</tbody>
</table>
It seems very likely that each lithium atom of 1-bromo-1-lithioethene 7 is chelated with *two* THF molecules and *one* bromide anion originating from the added LiBr. Given that, in a LiBr crystal, each bromide anion is surrounded with six lithium cations, it is possible that each bromide anion from added LiBr could be coordinated with up to 5 molecules of 7 (while the lithium cation from added LiBr is chelated with THF). This ratio would explain the necessity to add *ca* 0.2 to 0.3 eq of LiBr to stabilize the initially formed monomeric 7.

In summary, we have established conditions required for the reliable preparation of 1-bromo-1-lithioethene (7). The presence of 0.2-0.25 eq of LiBr, the proper reaction temperature (-112 to -115 °C) and inducing the crystallization of 7 via a frozen coolant bridge formation proved to be important factors in the reproducible synthesis of 1-bromo-1-lithioethene.

According to our computational work and literature data, the key reason for stability of 7 at -112 to -115 °C was its crystalline structure where the bromine atom of 7 was not participating in the lithium chelation. In contrast, bromide anion originating from the added LiBr plays an important role in suppressing the carbenoid character of 7 by chelation to the lithium atom.

Overall, with a convenient preparation of 7 in hand, we were now in a position to explore the synthetic utility of 7 as a building block in organic synthesis.
Chapter 3. Electrophilic trapping of 1-bromo-1-lithioethene

3.1. Reactions of 1-bromo-1-lithioethene (7) with simple carbonyl compounds

Using the previously optimized conditions for the preparation of 1-bromo-1-lithioethene (7), several simple carbonyl compounds were examined as electrophiles to obtain various α-bromoallylic alcohols (Scheme 11). These syntheses went uneventfully, resulting in the clean formation of the corresponding adducts 20-29 in high yields after a simple distillation (Table 4). We were delighted to observe the clean 1,2-addition to α,β-unsaturated carbonyl compounds (entries 6-10) without detectable amounts of 1,4-adducts. In each case, no evidence for the formation of the corresponding propargylic alcohols (such as 11, Scheme 24) or cyclopropanation products, which could potentially emerge from carbene 6 (Scheme 4), were seen based on GC and 1H NMR analysis of the crude reaction mixtures. These results offer the first practical entry to tertiary α-bromoallylic alcohols 10, 21-24 and 28 as well to interesting α-monobromo-bis-allylic alcohols 21 and 24 – 28.
Table 4. Reaction of 7 with simple carbonyl compound electrophiles

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile&lt;sup&gt;a&lt;/sup&gt;</th>
<th>product</th>
<th>product number</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O</td>
<td>[structure]</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>O&lt;sub&gt;Ph&lt;/sub&gt;</td>
<td>[structure]</td>
<td>20</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>O&lt;sub&gt;Me&lt;/sub&gt;</td>
<td>[structure]</td>
<td>21</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>O&lt;sub&gt;Me&lt;/sub&gt;</td>
<td>[structure]</td>
<td>22</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>O</td>
<td>[structure]</td>
<td>23</td>
<td>85</td>
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<td>6</td>
<td>O</td>
<td>[structure]</td>
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</tr>
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<td>7</td>
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<td>[structure]</td>
<td>25</td>
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<td>8</td>
<td>O</td>
<td>[structure]</td>
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<td>10</td>
<td>O&lt;sub&gt;Ph&lt;/sub&gt;</td>
<td>[structure]</td>
<td>28</td>
<td>85</td>
</tr>
</tbody>
</table>

<sup>a</sup> 7, LiBr (0.20-0.25 eq), Trapp solvent, -112-115 °C, then 8% ethereal AcOH
3.2. Reactions of 1-bromo-1-lithioethene (7) with protected α-hydroxy ketones

To evaluate the scope and limitations of the synthetic utility of 7, more structurally complex protected α-hydroxy ketones were next examined as electrophiles. Initial studies were focused on the reaction of 7 with glucose-derived ketone 29a. To our disappointment, only 9% (by $^1$H NMR analysis) of the desired bromoethenyl adduct 29b was formed (albeit as a single diastereomer; Scheme 35), accompanied by 46% of the starting ketone 29a and 45% of the acetylenic adduct 29c.

Scheme 35. An initial attempt to trap 7 with a glucose-derived ketone

It is important to note that 29c most probably did not originate from the bromoethenyl adduct 29b. In a separate experiment the very similar adduct 39b (see Table 6, entry 5) exhibited no reaction when it was subjected to a solution containing LDA or DBU, even at rt. Instead, it seems likely that 29c was formed via decomposition of 7 to ethynyllithium followed by nucleophilic addition to 29a.

The common additives HMPA and TMEDA caused extensive decomposition of 7 while CeCl$_3$ did not facilitate this reaction. After considerable experimentation, it was found that addition of CeBr$_3$ (0.1 eq) dramatically increased the yield of 29b (from 29a) as well as 31b (from 31a, Table 5, entries 1 and 3). Further experimentation revealed that Me$_3$SiCl (0.5 to 1 eq) also significantly improved the yields of the desired
1-bromoethenyl adducts (Table 5, entries 2, 4 and 5). Regardless of the additive used, it was also observed that a 1.5 to 2-fold excess of 1-bromo-1-lithioethene (7) was necessary to obtain reproducible results.

Carbohydrate-derived ketones with well-defined convex and concave faces formed corresponding adducts with 7 with complete diastereoselectivity resulting from attack at the less crowded face. Interestingly, the base-sensitive ketone 32a did not form any byproducts under the reactions conditions used. Ketone 32a is usually quite susceptible to E1cb elimination; indeed, it could be completely converted to the corresponding α, β-unsaturated ketone by treatment with DBU for 15 min at rt (eq 1). 50

This particular reaction demonstrates the low basisity of 1-bromo-1-lithioethene (7) which is quite unusual for an organolithium reagent.
Table 5. Addition of 7 to protected α-hydroxy ketones leading to a single α-bromoethenyl product

<table>
<thead>
<tr>
<th>entry</th>
<th>starting ketone&lt;sup&gt;a&lt;/sup&gt;</th>
<th>product</th>
<th>isolated yield, %</th>
<th>additive used</th>
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<tbody>
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<td><img src="image1" alt="" /></td>
<td><img src="image2" alt="" /></td>
<td>84</td>
<td>CeBr&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>2</td>
<td><img src="image3" alt="" /></td>
<td><img src="image4" alt="" /></td>
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<td>Me&lt;sub&gt;3&lt;/sub&gt;SiCl</td>
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<td>3</td>
<td><img src="image5" alt="" /></td>
<td><img src="image6" alt="" /></td>
<td>67</td>
<td>CeBr&lt;sub&gt;3&lt;/sub&gt;</td>
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<td><img src="image8" alt="" /></td>
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<td>Me&lt;sub&gt;3&lt;/sub&gt;SiCl</td>
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<tr>
<td>5</td>
<td><img src="image9" alt="" /></td>
<td><img src="image10" alt="" /></td>
<td>70</td>
<td>Me&lt;sub&gt;3&lt;/sub&gt;SiCl</td>
</tr>
</tbody>
</table>

<sup>a</sup> 7 (1.5 to 2 eq), additive (0.5-1 eq of Me<sub>3</sub>SiCl added to ketone or 0.1 eq of CeBr<sub>3</sub> added to 7), Trapp mixture at -112-115 °C then 8% ethereal AcOH.
Table 6. Addition of 7 to protected α-hydroxy ketones having sterically less well-differentiated π-faces

<table>
<thead>
<tr>
<th>entry</th>
<th>starting ketone</th>
<th>major product</th>
<th>isolated yield, %</th>
<th>dr</th>
<th>additive used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OTMS</td>
<td>61&lt;sup&gt;b&lt;/sup&gt;</td>
<td>88:12</td>
<td></td>
<td>CeBr&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>2</td>
<td>36a</td>
<td>35&lt;sup&gt;b&lt;/sup&gt;</td>
<td>91:9</td>
<td></td>
<td>CeCl&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>3</td>
<td>37a</td>
<td>63&lt;sup&gt;c&lt;/sup&gt;</td>
<td>89:11</td>
<td></td>
<td>Me&lt;sub&gt;3&lt;/sub&gt;SiCl</td>
</tr>
<tr>
<td>4</td>
<td>38d</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>88:12</td>
<td></td>
<td>Me&lt;sub&gt;3&lt;/sub&gt;SiCl</td>
</tr>
<tr>
<td>5</td>
<td>39a</td>
<td>69&lt;sup&gt;b&lt;/sup&gt;</td>
<td>95:5</td>
<td></td>
<td>Me&lt;sub&gt;3&lt;/sub&gt;SiCl</td>
</tr>
</tbody>
</table>

<sup>a</sup> 7 (1.5 to 2 eq), additive (0.5-1 eq of Me<sub>3</sub>SiCl added to ketone or 0.1 eq of CeBr<sub>3</sub> added to 7), Trapp mixture at -112-115 °C then 8% ethereal AcOH. <sup>b</sup> Isolated yield for a pure major diastereomer. <sup>c</sup> Isolated as an inseparable diastereomeric mixture.
Ketones without well defined convex / concave faces provided products resulting from attack of 7 on the less crowded face of the starting ketone (Table 6). Surprisingly high overall diastereoselectivities were observed even for ketones that do not possess an obvious intrinsic facial bias. For example, ketones 36a, 37a and 38d provided similar diastereomeric ratios (ca 88:12) of adducts. Except for 37b, the diastereomeric adducts were readily separated by column chromatography. The relative stereochemistry of 36b was assigned by analogy with published data.51 The relative stereochemistry for 37b, 38e and 39b was established on the basis of nOe studies.

In another example, ketone 39a (entry 5) afforded a 95 : 5 mixture of diastereomeric products. In contrast, reaction of 39a with 2-(trimethylsilyl)ethynyl lithium (THF, 0 °C) afforded only a 1.5 : 1 mixture of diastereomeric propargyl alcohol products, with the major diastereomer resulting from the same β-(axial) face attack at the ketone.52 These authors found that the use of more sterically demanding TBS protecting groups at C-3, C-4 and C-6 allowed for completely diastereoselective axial addition to the β-face. Similarly, addition of 1.2 eq ethynylmagnesium bromide to ketone 39a (THF, 0 °C) afforded a 1 : 1 mixture of diastereomeric adducts.53 More highly diastereoselective (4 : 1) β-face addition reactions were observed for the addition of 2-(trimethylsilyl)ethynyllithium to the corresponding β-anomer of 39a.52 Although the highly diastereoselective addition of vinylmagnesium bromide to the closely related β-anomeric A-ulose sugar derivatives has been reported54 (eq 2), these reactions afforded the epimeric adducts resulting from α-face attack at the ketone. The authors attributed the high α-selectivity to Mg$^{2+}$ chelation with the C-4 carbonyl oxygen and oxygen centers.
within the C-3 protecting group\textsuperscript{55} followed by nucleophilic attack from the less crowded equatorial direction.\textsuperscript{56}

\[
\text{O}_{\text{BnO}} \quad \text{OR} \quad \text{SiMe}_3 \quad \text{MgBr} \quad \text{O} \quad \text{BnO} \quad \text{OR} \quad \text{SiMe}_3
\]

(eq 2)

\[
R = \text{Bn}: \quad \alpha\text{-attack} : \beta\text{-attack} = 21 : 1
R = \text{t-BuMe}_2\text{Si}: \quad \alpha\text{-attack only}
\]

To test the compatibility of various protecting groups, ketone \textbf{38d} was synthesized from the known and cheaply accessible $\beta$-methylmannopyranoside derivative \textbf{38a}\textsuperscript{57} via the three-step sequence presented in Scheme 36.

\textbf{Scheme 36. Preparation of ketone 38d}

\[
\begin{array}{c}
\text{38a} \\
\text{Bu}_2\text{SnO} \quad \text{toluene, reflux 1 h} \\
\text{38b} \\
\text{53\%} \\
\end{array}
\]

\[
\begin{array}{c}
\text{38c} \\
\text{36\%} \\
\end{array}
\]

\[
\begin{array}{c}
\text{38d} \\
\text{66\%} \\
\end{array}
\]

The differentiation between three secondary hydroxy groups in \textbf{38a} was achieved through formation of a cyclic stannylene acetal with subsequent reaction with an electrophile. These kinds of reactions usually lead to a selective monoprotection of 1,2- and 1,3-polyols. Although many precedents for such kinds of chemistry have been
published, there is still no possibility to reliably predict which exact product will be formed. The treatment of 38b with acetic anhydride afforded a mixture of 2- and 4-acetyl-protected sugars with the 4-acetyl protected product being the major component (and luckily noticeably less polar on silica, which allowed for its clean separation). PCC oxidation of the last unprotected hydroxy group in 38c went uneventfully, allowing for a quite interesting electrophile 38d which contained three orthogonal protecting groups with poorly differentiated faces of the ketone carbonyl group. To our delight, 1-bromo-1-lithioethene (7) reacted with 38d, exhibiting a preparatively useful 88:12 selectivity with no evidence of protecting groups (especially acetate) being destroyed by 7. Interestingly, the axial anomeric methyl group in 38d was the most important “directing” substituent, leading to the preferential attack of 7 from the top face of 38d (Scheme 36, Table 6, entry 4).

Again, clean and high yielding addition of 7 to the protected α-hydroxyketones shown in Table 6 was possible only when specific Lewis acids (CeBr₃, NdBr₃ or Me₃SiCl) were used. It seemed that the solubility of the Lewis acid was very important at such low temperatures. The commonly used Lewis acid CeCl₃ is not soluble in THF at rt even after sonication. This was probably the primary reason for the lack of the catalytic activity of CeCl₃ in the addition of 7 to α-trimethylsiloxy cyclohexanone (Table 6, entry 2). In contrast, we observed that commercially available CeBr₃ slowly dissolved in THF after prolonged stirring at rt and formed a clear solution at a concentration of ca 1-2%. (There are very few reported examples of using CeBr₃ as a Lewis acid and it seems that no significant difference in reactivity between CeBr₃ and CeCl₃ was previously
observed.\textsuperscript{60b)

We have noticed that the order of addition of reagents was critical for high yielding addition of 7 in these reactions. For CeBr$_3$ and NdBr$_3$, the best results were obtained when the Lewis acid was added to a slurry of 7 and the reaction mixture (cream colored with CeBr$_3$ or bluish colored when NdBr$_3$ was used) was stirred for \textit{ca} 5 min before addition of the carbonyl compound. Significantly longer reaction times caused excessive decomposition of 7 and decreased the yields of the addition product.

In a control experiment, when ketone 31a (Table 5, entry 3) was premixed with CeBr$_3$ and the resulting clear homogeneous solution was added to 1-bromo-1-lithioethene, the yield of the bromoethenyl addition product 31b was less than 33%. Adding only small amounts (0.05 to 0.1 eq) of Lewis acid was also important - use of 0.5-0.6 equiv CeBr$_3$ caused extensive decomposition of 1-bromo-1-lithioethene (7) and formation of addition products derived from the resulting ethynyllithium. These results suggest that added cerium salts activated the organometallics (possibly via formation of organocerium compounds) rather than by coordinating with the carbonyl compound used. It is important, that no evidence for competing enolization was seen in any of the reactions reported in Table 5 and Table 6; the stereochemistry at each epimerizable stereogenic center appeared unchanged after each reaction.
3.3. Application of 1-bromo-1-lithioethene (7) toward the synthesis of a Physalin fragment

At this point we decided to examine the utility of 7 as a potential building block en route to more complex synthetic targets. Specifically, we targeted the core bicyclic framework of the Physalin natural products. The physalins are a family of complex seco-steroids isolated from Physalis angulata L. annual herb.\textsuperscript{61} These extracts are widely used in popular medicine for the treatment of a variety of pathologies. It was also reported that both physalin B and physalin F inhibited the growth of several human leukemia cell lines: K562 (erythroleukemia), APM1840 (acute T lymphoid leukemia), HL-60 (acute promyelocytic leukemia), KG-1 (acute myeloid leukemia), CTV1 (acute monocytic leukemia) and B cell (acute B lymphoid leukemia).\textsuperscript{62} According to the literature, no total synthesis of any representative member of the Physalin family has been completed.

Scheme 37. Potential usage of 7 in Physalin fragment synthesis
Interestingly, the most complex part of the Physalin skeleton arises from a row of spatially congested stereogenic centers (labeled as 2, 3, 4 and 5 on Scheme 37). We anticipated that this complex structural array could be conveniently generated from inexpensive commercially available D-mannose via D-mannosan. The most difficult part of constructing the targeted physalin fragment was anticipated to be the nucleophilic addition of 7 to the sterically congested mannosan core at C3. Thus, we decided to examine if this addition step would be feasible in reality. To prepare the corresponding precursor we first prepared the acetonide of mannosan (40) from D-mannose using a known procedure (see Scheme 38).63

Scheme 38. Synthesis of 43

Treatment of 40 with PDC in the presence of acetic anhydride as an oxidation promoter64 allowed for an 86% yield of 4-ulose 41 which was treated with ethereal MeMgBr to furnish 71% of the 4-methyl adduct 42 as a single diastereomer after a
simple crystallization. An attempt to protect 42 at C4 with \( t\)-BuMe\(_2\)SiCl/imidazole failed, while MOM protection (MOMCl, \( \theta\)-Pr\(_2\)NEt, dichloromethane) at the same site was successful. However, all attempts to selectively cleave the acetonide group led to complete deprotection of the acetonide and MOM groups and formation of triol 43. Therefore, we decided to remove the acetonide group from 42 to afford 43 (in 99% yield), and then use a selective oxidation of a cyclic stannylene acetal derivative of 43 with bromine\(^{65}\) in hope of obtaining a single product oxidized at C2 or C3. To our delight, this procedure afforded 94% of a single product 44 resulting from a selective oxidation of 43 at C3 (Scheme 39).

**Scheme 39. Synthesis of 44**

![Scheme 39](image)

In the next step, 44 was monoprotected with Me\(_3\)SiCl at C2 and then was reacted with 2 eq of 7 in the hope that the corresponding alkoxide of 45 would be reactive toward 7. Unfortunately, this was not observed and unreacted 45 was the only product obtained. The introduction of a MOM protecting group at C4 followed by reaction with 7 in the presence of Me\(_3\)SiCl allowed for 24% (\(^1\)H NMR yield) of the desired adduct 46 along with the recovered starting ketone 45a (Scheme 40). Unfortunately, 46 promptly hydrolyzed upon contact with silica and the attempted isolation by silica chromatography gave only 7% of impure 46.
We considered that these disappointing results were probably due to the insufficient hydrolytic stability of the Me₃Si ether as well as some excessive steric crowding introduced by this protecting group. Multiple attempts to introduce different protecting groups at C2 (allyl, SEM, Bn and methylcyclopropyl ethers, carbonate) and C4 (MOM) into 44 failed, so we decided to protect both the C2 and C4 positions in 44 with a small (MOM) protecting group (Scheme 41).

In this case, addition of 7 to 47 proceeded uneventfully and allowed clean formation of the single diastereomer 48 resulting from the attack of 7 from the bottom face of 47. A facile column chromatographic separation allowed for the isolation of 48 in 81% yield as a crystalline solid. This result clearly demonstrated that 7 can be used with quite crowded “real total synthesis” substrates and still provide preparatively useful yields.
The adduct 48 could be quantitatively deprotected with 25% aq AcOH to the corresponding triol 48a (Scheme 42), however, we were unable to efficiently oxidize 48a at the C2 position, which would have allowed us to further elaborate this center.

Oxidants such Dess-Martin periodinane,\textsuperscript{67} N-bromosuccinimide/Bu₂SnO,\textsuperscript{68} Pt/O₂, Ag₂CO₃ in ethyl acetate and toluene, and CuBr₂/LiBr\textsuperscript{69} were unreactive toward 48a, while Swern oxidation\textsuperscript{70} of 48a led to complex mixtures of products. Attempts to selectively protect the hydroxyl group at C3 in 48a, which potentially might interfere with the oxidation, employing Me₃SiCl/Et₃N, Et₃SiCl/Et₃N, Et₃SiCl/Bu₂SnO, \textit{t}-BuMe₂SiCl/Et₃N, acetone/TsOH, MOM-Cl/\textit{i}-Pr₂NEt, allyl iodide/Bu₂SnO, ethyl chloroformate/Bu₂SnO, Me₂S/benzoyl peroxide,\textsuperscript{71} SEM-Cl/Bu₂SnO and MeOCH₂OMe/P₂O₅\textsuperscript{72} also did not yield any useful results. It might be that the highly crowded α-face at C2 made C2(OH) oxidation problematic. We considered that the hydroxy group at the C2 position of 44 might usefully be inverted prior the addition of 7, so that the subsequent oxidation at C2 might become possible. However, at this point we decided to abandon our pursuit of the Physalin fragment synthesis to concentrate on a study of the general reactivity and synthetic applicability of 7. Despite not achieving our
initial goal, we had achieved a diastereoselective synthesis of complex advanced intermediate 48a in 11 steps from commercially available D-mannose. This adduct might prove a useful building block in natural product synthesis. Its synthesis effectively demonstrated the utility of 7 in construction of the complex synthetic targets.

3.4. Reaction of 1-bromo-1-lithioethene (7) with highly electrophilic aldehydes

As was observed before, simple ketones, and several conjugated aldehydes and ketones, react with 7 to give good yields of the desired addition products (see Table 4). In contrast, \( n \)-heptanal and propanal (a simple aliphatic aldehydes) afforded only modest yields of the corresponding 2-bromo-1-alken-3-ol product on reaction with 7 (Table 7, entry 1 and 5). Yields dropped even further when protected \( \alpha \)-hydroxy aldehydes were used as electrophiles to trap 7 (see later).

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>product</th>
<th>isolated yield, %</th>
<th>conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( n-C_6H_{13} )</td>
<td>( n-C_6H_{12} )OH ( 49 ) Br</td>
<td>50</td>
<td>1 eq of 7</td>
</tr>
<tr>
<td>2</td>
<td>( n-C_6H_{13} )</td>
<td>( n-C_6H_{12} )OH ( 49 ) Br</td>
<td>74</td>
<td>3 eq 7 + 2 eq Me(_3)SiCl</td>
</tr>
<tr>
<td>3</td>
<td>( F_3C)phenyl-CHO</td>
<td>( F_3C)phenyl-( 50 )BrOH</td>
<td>40</td>
<td>1 eq of 7</td>
</tr>
<tr>
<td>4</td>
<td>( F_3C)phenyl-CHO</td>
<td>( F_3C)phenyl-( 50 )BrOH</td>
<td>77</td>
<td>3 eq 7 + 2 eq Me(_3)SiCl</td>
</tr>
<tr>
<td>5</td>
<td>( n-C_6H_{13} )</td>
<td>( n-C_6H_{12} )OH ( 49 ) Br</td>
<td>46</td>
<td>1 eq of 7</td>
</tr>
</tbody>
</table>
Attempts to use various additives invariably led to even lower yields of the desired adducts. In every case, unreacted aldehyde was recovered as the major byproduct. Non-enolizable 4-trifluoromethylbenzaldehyde provided the same low yield of adduct as \( n \)-heptanal (Table 7, entry 3), indicating that competing aldehyde enolization was not the major problem during these reactions.

A separate experiment, in which the products derived from the reaction of 7 with \( n \)-heptanal were quenched by a slight excess of Me\(_3\)SiCl followed by careful removal of solvent under anhydrous conditions, unexpectedly provided a 1:1 mixture (by \(^1\)H NMR analysis) of 1-bromo-1-trimethylsilylethylene and 2-bromo-3-trimethylsiloxy-1-nonene (49a) (Scheme 43). No traces of silyl enol ethers derived from trapping the \( n \)-heptanal enolate could be observed.

**Scheme 43. Reaction of 7 with \( n \)-heptanal after anhydrous Me\(_3\)SiCl quench**

\[
\begin{align*}
\text{n-C}_6\text{H}_{13}^\text{O} &\quad + \quad \text{n-C}_6\text{H}_{13}^\text{Li}^\text{Br} &\quad \rightarrow \quad \text{n-C}_6\text{H}_{13}^\text{OSiMe}_3^\text{Br} &\quad + \quad \text{Me}_3\text{Si}^\text{Br} \\
\text{n-C}_5\text{H}_{11}^\text{O} &\quad \text{base} &\quad \rightarrow \quad \text{n-C}_5\text{H}_{11}^\text{OSiMe}_3 &\quad + \quad \text{n-C}_5\text{H}_{11}^\text{O}^\text{SiMe}_3 \\
\text{Me}_3\text{SiCl} &\quad \rightarrow \quad &\quad \text{Me}_3\text{Si}^\text{Br} &\quad \text{Me}_3\text{Si}^\text{Br}
\end{align*}
\]

*these products were not detected!*

The above results are consistent with a competitive trapping of the initially formed alkoxide adduct 52 (Scheme 44) by a second molecule of aldehyde, with the facility of this reaction depending on the electrophilicity of the aldehyde substrate. Less
electrophilic conjugated aldehydes such as benzaldehyde and $\alpha,\beta$-unsaturated aldehydes presumably react more sluggishly with 52, allowing efficient trapping of 7 by the aldehyde (Table 4, entries 2, 7-9). In contrast, more electrophilic aldehydes appear to compete effectively for alkoxide adduct 52, presumably leading eventually to the formation of an aldehyde oligomerization product 53 (Scheme 44).

**Scheme 44. Possible side reactions of 7 with highly electrophilic aldehydes**

If this mechanism was indeed operating, we considered that the competitive addition of 7 to an aldehyde in the presence of $\text{Me}_3\text{SiCl}$ might lead to the preferential silylation of alkoxide adduct 52 before it could react with a second molecule of the aldehyde. The success of this approach would depend on the relative rates of silylation for unreacted 7 and for the initially formed 52. Given the hard nature of the alkoxide anion 52, we anticipated that $\text{Me}_3\text{SiCl}$ might react preferentially with 52 over 7. In practice, addition of a mixture of 2 eq $\text{Me}_3\text{SiCl}$ and 1 eq $n$-heptanal to 3 eq 7 at –115 °C afforded a complex product mixture which contained trimethylsilyl ether 49a as the major product, as well as
some other byproducts. This reaction mixture promptly hydrolyzed upon contact with silica, precluding purification of the silyl ether 49a. However, deliberate hydrolysis of the silyl ether (aq CF₃COOH in CH₂Cl₂) followed by vacuum distillation afforded the desired allylic alcohol 49 in 74% yield (Table 7, entry 2). Similarly, reaction of 4-trifluoromethylbenzaldehyde under these conditions afforded allylic alcohol 50 in 77% yield (Table 7, entry 4).

In order to find the most efficient competitive trapping agent, several common silylating reagents were surveyed. Interestingly, the initially chosen Me₃SiCl provided the best overall yields of the desired adducts. Me₃SiI and Me₃SiOTf were excessively reactive toward 7, resulting in predominant formation of 1-bromo-1-trimethylsilylethene (Scheme 44), while Et₃SiCl and t-BuMe₂SiOTf were not sufficiently reactive to efficiently intercept anion 52.

In order to further explore the synthetic utility of 7 under these in situ silylation conditions, a series of protected α-hydroxy aldehydes were examined as electrophiles (Table 8). 2 Eq of Me₃SiCl and 3 eq of 7 were used as the standard conditions to suppress aldehyde polymerization. These reactions were complicated by the formation of bis-protected diols (eq 3) which had to be carefully hydrolyzed to afford the desired monoprotected diol product. (Only traces of the corresponding addition products were obtained without the Me₃SiCl additive.) Quite variable yields and diastereoselectivities were observed in these reactions, depending on the nature of the protecting group.
From a practical standpoint, the t-BuMe₂Si-protected α-hydroxy aldehydes turned out to be the most useful substrates because of the preparatively useful diastereomeric ratios (89:11 and above) obtained with these substrates.

Table 8. Reactions of 7 with protected linear α-hydroxy aldehydes followed by hydrolysis

| entry | aldehyde(a) | product (major diastereomer) | dr     | isolated yield b, % | isolated yield is given for:
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MOMO</td>
<td>54a</td>
<td>77 : 23</td>
<td>62</td>
<td>inseparable mixture of diastereomers</td>
</tr>
<tr>
<td>2</td>
<td>BnO</td>
<td>55a</td>
<td>60 : 40</td>
<td>53</td>
<td>inseparable mixture of diastereomers</td>
</tr>
<tr>
<td>3</td>
<td>t-BuMe₂SiO</td>
<td>56a</td>
<td>93 : 7</td>
<td>49</td>
<td>isolated major diastereomer</td>
</tr>
<tr>
<td>4</td>
<td>t-BuPh₂SiO</td>
<td>57a</td>
<td>68 : 32</td>
<td>35</td>
<td>inseparable mixture of diastereomers</td>
</tr>
<tr>
<td>5</td>
<td>t-BuMe₂SiO</td>
<td>58a</td>
<td>89 : 11</td>
<td>50</td>
<td>isolated major diastereomer</td>
</tr>
<tr>
<td>6</td>
<td>Et₃SiO</td>
<td>59a</td>
<td>93 : 7</td>
<td>35</td>
<td>isolated major diastereomer</td>
</tr>
</tbody>
</table>

a A mixture of aldehyde (1 eq) with Me₂SiCl (2 eq) was added to 7 (3 eq) at -112-115 °C (Trapp mixture).

b After hydrolysis with aq CF₃COOH in CH₂Cl₂.
Also it was possible to selectively remove the Me$_3$Si group while the more robust t-BuMe$_2$Si group remained intact, and then cleanly isolate the products as single diastereomers by conventional flash chromatography (Table 8, entries 3 and 5.)

Again, these results showed that a chelation mechanism did not operate during the addition of 7 to variously protected $\alpha$-hydroxy aldehydes. In every case the major diastereomer of the deprotected product was the *anti*-diol, suggesting Felkin-Ahn control during the addition of 7 to the aldehyde.

The *anti*-configuration of the products 56b and 58b (Table 8, entries 3 and 5,) was established after complete deprotection to the corresponding diols 61 and 60, followed by conversion to the cyclic acetonides 61a and 60a. A comparison of the observed $^3$J$_{H3-H4}$ coupling constants with very closely related literature compounds$^{73}$ allowed determination of the *anti*-stereochemistry (Scheme 45).

**Scheme 45. Establishing the configuration of the major diastereomers of 56b and 58b**

![Scheme 45](image)
High levels of Felkin-Ahn diastereoselectivity were seen with some \( \alpha \)-siloxyl aldehydes (e.g. Table 8, entries 3, 5 and 6). The much lower levels of stereocontrol observed for \( \alpha \)-methoxymethyloxy and \( \alpha \)-benzyloxy aldehydes (Table 8, entries 1 and 2) is consistent with the smaller size of the benzyloxy and methoxymethyloxy groups when compared to the siloxy moieties (entries 3 – 6). Somewhat surprising is the low level of Felkin-Ahn selectivity seen for the \( t \)-BuPh\(_2\)SiO-protected substrate (Table 8, entry 4) while \( t \)-BuMe\(_2\)SiO- and Et\(_3\)SiO- protected \( \alpha \)-hydroxy aldehydes react with very high Felkin-Ahn control. It also interesting to note that high levels of diastereoselection were seen only for some \( \alpha \)-siloxyl aldehydes, while the analogous reactions of 1-bromo-1-lithio-2-methylpropene with MEM protected aldehyde proceeded with very high Felkin-Ahn diastereoselectivity (see Scheme 5). We currently have no explanation for these observations.

### 3.5. Reaction of 1-bromo-1-lithioethene (7) with acetyltrimethylsilane

Since acetyltrimethylsilanes are often used as masked aldehydes\(^{74} \), we felt that it would be of some interest to examine commercially available acetyltrimethylsilane as a trapping reagent for 7. Somewhat discouragingly, it was reported that reactions of \( \alpha \)-substituted vinylmetals with acetyltrimethylsilanes are not clean, and the expected products are susceptible to Brook rearrangement\(^{75} \). However, to our surprise, acetyltrimethylsilane reacted cleanly with 7, providing the \( \alpha \)-silyl alcohol \( \textbf{62} \) after a vacuum distillation in good yield (Scheme 46). No evidence for any Brook rearrangement products was observed.
3.6. Electrophilic trapping of 1-bromo-1-lithioethene (7) with non-carbonyl electrophiles

3.6.1. Trapping 7 with silicon-based electrophiles

All the synthetic work presented so far was concerned with electrophilic trapping of 7 with various carbonyl compounds. In order to further explore the scope and limitations of this reagent, we were interested to examine the feasibility of intercepting 7 with various non-carbonyl electrophiles. Prior to our studies, it was known that 1-bromo-1-lithioethene
(7) could be trapped in situ with Me$_3$SiCl.$^{21}$

Scheme 47. Potential one step synthesis of 1-bromo-1-chlorosilylenes

With a potential one step synthesis of 1-bromo-1-chlorosilylenes in mind as potential synthetic building blocks (Scheme 47),$^{77}$ we have examined the use of several chlorosilanes as electrophiles to trap 7. The results of these trapping reactions are presented in the Table 9.

Table 9. Trapping of 1-bromo-1-lithioethene (7) with silicon-based electrophiles

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>product</th>
<th>isolated yield, % (slow addition)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeSiClClMe</td>
<td>MeSiClClBr</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>MeSiClNEt$_2$</td>
<td>no reaction</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PhSiClPh</td>
<td>no reaction</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>EtSiClEt</td>
<td>EtSiBrCl</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>ClSiClCl</td>
<td>ClSiBrCl</td>
<td>47</td>
</tr>
</tbody>
</table>

$^a$The chlorosilane electrophile was added slowly to 7 over 10 to 20 min at -112 to -115 °C
The low degree of steric crowding in dichlorodimethylsilane resulted in bis-coupling with 7 to afford the bis-ethenylsilane 67 in good yield (entry 1). The corresponding chloro-N,N-diethylaminodimethylsilane did not react with 7 (entry 2), nor did the more crowded dichlorodiphenylsilane (entry 3). It was possible to achieve selective monocoupling with 7 using dichlorodiethylsilane to afford the ethenylchlorosilane 68, albeit in low yield. Much more respectable yields of selective monocoupling products were seen for the more crowded dichlorodisopropylsilane, leading to the isolation of 69 in 47% yield (entry 5).

Scheme 48. The published precedent of employing 64 in an intramolecular radical cyclization

Compound 69 is a more crowded variant of the bromoethenyl chlorosilane 64 initially employed by Tamao et al. for directing an intramolecular radical cyclization reaction (Scheme 48). However, we found that 69 has two advantages over 64: its preparation requires only one step (instead of 3 steps for 64) and all intermediates (e.g. 70 and 71, Scheme 49) are sufficiently stable to be isolated by conventional flash chromatography. In contrast, the corresponding dimethylsilyl analogs 65 and 66 are labile on silica which precluded the isolation of the final cyclized product 66.77

Because of the increased steric congestion around the silicon atom in 69, the corresponding silyl ethers (such as 70 and 71) exhibited similar stability to hydrolytic
cleavage as $t$-BuMe$_2$Si-protected alcohols.

Scheme 49. Using more crowded 1-bromo-1-chlorosilylene 69 to direct radical cyclization

For example, compound 72 (Scheme 50) underwent clean reduction upon treatment with DIBAH, and more importantly, survived the aqueous workup necessary to cleave the resulting aluminum complex after the reduction. In other words, 69 (unlike it known analog 64) potentially could be used as an alcohol protection group with latent functionality.

Scheme 50. An example of using 69 as a protecting group

Radical translocation reactions$^{78}$ are another interesting area where 69 potentially could be used. In specifically designed substrates under appropriate conditions, the initially formed radical can undergo a 1,5- (or, rarely, a 1,6-) intramolecular hydrogen
shift with formation of a new “translocated” radical which could be, in turn, intercepted.

Scheme 51. An example of a radical translocation reaction

Bromoalkenes are especially interesting in this regard because the double bond of the reagent itself can intercept this newly formed “translocated” radical leading to a functionalized methylecyclopentane (Scheme 51). Bromoethenyl chlorosilane 69 potentially could be employed in such chemistry. By analogy with published data, we anticipated that functionalized glucose might be a suitable molecule for the aforementioned chemistry, allowing for a method of direct functionalization of an unactivated sugar backbone (Scheme 52)

Scheme 52. The expected translocation reaction pathway of glucose derivative 74
The single substrate 74 that we prepared from 69 unexpectedly provided the 1,6-
translocation product 75 rather than the expected 1,5-translocation product 74a, albeit in
very poor isolated yield (6-7% along with the reduced material 74b) (Scheme 53).

Scheme 53. The observed radical translocation reaction of glucose derivative 74

We were unable to optimize this reaction by varying the hydride reagent (Bu3SnH,
(Me3Si)3SiH), solvent (benzene, t-butylbenzene), hydride reagent concentration (0.1M to
0.001M), radical initiator (AIBN or Et3B) or temperature (60-130 °C).

Scheme 54. Synthesis of a potential radical translocation tether 78
We also tried to change the geometry of the tether by using 76 as an electrophile to trap 1-bromo-1-lithioethene (7) in the first place. The chloromethylsilane derivative 77 was not isolated, but instead it was directly transformed into the corresponding iodomethylsilane derivative 78 using NaI. Unfortunately, 78 turned out to be completely unreactive toward a secondary hydroxy group under the range of conditions examined (K$_2$CO$_3$/acetone, NaH/DMF, Ag$_2$O/DMF).

3.6.2. Trapping 7 with tributylchlorostannane and iodine

We also were interested in the preparation of bromoethenylstannane 79 as a potential building block for organic synthesis. 1-Iodoethenylstannane was obtained previously in 40% ($^1$H NMR yield, see Scheme 7) but was not isolated. However, the corresponding 2-haloethenylstannanes have been isolated$^{79}$ and, in one case, were shown to be useful substrates for transmetallation and Diels-Alder cycloaddition.$^{80}$ Trapping 7 with Bu$_3$SnCl afforded 79 in moderate yield (Table 10, entry 1A) along with unreacted Bu$_3$SnCl. During this experimental work we noticed that fast addition (over 5-10 sec instead of the usual 5-25 min) of a precooled Bu$_3$SnCl solution to a slurry of 7 gave much better yields of the desired bromoethenylstannane 79 (85%, Table 10, entry 1B).

Campos et al.$^{19}$ had previously reported the low yielding trapping of 1-iodo-1-lithioethene by I$_2$ (25% $^1$H NMR yield, see Scheme 7). Slow addition of an I$_2$ solution in ether (9% solutions of I$_2$ in ether do not crystallize at –112 °C while I$_2$ dissolved in THF precipitates out from the solution below –100 °C at much lower concentrations) to 7 afforded disappointing results when I$_2$ was added slowly (0-10% isolated yield, Table 10,
entry 2A). However, a more respectable 40\% isolated yield was obtained when the I\textsubscript{2} was added rapidly (Table 10, entry 2B). Surprisingly, 1-bromo-1-iodoethene (13) has not previously been reported.\textsuperscript{81} However, given the utility of (E)-1-bromo-2-iodoethene as a synthetic building block,\textsuperscript{82} we anticipate that 1-bromo-1-iodoethene will be a useful 1,1-difunctionalized ethenyl synthon.

Table 10. Trapping of 7 with tributylchlorostannane and iodine

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>product</th>
<th>isolated yield, % (slow addition)a</th>
<th>isolated yield, % (fast addition)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu\textsubscript{3}SnCl</td>
<td>Bu\textsubscript{3}SnCl</td>
<td>40-60</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>I\textsubscript{2}</td>
<td>Br\textsubscript{3}SnBu\textsubscript{3} 79</td>
<td>0-10</td>
<td>40</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Electrophile added over 10 - 15 min.
\textsuperscript{b}Electrophile added over 5 - 10 sec.

It seems plausible that lithium halides, which were forming along with the desired product in these reactions, were crystallizing on the surface of the solid 7 during the slow addition of the electrophile, thus isolating it from the electrophile. On the subsequent warm-up step, the rate of diffusion of the electrophile through a crust of lithium salts might be lower than the rate of thermal decomposition of residual 7, resulting in incomplete trapping of the electrophile. Conversely, fast addition of the electrophile caused the internal reaction temperature to rise up to \(\text{–90} \, ^\circ\text{C}\). At this temperature, 7 became soluble and would be expected to decompose, however, the rate of trapping of dissolved 7 with the added electrophiles was apparently much faster than the rate of its thermal decomposition, allowing the generation of the adducts 79 and 13 in reasonable
During our experimental work we have encountered some limitations with the synthetic utility of 1-bromo-1-lithioethene (7). We found that epoxides were completely unreactive toward 7 even in the presence of BF$_3$•Et$_2$O or CeBr$_3$. In addition, crowded ketones such as 2,6-dimethylcyclohexanone provided only traces of addition product, independent of the conditions used. Finally, attempts to conduct transmetallation reactions by using derivatives of more electropositive elements than Si or Sn (e.g. ZnCl$_2$, ZnBr$_2$, Zn(OTf)$_2$, B(OMe)$_3$, CeCl$_3$, CeBr$_3$, ClTi(O$_{i}$-Pr)$_3$, Cl$_2$Ti(O$_{i}$-Pr)$_2$ and BeCl$_2$) under various conditions have failed, to date, to afford any synthetically useful results.

Overall 1-bromo-1-lithioethene (7) has proved to be a synthetically useful reagent. In most cases, good yields and preparatively useful levels of diastereoselectivities were observed in reactions of 7 with carbonyl compounds. In all cases, the less crowded side of the carbonyl group was attacked preferentially regardless of other substituents present in the electrophile. In case of α- or α,β-oxygenated aldehydes and ketones, the addition of 7 provides a facile approach to products which are not easily available via conventional organometallic reagents due to intramolecular chelation.

Trapping 7 with various non-carbonyl-based electrophiles provided a convenient one-step access to multifunctional compounds such as 1-bromoethenyl dialkylchlorosilanes, 1-bromoethenyl tributylstannane and, to 1-iodo-1-bromoethene. These compounds, in turn, could be useful as building blocks for organic synthesis.
Chapter 4. Ireland-Claisen rearrangement of α-bromoallylic esters

4.1. Introduction

The Ireland-Claisen rearrangement is a powerful tool for the synthesis of γ,δ-unsaturated carboxylic acids starting from easily accessible esters of allylic alcohols (Scheme 55).

Scheme 55. Mechanism of Ireland Claisen rearrangement

The Ireland-Claisen rearrangement of α-bromoallylic esters is interesting synthetically due to the possibility of the further elaboration of the obtained γ-bromo-γ,δ-pentenoic acids (eq 4).

However, the halogen atom present in the starting ester potentially poses some problems during this transformation due to possible dehydrobromination during the preparation of the required silylketene acetal derivative (Scheme 55).

The available literature precedents concerning the use of α-haloallylic esters (where halo is Cl, Br or I) as substrates for Ireland-Claisen rearrangement are confined
exclusively to a few examples involving secondary \( \alpha \)-bromoallylic esters. In addition, in most cases, the variety of \( \alpha \)-bromoallylic esters used is limited to those derived from 6- or 5-membered 2-bromocycloalk-2-en-1-ols\(^{85,86,87} \) (Scheme 56). These examples proceeded in moderate to good yields and with moderate to high diastereoselectivity.

**Scheme 56. Published precedents of Ireland-Claisen rearrangement of cyclic \( \alpha \)-bromoallylic esters**

A recent report indicated a failure to induce Ireland-Claisen rearrangement of a series of acyclic \( \alpha \)-bromoallylic esters with the Corey reagent due to a lack of reactivity.\(^{88} \)
The introduction of a bulky silyl substituent in the starting $\alpha$-bromoallylic ester, as well as changing the conditions for the intermediate silyl ketene acetal preparation, allowed the authors to obtain the rearranged product in a good yield as a single enantiomer after debromosilylation (Scheme 57).\(^{88}\)

**Scheme 57. Precedent of Ireland-Claisen rearrangement of acyclic $\alpha$-bromoallylic ester**

To the best of our knowledge, no attempts have been made to use tertiary $\alpha$-bromoallylic esters as substrates for Ireland-Claisen rearrangement.

The enolate generation step is an indispensable part of the Ireland-Claisen transformation. The very first approach, developed by Ireland, relied upon the observed fact that esters predominantly produced $(E)$-silyl ketene acetals if treated with LDA in THF and then trapped with $t$-BuMe$_2$SiCl in THF at $-78 \, ^{\circ}$C. The same sequence of reactions allowed predominantly $(Z)$-silyl ketene acetals in the presence of HMPA (Scheme 58).\(^{89}\)

**Scheme 58. Selective formation of $(E)$-and $(Z)$-silyl ketene acetals**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>$E$ products ratio</th>
<th>$Z$ products ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDA (1.1 eq) in THF, $-78 , ^{\circ}$C, then $t$-BuMe$_2$SiCl</td>
<td>91 : 9</td>
<td>16 : 84</td>
</tr>
</tbody>
</table>
These conditions have found widespread application in organic synthesis, and they remain the standard conditions for the preparation of Ireland-Claisen precursors.

Several different approaches also have been developed for the generation of silyl ketene acetals. Using one set of conditions that were developed for use with base sensitive-substrates, an α-fluoroacetate ester was almost quantitatively converted into the corresponding silyl ketene acetal upon treatment with Me$_3$SiOTf / Et$_3$N in dichloromethane at –78 °C to rt. The geometry of the major product obtained implied the predominant formation of a (Z)-silyl ketene acetal intermediate, assuming the operation of a chair-like transition state (Scheme 59). Similar sets of conditions for silyl ketene acetal preparation, including Me$_3$SiOTf/Et$_3$N, $t$-BuMe$_2$SiOTf/tertiary amine, Me$_3$SiOTf/2,6-lutidine and polymer-supported diethylsilyltriflate/tertiary amine mixtures were used for Ireland-Claisen rearrangement of sensitive substrates.

**Scheme 59. α-Fluoroacetate enolization using Me$_3$SiOTf/Et$_3$N**

\[
\begin{align*}
\text{F} & \quad \text{Me$_3$SiOTf (1.1 eq)} \\
\text{O} & \quad \text{Et$_3$N, CH$_2$Cl$_2$} \\
\text{Me} & \quad -78 \degree C \text{ to rt} \\
\text{Me} & \quad \text{O} \\
\text{F} & \quad \text{OTMS} \\
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{OH}
\end{align*}
\]

In another approach, it was found that quite stable manganese kinetic enolates could be obtained upon treatment of ketones with PhN(Me)MnCl, which was prepared *in situ* from $n$-BuLi, PhNHMe and MnCl$_2$. The approach was further developed by Kazmaier who used chelated manganese enolates in Ireland-Claisen rearrangement reactions (Scheme 60).
Scheme 60. Chelated manganese enolate Ireland-Claisen (or Kazmaier-Claisen) rearrangement

In general, the replacement of silyl ketene acetals with metal enolates has proved to be a fruitful area for Ireland-Claisen rearrangement chemistry. Recently, chiral (using quinine as a chiral ligand) variants of Ireland-Claisen rearrangements of magnesium and aluminum enolates were reported (Scheme 61). Zinc enolates have also proved to be suitable substrates for the Ireland-Claisen rearrangement.

Scheme 61. Chiral variant of Ireland-Claisen rearrangement of magnesium enolates

It is ironic that Ireland’s original Claisen rearrangement chemistry was developed after it was found that lithium enolates often were too labile to be useful in such rearrangement reactions. Excluding very few specific substrates, no good yields of the rearranged products could be obtained from lithium enolates due to enolate fragmentation and other competing reactions.

Given that α-bromoallylic alcohols are easily accessible through the trapping of 1-bromo-1-lithioethene (7) with various carbonyl compounds (see Chapter 3), we were
interested in determining the scope and limitations of the Ireland-Claisen rearrangement reaction using $\alpha$-bromoallylic esters.

4.2. Ireland-Claisen rearrangement of simple $\alpha$-bromoallylic propionates

A series of $\alpha$-bromoallylic alcohols obtained by reaction of 1-bromo-1-lithioethene (7) with aldehydes or ketones (see Chapter 3) were uneventfully converted into the corresponding propionate or acetate esters upon treatment with DMAP (1.2 eq) and either propionic anhydride or acetic anhydride. Secondary $\alpha$-bromoallylic alcohols reacted rapidly at rt while tertiary $\alpha$-bromoallylic alcohols required heating at 40 to 50 °C for 24 to 48 h (see Table 11).

As we proceeded with these $\alpha$-bromoallylic ester substrates in Ireland-Claisen rearrangement chemistry, we recognized that the potential liability of $\alpha$-bromoallylic esters to undergo dehydrobromination would require a careful choice of reaction conditions for initial enolate generation. Indeed, an attempt to enolize bromoallyl propionate $80a$ under original Ireland conditions$^{84}$ (LDA, THF, -78 °C to rt, then $t$-BuMe$_2$SiCl) gave a mixture of intractable products. However, use of a milder base LiN(SiMe$_3$)$_2$ afforded the desired propenoic acid Ireland-Claisen rearrangement product $80b$ in 56% yield (Scheme 62). The (Z)-stereochemistry of the resulting bromoalkene was exactly as expected based on a chair-like transition state for the rearrangement step (Scheme 62). The structure of $80b$ does not allow unambiguous assignment of the intermediate silyl ketene acetal stereochemistry,
Table 11. Esterification of various α-bromoallylic alcohols

<table>
<thead>
<tr>
<th>entry</th>
<th>starting material</th>
<th>product structure</th>
<th>product number</th>
<th>time, h</th>
<th>temperature, °C</th>
<th>isolated yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td><img src="image1.png" alt="Structure Image 1" /></td>
<td>80a</td>
<td>3</td>
<td>rt</td>
<td>80%</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td><img src="image2.png" alt="Structure Image 2" /></td>
<td>81a</td>
<td>48</td>
<td>40</td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td><img src="image3.png" alt="Structure Image 3" /></td>
<td>83a(R=Me)</td>
<td>48</td>
<td>40</td>
<td>80%</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td><img src="image4.png" alt="Structure Image 4" /></td>
<td>84a(R=H)</td>
<td>48</td>
<td>40</td>
<td>85%</td>
</tr>
<tr>
<td>5</td>
<td>29b</td>
<td><img src="image5.png" alt="Structure Image 5" /></td>
<td>85a</td>
<td>48</td>
<td>60</td>
<td>97%</td>
</tr>
<tr>
<td>6</td>
<td>30b</td>
<td><img src="image6.png" alt="Structure Image 6" /></td>
<td>86a(R=Me)</td>
<td>48</td>
<td>rt</td>
<td>86%</td>
</tr>
<tr>
<td>7</td>
<td>30b</td>
<td><img src="image7.png" alt="Structure Image 7" /></td>
<td>87a(R=H)</td>
<td>48</td>
<td>rt</td>
<td>89%</td>
</tr>
<tr>
<td>8</td>
<td>21</td>
<td><img src="image8.png" alt="Structure Image 8" /></td>
<td>88a</td>
<td>48</td>
<td>40</td>
<td>78%</td>
</tr>
<tr>
<td>9</td>
<td>21</td>
<td><img src="image9.png" alt="Structure Image 9" /></td>
<td>89a</td>
<td>16</td>
<td>rt</td>
<td>80%</td>
</tr>
<tr>
<td>10</td>
<td>24b</td>
<td><img src="image10.png" alt="Structure Image 10" /></td>
<td>90a(R=Me)</td>
<td>19</td>
<td>40</td>
<td>75%</td>
</tr>
<tr>
<td>11</td>
<td>24b</td>
<td><img src="image11.png" alt="Structure Image 11" /></td>
<td>91a(R=H)</td>
<td>19</td>
<td>40</td>
<td>86%</td>
</tr>
<tr>
<td>12</td>
<td>25</td>
<td><img src="image12.png" alt="Structure Image 12" /></td>
<td>92a</td>
<td>3h</td>
<td>rt</td>
<td>81%</td>
</tr>
<tr>
<td>13</td>
<td>25</td>
<td><img src="image13.png" alt="Structure Image 13" /></td>
<td>93a</td>
<td>16</td>
<td>rt</td>
<td>82%</td>
</tr>
<tr>
<td>14</td>
<td>27</td>
<td><img src="image14.png" alt="Structure Image 14" /></td>
<td>94a</td>
<td>3</td>
<td>rt</td>
<td>80%</td>
</tr>
</tbody>
</table>
although this reaction would be expected to proceed via an (E)-silylketene acetal when using LiN(SiMe$_3$)$_2$ as a base in the absence of HMPA.

**Scheme 62. Ireland-Claisen Rearrangement of the secondary α-bromoallylic ester 80a**

In stark contrast, *tertiary* α-bromoallylic ester 81a yielded only 6% of the corresponding pentenoic acid 81b under the same reaction conditions (Scheme 63). In an attempt to increase the yield, we decided to explore other methods of enolate formation. Enolization using LiN(SiMe$_3$)$_2$ in the presence of HMPA allowed for a 47% yield of 81b, while Me$_3$SiOTf / Et$_3$N conditions$^{90}$ provided a further increase in the yield of 81b up to 77%.

**Scheme 63. Ireland-Claisen rearrangement of the tertiary α-bromoallylic ester 81a**

conditions: isolated yield of 81b, %
1. LiN(SiMe$_3$)$_2$, THF,
2. t-BuMe$_2$SiCl, (-78 °C to rt)
1. LiN(SiMe$_3$)$_2$, THF-HMPA (77:23),
2. t-BuMe$_2$SiCl, (-78 °C to rt)
Me$_3$SiOTf, Et$_3$N,
CH$_2$Cl$_2$, -78°C to rt

87
This unexpected behavior can be indirectly rationalized by comparing the calculated (at HF6-31G* level of theory) transition state (TS) energies for Ireland-Claisen rearrangements employing the closely related silyl ketene acetals 82a and 82b (Scheme 63) (these compounds were initially calculated for a different purpose; the detailed discussion will be presented later in the text). For silyl ketene acetals 82a and 82b, all possible transition states leading to the rearranged product were located. The two lowest energy transition states from each silyl ketene acetal stereoisomer are presented in Fig. 13.

Fig. 13. Lowest energy TS leading to Ireland-Claisen rearrangement from silylketene acetals 82a and 82b

The indicated 7.0 kcal/mol difference in TS barriers for Ireland-Claisen rearrangement of the (E)- and (Z)- silyl ketene acetals corresponds to an approximately $1.3\times10^5$ ratio of reaction rates at rt. For TS-E, the methyl group derived from the enolized
propionate is forced into an axial position where it ends up in close proximity to a pseudoaxial bromine atom. The resulting steric crowding leads to a less symmetrical TS geometry with a shorter C-O bond and a longer C-C bond (Fig. 13), raising the energy of the TS. In addition, the total count of axial / pseudoaxial substituents in TS-E is four (Br, OSiMe₃, the methyl group and the vinyl group) which leads to a quite congested TS and thus to an impractically slow rate of reaction. For TS-Z, the methyl group resulting from the enolized propionate is in an equatorial orientation while the total count of axial / pseudoaxial substituents in TS-Z is only three (Br, OSiMe₃, and the vinyl group).

Therefore, the lower energy TS derives from rearrangement of the (Z)-silyl ketene acetal.

In comparison, silyl ketene acetals resulting from secondary α-bromoallylic alcohols would have a decreased number of axial / pseudoaxial substituents in the corresponding TSs: three for TSs derived from an (E)-silyl ketene acetal and two TSs derived from a (Z)-silyl ketene acetal. Overall, this means that esters of secondary α-bromoallylic alcohols should be more reactive than esters of tertiary α-bromoallylic alcohols. In both cases, (Z)-silyl ketene acetals should rearrange faster than their (E)- counterparts.

Scheme 64. Ireland-Claisen rearrangement of an unsymmetrical tertiary α-bromoallylic ester 83a

Given the better isolated yields of rearranged products under LiN(SiMe₃)₂/
\( \text{t-BuMe}_2\text{SiCl} / \text{HMPA} \) and \( \text{Me}_3\text{SiOTf} / \text{Et}_3\text{N} \) enolization conditions, which both facilitated (Z)-silyl ketene acetal formation, the above calculation results seems to be in a good agreement with the experimental data.

With unsymmetrical tertiary \( \alpha \)-bromoallylic esters \( ({}^1\text{R} \neq {}^2\text{R}, \text{eq 6}) \), however, one could not expect any useful \( E/Z \) selectivity unless \( {}^1\text{R} \) and \( {}^2\text{R} \) differ significantly. Indeed, propionate \( 83\text{a} \) gave a 57:43 mixture of \( E/Z \) isomers \( 83\text{b} \) in 50\% yield under \( \text{Me}_3\text{SiOTf} / \text{Et}_3\text{N} \) enolization conditions. Identical selectivity was observed when acetate \( 84\text{a} \) was subjected to the same enolization conditions (Scheme 64). Thus, we became interested in understanding which types of substituents \( {}^1\text{R} \) and \( {}^2\text{R} \) (eq 4) in the starting ester would exhibit preparatively useful \( E/Z \) alkene selectivities during Ireland-Claisen rearrangement.

### 4.3. Synthesis of 6-hydroxy-4-bromopent-4-enoic acids

The availability of functionalized \( \alpha \)-bromoallylic alcohols resulting from addition of 1-bromo-1-lithioethene (7) to various \( \alpha \)-hydroxy ketones prompted us to examine their corresponding esters as substrates for Ireland-Claisen rearrangement. The carbohydrate derived ketones were interesting substrates because of the possibility of the asymmetric induction from the carbohydrate moiety. We decided to focus our efforts on the glucose derived propionate \( 85\text{a} \) (Scheme 65), which was prepared from from ketone \( 29\text{a} \) via addition of 7 (Table 5, entry 1) followed by treatment of the \( \alpha \)-bromoallylic alcohol \( 29\text{b} \) with propionic anhydride in the presence of DMAP (Table 11, entry 5).
Unfortunately, compound 85a proved to be a relatively unreactive substrate for the desired Ireland-Claisen rearrangement. After extensive experimentation it was found that only the silyl triflate / tertiary amine enolization method could induce the desired rearrangement to some extent, while all other approaches led to the recovery of unchanged starting material 85a after workup. This outcome might reasonably be rationalized by the undesired intramolecular chelation of the intermediate metal enolate derived from 80a with the C-2 acetonide oxygen (Fig. 14) which would lock the substrate in a conformation which would prevent Ireland-Claisen rearrangement. However, currently we do not have any solid computational or experimental evidence for the formation of such an intermediate.

**Fig. 14. Possible intramolecular chelated metal enolate of derived from 85a**

Among the various silyl triflates studied only t-BuMe₂SiOTf proved to be useful
reagent for mediating Ireland-Claisen rearrangement of 85a. Me$_3$SiOTf led to an unselective opening of both cyclic ketals in 85a (eq 5), while i-Pr$_3$SiOTf exhibited no reactivity toward 85a.

![Chemical diagram](image)

(ratio determined from $^1$H NMR analysis of crude reaction mixture)

When using tBuMe$_2$SiOTf, careful optimization of the reaction conditions afforded a 33-35% isolated yield of 85b which was obtained by slow addition of t-BuMe$_2$SiOTf (1.5 eq, 10h, syringe pump) to a mixture of 85a and Et$_3$N (5.0 eq) in CH$_2$Cl$_2$ at rt (Scheme 65). Despite of the mediocre yield of 85b, the asymmetric induction from the carbohydrate moiety was complete and only a single diastereomer of 85b was observed in the crude reaction mixture by $^1$H NMR. The stereochemistry of 85b was initially determined by nOe studies and was further confirmed by a single crystal X-ray analysis of the solid cesium salt 85c.

Esters of $\alpha$-bromoallylic alcohols derived from addition of 1-bromo-1-lithioethene (7) to acyclic $\alpha$-hydroxy ketones proved to be much less useful substrates for the Ireland-Claisen rearrangement. For example, propionate ester 86a (Scheme 66) gave only an 8% combined yield of target acids under the previously optimized conditions, albeit with acceptable alkene (4:1) $E/Z$ stereo-selectivity. The rest of the starting material 86a was consumed by some unidentified side reactions. In contrast, acetate ester 87a provided a
good yield of the rearranged product but with decreased alkene E/Z selectivity (Scheme 66).

Scheme 66. Synthesis of acyclic 6-hydroxy-4-bromopent-4-enoic acid derivatives

To establish the alkene configuration the acid mixture \( 87b+87c \) was treated with ethereal diazomethane to obtain the corresponding methyl esters and then the mixture was partially separated (only the less polar major component \( 87d \) could be obtained as a relatively pure substance). NOe studies proved the \((E)\)-geometry of the major product \( 87d \) (and thus \( 87b \)). The alkene configuration for propionate derivative \( 86b \) was assumed to be analogous to \( 87b \).

Overall, the introduction of the protected \( \alpha' \)-hydroxy substituent into the starting tertiary \( \alpha \)-bromoallylic alcohol significantly lowered the rate of the Ireland-Claisen
rearrangement, rendering these kinds of substrates only marginally useful for preparative synthesis.

4.4. Synthesis of 3-bromo-3,5-pentadienoic acids

Another group of tertiary α-bromoallylic alcohols which could potentially exhibit useful alkene E/Z selectivity were adducts of 1-bromo-1-lithioethene (7) with α,β-unsaturated ketones. These bis-allylic alcohol derived substrates were especially interesting because of the added possibility of selectively engaging the bromine-bearing π-bond versus the non-halogenated alkene moiety (Scheme 67).

Scheme 67. Regioselectivity during rearrangement of esters of bis-allylic alcohols

Esterification of 21 (Table 4, entry 3) with a propionic anhydride / DMAP mixture in CH₂Cl₂ (rt, 48h) afforded a 78% yield of the propionate 88a (Table 11, entry 8) which was then treated with Me₃SiOTf in the presence of excess Et₃N (CH₂Cl₂, rt, 24h).

Scheme 68. Possible decomposition pathway for 88a in the presence of silyltriflates
We were unable to isolate any acidic material by aq K$_2$CO$_3$ extraction from the resulting product solution, while $^1$H NMR analysis of the crude reaction mixture was intractable (Table 12, entry 1). Exactly the same outcome was observed when $t$-BuMe$_2$SiOTf was employed instead of Me$_3$SiOTf (Table 12, entry 2). These results could be rationalized by assuming that, after the silyl triflates attacked the ester carbonyl oxygen atom in 88a, the desired $\alpha$-deprotonation reaction was outcompeted by formation of a tertiary bis-allylic carbocation and subsequent further uncontrollable polymerization (Scheme 68).

Table 12. Optimization of the reaction conditions for Ireland-Claisen rearrangement of 88a

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>temperature, °C (time, h)</th>
<th>combined yield</th>
<th>ratio of 83b</th>
<th>83c</th>
<th>83d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me$_3$SiOTf / Et$_3$N</td>
<td>rt (62)</td>
<td>0%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>$t$-BuMe$_2$SiOTf / Et$_3$N</td>
<td>rt (24)</td>
<td>0%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>LiN(SiMe$_3$)$_2$ / Me$_3$SiCl</td>
<td>rt (62)</td>
<td>4%</td>
<td>60</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>LiN(SiMe$_3$)$_2$ / Me$_3$SiCl / HMPA</td>
<td>rt (5)</td>
<td>24%</td>
<td>80</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>3.0 eq LiN(SiMe$_3$)$_2$ / 1.0 eq ZnBr$_2$</td>
<td>60 (48)</td>
<td>35%</td>
<td>67</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>1.5 eq LiN(SiMe$_3$)$_2$ / 1.1 eq MnCl$_2$</td>
<td>70 (18)</td>
<td>9%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>2.0 eq LiN(SiMe$_3$)$_2$ / 1.1 eq MnCl$_2$</td>
<td>60 (18)</td>
<td>43%</td>
<td>87</td>
<td>13</td>
<td>n/a</td>
</tr>
<tr>
<td>8</td>
<td>3.0 eq LiN(SiMe$_3$)$_2$ / 1.1 eq MnCl$_2$</td>
<td>80 (20)</td>
<td>80%</td>
<td>83</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

*Isolated yields after extraction with base from crude reaction mixture followed by reprotonation with 1M aq HCl. Determined by $^1$H NMR analysis of the crude reaction mixture.
At this point we decided to return to the more traditional modified Ireland-Claisen enolization conditions that we exploited earlier in our studies, using LiN(SiMe₃)₂ as the base. In accordance with earlier observed trends, treatment of 88a with LiN(SiMe₃)₂ / Me₃SiCl resulted in a very poor yield of the desired acids (Table 12, entry 3), most probably because of the initial formation of an unreactive (E)-silylketene acetal (Scheme 58). An attempt to run the enolization step in the presence of 23 vol % of HMPA, which favors the formation of (Z)-silylketene acetal, provide only 24% of the desired product mixture (Table 12, entry 4). Interestingly, the brominated double bond in 88a was preferentially engaged in the Ireland-Claisen rearrangement with the predominant formation of (E)-alkene 88b. In an attempt to increase the yield of these Ireland-Claisen rearrangement reactions, we decided to try to conduct the rearrangement via metal enolates instead of silyl ketene acetals. Although zinc enolates were previously used in Ireland-Claisen rearrangement, we observed only a marginal improvement in the product yield under these conditions, while regioselectivity was eroded (Table 12, entry 5). After some experimentation we have found that the manganese enolate of 88a allowed for good overall yields of the desired product acids with preparatively useful levels of regio- and stereoselectivity (Table 12, entry 8).

After extraction with a base followed by reacidification, the resulting mixture of acids was treated with ethereal diazomethane which allowed for chromatographic separation of clean methyl ester 88e in 52% isolated yield (eq 6). The (E)-geometry of the double bond was established by nOe studies (eq 6).
Table 13. Calculated TS for rearrangement of 88a under LiN(SiMe$_3$)$_2$/Me$_3$SiCl/HMPA conditions (proceeding via the (Z)-silyketene acetal)

<table>
<thead>
<tr>
<th>entry</th>
<th>transition state geometry</th>
<th>product (after hydrolysis)</th>
<th>relative activation barrier, kcal/mol (relative reaction rate at 343K) in THF</th>
<th>relative reaction rate at 343K in vacuum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Transition State 1" /></td>
<td><img src="image2.png" alt="Product 1" /></td>
<td>$0 (1)$</td>
<td>$0 (1)$</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Transition State 2" /></td>
<td><img src="image4.png" alt="Product 2" /></td>
<td>$+1.8 (1/14)$</td>
<td>$+2.1 (1/23)$</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Transition State 3" /></td>
<td><img src="image6.png" alt="Product 3" /></td>
<td>$+2.5 (1/42)$</td>
<td>$+2.4 (1/34)$</td>
</tr>
</tbody>
</table>
Table 14. Calculated TS for rearrangement of 88a under LiN(SiMe₃)₂/Me₃SiCl conditions
(proceeding via the (E)-silylketene acetal)

<table>
<thead>
<tr>
<th>entry</th>
<th>transition state geometry</th>
<th>product (after hydrolysis)</th>
<th>relative activation barrier, kcal/mol in THF</th>
<th>relative reaction rate at 343K in THF</th>
<th>relative reaction rate at 343K in vacuum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Transition state 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>0 (1)</td>
<td>0 (1)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Transition state 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>+0.5 (1/2)</td>
<td>+0.2 (1/1.4)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Transition state 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>+0.9 (1/4)</td>
<td>+1.6 (1/10)</td>
<td></td>
</tr>
</tbody>
</table>
We were interested to gain some insight into the origin of the high selectivity seen during the rearrangement of \(88a\) by performing \textit{ab initio} calculations on possible reaction transition states. For this reaction we have located 12 transition states starting from the (Z)-trimethylsilyl ketene acetal of \(88a\) and 12 transition states starting from the (E)-trimethylsilyl ketene acetal of \(88a\) at the HF6-31G* level of theory (available within GAMESOL package\textsuperscript{45}). Within each group, 6 TSs corresponded to chair-like conformations and 6 to boat-like conformations. Within each subgroup, 2 TSs corresponded to the situation when a halogenated double bond (bond \(b\) in Scheme 67) was participating in the rearrangement and, in the remaining 4 TSs, the non-halogenated double bond (bond \(a\) on Scheme 67) was engaged. We were unable to locate other transition states for this reaction beyond the 24 TSs described above.

Only chair-like transition states were found to be important in this reaction because the corresponding boat like TSs were always at least 6 kcal/mol higher in energy. The three lowest energy TSs which emerged from rearrangement of the (Z)-silyl ketene acetal of \(88a\) (LiN(SiMe\textsubscript{3})\textsubscript{2} / Me\textsubscript{3}SiCl / HMPA enolization conditions) are presented in Table 13. HF6-31G* calculations in vacuum correctly predicted \(88b\) (Table 12, entry 4 and probably 8) being the major product, followed by \(88c\) and \(88d\). However, the predicted product selectivities (at 25 °C) were better than observed in reality (Table 15). Thus, we have subjected the 4 lowest energy TSs to HF6-31G* / SM5.42R solvated state...
calculations\textsuperscript{45} (in ether and THF). After this step the predicted ratio of products became somewhat closer to reality (Table 15, entries 2 and 3), although the experimental levels of selectivity were still somewhat lower that suggested by these calculations.

Table 15. Summary of predicted versus observed outcomes for Ireland-Claisen rearrangement of 88a

<table>
<thead>
<tr>
<th>entry</th>
<th>enolate</th>
<th>calculation method</th>
<th>predicted ratio of 88b : 88c : 88d</th>
<th>observed ratio of 88b : 88c : 88d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Z</td>
<td>HF6-31G* (vacuum)</td>
<td>93 : 4 : 3</td>
<td>80 : 12 : 8</td>
</tr>
<tr>
<td>2</td>
<td>Z</td>
<td>HF6-31G*/SM5.42R (THF)</td>
<td>91 : 6 : 3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>E</td>
<td>HF6-31G* (vacuum)</td>
<td>55 : 5 : 40</td>
<td>60 : 13 : 27</td>
</tr>
<tr>
<td>4</td>
<td>E</td>
<td>HF6-31G*/SM5.42R (THF)</td>
<td>54 : 15 : 31</td>
<td></td>
</tr>
</tbody>
</table>

For the (E)-enolate of 88a, both vacuum and solvated state calculations predict much lower regioselectivity, which also was in good agreement with the experimental results (Table 15, entries 3 and 4).

The weak dependence of the calculated outcome for vacuum computations versus THF solvated computations rendered solvent optimization as being most likely useless for improving the selectivity of the reaction. Instead, we decided to switch to different substrates to test the scope and limitations of the reaction.

TFA-protected proline ester 89a (Table 11, entry 8) provided an excellent yield during the Ireland-Claisen rearrangement step, but a noticeable decrease in regioselectivity (2:1) and alkene E/Z selectivity when compared to the propionate ester of 88a was observed (Scheme 69). It is interesting that the additional crowding introduced by the proline ring did not decreased the reaction rate in comparison with propionate ester.
88a. In contrast, the less crowded acetate 87a exhibited a significant increase in the reaction rate over the slightly more crowded propionate 86a (Scheme 66).

Scheme 69. Ireland-Claisen rearrangement of proline ester 86a

The crude mixture of carboxylic acids 89b-d was treated with diazomethane and the methyl ester of 89b was partially separated by column chromatography. NOe studies were conducted on this ester to establish the alkene stereochemistry for 89b.

Scheme 70. Rearrangement of cyclic bis-allylic alcohols

Substrates with one double bond incorporated into a ring offered complete regioselectivity during Ireland-Claisen rearrangement (Scheme 70). The formation of another regioisomer presumably was suppressed by the increased steric strain in the
transition state. Good alkene E/Z selectivity (9:1) was observed for propionate ester 90a while acetate ester 91a provided a less attractive 4:1 ratio of acids 91c and 91b. The (E)-geometry of the major product 90c was established by nOe studies while 91c was assumed to have the (E)-configuration by analogy with 90c.

Interestingly, a very similar kind of chemistry was reported recently\textsuperscript{100} (Scheme 71), albeit for an isobutyric ester of a bis-allylic alcohol structurally similar to 90a. Much lower E/Z alkene selectivity (3:1 instead of 10:1 for 90a) was observed for the Ireland-Claisen rearrangement of this ester.

Scheme 71. Reported competitive Ireland-Claisen rearrangement of a bis-allylic ester

\[ \begin{array}{c}
\text{O} & \text{O} \\
\text{HOOC} & \text{COOH} \\
\end{array} \]

Overall, esters of \textit{tertiary} bis-allylic alcohols provided reasonable alkene E/Z selectivities ranging from 4:1 to 9:1. In each case, the major isomer had the bromine substituent \textit{cis} to an \textit{sp}^3 carbon originating from the parent \textit{α,β}-unsaturated ketone. The \textit{CH}_2 group originating from the terminal methylene group of 1-bromo-1-lithioethene (7) was always in a \textit{cis}- relationship to the \textit{sp}^2 carbon originating from the starting \textit{α,β}-unsaturated ketone (compounds 88b, 89b, 90c and 91c).

In contrast, esters of \textit{secondary} bis-allylic alcohols 25 and 27 (Table 4) derived from trapping acrolein and methacrolein with 1-lithio-1-bromoethene (7) (Table 4, entries 7
and 9) did not show useful regioselectivity during Ireland-Claisen rearrangement (Table 16). This observation means that the bromine substituent does not change noticeably the reactivity of a double bond in 92a-94a. For propionate esters 92a and 94a, better yields of products were observed under Me$_3$SiOTf / Et$_3$N enolization conditions (Table 16, entry 1; compare to entries 2-5) while proline ester 93a provided an excellent yield under LiN(SiMe$_3$)$_2$ / MnCl$_2$ conditions (Table 16, entry 6).

Table 16. Ireland-Claisen rearrangement of esters of secondary bis-allylic alcohols

<table>
<thead>
<tr>
<th>entry</th>
<th>starting ester</th>
<th>conditions</th>
<th>products</th>
<th>product ratio</th>
<th>combined yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>92a</td>
<td>Me$_3$SiOTf / Et$_3$N</td>
<td>53:47</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>92a</td>
<td>LiN(SiMe$_3$)$_2$ / Me$_3$SiCl</td>
<td>58:42</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>92a</td>
<td>LiN(SiMe$_3$)$_2$ / t-BuMe$_3$SiCl</td>
<td>63:37</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>92a</td>
<td>LiN(SiMe$_3$)$_2$ / Me$_3$SiCl / HMPA</td>
<td>72:28</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>92a</td>
<td>LiN(SiMe$_3$)$_2$ / MnCl$_2$</td>
<td>decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>93a</td>
<td>LiN(SiMe$_3$)$_2$ / MnCl$_2$</td>
<td>50:50</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>94a</td>
<td>Me$_3$SiOTf / Et$_3$N</td>
<td>56:44</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>94a</td>
<td>LiN(SiMe$_3$)$_2$ / Me$_3$SiCl</td>
<td>54:46</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>94a</td>
<td>LiN(SiMe$_3$)$_2$ / Me$_3$SiCl / HMPA</td>
<td>56:44</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>94a</td>
<td>LiN(SiMe$_3$)$_2$ / MnCl$_2$</td>
<td>decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>95a</td>
<td>Me$_3$SiOTf / Et$_3$N</td>
<td>decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>95a</td>
<td>LiN(SiMe$_3$)$_2$ / Me$_3$SiCl / HMPA</td>
<td>decomposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>95a</td>
<td>LiN(SiMe$_3$)$_2$ / MnCl$_2$</td>
<td>decomposition</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CH$_2$Cl$_2$, -78 ºC to rt, then 48 h at rt. *THF, -78 ºC to rt, then 2 h at rt. *THF, -78 ºC to rt, then 5 h at rt. *THF - HMPA mixture (77:23 vol), -78 ºC to rt, then rt 1-2 h. *THF, -78 ºC to rt, then 16-24 h at 60-80 ºC.
Crotyl ester 95a (derived from bis-allylic alcohol 26, Table 4, entry 3) proved to be unstable under various enolization conditions and only intractable mixtures of products were obtained (Table 16, entry 11-13).

Good alkene E/Z selectivities were observed in all cases. Very little (less than 2%) of the possible (E)-isomers of 92b, 93b and 94b could be observed by 1H NMR analysis of the crude reaction mixture, which demonstrates that the bromine atom in these cases behaves as a non-bulky substituent.

The mixtures of acids (92b+92c, 93b+93c and 94b+94c) extracted from the reaction mixture with an aqueous base (K₂CO₃) were sufficiently clean for further use based on 1H and 13C NMR analysis. To characterize the individual acids, the corresponding mixture was treated with ethereal diazomethane and the methyl esters thus obtained were partially separated on a silica column. Alkene geometries were confirmed with nOe studies (see Experimental Section) or (for 92c and 93c) by the 3JHH coupling constant value (ca 16 Hz) which corresponds to a trans-substitution pattern at the double bond.

At this point we were interested to apply the Ireland-Claisen rearrangement of esters derived from α-bromoallylic alcohols (8) in the partial synthesis of a natural product to demonstrate the synthetic utility of this chemistry in complex molecule synthesis.

4.5. Attempted partial synthesis of VM55599

Paraherquamides, brevianamides, and asperparalines are members of an unusual family of fungal metabolites that possess a bicyclo[2.2.2]diazaoctane core ring system (Fig. 15). Some paraherquamides have displayed useful levels of anthelmintic and
antinematodal activity and are under investigation for use in veterinary medicine to treat intestinal parasites.\textsuperscript{102}

**Fig. 15. Structures of Paraherquamide A and Brevianamide A**

![Paraherquamide A and Brevianamide A](image)

VM55599 is a minor metabolite isolated from culture extracts of a Penicillium sp. (IMI332995) that also produces paraherquamide A and it is also based on a bicyclo[2.2.2]diazaoctane core. The total synthesis of VM55599 was published recently (Fig. 16).\textsuperscript{103}

**Fig. 16. Structure of VM55599 and key Diels-Alder cyclization step employed in its synthesis**

![VM55599 synthesis](image)
However, an intramolecular Diels Alder reaction which was employed as the key step of the synthetic sequence led to a mixture of three products in a 58 : 25 : 17 ratio with 60% combined yield. L-leucine was used as a chiral starting material for this synthesis, rendering access to the opposite enantiomer of VM55599 difficult.

We were interested in a different synthetic approach which potentially could allow an easier access to the bicyclo[2,2,2]diazaoctane ring system common to VM55599, the paraherquamides and the brevianamides, starting from proline (or 2-methylproline) esters.

**Scheme 72. Retrosynthetic approach to VM55599 synthesis**

Our goal was to prepare early intermediate 100 using our previously established Ireland-Claisen rearrangement chemistry (see above). This would serve to showcase our chemistry in a more complex target synthesis.
There are some potential complications in the cyclization step (96 to VM55599) in terms of regioselectivity. Molecular mechanics modeling of the corresponding products showed that the needed regioselectivity might be preferential. A simple rotation of the amide group brings a properly oriented nitrogen atom in close proximity to the \( \pi \)-bond to achieve 6-endo-trig cyclization. Of course 5-exo-trig cyclization is also possible here, but the distance between the C and N atoms is a little larger (\( ca \) by 0.15 Å). However, if the regioselectivity would be a problem, the a double bond in 96 might be placed in an exocyclic position by changing the 97 to 96 step appropriately.

**Scheme 73. Synthesis of amide 100**

In order to explore this chemistry, we elected to initially target the desmethyl analog of VM55599 (R=H) allowing use of the easy accessible proline instead commercially unavailable 2-methylproline. However, the latter unnatural amino acid is easily available in an enantiopure form by zinc enolate carbocyclization of substituted N-homoallyl glycine\(^{104}\) and other methods.\(^{105}\)
As was shown above, we knew that proline esters provided good yields of Ireland-Claisen rearranged products under LiN(SiMe$_3$)$_2$ / MnCl$_2$ enolization conditions but with a complete lack of stereoselectivity. Given that the conversion of 101 to 100 is not complicated with alkene E/Z selectivity issues, this approach seemed quite attractive.

At the beginning of the sequence, (S)-proline was protected with an ethyl trifluoroacetate / Et$_3$N mixture$^{106}$ in 85% yield. Given the crowded nature of the $\alpha$-bromoallylic alcohol 10, a modified esterification procedure was employed. At first we attempted to react 10 with diisopropylcarbodiimide in the presence of a CuCl catalyst$^{107}$ to obtain the corresponding isourea which was then reacted with the protected proline 102. However, no product 103 was formed under these conditions, so we resorted back to a more standard esterification procedure which allowed a 64% yield of 103 (Scheme 73). The product uneventfully underwent Ireland-Claisen rearrangement via the corresponding manganese enolate to afford acid 104 in excellent yield.

Scheme 74. Synthesis of diene 107

An attempt to convert the free acid 104 into an amide upon treatment with an ethyl chloroformate/Et$_3$N mixture$^{108}$ failed, but successful amide formation was achieved under diisopropylcarbodiimide / HOBT / NH$_3$ conditions.$^{109}$ The immediate product was not
isolated but instead it was deprotected under standard conditions,\textsuperscript{110} affording 84\% of crystalline amide 105.

At this point we decided to explore an obscure possibility of a Diels-Alder reaction which would provide a shortcut to the VM55599 core. Amide 105 was alkylated with allyl iodide and an intramolecular Heck reaction afforded crystalline diene 107 in good yield (Scheme 74). It was known that N-tosyl-3-nitroindole is a reasonably good dienophile substrate for Diels Alder reactions\textsuperscript{111} so we attempted a direct reaction between 107 and N-tosyl-3-nitroindole (eq 7).

\[
\begin{array}{c}
\text{N} \\
\text{CONH}_2 \\
\text{N} \\
\text{PhSO}_2 \\
\end{array}
+ \begin{array}{c}
\text{N} \\
\text{CONH}_2 \\
\text{N} \\
\text{PhSO}_2 \\
\end{array}
\xrightarrow{\text{-HONO}} \begin{array}{c}
\text{N} \\
\text{CONH}_2 \\
\text{N} \\
\text{PhSO}_2 \\
\end{array}
\]

(eq 7)

However, the cycloaddition could not be induced even at 200 °C or under microwave irradiation. More reactive dienophiles such as ethyl propiolate or the diethyl ester of acetylenedicarboxylic acid also did not participate in the Diels-Alder reaction with 107. Given the high degree of steric crowding in diene 107, it is perhaps not too surprising that it is relatively unreactive toward Diels-Alder cycloaddition. Interestingly, the fixed s-cis diene conformation was not sufficient to permit cycloaddition.

We next decided to try to incorporate the indole ring in a stepwise fashion to avoid the Diels-Alder cycloaddition step. The initial step required N-alkylation of the pyrrolidine ring nitrogen in 105 using mesylate 108 (or a similar alkylating agent) (see
Scheme 75). Regretably, the required mesylate 108 (and other related alkylating agents) turned out to be unknown compounds. Even though alcohol 110 is known and was synthesized by us according to the published procedure,\textsuperscript{112} it was not possible to obtain the corresponding mesylate, tosylate or iodide from 110 (R=Ts or Bn) under a variety of conditions. Also, there are no literature precedents available which would demonstrate the use of derivatives of 110 as an alkylating agent.

**Scheme 75. Planned approach to compound 109**

An alternative approach which would include Suzuki coupling of the 9-BBN adduct of 107 with an N-protected 3-iodoindole (Scheme 76) also did not provide any coupling products, presumably because of reaction of the amine or amide functionality in 107 at
the boron center.

In a third and final approach, we decided to use \((Z)\)-1-iodo-3-bromoprop-1-ene\(^{113}\) as a linking group to prepare the precursor to the VM55599 core. The tertiary amine 111 was obtained in a good yield upon treatment of 105 with 1.3 eq of \((Z)\)-1-iodo-3-bromoprop-1-ene (see Scheme 77). However, an attempt to cross-couple 111 with N-tosyl-protected indole-3-boronic acid\(^{114}\) using TBAF as a base to provide anhydrous conditions\(^{115}\) afforded only acetylenic compound 112 in a good yield.

Scheme 77. Attempted Suzuki coupling of 111 using TBAF as a base

Completely different results were obtained when aq \(K_2CO_3\) was used as a base. In contrast to a known precedent,\(^{116}\) the N tosyl-protected indole-3-boronic acid proved to be hydrolytically unstable under these conditions. Unexpectedly, the primary amide group in 111 participated in a cyclization reaction, presumably forming an intermediate alkylpalladium species (via 114) which, in turn, reacted with N-tosyl-indole 3-boronic acid. In addition, the crowded alkenyl bromide group in 114 was also sufficiently reactive under the conditions employed leading to a doubly-coupled product 115 (Scheme 78).
Scheme 78 Attempt of Suzuki coupling of 111 using aq K₂CO₃ as a base

Given that this particular total synthesis was not a primary objective of our study we decided not to further pursue the final steps of our planned synthesis of the VM55599 core. Overall, it was demonstrated that products originating from Ireland-Claisen rearrangement of α-bromoallylic esters are versatile substances which are compatible with a variety of conditions. As such, they should have considerable utility in the synthesis of complex molecules.
Chapter 5. Conclusions

An inexpensive all glass low temperature reactor was designed and optimized to allow routine chemical transformations at –100 to -125°C. The conditions for 1-bromo-1-lithioethene (7) synthesis were optimized and reasons for published erratic yields of 1-halo-1-lithioethenes were revealed. Experimental observations along with computational evidence suggest that 7 exists in a crystalline form while its bromine atom remains non-chelated. Instead, bromide ion originating from added LiBr is most probably chelated to the lithium atom in 7, possibly connecting molecules of 7 into a crystal lattice.

1-Bromo-1-lithioethene (7) has proven to be a useful practical reagent for the selective introduction of the 1-bromoethenyl group into various organic and organometallic substrates. At -110 to -115 °C, 7 affords clean 1,2-addition to carbonyl compounds. It possesses low basicity and is compatible with acetate, allyl ether and tosylate protecting groups. The addition of 7 to chiral aldehydes and ketones proceeded under Felkin-Ahn diastereocontrol, providing high diastereomeric ratios (88:12 to 92:8) of adducts in some cases. Among simple protected α-hydroxy aldehydes, t-BuMe₂Si-protected compounds provided the highest diastereoselectivities (up to 93:7). For aliphatic aldehydes and protected α-hydroxy aldehydes, Me₃SiCl was necessary as an additive to suppress undesirable side reactions. Epoxides and crowded ketones were not sufficiently electrophilic to react with 7. However, several dichlorosilanes, tributyltin chloride and iodine proved to be efficient electrophiles for trapping 7, providing one-step access to potentially useful small 1,1-difunctionalized ethene building blocks.
Esters of α-bromoallylic alcohols undergo Ireland-Claisen rearrangement under mildly basic enolization conditions. Esters of tertiary bis-allylic alcohols (originating from trapping of 7 with α,β-unsaturated ketones) provided the best yields of rearranged products under Li(NSiMe₃)₂ / MnCl₂ conditions with preparatively useful levels (ca 1:10) of alkene E/Z selectivity and good regioselectivities. According to ab initio calculations and the experimentally observed trends, the rearrangement of (Z)-silyl ketene acetals of these tertiary α-bromoallylic esters is faster and much more selective than the rearrangement of the corresponding (E)-silylketene acetals.

For other substrates, trialkylsilyl triflate / triethylamine enolization conditions proved to be optimal but, in some cases, observed alkene E/Z selectivities were lower (1 : 4 to 2 : 3) and no regioselectivity was observed for secondary bis-allylic alcohols (originating from trapping of 7 with α,β-unsaturated aldehydes).

1-Bromo-1-lithioethene (7) was successfully applied in partially developed synthetic approaches toward Physalin and VM55599, showing its potential as a building block in natural products syntheses.
Chapter 6. Experimental details

6.1. General

All manipulations were conducted under a dry argon atmosphere. All glassware used was dried in vacuum (0.5 – 0.1 mmHg) for at least 1 h at rt. THF and ether were distilled from sodium/benzophenone immediately prior to use. LiBr was heated in a short test tube until it started to melt and then was cooled under a flow of argon. The same test tube fitted with a septum was used to prepare the LiBr solution. Bromoethene (Aldrich) was dried by passing it through a tube (200 mm length, 16 mm outer diameter) filled with CaCl₂ granules and was condensed in a small graduated test tube (cooled in an ice bath) fitted with a septum. The remaining solvents and reagents, including CeBr₃ (ultra dry, Alfa Aesar) and pentane (anhydrous, Acros), were used as supplied. Thin layer chromatography was performed using Whatman silica gel F-254 aluminium backed plates. Flash chromatographic separations were carried out on Fisher 170 – 400 mesh silica gel 60. Gas chromatography was performed on an HP 5890 Gas Chromatograph using an HP-1 capillary column (15 m × 0.53 mm, 1.5µm film). Melting point determinations were conducted on a Mettler FP52 hotstage and are uncorrected. NMR spectra were recorded on a Bruker AMX 300 or Bruker Avance 400 NMR spectrometer. Chemical shifts are reported relative to Me₄Si (δ 0.0) for ¹H NMR and chloroform (δ 77.0) for ¹³C NMR spectra.
6.2. Low temperature reactor design

A low temperature glass reactor (Fig. 17) was constructed to allow easy addition of cold solutions and slurries to a reaction mixture at uniform (± 5 °C) temperatures as low as –127 °C. All parts of the reactor contacting with all solutions during an experiment were beneath the level of the stirred coolant. The entire setup, which includes the reactor equipped with a mechanical stirrer (450 rpm) and a thermometer, a coolant bath stirrer (450 rpm) and a heat exchanger (a large glass test tube with 30 mm outer diameter, 200 mm length or a semi-cylinder soldered from thin sheet brass) was inserted in a standard Dewar flask (120 mm inner diameter, 190 mm inside depth, 1.9 L volume) filled with methylecyclohexane. The reactor was cooled by addition of liquid nitrogen into the heat exchanger.

Operating the unit requires two argon lines from a standard manifold. A mercury manometer in the argon line is highly desirable. The usual working argon pressure was 10-60 mmHg above atmospheric pressure. One argon line was attached directly to the *main argon inlet* of the unit. The second argon line was attached through a flow regulator to the *auxiliary argon inlet* of the unit. The flow regulator was made from a piece of a capillary tube from a laboratory thermometer with an attached bypass stopcock: see bottom of Fig. 17. The actual rate of addition was regulated by changing the argon pressure in the 10 to 100 mmHg range which resulted in *ca* 0.5 to 5 mL/min addition rates.
Fig. 17. Schematic Representation of Low Temperature Reactor

All dimensions are in mm
6.2.1. Modes for operation of the reactor

There are three modes for operation of the reactor:

1. Waiting – both bubblers are open;
2. Addition – the auxiliary bubbler is stopped and the main bubbler is open; the rate of addition of the side tube contents can be regulated by the auxiliary argon flow regulator;
3. Side tube content stirring – the main bubbler is stopped and the auxiliary bubbler is open. In this mode, argon bubbling through the side tube prevents particulate material from sedimenting and clogging the capillary tube of the unit.

It is important to use a mechanical stirrer inside of the main flask because of the considerable viscosity of the reaction mixture at the low reaction temperature employed.

The maximum capacity of the side tube of the reactor is 35 mL while the total useful volume of the reactor is 100 mL. Thus, the molar amount of $n$-BuLi that can be added in one pass is limited to ca 14 mmol (2.0 M solution of $n$-BuLi in pentane was typically used). This allows for the preparation of up to maximum 12 mmol (for method A; 6 mmol for method B) of the final addition product in a single run.

6.2.2. Notes on setting up the reactor

The reactor vessel equipped with a mechanical stirrer and thermometer was placed in a standard 1.9 L (120 mm inner diameter, 190 mm inside depth) cylindrical Dewar flask. The heat exchange tube should be inserted into the Dewar flask near the reactor in such a
A second mechanical stirrer fitted with a narrow and long blade, is placed into the Dewar flask near the heat exchanger tube. Liquid nitrogen should always be poured into the heat exchanger tube to prevent dangerous stresses within the setup and to keep losses of the coolant to a minimum. This setup requires approximately 1.6 L of methylcyclohexane and about 4 L of liquid nitrogen to perform a typical reaction.

A –200°C liquid filled thermometer was used to measure temperatures within the cooling bath, while commercially available long stem thin bore pentane filled thermometers graduated up to –100°C typically were used to monitor the inner temperature (the contents of these thermometers freeze at about –125°C). An RTD probe placed in a glass well occasionally was used for more precise measurements of the inner temperature.

### 6.3. Experimental details for Chapter 3

**General Procedure A: Reaction of 1-bromo-1-lithioethene (7) with acetone – preparation of 3-bromo-2-methylbut-3-en-2-ol (10).**

A solution of bromoethene (3.0 mL, 42.5 mmol), lithium bromide (0.23 g, 3.2 mmol) and the Trapp mixture (THF : ether : pentane, 4 : 1 : 1 by volume) (20 mL) was placed into the central flask of the low temperature reactor described in the in Section 6.2. A mixture of anhydrous THF (19 mL) and anhydrous ether (7 mL) was placed into the side tube. The reactor was cooled down to –70 °C (methylcyclohexane / liquid N₂) and n-butyl lithium (8.1 mL, 16.1 mmol, 2M in pentane, Aldrich) was added to the side tube.
The main bubbler was temporarily stopped for *ca* 10 sec (argon started to bubble through the side tube, mixing the contents of the side tube) and then the unit was further cooled down with liquid nitrogen to –110 °C. At this point the auxiliary bubbler was stopped and the contents of the side tube were slowly transferred to the main flask with argon pressure. (To achieve good yields, this addition should be done over 15 - 30 min, while the temperature should be in the –110 to –115 °C range). After the addition, the side tube was washed with the Trapp mixture (2 x 1.5 mL). Liquid nitrogen was added to the heat exchanger tube until the bridge of the frozen coolant between the reactor and the heat exchanger was formed (Fig. 7 and Fig. 17). This condition was indicated by attempting to move slightly an outer Dewar vessel. When the bridge is formed, the Dewar vessel cannot be moved any more. At this moment, the crystallization of 7 had usually occurred. Addition of liquid nitrogen was ceased until the bridge of the frozen coolant had melted (temperature should not rise above –112 °C). This process usually was completed in 20 to 40 min. The cloudy mixture was stirred for 30 – 40 min at –112 – 115 °C to complete the deprotonation of bromoethene.

A solution of acetone (1.0 mL, 14 mmol) in the Trapp mixture (10 mL) was placed into the side tube. After thermal equilibration (usually 5-10 min), the contents of the side tube were transferred as described above to the central flask over 2-15 min. (The time for this addition was not so critical). The reaction mixture was stirred at –110 to –105 °C for 30 min. A solution of acetic acid (1.05 mL, 1.25 mmol) in the Trapp mixture (15 mL) was placed into the side tube and, five minutes later, it was transferred into the central flask. The cooling bath was removed and the contents were transferred to a separatory
funnel. The organic layer was washed with 4% aq NaHCO₃ (10 mL), brine (10 mL),
dried (MgSO₄) and concentrated at atmospheric pressure. Vacuum distillation gave 3-
bromo-2-methylbut-3-en-2-ol (10) (1.79 g, 77%) as a colorless liquid which was 99.5% 
pure by GC, bp 53 °C at 17mmHg. ¹H NMR (300 MHz, CDCl₃): δ 1.49 (s, 6H), 2.10 (br 
s, 1H, OH), 5.49 (d, ²J=2.3 Hz, 1H), 5.89 (d, ²J=2.3 Hz, 1H); ¹³C NMR δ 28.7, 74.1, 

1-Bromo-1-iodoethene (13), prepared according to General Procedure A (with the 
exception of that a solution of AcOH was not added) from iodine (3.09 g) as a yellowish 
liquid (1.13 g, 40%), bp 80 – 81 °C at 160 mmHg. ¹H NMR (300 MHz, CDCl₃): δ 6.72 
(d, J = 3.3 Hz, 1H), 6.92 (d, J = 3.3 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 55.3, 134.9.

2-Bromo-1-phenylprop-2-en-1-ol (20),¹¹⁷ prepared according to General Procedure A 
from benzaldehyde (1.29 g) as a colorless liquid (2.10 g, 81%), bp 87-88 °C at 0.6 
mmHg, GC purity was 99.5%. ¹H NMR (300 MHz, CDCl₃): δ 2.74 (br s, OH, 1H), 5.20 
(s, 1H), 5.64 (d, J=2.0 Hz, 1H), 6.00 (dd, J=1.9, 1.1, 0.2 Hz, 1H), 7.30-7.38 (m, 5H); ¹³C 
NMR: 78.0, 117.9, 126.9, 128.6, 128.7, 135.8, 139.9.

2-Bromo-3-methylpenta-1,4-dien-3-ol (21), prepared according to General Procedure A 
from 3-buten-2-one (0.850 g) as a colorless liquid (1.68 g, 78%), bp 63 °C at 14 mmHg, 
GC purity was 98%. ¹H NMR (400 MHz, CDCl₃): δ 1.55 (s, 3H), 2.25 (s, 1H), 5.23 (dd, 
³J₁ = 10.6 Hz, ²J₂ = 0.8 Hz, 1H), 5.40 (dd, ³J₁ = 17.2 Hz, ²J₂ = 0.8 Hz, 1H), 5.57 (d, ²J =
2.3 Hz, 1H), 5.94 (d, $^2J = 2.3$ Hz, 1H), 6.01 (dd, $^3J_1 = 17.3$ Hz, $^3J_2 = 10.7$ Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): δ 26.7, 76.1, 114.5, 116.6, 140.2, 141.5. Anal. Calcd for C$_6$H$_9$BrO: C, 40.71; H, 5.12. Found: C, 40.77; H, 5.25.

2-Bromo-3-methylhepta-1,6-dien-3-ol (22), prepared according to General Procedure A from 5-hexen-2-one (1.19 g) as a colorless liquid (2.09 g, 84%), bp 89 - 91 °C at 14 mmHg, a single peak by GC analysis. $^1$H NMR (300 MHz, CDCl$_3$): δ 1.46 (s, 3H), 1.73 (ddd, $^2J_1 = 13.8$ Hz, $^3J_2 = 9.6$ Hz, $^3J_3 = 7.1$ Hz, 1H), 1.89 (ddd, $^2J_1 = 13.8$ Hz, $^3J_2 = 9.6$ Hz, $^3J_3 = 6.2$ Hz, 1H), 2.03-2.15 (m, 2H), 2.30 (br s, 1H, OH), 4.98 (dm, $^3J = 10.1$ Hz, 1H), 5.05 (ddd, $^3J_1 = 17.2$ Hz, $^2J_1 = 3.2$ Hz, $^4J_1 = 1.6$ Hz, 1H), 5.56 (d, $^2J = 2.1$ Hz, 1H), 5.83 (ddt, $^3J_1 = 16.9$ Hz, $^3J_2 = 10.3$ Hz, $^3J_3 = 6.7$ Hz, 1H), 5.92 (dd, $^2J_1 = 2.1$ Hz, $^4J_2 = 0.36$ Hz, 1H); $^{13}$C NMR δ 27.2, 28.5, 39.4, 76.8, 115.2, 116.5, 138.5, 140.6. Calcd for C$_8$H$_{13}$BrO: C, 46.85; H, 6.39. Found: C, 47.15; H, 6.51.

1-(1-Bromoethenyl)cyclohexanol (23), prepared according to General Procedure A from cyclohexanone (1.19 g) as a colorless oil (2.10 g, 85%), bp 62 °C at 1 mmHg, GC purity was 98.8%. $^1$H NMR (400 MHz, CDCl$_3$): δ = 1.20 – 1.30 (m, 1H), 1.54 – 1.72 (m, 5H), 1.74 – 1.82 (m, 5H), 5.57 (d, $^2J = 2.3$ Hz, 1H), 5.91 (d, $^2J = 2.3$ Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): δ = 21.9, 25.4, 36.0, 74.4, 115.5, 143.6. Anal. Calcd for C$_8$H$_{13}$BrO: C, 46.85; H, 6.39. Found: C, 47.08; H, 6.43.
1-(1-Bromoethenyl)-4,4-dimethylcyclohex-2-enol (24), prepared according to General Procedure A from 4,4-dimethylcyclohex-2-enone (1.51 g) as a colorless oil (2.23 g, 80%) bp 64-65 °C at 1 mmHg, GC purity was 96%. $^1$H NMR (400 MHz, CDCl$_3$): δ = 0.99 (s, 3H), 1.03 (s, 3H), 1.45 (ddd, $J_1 = 13.2$ Hz, $J_2 = 9.7$ Hz, $J_3 = 3.3$ Hz, 1H), 1.59 (ddd, $J_1 = 14.3$ Hz, $J_2 = 9.2$ Hz, $J_3 = 3.8$ Hz, 1H), 1.74 (ddd, $J_1 = 12.9$ Hz, $J_2 = 9.2$ Hz, $J_3 = 2.8$ Hz, 1H), 2.11 (ddd, $J_1 = 12.6$ Hz, $J_2 = 8.6$ Hz, $J_3 = 3.2$ Hz, 1H), 2.26 (s, 1H), 5.50 (d, $^2$J = 10.0 Hz, 1H), 5.60 (d, $^2$J = 2.0 Hz, 1H), 5.68 (d, $^2$J = 10.0 Hz, 1H), 5.91 (d, $^2$J = 2.0 Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): δ = 28.5, 28.8, 32.2, 33.3, 74.1, 118.0, 126.5, 140.6, 142.2. Anal. Calcd for C$_{10}$H$_{15}$BrO: C, 51.97; H, 6.54. Found: C, 52.13; H, 6.74.

2-Bromopenta-1,4-dien-3-ol (25), prepared according to General Procedure A from acrolein (0.681 g) as a colorless liquid (1.47 g, 74%), bp 67 °C at 14 mmHg, GC purity was 98.6%. $^1$H NMR (400 MHz, CDCl$_3$): δ = 2.15 (s, 1H), 4.68 (s, 1H), 5.32 (dt, $^3$J$_1 = 10.4$ Hz, $^2$J$_2 = 1.2$ Hz, 1H), 5.43 (dt, $^3$J$_1 = 17.2$ Hz, $^2$J$_2 = 1.2$ Hz, 1H), 5.61 (d, $^2$J = 2.0 Hz, 1H), 5.91 (ddd, $^3$J$_1 = 17.2$ Hz, $^3$J$_2 = 10.4$ Hz, $^3$J$_3 = 5.6$ Hz, 1H), 5.96 (dd, $^2$J$_1 = 2.1$ Hz, $^4$J$_2 = 1.0$ Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): δ = 76.6, 117.4, 117.6, 135.2, 136.8. Anal. Calcd for C$_5$H$_7$BrO: C, 36.84; H, 4.33. Found: C, 36.59; H, 4.48.

(E)-2-Bromohexa-1,4-dien-3-ol (26), prepared according to General Procedure A from crotonic aldehyde (0.853 g) as a colorless liquid (1.29 g, 60%) after column chromatography (silica, pentane : ether 2:1). $^1$H NMR (300 MHz, CDCl$_3$): δ 1.76 (ddd, $J_1 = 6.5$ Hz, $J_2 = 1.6$ Hz, $J_3 = 0.8$ Hz, 3H), 2.90 (s, 1H), 4.62 (d, $J = 6.6$ Hz, 1H), 5.55
(ddq, J₁ = 16.1 Hz, J₂ = 5.8 Hz, J₃ = 1.6 Hz, 1H), 5.58 (dd, J₁ = 1.9 Hz, J₂ = 0.4 Hz, 1H), 5.85 (ddd, J₁ = 15.3 Hz, J₂ = 6.5 Hz, J₃ = 1.1 Hz, 1H), 5.96 (dd, J₁ = 1.9 Hz, J₂ = 1.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 17.9, 76.5, 116.7, 116.8, 129.9, 136.2.

2-Bromo-4-methylhexa-1,4-dien-3-ol (27), prepared according to General Procedure A from metacroleine (0.950 g) as a colorless liquid (1.50 g, 70%), bp 77-78 °C at 14 mmHg. ¹H NMR (300 MHz, CDCl₃): δ 1.75 (s, 3H), 2.50 (br s, 1H), 4.63 (s, 1H), 5.10 (br q, J = 1.2 Hz, 1H), 5.20 (br t, J = 1.0 Hz, 1H), 5.70 (d, J = 1.9 Hz, 1H), 6.04 (dd, J₁ = 1.9 Hz, J₂ = 1.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 18.2, 79.4, 114.1, 118.4, 134.6, 143.0.

(E)-4-Bromo-3-methyl-1-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-1,4-dien-3-ol (28), prepared according to General Procedure A from β-ionone (1.35 g) as a colorless oil (1.93 g, 92%) after filtration through a silica plug. ¹H NMR (300 MHz, CDCl₃): δ 1.01 (d, J = 1.9 Hz, 1H), 1.42-1.50 (m, 2H), 1.55-1.65 (m, 5H), 1.68 (d, J = 0.9 Hz, 3H), (br t, J = 6.3 Hz, 2H), 2.23 (br s, 1H), 5.53 (d, J = 16.1 Hz, 1H), 5.59 (d, J = 2.3 Hz, 1H), 5.97 (d, J = 2.3 Hz, 1H), 6.22 (dq, J₁ = 16.1 Hz, J₂ = 1.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 19.4, 21.5, 27.0, 28.9, 32.8, 34.3, 39.49, 76.3, 116.3, 128.1, 129.0, 136.7, 140.0, 141.2.

1,2:5,6-Di-O-(1-methylethylidene)-α-D-ribo-3-hexulofuranose (29a)¹¹⁸: 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (5.10 g, 20 mmol), 3Å powdered molecular sieves (18 g, Alfa Aesar brand; activated at 350 °C for 12 h) and PCC (10.6 g, 48.9 mmol) was
stirred in dichloromethane (50mL) for 17 h at rt. Most of the dichloromethane was removed under vacuum (100 mmHg) and anhydrous ether (100 mL) was added to the brown residue. The mixture was stirred for 2 h at rt (no large pieces of solid should remain at this point) and petroleum ether (100 mL) was added. The slurry was promptly filtered through a short pad of silica (predried at 150°C for 12 h because 29a is extremely hygroscopic) and the solid was washed with 1:1 petroleum ether : anhydrous ether (2 x 50 mL). Concentration *in vacuo* gave 4.02 g (79%) of 29a as a clear oil which was sufficiently clean by 1H NMR analysis to be used directly in the next step. 1H NMR (300 MHz, CDCl3): δ 1.34 (s, 6H), 1.44 (br d, J=0.5 Hz, 3H), 1.46 (s, 3H), 4.00-4.05 (m, 2H), 4.33-4.43 (m, 3H), 6.15 (d, J=4.5 Hz, 1H, H-1); 13C NMR (75 MHz, CDCl3): δ 25.4, 26.1, 27.3, 27.7, 64.4, 76.5, 77.4, 79.1, 103.2, 110.4, 114.3, 209.0.

**General Procedure B:** 3-C-(1-bromoethenyl)-1,2:5,6-bis-O-(1-methylethylidene)-α-D-allofuranose (29b): Anhydrous CeBr₃ (0.588 g, 1.55 mmol) was stirred in the Trapp mixture (14 mL) for 4 h at rt in a separate flask. Bromoethene (5.45 ml, 77.4 mmol), lithium bromide (0.35 g, 4.2 mmol) and the Trapp mixture (18 mL) were placed into the central flask of the low temperature reactor (described above). Anhydrous ether (10 mL) and anhydrous THF (10 mL) were placed into the side tube. The low temperature reactor was cooled down to −60 °C (methylcyclohexane/liquid nitrogen was used as coolant) and the first aliquot of n-butyllithium (9.7 mL, 19.4 mmol, 2.0 M in pentane) was added into the side tube. The reactor was further cooled with liquid nitrogen to −110 °C and the contents of the side tube were displaced into the central flask over 25 min. Then,
anhydrous ether (10 mL), anhydrous THF (10 mL) and the second aliquot of n-butyllithium (9.7 mL, 19.4 mmol, 2.0M in pentane) were placed into the side tube. After thermal equilibration (5 min) the contents of the side tube were again displaced into the central flask. The side tube was washed with the Trapp mixture (4 mL). Liquid nitrogen was added into the heat exchanger until a frozen coolant bridge was formed and then the temperature of the reaction mixture was allowed to rise to –112 °C. The whole process of addition took 1 h 30 min. (The addition of n-BuLi was done in two steps because of the insufficient volume of the side tube). The slurry of CeBr3 in the Trapp mixture (prepared as described earlier) was added to the side tube. The main bubbler of the unit was stopped for 3 min which allowed gentle bubbling of argon through the contents of the side tube (this was necessary to prevent the precipitation of cerium (III) bromide). Then, the stopper was removed from the main bubbler and was placed on the auxiliary bubbler. The argon pressure developed in the side tube (10-20 mmHg) transferred its contents to the central flask in ca 10 sec. This addition should be done fast to avoid clogging of the capillary tube of the reactor. No rise in reaction temperature was observed. The yellowish mixture was stirred for 5 min and a solution of the starting ketone 29a (4.02 g, 15.5 mmol) in the Trapp mixture (20 mL) was placed into the side tube. After thermal equilibration (5 min), the contents of the side tube were slowly added over ca 5 min to the central flask at -110 °C. The side tube was washed with the Trapp mixture (4 mL). The slurry was stirred for 45 min at –110 to –108 °C and then quenched by addition of a solution of acetic acid (3.5 mL, 62 mmol) in the Trapp mixture (25 mL). The cooling bath was removed and sat. aq NaHCO3 (25 mL) was added at –20 °C to the flask. The
mixture was stirred overnight, and then the organic layer was separated, dried over anhydrous sodium sulfate (5 g) and evaporated. Column chromatography (40 g silica, petroleum ether : ethyl acetate, 6:1) gave the title compound **29b** as a white solid (4.76 g, 84%), mp 113-115 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.35 (s, 3H), 1.41 (s, 3H), 1.45 (s, 3H), 1.63 (s, 3H), 3.28 (s, 1H), 3.96 (d, $J = 7.5$ Hz, 1H) 4.00 (dd, $J_1 = 8.5$ Hz, $J_2 = 5.8$ Hz, 1H), 4.09 (dd, $J_1 = 8.5$ Hz, $J_2 = 6.1$ Hz, 1H), 4.26 (dt, $J_1 = 7.5$ Hz, $J_2 = 5.9$ Hz, 1H), 4.55 (d, $^3J = 3.9$ Hz, 1H), 5.86 (d, $^2J = 1.7$ Hz, 1H), 5.97 (d, $^3J = 4.0$ Hz, 1H), 6.34 (d, $^2J = 1.8$ Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ 25.5, 26.56, 26.65, 26.8, 67.1, 73.6, 81.7, 83.0, 83.9, 105.4, 109.5, 112.9, 120.6, 127.9. Anal. Calcd for C$_{14}$H$_{21}$BrO$_6$: C, 46.04; H, 5.80. Found: C, 46.25; H, 5.68.

**General Procedure C**: 3-Bromo-1-(tert-butyldiphenylsilanyloxy)-2-methylbut-3-en-2-ol (**30b**) was obtained from **30a** using the same approach as described in General Procedure A, except that a solution of ketone **30a** (3.31 g, 10.5 mmol) and Me$_3$SiCl (1.33 mL, 10.5 mmol, 1 eq) in the Trapp mixture was slowly added to the preformed slurry of **7** (2 eq) over 5 – 10 min at –112 °C. Column chromatography (silica, petroleum ether : ether, 10 : 1) gave the title compound **30b** (3.55 g, 80%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.12 (s, 9H), 1.39 (s, 3H), 3.17 (d, $J = 0.5$ Hz, 1H), 3.53 (d, $J = 9.9$ Hz, 1H), 4.01 (d, $J = 9.9$ Hz, 1H), 5.70 (d, $J = 1.8$ Hz, 1H), 6.17 (d, $J = 1.8$ Hz, 1H), 7.40-7.50 (m, 6H), 7.70-7.80 (m, 4H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ 19.0, 23.1, 26.9, 68.8, 117.4, 127.82, 127.87, 129.94, 129.97, 132.57, 132.87, 135.57, 135.76, 138.0. Anal. Calcd for C$_{21}$H$_{27}$BrO$_3$Si: C, 60.14; H, 6.49. Found: C, 60.01; H, 6.38.
5-O-tert-Butyldiphenylsilyl-1,2-O-(1-methylethylidene)-β-L-threo-pentofuranose-3-ulose (31a): Compound 31a was prepared in 60% yield as a colorless oil from 5-O-tert-butyldiphenylsilyl-L-1,2-O-1-methylethylidene arabinofuranose\textsuperscript{119} by the same procedure as for the preparation of 29a. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 1.07 (s, 9H), 1.37 (s, 3H), 1.39 (s, 3H), 3.93 (dd, J=11.2, 6.2 Hz, 1H, H-5), 3.98 (dd, J=11.2, 4.3 Hz, 1H, H-5), 4.30 (dd, J=6.2, 4.3 Hz, 1H, H-4), 4.40 (dd, J=4.3, 0.7 Hz, 1H, H-2), 6.04 (d, J=4.3 Hz, 1H, H-1), 7.35-7.45 (m, 6H), 7.66-7.74 (m, 4H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ 19.4, 26.9, 27.6, 64.6, 76.9, 82.5, 102.8, 116.0, 127.9, 129.9, 133.0, 133.3, 135.8, 135.9, 206.9.

3-C-(1-Bromoethenyl)-5-O-tert-butyldiphenylsilyl-1,2-O-(1-methylethylidene)-β-L-lyxofuranose (31b): The title product 31b was obtained from 31a using General Procedure C with the exception that the addition of \textit{n}-butyllithium was done in a single step due to smaller loading. Column chromatography (silica, petroleum ether : diethyl ether, 6:1) gave 67% of 31b as a colorless oil. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 1.06 (s, 9H), 1.45 (s, 3H), 1.58 (s, 3H), 3.63 (d, J=0.5 Hz, 1H, OH), 3.87 (dd, J=11.0, 6.0 Hz, 1H, H-5), 4.00 (dd, J=11.0, 5.0 Hz, 1H, H-5), 4.39 (t, J=5.5 Hz, 1H, H-4), 4.81 (d, J=4.2 Hz, 1H, H-2), 5.62 (d, J=1.9 Hz, 1H), 5.80 (d, J=4.2 Hz, 1H, H-1), 6.19 (d, J=1.9 Hz, 1H), 7.30-7.50 (m, 6H), 7.70-7.85 (m, 4H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): δ 19.4, 27.0, 27.8, 28.0, 62.7, 79.5, 83.6, 85.4, 105.0, 116.3, 118.6, 127.9, 129.9, 133.4, 133.7, 133.9, 135.9, 136.0.
4-C-(1-bromoethenyl)-2,3-O-(1-methylethylidene)-6-O-tosyl-α-D-methyltalopyranoside (32b), was obtained from 32a\(^50\) (1.65 g, 4.27 mmol) using General Procedure C. Column chromatography (silica, petroleum ether : ethyl acetate, 3:1) gave the title compound 32b (1.35 g, 64%) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.35\) (s, 3H), 1.54 (s, 3H), 2.43 (s, 3H), 3.01 (s, 1H), 3.39 (s, 3H), 4.08 - 4.17 (m, 2H), 4.18 (dd, \(J_1 = 11.1\) Hz, \(J_2 = 2.6\) Hz, 1H), 4.33 (dd, \(J_1 = 8.33\) Hz, \(J_2 = 2.7\) Hz, 1H), 4.62 (d, \(J = 6.4\) Hz, 1H), 4.94 (s, 1H), 5.70 (d, \(^2\)J = 1.8 Hz, 1H), 6.20 (d, \(^2\)J = 1.8 Hz, 1H). \(^13\)C NMR (100.6 MHz, CDCl\(_3\)): \(\delta = 21.6, 24.7, 25.9, 55.3, 67.8, 68.3, 72.2, 72.9, 73.5, 97.7, 109.9, 120.9, 128.0, 129.9, 130.9, 132.9, 144.9\). NOE (400 MHz): irradiation of the vinylic proton (at 6.20 ppm) resulted in enhancement of the OMe group (at 3.39 ppm). Calcd for C\(_{11}\)H\(_{15}\)BrO\(_5\): C, 43.02%; H, 4.92%. Found: C, 43.09; H, 4.97.

4-C-(1-Bromoethyl)-1,6-anhydro-2,3-O-(1-methylethylidene)-β-D-talopyranose (33b), was obtained from 33a\(^120\) (1.15 g, 5.74 mmol) using General Procedure C. Column chromatography (silica, petroleum ether : ethyl acetate, 3:1) gave the title compound 33b (1.23 g, 70%) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.30\) (s, 3H), 1.52 (s, 3H), 3.59 (s, 1H), 3.69 (dd, \(J_1 = 7.9\) Hz, \(J_2 = 5.8\) Hz, 1H), 4.07 (dd, \(J_1 = 5.8\) Hz, \(J_2 = 3.0\) Hz, 1H), 4.27 (d, \(J = 8.0\) Hz, 1H), 4.40 (t, \(J = 6.3\) Hz, 2H), 5.26 (d, \(J = 3.2\) Hz, 1H), 5.79 (d, \(J = 2.8\) Hz, 1H), 6.08 (d, \(J = 2.9\) Hz, 1H). \(^13\)C NMR (100.6 MHz, CDCl\(_3\)): \(\delta = 25.9, 26.2, 64.3, 73.1, 74.8, 75.0, 75.7, 99.2, 111.1, 120.4, 136.5\). Calcd for C\(_{19}\)H\(_{25}\)BrO\(_8\)S: C, 46.26; H, 5.11. Found: C, 45.64; H, 5.08.
2-Trimethylsiloxy-1-cyclohexene (36a). Although the title compound is well known,\textsuperscript{121} our attempts to reproduce literature methods for its preparation were not successful. The product was always severely contaminated with 2-hydroxy-1-cyclohexene which was slowly dimerizing. (The limited commercial availability of adipic acid, the dimer of 2-hydroxy-1-cyclohexene, prevented the effective use of another approach.\textsuperscript{122}) The origin of the failure was in the acidic admixtures which were still present in the crude 2-trimethylsiloxy-1-cyclohexene and which caused its decomposition during distillation. The following modification of the known procedure\textsuperscript{121} allowed successful isolation of the title compound, albeit in mediocre yield: 1-trimethylsiloxy-1-cyclohexene (8.1 g, 48 mmol) was dissolved in dichloromethane (100 mL) and a solution of potassium carbonate (5.3 g, 38 mmol) in water (50 mL) was added. The mixture was cooled down to 0 °C (NaCl/ice bath) and mCPBA (11 g (75% assay), 48 mmol) was added over 30 min so that the temperature did not rise above 0 °C. The mixture was stirred for 1 h at 0 °C, then filtered and the organic layer was dried over Na$_2$SO$_4$. Concentration in vacuo (100 mmHg) at rt afforded a colorless oil which was dissolved in petroleum ether (100 mL). Oven-dried (24 h at 130 °C) silica (10 g) was added to the solution. The slurry was stirred for 6 h at rt. During this time a significant amount of $m$-chlorobenzoic acid was precipitated. The solution was filtered, the precipitate was washed with petroleum ether (2×30 mL) and the combined organic layers were filtered again through a small pad of dried silica. Vacuum distillation gave 4.4 g (50%) of 2-trimethylsiloxy-1-cyclohexene 36a as a colorless liquid, bp 95-100°C at 17 mmHg, which was 95% pure by GC and $^1$H NMR analysis. $^1$H NMR (300 MHz, C$_6$D$_6$): $\delta$ 0.18 (s, 9H), 1.05-1.27 (m, 2H), 1.35-1.60
(m, 3H), 1.72-1.93 (m, 2H), 2.28 (dt d J=13.4, 4.4, 1.9 Hz, 1H), 3.91 (ddd, J=10.1, 5.6, 1.2 Hz, 1H); $^{13}$C NMR (75 MHz, C$_6$D$_6$) δ 0.9, 23.5, 27.6, 37.6, 40.3, 77.2, 208.2.

1-(1-Bromoethyl-2-trimethylsiloxy-cyclohexanols (36b and 36c): the title compounds were prepared from 2-trimethylsiloxycyclohexanone following General Procedure B. $^1$H NMR analysis of the crude reaction mixture showed an 88:12 ratio of diastereomeric 36b and 36c. Column chromatography (silica, petroleum ether : ether, 8:1) afforded 61% yield of the major diastereomer 36b as a white solid, mp 73-74 °C, and 9% yield of the minor diastereomer 36c as a colorless oil.

Spectral data for 36b: $^1$H NMR (300 MHz, CDCl$_3$): δ 0.10 (s, 9H), 1.33-1.40 (m, 1H), 1.50-1.65 (m, 5H), 1.80-1.95 (m, 1H), 1.97 (d, J=1.2 Hz, 1H, OH), 2.03-2.15 (m, 1H), 3.84 (br t, J=3.6 Hz, 1H, H-2), 5.63 (d, J=2.5 Hz, 1H), 5.82 (d, J=2.5 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 0.5, 19.5, 21.7, 29.5, 30.5, 71.6, 76.2, 118.6, 142.2.

Spectral data for 36c: $^1$H NMR (300 MHz, CDCl$_3$): δ 0.11 (s, 9H), 1.10-1.30 (m, 1H), 1.40-1.60 (m, 3H), 1.62-1.75 (m, 3H), 1.92 (dddd, J=14.4, 11.8, 5.4, 2.6 Hz, 1H), 2.90 (d, J=2.6 Hz, 1H, OH), 4.05 (dd, J=10.7, 4.9 Hz, 1H, H-2), 5.56 (d, J=1.6 Hz, 1H), 6.09 (d, J=1.6 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 0.6, 20.7, 24.1, 31.4, 34.1, 71.6, 78.2, 117.2, 140.2.

(2S, 3R, 3aS, 9aS)-3-(1-bromoethyl)-5,5,7,7-tetraisopropyl-2-methoxy-1,4,6,8-tetraoxa-5,7-disilabicyclo[6.3.0]undecan-3-ol (37b) was prepared from ketone 37a (1.2 g, 3.74 mmol, 1 eq) following General Procedure C. Column chromatography (silica,
petroleum ether : ethyl acetate, 10:1) gave the title compound 37b (1.01 g, 63%, colorless oil) as an inseparable 89:11 mixture of diastereomers. Major diastereomer: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.90 – 1.00 (m, 2H), 1.02 – 1.15 (m, 24H), 3.25 (s, 1H), 3.51 (s, 3H), 3.85 (dd, $J_1$ = 11.1 Hz, $J_2$ = 7.6 Hz, 1H), 3.98 (dd, $J_1$ = 6.8 Hz, $J_2$ = 3.4 Hz, 1H), 4.03 (dd, $J_1$ = 11.0 Hz, $J_2$ = 3.4 Hz, 1H), 4.38 (d, $J$ = 6.7 Hz, 1H), 4.90 (s, 1H), 5.84 (d, $^2$J = 1.8 Hz, 1H), 6.29 (d, $^2$J = 1.8 Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 56.1, 65.2, 81.1, 81.7, 104.5, 120.4, 130.2 (resonances due to isopropylsilyl groups are omitted). NOE (400 MHz): irradiation of the vinylic proton (at 6.29 ppm) resulted in enhancement of H$_1$ (at 4.90 ppm). Calcd for C$_{20}$H$_{39}$BrO$_6$Si$_2$: C, 46.95; H, 7.68. Found: C, 46.73; H, 7.76.

3-O- Allyl- 6- tert- butyldiphenylsiloxyl- $\beta$- methylmannopyranoside (38b). A slurry of 38a$^{124}$ (4.93 g, 11.4 mmol) and $n$-Bu$_2$SnO (2.84 g, 11.4 mmol) in toluene (40 mL) was refluxed in a round bottom flask fitted with a Dean-Stark adapter for 1 h. The Dean-Stark adapter was removed, allyl iodide (1.4 mL, 15 mmol) was added and reflux was continued for 45 h. Toluene was removed at 50 $^\circ$C (20 mmHg), ethyl acetate (20 mL) and water (5 mL) were added and the solution was stirred for 10 min at rt. The organic layer was separated, dried (MgSO$_4$) and concentrated at 50 $^\circ$C (20 mmHg). Column chromatography (100 g of silica, petroleum ether : ethyl acetate, 2 : 1) gave title compound 38b as a colorless oil (2.88 g, 53 %). $^1$H NMR (400 MHz, C$_6$D$_6$ after D$_2$O exchange): $\delta$ = 1.23 (s, 9H), 3.15 (s, 3H), 3.70 (dd, $J_1$ = 9.1 Hz, $J_2$ = 3.4 Hz, 1H), 3.85 – 3.95 (m, 3H), 4.01 (dd, $J_1$ = 3.4 Hz, $J_2$ = 1.6 Hz, 1H), 4.07 (t, $J$ = 9.6 Hz, 1H), 4.12 (dd, $J_1$ = 10.7 Hz, $J_2$ = 5.2 Hz, 1H), 4.15 (dd, $J_1$ = 10.7 Hz, $J_2$ = 3.6 Hz, 1H), 4.86 (d, $J$ = 1.5 Hz,
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.06 (s, 9H), 1.91 (s, 3H), 2.69 (d, $J$ = 2.3 Hz, 1H), 3.42 (s, 3H), 3.65 – 3.72 (m, 2H), 3.75 – 3.83 (m, 2H), 3.99 (ddt, $J_1$ = 13.0 Hz, $J_2$ = 5.7 Hz, $J_3$ = 1.4 Hz, 1H), 4.02 (dd, $J_1$ = 3.7 Hz, $J_2$ = 2.1 Hz, 1H), 4.12 (ddt, $J_1$ = 14.4 Hz, $J_2$ = 5.5 Hz, $J_3$ = 1.4 Hz, 1H), 4.82 (d, $J$ = 1.7 Hz, 1H), 5.15 (t, $J$ = 9.6 Hz, 1H), 5.17 (dq $J_1$ = 9.2 Hz, $J_2$ = 1.5 Hz, 1H), 5.26 (dq, $J_1$ = 17.2 Hz, $J_2$ = 1.6 Hz, 1H), 5.84 (ddt, $J_1$ = 17.1 Hz, $J_2$ = 9.3 Hz, $J_3$ = 4.5 Hz, 1H), 7.35 – 7.41 (m, 6H), 7.64 – 7.69 (m, 4H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 19.3, 20.1, 26.9, 55.0, 63.6, 68.2, 68.6, 71.1, 71.9, 77.3, 100.1, 117.4, 127.65, 127.69, 129.65, 129.66, 133.39, 133.45, 134.3, 135.68, 135.74.

4-O-Acetyl-3-O-allyl-6-tert-butyldiphenylsiloxy-β-methylmannopyranoside (38c).

Acetic anhydride (0.57 mL, 6.09 mmol) was slowly added to a stirred solution of 38b and DMAP (0.82 g, 6.7 mmol) in anhydrous dichloromethane (10 mL) at +5 °C (syringe pump, 1 h addition time). The reaction mixture was kept in a refrigerator (at about +5 to +8 °C) for 90 h. The reaction mixture was warmed up to rt and water (5 mL) was added. The solution was extracted with dichloromethane (2 x 5 mL), the organic extracts were dried (MgSO$_4$) and concentrated. Column chromatography (100 g of silica, petroleum ether : ethyl acetate, 5 : 2) gave the title compound 38c as a colorless oil (1.14 g, 36%, R$_f$ = 0.25). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.06 (s, 9H), 1.91 (s, 3H), 2.69 (d, $J$ = 2.3 Hz, 1H), 3.42 (s, 3H), 3.65 – 3.72 (m, 2H), 3.75 – 3.83 (m, 2H), 3.99 (ddt, $J_1$ = 13.0 Hz, $J_2$ = 5.7 Hz, $J_3$ = 1.4 Hz, 1H), 4.02 (dd, $J_1$ = 3.7 Hz, $J_2$ = 2.1 Hz, 1H), 4.12 (ddt, $J_1$ = 14.4 Hz, $J_2$ = 5.5 Hz, $J_3$ = 1.4 Hz, 1H), 4.82 (d, $J$ = 1.7 Hz, 1H), 5.15 (t, $J$ = 9.6 Hz, 1H), 5.17 (dq $J_1$ = 9.2 Hz, $J_2$ = 1.5 Hz, 1H), 5.26 (dq, $J_1$ = 17.2 Hz, $J_2$ = 1.6 Hz, 1H), 5.84 (ddt, $J_1$ = 17.1 Hz, $J_2$ = 9.3 Hz, $J_3$ = 4.5 Hz, 1H), 7.35 – 7.41 (m, 6H), 7.64 – 7.69 (m, 4H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 19.3, 20.1, 26.9, 55.0, 63.6, 68.2, 68.6, 71.1, 71.9, 77.3, 100.1, 117.4, 127.65, 127.69, 129.65, 129.66, 133.39, 133.45, 134.3, 135.68, 135.74.
4-O-Acetyl-3-O-allyl-6-O-(tert-butyldiphenylsilyl)-1-O-methyl-α-D-arabino-hexopyranosulose (38d). Acetic anhydride (0.84 mL, 8.9 mmol) was added to a suspension of pyridinium chlorochromate (0.95 g, 4.4 mmol) and 38c (1.14 g, 2.21 mmol) in anhydrous dichloromethane (10 mL). The slurry was stirred for 16 h at 27 to 30 °C and the solvent was then removed at 30 °C (20 mmHg). A mixture of ethyl acetate (30 mL) and petroleum ether (30 mL) was added to the thick black reaction mixture. The slurry was stirred for 2 h at rt and then was filtered through a pad of silica (20 g). The silica pad was washed with the same solvent mixture (30 mL) and the combined filtrates were concentrated in vacuo to afford the title compound 38d as a yellowish oil (0.748 g, 66%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.22\) (s, 9H), 1.71 (s, 3H), 3.10 (s, 3H), 3.87 (d, \(J = 3.8\) Hz, 1H), 3.90 – 3.96 (m, 1H), 4.20 (dt, \(J_1 = 7.5\) Hz, \(J_2 = 3.8\) Hz, 1H), 4.39 (ddt, \(J_1 = 13.2\) Hz, \(J_2 = 4.8\) Hz, \(J_3 = 1.6\) Hz, 1H), 4.51 (d, \(J = 9.9\) Hz, 1H), 4.70 (s, 1H), 5.04 (dq, \(J_1 = 10.5\) Hz, \(J_2 = 1.4\) Hz, 1H), 5.24 (dq, \(J_1 = 17.3\) Hz, \(J_2 = 1.7\) Hz, 1H), 5.59 (t, \(J = 10.0\) Hz, 1H), 5.81 (ddt, \(J = 17.3\) Hz, \(J = 10.4\) Hz, \(J = 4.8\) Hz, 1H), 7.27 – 7.31 (m, 6H), 7.83 – 7.88 (m, 4H). \(^13\)C NMR (100.6 MHz, CDCl\(_3\)): \(\delta = 19.4, 20.2, 26.9, 55.0, 63.2, 71.8, 72.1, 81.3, 100.7, 116.6, 127.5, 127.8, 128.1, 133.3, 134.4, 135.9, 196.8\).

2-C-(1-bromoethenyl)-3-O-allyl-4-O-acetyl-6-tert-butyldiphenylsiloxy-α-D-methyl-glucopyranoside (38e), was obtained from 38d (0.90 g, 1.76 mmol) using General Procedure C. Column chromatography (silica, petroleum ether : ethyl acetate, 10:1) gave the title compound 38e (0.545 g, 50%) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.07\) (s, 9H), 1.97 (s, 3H), 3.00 (s, 1H), 3.51 (d, \(J = 6.0\) Hz, 3H), 3.65 – 3.80 (m, 2H),
3.84 (ddd, J₁ = 9.9 Hz, J₂ = 4.8 Hz, J₃ = 2.9 Hz, 1H), 3.90 (d, J = 9.1 Hz, 1H), 4.17 (ddt, J₁ = 13.0 Hz, J₂ = 5.6 Hz, J₃ = 1.53 Hz, 1H), 4.39 (ddt, J₁ = 13.0 Hz, J₂ = 5.3 Hz, J₃ = 1.5 Hz, 1H), 4.96 (s, 1H), 5.15 (dq, J₁ = 10.4 Hz, J₂ = 1.6 Hz, 1H), 5.25 (dq, J₁ = 17.2 Hz, J₂ = 1.7 Hz, 1H), 5.33 (t, J = 9.5 Hz, 1H), 5.87 (ddt, J₁ = 17.2 Hz, J₂ = 10.5 Hz, J₃ = 5.3 Hz, 1H), 5.96 (d, J = 2.6 Hz, 1H), 6.53 (d, J = 2.6 Hz, 1H) 7.35 – 7.45 (m, 6H), 7.65 – 7.75 (m, 6H). 13C NMR (100.6 MHz, CDCl₃): δ = 19.2, 20.9, 26.7, 55.5, 62.9, 68.6, 71.5, 74.4, 78.0, 82.1, 101.0, 116.6, 124.0, 127.7, 129.66, 129.70, 131.9, 133.31, 134.7, 135.7, 169.4. NOE (400 MHz): irradiation of the vinylic proton (at 6.53 ppm) resulted in enhancement of H₄ (at 5.33 ppm); irradiation of the OH group (at 3.00 ppm); resulted in enhancement of H₃ (at 3.90 ppm).

4-C-(1-bromoethenyl)-2,3,6-tri-O-benzyl-α-D-methylglucopyranoside (39b), was obtained from 39a₁²⁵ (0.95 g, 2.05 mmol) using General Procedure C. Column chromatography (silica, petroleum ether : ethyl acetate, 3:1) gave the title compound 39b (0.805 g, 69%) as a colorless oil. ¹H NMR (400 MHz, 80% C₆D₆ + 20% CDCl₃): δ = 3.18 (s, 3H), 3.60 (dd, J₁ = 9.5 Hz, J₂ = 6.2 Hz, 1H), 3.64 (s, 1H), 3.79 (dd, J₁ = 9.4 Hz, J₂ = 6.8 Hz, 1H), 4.08 (dd, J₁ = 10.1 Hz, J₂ = 3.9 Hz, 1H), 4.20 (d, J = 8.9 Hz, 1H), 4.21 (s, 2H), 4.27 (t, J = 6.5 Hz, 1H), 4.48 (d, J = 11.9 Hz, 1H), 4.60 (d, J = 3.9 Hz, 1H), 4.66 (d, J = 11.9 Hz, 1H), 4.86 (d, J = 11.7 Hz, 1H), 4.97 (d, J = 11.7 Hz, 1H), 5.81 (d, J = 1.8 Hz, 1H), 6.19 (d, J = 1.8 Hz, 1H), 7.15 (m, 11H), 7.27 (d, J = 6.7 Hz, 2H), 7.40 (d, J = 6.7 Hz, 2H). ¹³C NMR (100.6 MHz, C₆D₆): δ = 54.9, 69.9, 71.0, 73.2, 73.4, 75.7, 78.0, 79.17, 83.6, 98.6, 120.6, 127.44, 127.48, 127.67, 127.70, 128.18, 128.29, 128.31, 128.44.
NOE (400 MHz): irradiation of the OH group (at 3.64 ppm) resulted in enhancement of the H$_6$ (at 3.79 ppm) and H$_5$ (at 4.27 ppm) protons of the carbohydrate backbone; irradiation of the vinylic proton (at 5.81 ppm) resulted in enhancement of H$_2$ (at 4.08 ppm).

(1R, 2S, 6R, 8R)-4,4-Dimethyl-3,5,10,11-tetraoxa-tricyclo[6.2.1.0$^{2,6}$]undecan-7-one (41). A slurry of D-mannosan-2:3-O-acetonide (40) (6.80 g, 33.6 mmol), PDC (7.46 g, 19.8 mmol) and acetic anhydride (10.5 mL, 111 mmol) in CH$_2$Cl$_2$ (67 mL) was stirred for 2 h at rt. The black oily mixture was concentrated at 30 °C (15 mmHg) for 30 min and then at 30 °C (0.5 mmHg) for 20 min. Ethyl acetate (170 mL) was added and the dark brown slurry was stirred for 30 min at rt. Hexanes (30 mL) were added and the slurry was transferred to a column filled with silica (50 g) in a petroleum ether : ethylacetate (1 : 5) mixture. The column was eluted with the same mixture (500 mL). The blue band of chromium (III) salts moved approximately through 2/3 of the column height. The colorless eluant was concentrated to give the title compound 40 as a colorless oil (5.74 g, 86%). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.32 (s, 3H), 1.48 (s, 3H), 3.87 (dd, $J_1$ = 7.9 Hz, $J_2$ = 5.7 Hz, 1H), 4.01 (dd, $J_1$ = 8.0 Hz, $J_2$ = 1.0 Hz, 1H), (dt, $J_1$ = 7.6 Hz, $J_2$ = 1.2 Hz, 1H), 4.48 (dd, $J_1$ = 7.6 Hz, $J_2$ = 3.2 Hz, 1H), 4.58 (dt, $J_1$ = 5.6 Hz, $J_2$ = 1.1 Hz, 1H), 5.61 (dd, $J_1$ = 3.2 Hz, $J_2$ = 0.5 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 25.4, 26.0, 66.9, 75.4, 76.3, 76.9, 99.2, 112.9, 200.9.
(1R, 2S, 6R, 7S, 8R)-4,4,7-Trimethyl-3,5,10,11-tetraoxa-tricyclo[6.2.1.0*2,6*]undecan-7-ol (42). A solution of ketone 41 (4.29 g, 21.4 mmol) in anhydrous ether (60 mL) was added to a stirred solution of methylmagnesium bromide (11.4 mL, 34.2 mmol, 3.0 M in THF) in ether (60 mL) at –30 to –20 °C (internal temperature) over 20 min. The thick white slurry was stirred at –40 °C for 1 h and then quenched with methanol (1 mL) at –40 °C. Aq sat. NH₄Cl (10 mL) was added at rt and the mixture was stirred until the magnesium salts were dissolved. The organic layer was separated, dried (MgSO₄) and concentrated. The residue was crystallized from methylecyclohexane (40 mL) to afford the title compound 42 as white crystals (3.27 g, 71%), mp 134-136 °C (subl.) ¹H NMR (300 MHz, CDCl₃): δ = 1.32 (s, 3H), 1.42 (s, 3H), 1.55 (s, 3H), 3.04 (br s, 1H), 3.66 (dd, J₁ = 7.6 Hz, J₂ = 5.7 Hz, 1H), 4.02-4.09 (m, 2H), 4.19 (d, J = 7.7 Hz, 1H), 5.25 (d, J = 2.4 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 25.8, 26.1 (2 signals), 63.4, 69.3, 74.9, 77.9, 78.1, 99.1, 111.0.

(1R, 2R, 3R, 4S, 5R)-2-Methyl-6,8-dioxa-bicyclo[3.2.1]octane-2,3,4-triol (43). A solution of 42 (3.0 g, 13.9 mmol) in an acetic acid (8 mL) – water (32 mL) mixture was kept at 80 °C for 3 h and then volatiles were removed at 50 °C (16 mmHg). The oily residue was coevaported with toluene (2 x 30 mL) and finally dried at 0.5 mmHg overnight. The title product 43 was obtained as a yellowish powder (2.41 g, 99%) mp 112-114 °C. ¹H NMR (300 MHz, CDCl₃): δ = 1.42 (s, 3H), 3.10 (br s, 1H), 3.47 (br s, 2H), 3.69 (dd, J₁ = 7.8 Hz, J₂ = 5.2 Hz, 1H), 3.74 (dd, J₁ = 5.0 Hz, J₂ = 1.9 Hz, 1H), 3.79 (br d, J = 4.9 Hz, 1H), 3.75 (d, J = 5.2 Hz, 1H), 4.31 (d, J = 8.2 Hz, 1H), 5.35 (t, J = 1.4

(1R, 2R, 3R, 4S, 5R)-2-Methyl-6,8-dioxa-bicyclo[3.2.1]octane-2,3,4-triol (43). A solution of 42 (3.0 g, 13.9 mmol) in an acetic acid (8 mL) – water (32 mL) mixture was kept at 80 °C for 3 h and then volatiles were removed at 50 °C (16 mmHg). The oily residue was coevaported with toluene (2 x 30 mL) and finally dried at 0.5 mmHg overnight. The title product 43 was obtained as a yellowish powder (2.41 g, 99%) mp 112-114 °C. ¹H NMR (300 MHz, CDCl₃): δ = 1.42 (s, 3H), 3.10 (br s, 1H), 3.47 (br s, 2H), 3.69 (dd, J₁ = 7.8 Hz, J₂ = 5.2 Hz, 1H), 3.74 (dd, J₁ = 5.0 Hz, J₂ = 1.9 Hz, 1H), 3.79 (br d, J = 4.9 Hz, 1H), 3.75 (d, J = 5.2 Hz, 1H), 4.31 (d, J = 8.2 Hz, 1H), 5.35 (t, J = 1.4
(1R, 2S, 4R, 5R)-2,4-Dihydroxy-2-methyl-6,8-dioxa-bicyclo[3.2.1]octan-3-one (44). A slurry of 43 (0.923 g, 5.24 mmol) and dibutyltin oxide (1.30 g, 5.24 mmol) was refluxed in benzene (45 mL) with a Dean Stark adapter for 3 h. The clear colorless solution was cooled to 10 °C and a solution of bromine (0.838 g, 5.24 mmol) in anhydrous CH2Cl2 (10 mL) was added dropwise. The resulting yellowish solution was stirred for 30 min at rt and then was concentrated at 30 °C (16 mmHg). Column chromatography (40 g of silica, petroleum ether : ethylacetate 1 : 1) gave the title product 44 as a thick yellowish oil (0.78 g, 86%). 1H NMR (400 MHz, CDCl3): δ = 1.53 (s, 1H), 1.57 (s, 1H), 3.16 (d, J = 6.8 Hz, 1H), 3.70-3.75 (m, 2H), 3.91 (dd, J1 = 8.3 Hz, J2 = 0.8 Hz, 1H), 4.42 (dd, J1 = 6.7 Hz, J2 = 2.4 Hz, 1H), 4.47 (d, J = 4.6 Hz, 1H), 5.61 (d, J = 2.4 Hz, 1H). 13C NMR (75 MHz, CDCl3): δ = 23.8, 65.8, 75.9, 77.9, 81.1, 103.7, 209.3.

(1R, 2S, 4R, 5R)-2-Hydroxy-2-methyl-4-trimethylsilanyloxy-6,8-dioxa-bicyclo[3.2.1]octan-3-one (45). Chlorotrimethylsilane (0.74 mL, 5.86 mmol) was added to a solution of ketone 44 (680 mg, 3.90 mmol) and triethylamine (1.1 mL, 7.81 mmol) in anhydrous dichloromethane (15 mL). The white slurry was stirred for 1 h at rt. Cold water (10 mL) was added and the mixture was stirred for 5 min at ca 5 °C. The organic layer was dried (MgSO4), filtered through a pad of silica and the solvent was removed at 40 °C (15 mmHg). The residual oil was identified as the title compound 45 (0.939 g, 98%), which was sufficiently clean to be used directly on the next step. 1H NMR (300
MHz, CDCl₃): δ = 0.19 (s, 9H), 1.53 (s, 3H), 3.74 (dd, J₁ = 8.3 Hz, J₂ = 5.1 Hz, 1H), 3.89 (s, 1H), 3.98 (dd, J₁ = 8.3 Hz, J₂ = 0.9 Hz, 1H), 4.41 (d, J = 2.4 Hz, 1H), 4.45 (dd, J₁ = 5.0 Hz, J₂ = 0.8 Hz, 1H), 5.51 (d, J = 2.4 Hz, 1H), 13C NMR (75 MHz, CDCl₃): δ = 0.2, 24.9, 65.9, 76.6, 77.9, 80.8, 104.5, 208.2.

(1R, 2S, 4R, 5R)-2-Methoxymethoxy-2-methyl-4-trimethylsilanyloxy-6,8-dioxa-bicyclo[3.2.1]octan-3-one (45a). A solution of 45 (462 mg, 1.88 mmol), chloromethyl methyl ether (0.28 mL, 3.75 mmol) and diisopropylethylamine (1.14 mL, 6.56 mmol) in dichloromethane (5 mL) was refluxed for 60 h. Ether (30 mL) and water (10 mL) were added to the reaction mixture. Layers were separated, aq layer was extracted with ether (2 x 10 mL), combined organic layers were dried (MgSO₄) and filtered through a silica plug. The solvent was removed in vacuo and the residue was coevaporated with benzene (50 mL) which allowed the title compound 45a as a colorless oil (0.437 g, 80%) sufficiently clean to be used in the next step. ¹H NMR (300 MHz, CDCl₃): δ = 0.15 (s, 9H), 1.60 (s, 3H), 3.34 (s, 3H), 3.78 (dd, J₁ = 8.1 Hz, J₂ = 5.3 Hz, 1H), 4.11 (dd, J₁ = 8.1 Hz, J₂ = 0.9 Hz, 1H), 4.24 (d, J = 2.5 Hz, 1H), 4.44 (dd, J₁ = 5.2 Hz, J₂ = 0.9 Hz, 1H), 4.76 (d, J = 7.5 Hz, 1H), 5.11 (d, J = 7.5 Hz, 1H), 5.47 (d, J = 2.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 0.3, 20.2, 55.9, 66.2, 76.9, 80.4, 82.5, 92.8, 103.9, 205.2.

(1R, 2S, 3R, 4S, 5R)-3-(1-Bromoethenyl)-2-methoxymethoxy-2-methyl-4-trimethyl-silanyloxy-6,8-dioxa-bicyclo[3.2.1]octan-3-ol (46) was obtained from 45a (0.437 g, 1.50 mmol) using General Procedure C. Column chromatography (silica, petroleum ether :
ethyl acetate, 10:3) gave the title compound 46 (0.044 g, 7%) as a colorless oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.22\) (s, 9H), 1.58 (s, 3H), 3.33 (s, 3H), 3.65 (dd, \(J_1 = 6.8\) Hz, \(J_2 = 5.6\) Hz, 1H), 3.68 (s, 1H), 4.25 (d, \(J = 5.1\) Hz, 1H), 4.35 (d, \(J = 2.3\) Hz, 1H), 4.65 (d, \(J = 7.7\) Hz, 1H), 4.75 (d, \(J = 7.0\) Hz, 1H), 4.99 (d, \(J = 7.7\) Hz, 1H), 5.26 (d, \(J = 2.3\) Hz, 1H), 5.82 (d, \(J = 1.5\) Hz, 1H), 6.21 (d, \(J = 1.5\) Hz, 1H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 0.9, 22.5, 55.8, 65.2, 72.0, 77.9, 80.3, 91.8, 101.3, 105.2, 122.9\).

\((1R, 2S, 4R, 5R)-2,4\text{-Bis-methoxymethoxy-2-methyl-6,8-dioxoa-bicyclo[3.2.1]octan-3-one (47)}\). A solution of ketone 44 (0.65 g, 3.73 mmol), chloromethyl methyl ether (1.13 mL, 14.9 mmol) and diisopropylethylamine (3.90 mL, 22.4 mmol) in dichloromethane (18 mL) was refluxed for 44 h. The solvent was removed \(\text{in vacuo}\), ethyl acetate (20 mL) was added and the thick yellowish solid was stirred for 1 h. The slurry was filtered through a pad of silica (ethyl acetate) and the ethyl acetate was removed at 30 °C (20 mmHg). The residual oil proved to be sufficiently clean 47 (0.990 g, 99%) which was used directly in the next step. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.70\) (s, 3H), 3.41 (s, 3H), 3.48 (s, 3H), 3.87 (dd, \(J_1 = 8.2\) Hz, \(J_2 = 5.3\) Hz, 1H), 4.20 (dd, \(J_1 = 8.1\) Hz, \(J_2 = 1.1\) Hz, 1H), 4.30 (d, \(J = 2.5\) Hz, 1H), 4.52 (dd, \(J_1 = 5.2\) Hz, \(J_2 = 1.0\) Hz, 1H), 4.75-4.90 (m, 3H), 5.15 (d, \(J = 7.5\) Hz, 1H), 5.68 (d, \(J = 2.5\) Hz, 1H).

\((1R, 2S, 3R, 4S, 5R)-3\text{-}(1\text{-Bromoethenyl)-2,4-bis-methoxymethoxy-2-methyl-6,8}
\text{-dioxoa-bicyclo[3.2.1]octan-3-ol (48)}\) was obtained from 47 (0.328 g, 1.25 mmol) using General Procedure C. Column chromatography (silica, petroleum ether : ethyl acetate, 1 :
2) gave the title compound 48 (0.358 g, 81%) as a thick colorless syrup. ¹H NMR (300 MHz, CDCl₃): δ = 1.58 (s, 3H), 3.35 (s, 3H), 3.45 (s, 3H), 3.61 (s, 1H), 3.70 (dd, J₁ = 7.0 Hz, J₂ = 5.6 Hz, 1H), 4.25 (d, J = 2.3 Hz, 1H), 4.28 (d, J = 5.0 Hz, 1H), 4.65 (d, J = 7.8 Hz, 1H), 4.73 (d, J = 7.0 Hz, 1H), 4.77 (d, J = 7.0 Hz, 1H), 4.92 (d, J = 7.0 Hz, 1H), 5.00 (d, J = 7.8 Hz, 1H), 5.57 (d, J = 2.2 Hz, 1H), 5.87 (d, J = 1.9 Hz, 1H), 6.21 (d, J = 1.9 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 21.1, 55.9, 56.2, 65.6, 76.5, 77.8, 80.0, 80.4, 91.71, 91.81, 100.7, 122.6, 134.3.

**(1R, 2S, 3R, 4S, 5R)-3-(1-Bromoethenyl)-2-methyl-6,8-dioxa-bicyclo[3.2.1]octane-2,3,4-triol (48a).** A solution of 48 (0.957 g, 2.69 mmol) in a mixture of water (16 mL) and acetic acid (4 mL) was kept at 95 °C for 17 h. Solvents were removed at 50 °C (16 mmHg), the residue was coevaporated with toluene (2 x 30 mL) and then dried at rt (0.5 mmHg) overnight. The triol 48a was obtained as white crystals (0.700 g, 93%) mp 164-166 °C. ¹H NMR (300 MHz, CDCl₃): δ = 1.50 (s, 3H), 2.64 (d, J = 9.3 Hz, 1H, C₂-OH), 2.90 (s, 1H C₃-OH), 3.68 (dd, J₁ = 7.7 Hz, J₂ = 5.5 Hz, 1H, H₅), 3.81 (s, 1H, C₄-OH), 4.07 (d, J = 5.3 Hz, 1H, H₆), 4.19 (dd, J₁ = 9.2 Hz, J₂ = 2.4 Hz, 1H, H₂), 4.39 (d, J = 7.9 Hz, 1H, H₆), 5.43 (d, J = 2.5 Hz, 1H, H₁), 5.88 (d, J = 2.8 Hz, 1H), 6.09 (d, J = 2.8 Hz, 1H).

**General Procedure D: 2-Bromonon-1-en-3-ol (49)** was obtained from n-heptanal using the same approach as described in General Procedure A, except that a solution of n-heptanal (1.05 g, 9.19 mmol) and Me₃SiCl (2.3 mL, 18.4 mmol, 2 eq) in the Trapp mixture was slowly added to the preformed slurry of 7 (3 eq) over 5 – 10 min at –112 °C.
The crude reaction mixture was hydrolyzed by vigorous stirring with a mixture of CH$_2$Cl$_2$ : water : CF$_3$COOH (1 : 1 : 0.1 by volume) overnight at 30 – 35 °C. Column chromatography (silica, petroleum ether : ethyl acetate, 20:3) gave the title compound 49 (1.50 g, 74%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.90 (t, $J$ = 6.8 Hz, 3H), 1.25 – 1.35 (m, 8H), 1.55 – 1.75 (m, 2H), 2.14 (s, 1H), 4.09 (t, $J$ = 6.5 Hz, 1H), 5.56 (d, $^2J$ = 1.9 Hz, 1H), 5.88 (d, $^2J$ = 1.1 Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 14.1, 22.6, 25.1, 29.0, 31.7, 35.3, 76.1, 116.9, 137.7. Calcd for C$_9$H$_{17}$BrO: C, 48.88; H, 7.75. Found: C, 49.08; H, 7.80.

1-(4-Trifluoromethylphenyl)-3-propen-1-ol (50), prepared according to General Procedure D from $p$-trifluoromethylbenzaldehyde (1.22 g, 7.0 mmol). The crude reaction mixture was hydrolyzed by vigorous stirring with a mixture of CH$_2$Cl$_2$ : water : CF$_3$COOH (1 : 1 : 0.1 by volume) overnight at 30 – 35 °C. Column chromatography (silica, petroleum ether : ethyl acetate, 5:1) gave the title compound 50 (1.52 g, 77%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.81 (s, 1H), 5.32 (s, 1H), 5.72 (d, $J$ = 1.8 Hz, 1H), 6.06 (dd, $J_1$ = 2.1 Hz, $J_2$ = 1.0 Hz, 1H), 7.54 (d, $J$ = 8.7 Hz, 2H), 7.64 (d, $J$ = 8.2 Hz, 2H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 77.3, 118.5, 122.7, 125.45, 125.49, 127.0, 134.9, 143.6. Calcd for C$_{10}$H$_8$BrF$_3$O: C, 42.73; H, 2.87. Found: C, 43.31; H, 2.94.

2-Bromopent-1-en-3-ol (51): prepared according to General Procedure A from propanal (0.71 g, 12 mmol) as a colorless liquid (0.93 g, 46%), bp 67-69°C at 14 mmHg, GC purity was 99%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.92 (t, $J$=7.5 Hz, 3H), 1.62-1.75
(m, 2H), 2.41 (s, 1H, OH), 4.02 (td, J=6.5, 0.7 Hz, 1H), 5.57 (d, J=1.9 Hz, 1H), 5.87 (dd, J₁ = 1.9 Hz, J₂ = 0.8 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 9.6, 28.3, 77.5, 117.3, 137.3.

**2-Methoxymethoxyhexanal (54a).**¹²⁷ A solution of hept-1-en-3-ol (1.14 g, 10 mmol), chloromethyl methyl ether (0.97 g, 12 mmol) and diisopropylethylamine (2.58 g, 20 mmol) in anhydrous dichloromethane (20 mL) was refluxed for 4 h. Dichloromethane was removed in vacuo, ethyl acetate (20 mL) was added and the solution was filtered through a small pad of silica. Ethyl acetate was removed at rt (20 mmHg). The residue was dissolved in dichloromethane (30 mL), cooled in a dry ice – acetone bath and a stream of ozone was bubbled through the solution until a bluish coloration persisted. A solution of triphenylphosphine (2.88 g, 11 mmol) in dichloromethane (10 mL) was added and the reaction mixture was slowly warmed up to rt. After the evolution of formaldehyde has ceased (ca 30 min at rt), dichloromethane was removed at rt (20 mmHg) and hexanes (30 mL) were added. The thick yellowish precipitate was filtered off and the filtrate was concentrated in vacuo. Vacuum distillation of the residue gave the title compound 54a (1.04 g, 65%) as a colorless liquid, bp 63 °C at 17 mmHg. ¹H NMR (300 MHz, CDCl₃): δ = 0.93 (t, J = 7.3 Hz, 3H), 1.30 – 1.50 (m, 4H), 1.65 – 1.75 (m, 2H), 3.43 (s, 3H), 3.92 (dt J₁ = 7.6 Hz, J₂ = 2.0 Hz, 1H), 4.72 (d, J = 6.9 Hz, 1H), 4.76 (d, J = 6.9 Hz, 1H), 9.64 (d, J = 2.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 14.0, 22.7, 27.1, 29.9, 56.1, 82.6, 96.9, 203.1.
2-Bromo-4-methoxymethyloxyoct-1-en-3-ol (54b) (mixture syn and anti products, Table 8, entry 1) was prepared from 2-methoxymethoxyhexanal 54a according to the General Procedure D. The crude mixture was hydrolyzed by vigorous stirring with a mixture of CH₂Cl₂ : water : CF₃COOH (1 : 1 : 0.1 by volume) overnight at 30 – 35 °C. Column chromatography (silica, petroleum ether : ethyl acetate, 4:1) gave the title compound 54b in 62% yield as a 77 : 23 diastereomeric mixture. The diastereomeric ratio was determined from integration of selected ¹H NMR resonances (300 MHz, CDCl₃): H₁ (vinylic) protons (δ = 6.04 (dd, J₁= 1.7 Hz, J₂ = 1.4 Hz, 0.77H) and δ = 6.00 (dd, J₁= 1.8 Hz, J₂ = 1.0 Hz, 0.24H)) and H₃ (δ = 4.30 (d, J = 4.3 Hz, 0.77H) and δ = 4.00 (d, J = 5.2 Hz, 0.22H)). The mixture was completely deprotected by treating with 20% aq acetic acid (20 h at 30 °C) and anti diol 61 was observed as the major product in the crude reaction mixture (characterized by comparison of the ¹H NMR spectrum with an authentic sample prepared via another approach – see p. 146).

4-Benzylxy-2-bromooct-1-en-3-ol (55b) (mixture syn and anti products, Table 8 entry 2) was prepared from 2-benzylxyhexanal (55a)¹²⁸ according to General Procedure D. The crude mixture was hydrolyzed by vigorous stirring with a mixture of CH₂Cl₂ : water : CF₃COOH (1 : 1 : 0.1 by volume) overnight at 30 – 35 °C. Column chromatography (silica, petroleum ether : ether, 10:1) gave the title compound 55b in 53% yield as a 60 : 40 diastereomeric mixture. The diastereomeric ratio was determined from integration of selected ¹H NMR resonances (300 MHz, CDCl₃): H₁ (vinylic) protons (δ = 5.65 (dd, J₁= 1.9 Hz, J₂ = 0.8 Hz, 0.40H) and δ = 5.62 (dd, J₁= 1.9 Hz, J₂ = 1.7 Hz, 0.59H)) and H₃ (δ =
4.03 (ddt, $J_1 = 7.4$ Hz, $J_2 = 1.6$ Hz, $J_3 = 0.8$ Hz, 0.41H) and $\delta = 4.30 – 4.35$ (m, 0.60H)).

**anti-2-Bromo-4-tert-butyldimethylsiloxyl-oct-1-en-3-ol (56b),** prepared according to General Procedure C from 2-tert-butyldimethylsiloxylhexanal (56a)\(^{129}\) (1.61 g, 7.0 mmol). The crude mixture was hydrolyzed by vigorous stirring with a mixture of CH\(_2\)Cl\(_2\) : water : CF\(_3\)COOH (1 : 1 : 0.1 by volume) overnight at 30 – 35 °C. Column chromatography (silica, petroleum ether : ether, 93 : 7) gave the title compound 56b (1.18 g, 49%) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): $\delta = 0.11$ (s, 3H), 0.12 (s, 3H), 0.92 (s, 9H), 1.20 – 1.55 (m, 6H), 2.63 (s, 1H), 4.01 (apparent quintet, $J = 3.1$ Hz, 1H), 4.19 (br d, $J = 4.3$ Hz, 1H), 5.62 (t, $J = 1.4$ Hz, 1H), 6.06 (dd, $J_1 = 1.6$ Hz, $J_2 = 1.2$ Hz, 1H). \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)): $\delta = -1.83$, -1.76, 15.9, 17.0, 24.2, 27.1, 28.6, 30.7, 71.5, 76.5, 114.1, 127.4. Calcd for C\(_{14}\)H\(_{29}\)BrO\(_2\)Si: C, 49.84; H, 8.66. Found: C, 50.38; H, 8.93.

**2-Bromo-4-(tert-butyldiphenylsiloxyl)-pent-1-en-3-ol (57b)** (mixture syn and anti products, Table 8 entry 4) was prepared from 2-(tert-butyldiphenylsiloxyl)propanal\(^{130}\) according to General Procedure D. The crude mixture was hydrolyzed by vigorous stirring with a mixture of (1 : 1 : 0.1 by volume) CH\(_2\)Cl\(_2\) : water : CF\(_3\)COOH overnight at 30 – 35 °C. Column chromatography (silica, petroleum ether : ethyl acetate, 10:1) gave the title compound 57b in 35% yield as a 68 : 32 diastereomeric mixture. The diastereomeric ratio was determined from the integration of selected \(^1\)H NMR resonances (300 MHz, CDCl\(_3\)) data for H\(_1\) (vinyllic) protons ($\delta = 5.66$ (dd, $J_1 = 1.8$ Hz, $J_2 = 0.7$ Hz, 0.48H) and $\delta = 5.60$ (d, $J_1 = 1.6$ Hz, $J_2 = 1.0$ Hz, 1.00H)) and H\(_3\) ($\delta = 3.11$ (d, $J_1 = 7.1$ Hz,
$0.45H)$ and $\delta = 2.72$ (d, $J = 3.2$ Hz, 1.01H)).

**anti-2-Bromo-4-tert-butyldimethylsiloxy-pent-1-en-3-ol (58b)**, prepared according to General Procedure C from 2-tert-butyldimethylsiloxypropanal\textsuperscript{131} (1.32 g, 7.0 mmol). The crude mixture was hydrolyzed by vigorous stirring with a mixture of CH$_2$Cl$_2$ : water : CF$_3$COOH (1 : 1 : 0.1 by volume) overnight at 30 – 35 °C. Column chromatography (silica, petroleum ether : ether, 93 : 7) gave the title compound 58b (1.01 g, 50\% yield) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.10$ (s, 6H), 0.90 (s, 9H), 1.09 (d, $J = 6.1$ Hz, 3H), 2.65 (d, $J = 2.0$ Hz, 1H), 4.05 – 4.16 (m, 2H), 5.61 (dd, $J_1 = 1.6$ Hz, $J_2 = 1.0$ Hz, 1H), 6.02 (t, $J = 1.5$ Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta = -5.0$, -4.5, 16.8, 25.8, 68.9, 78.7, 117.6, 132.1. Calcd for C$_{11}$H$_{23}$BrO$_2$Si: C, 44.74; H, 7.85. Found: C, 45.24; H, 7.96.

**anti-2-Bromopent-1-en-3,4-diol (60).**

1. Prepared from triethylsilylactaldehyde\textsuperscript{132} 59a (2.44 g, 12.9 mmol) according to General Procedure C. The crude mixture was hydrolyzed by vigorous stirring with a mixture of CH$_2$Cl$_2$ : water : CF$_3$COOH (1 : 1 : 0.1 by volume) overnight at 30 – 35 °C. TLC showed a significant amount of 60 formed along with various less polar substances. The crude reaction product was dissolved in dichloromethane (25 mL) and treated with pyridine (5 mL) and HF*pyridine complex (0.80 g, 70\% HF) in a polyethylene bottle overnight at rt. Water (15 mL) was added followed by solid NaHCO$_3$ (5 g) and the mixture was extracted with dichloromethane (2 x 10 mL). The organic layer was concentrated and dried at 30 °C (0.5 mmHg) for 3 h. Column
chromatography (silica, ether) gave the diastereomerically pure title compound 60 as a thick colorless oil (1.17 g, 35%)

2. Prepared from 58b: compound 58b (0.12 g, 0.41 mmol) was stirred with a solution of pyridine (0.25 mL) and hydrogen fluoride-pyridine (0.05 g, ca 70% HF) in CH₂Cl₂ (1.5 mL) at rt for 20 h (polyethylene bottle). The reaction mixture was treated with sat. aq NaHCO₃ (10 mL). The aqueous layer was extracted with ethyl acetate (4 x 5 mL). The organic extracts were dried (MgSO₄) and concentrated in vacuo. Column chromatography (silica, petroleum ether : ethyl acetate, 3 : 1) gave the title compound 60 (59 mg, 80%) as a colorless oil.

1H NMR (400 MHz, CDCl₃): δ = 1.18 (d, J = 6.4 Hz, 3H), 2.75 (d, J = 5.7 Hz, 1H), 3.40 (d, J = 4.9 Hz, 1H), 4.08 (q, J = 5.4 Hz, 1H), 4.16 (t, J = 4.7 Hz, 1H), 5.68 (d, J = 1.2 Hz, 1H), 6.03 (t, J = 1.5 Hz, 1H). 13C NMR (100.6 MHz, CDCl₃): δ = 16.6, 68.3, 76.8, 77.1, 77.4, 78.6, 118.5, 132.3. Calcd for C₅H₉BrO₂: C, 33.17; H, 5.01. Found: C, 33.38; H, 5.19.

4-(1-Bromoethenyl)-2,2,5-trimethyl-1,3-dioxolane (60a). Compound 60 (60 mg, 0.33 mmol) was dissolved in anhydrous acetone (5 mL) and TsOH (ca 5 mg) was added to the solution. The reaction mixture was stirred for 1 h at rt and then ammonia gas was bubbled through the reaction mixture (1 min). The solution was filtered through a short plug of silica. Concentration of the solution gave title compound 60a as a colorless oil (72 mg, 99%). 1H NMR (400 MHz, CDCl₃): δ = 1.27 (d, J = 6.4 Hz, 3H), 1.38 (s, 3H), 1.56 (s, 3H), 4.50 (quintet, J = 6.4 Hz, 1H), 4.73 (d, J = 6.6 Hz, 1H), 5.69 (dd, J₁ = 5.1
Hz, J₂ = 0.5 Hz, 1H), 6.04 (t, J = 1.5 Hz, 1H). ¹³C NMR (100.6 MHz, CDCl₃): δ = 15.9,
25.3, 27.4, 73.8, 81.4, 117.8, 117.9, 128.6. Calcd for C₈H₁₃BrO₂: C, 43.46; H, 5.93.
Found: C, 43.25; H, 6.03.

**anti-2-Bromooc-1-en-3,4-diol (61).** Compound 56b (0.10 g, 0.29 mmol) was stirred
with a solution of pyridine (0.25 mL) and hydrogen fluoride-pyridine (0.05 g, ca 70%
HF) in CH₂Cl₂ (1.5 mL) at rt for 10 h (polyethylene bottle). The reaction mixture was
treated with sat. aq solution of NaHCO₃ (10 mL). The aqueous layer was extracted with
CH₂Cl₂ (3 x 5 mL) dried (MgSO₄). The organic extracts were concentrated *in vacuo.*
Column chromatography (silica, petroleum ether : ethyl acetate, 4 : 1) gave the title
compound 61 (60 mg, 90%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 0.91 (t, J
= 7.1 Hz, 3H), 1.25 – 1.60 (m, 6H), 2.41 (s, 1H), 3.24 (d, J = 5.4 Hz, 1H), 3.83 (s, 1H),
4.14 (t, J = 4.9 Hz, 1H), 5.68 (d, J² = 1.7 Hz, 1H), 6.01 (t, J = 1.5 Hz, 1H). ¹³C NMR
(100.6 MHz, CDCl₃): δ = 14.0, 22.6, 28.0, 30.5, 72.3, 78.3, 118.9, 132.6. Calcd for
C₈H₁₅BrO₂: C, 43.07; H, 6.78. Found: C, 43.22; H, 6.92.

**4-(1-Bromoethenyl)-5-butyl-2,2-dimethyl-1,3-dioxolane (61a).** Compound 61 (60 mg,
0.27 mmol) was dissolved in anhydrous acetone (5 mL) and TsOH (ca 5 mg) was added
to the solution. The reaction mixture was stirred for 1 h at rt and then ammonia gas was
bubbled through the reaction mixture (1 min). The solution was filtered through a short
plug of silica. Concentration of the solution gave title compound 61a as a colorless oil
(70 mg, 99%). ¹H NMR (400 MHz, CDCl₃): δ = 0.91 (t, J = 7.2 Hz, 3H), 1.350 – 1.40 (m,
6H), 1.50 – 1.60 (m, 6H), 4.27 (dt, J1 = 8.9 Hz, J2 = 6.4 Hz, 1H), 4.70 (d, J = 6.5 Hz, 1H), 5.66 (dd, J1 = 1.0 Hz, J2 = 0.5 Hz, 1H), 6.00 (t, J = 1.5 Hz, 1H). 13C NMR (100.6 MHz, CDCl3): δ = 14.0, 22.6, 25.5, 27.5, 28.5, 29.5, 78.0, 81.3, 109.0, 118.1, 128.8. Calcd for C11H19BrO2: C, 50.20; H, 7.28. Found: C, 50.44; H, 7.33.

3-Bromo-2-trimethylsilyl-3-buten-2-ol (62), obtained according to General Procedure A from acetyltrimethylsilane (1.63 g, 14 mmol) as a colorless liquid (2.03 g, 65%), bp 45 – 46 °C at 0.6 mmHg. (To prevent spontaneous rearrangement to 63, the distillation glassware was soaked in 40 % aq NaOH for 3 min and then thoroughly rinsed with distilled water prior to use. 1 % (v/v) Pyridine was added to the product immediately after distillation to stabilize the purified product.) 1H NMR (300 MHz, C6D6): δ = 0.18 (s, 9H), 1.37 (s, 3H), 5.41 (d, J = 1.8 Hz, 1H), 5.67 (d, J = 1.8 Hz, 1H). 13C NMR (75 MHz, C6D6): δ = -3.2, 25.1, 72.0, 113.5, 141.3.

3-Bromo-3-trimethylsilylbutan-2-one (63). A solution of 62 in CH2Cl2 (ca 1 M) was kept in a glass vessel under argon for 72 h at rt. After the solvent was removed (rt at 20 mmHg), the crude title compound 63 was obtained as a 10:1 mixture with 62. 1H NMR (300 MHz, CDCl3): δ = 0.17 (s, 9H), 1.81 (s, 3H), 2.38 (s, 3H). 13C NMR (75 MHz, CDCl3): δ = -3.0, 24.9, 61.6, 207.5.

Bis(1-bromoethenyl)dimethylsilane (67), prepared according to General Procedure A (with the exception that a solution of AcOH was not added) from dichlorodimethylsilane
(1.81 g, 14 mmol) with slow addition of dichlorodiethylsilane over 10-20 min at −112 to −115 °C, affording 67 as a colorless liquid (1.21 g, 64%), bp 86-88°C at 16 mmHg. $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 0.41 (s, 6H), 6.38 (d, J = 2.0 Hz, 1H), 6.45 (d, J = 2.0 Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta =$ -3.7, 132.9, 133.5. Calcd for C$_6$H$_{10}$Br$_2$Si: C, 26.69; H, 3.73. Found: C, 26.68; H, 3.83.

**General Procedure E: Preparation of (1-Bromoethenyl)chlorodiethylsilane (68)**

from dichlorodiethylsilane. General Procedure A was used but with a different work-up procedure: instead of the addition of an AcOH solution, the reaction mixture was warmed up and diluted with a three-fold excess (by volume) of anhydrous pentane. The lithium salts were filtered off and the solvents were removed from the filtrate by distillation at atmospheric pressure. Vacuum distillation of the residual oil gave title compound 68 as a colorless oil (1.01 g, 26%), bp 72 – 74 °C at 17 mmHg. $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 0.96 – 1.10 (m, 10H), 6.48 (d, J = 1.9 Hz, 1H), 6.56 (d, J = 1.9 Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta =$ 6.5, 7.0, 130.2, 133.9.

(1-Bromoethenyl)-chlorodisopropylsilane (69), prepared according to General Procedure E from dichlorodisopropylsilane (2.59 g, 14 mmol) as a colorless liquid (1.68 g, 47%), bp 94 – 96 °C at 16 mmHg. $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 1.08 – 1.10 (m, 12 H), 1.41 (septet, J = 7.4 Hz, 2H), 6.53 (d, J = 1.9 Hz, 1H), 6.59 (d, J = 1.9 Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta =$ 13.2, 16.7, 17.3, 128.5, 134.7.
(1-Bromoethenyl)-(3,5,5-trimethylcyclohex-2-enyloxy) diisopropylsilane (70).

(1-bromoethenyl)-chlorodiisopropylsilane (69) (100 mg, 0.39 mmol) was added to a stirred solution of isophorol (55 mg, 0.39 mmol) and imidazole (53 mg, 0.78 mmol) in THF (3 mL). The mixture was stirred at rt for 2 h during which time a white precipitate was formed. Pentane (10 mL) and water (2 mL) were added, the organic layer was separated, dried (MgSO4) and concentrated in vacuo. The residue was dissolved in pentane (5 mL) and filtered through a short plug of silica. Concentration of the solution gave title compound 70 as a colorless oil (123 mg, 90%). 1H NMR (400 MHz, CDCl3): δ = 0.66 (s, 3H), 0.74 (s, 3H), 1.10-1.20 (m, 13H), 1.22-1.36 (m, 2H), 1.03 (dd, J1 = 12.5 Hz, J2 = 8.8 Hz, 1H), 1.19 (br d, J = 17.6 Hz, 1H), 1.25 (s, 3H), 1.29 (ddt, J1 = 12.5 Hz, J2 = 6.1 Hz, J3 = 1.3 Hz, 1H), 1.39 (br d, J = 17.1 Hz, 1H), 5.40-5.44 (m, 1H), 4.07 (d, J = 1.6 Hz, 1H). 13C NMR (100.6 MHz, CDCl3): δ = 12.0, 17.4, 17.7, 23.8, 26.7, 31.2, 31.4, 44.2, 45.3, 68.5, 124.1, 132.86, 132.96, 135.6. Calcd for C17H31BrOSi: C, 56.81; H, 8.69. Found: C, 56.88; H, 8.77.

2,2-Diisopropyl-4,6,6-trimethyl-3-methylene-octahydro-1,2-benzoxasilole (71). A solution of 70 (119 mg, 0.33 mmol), tributyltin hydride (116 mg, 0.39 mmol) and triethylborane (0.07 mL of 1M solution in hexanes) were stirred in benzene (20 mL) at rt for 24 h. The mixture was concentrated in vacuo. Purification of the crude product by column chromatography (silica, pentane : ether, 20 : 1) gave the title compound 71 (46 mg, 50%) as a colorless oil. 1H NMR (400 MHz, CDCl3): δ = 0.90 (d, J = 3.1 Hz, 6H),
1.00 – 1.05 (m, 9H), 1.06 – 1.10 (m, 8H), 1.27 (d, J = 7.3 Hz, 3H), 1.39 (t, J = 13.2 Hz, 1H),
1.51 (dq, J1 = 13.4, J2 = 0.8, 1H), 2.00-2.10 (m, 1H), 2.78 (sextet, J1 = 0.8 Hz, 1H),
4.19 (quintet, J = 6.3 Hz, 1H), 5.52 (t, J = 2.7 Hz, 1H), 5.98 (t, J = 2.6 Hz, 1H). 13C NMR
(75 MHz, CDCl3): δ = 12.7, 13.2, 17.3, 17.6, 17.7, 17.9, 20.0, 25.1, 30.2, 32.2, 33.2, 41.2,
45.0, 51.5, 76.5, 123.5, 147.4. NOE (400 MHz): irradiation of the vinylic proton (at 5.52
ppm) resulted in enhancement of the Me group (at 1.27 ppm). Calcd for C17H32OSi: C,
72.79; H, 11.50. Found: C, 72.58; H, 11.60.

(S)-2-[(1-Bromoethenyl)-diisopropylsilanyloxy]-propionic acid ethyl ester (72).
Chlorosilane 69 (200 mg, 0.782 mmol) was added to a solution of (S)-ethyl lactate (92
mg, 0.782 mmol) and imidazole (106 mg, 1.56 mmol) in anhydrous THF (2 mL). The
mixture was stirred overnight at rt. The volatiles were removed at 30 °C (16 mmHg) and
the residue was extracted with petroleum ether (2 x 10 mL). The combined extracts were
filtered through a silica plug and concentrated at 30 °C (16 mmHg). The product 72 was
obtained as a thick colorless oil (209 mg, 80%). 1H NMR (300 MHz, CDCl3): δ = 1.05-
1.10 (m, 12H), 1.20-1.27 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.46 (d, J = 6.7 Hz, 3H), 4.19
(q, J = 7.1 Hz, 2H), 4.51 (d, J = 6.7 Hz, 1H), 6.46 (d, J = 1.7 Hz, 1H), 6.48 (d, J = 1.7 Hz,
1H). 3C NMR (75 MHz, CDCl3): δ = 11.8, 14.3, 17.05, 17.09, 17.4, 21.7, 61.0, 69.1,
131.4, 133.4, 173.7.

(S)-2-[(1-Bromoethenyl)-diisopropylsilanyloxy]-propionaldehyde (73). DIBAH (0.65
mL, 1M in hexanes) was added to a solution of 72 (206 mg, 0.611 mmol) in anhydrous
ether (5 mL) at -70 °C. The mixture was stirred at the same temperature for 2 h and a solution of acetic acid (0.3 mL) in ether (3 mL) was added. The mixture was warmed to rt and poured onto a solution of Rochelle salt (15 g) in water (15 mL). The mixture was vigorously stirred for 1 h at rt and then extracted with ether (2 x 10 mL). The combined organic layers were dried (MgSO₄) and concentrated. The residual oil was found to be ca 95% pure 73 (107 mg, 60%). ¹H NMR (300 MHz, CDCl₃): δ = 1.05-1.15 (m, 12H), 1.20-1.30 (m, 2H), 1.36 (d, J = 6.9 Hz, 3H), 4.29 (ddd, J₁ = 24.4 Hz, J₂ = 24.4 Hz, J₃ = 18.8 Hz, 1H), 6.41 (d, J = 1.9 Hz, 1H), 6.51 (d, J = 1.8 Hz, 1H), 9.69 (d, J = 1.3 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 11.9, 17.2, 17.4, 18.8, 74.5, 133.4, 133.6, 203.6.

1,2,5,6-diisopropylidene-3-[(1-bromoethenyl)-diisopropylsilanyloxy]-D-glucose (74).
Chlorosilane 69 (100 mg, 0.391 mmol) was added to a solution of diacetoneglucose (102 mg, 0.391 mmol) and imidazole (53 mg, 0782 mmol) in anhydrous THF (1.0 mL). The mixture was stirred at rt for 6 h. The solvent was evaporated at rt (20 mmHg) and the solid white residue was extracted with ether (2 x 3 mL). Combined ethereal extracts were concentrated in vacuo. Column chromatography (silica, petroleum ether : ether, 10 : 1) gave the title compound 74 as a colorless oil (155 mg, 82%). ¹H NMR (300 MHz, CDCl₃): δ = 1.10-1.15 (m, 12H), 1.23-1.30 (m, 2H), 1.31 (s, 3H), 1.32 (s, 3H), 1.41 (s, 3H), 1.50 (s, 3H), 3.97 (dd, J₁ = 8.5 Hz, J₂ = 5.9 Hz, 1H), 4.04 (dd, J₁ = 8.4 Hz, J₂ = 2.8 Hz, 1H), 4.13 (dd, J₁ = 8.5 Hz, J₂ = 6.2 Hz, 1H), 4.30 (dt, J₁ = 8.3 Hz, J₂ = 6.1 Hz, 1H), 4.50 (d, J = 2.7 Hz, 1H), 4.53 (d, J = 3.7 Hz, 1H), 5.89 (d, J = 3.6 Hz, 1H), 6.50 (d, J = 2.0 Hz, 1H), 6.52 (d, J = 1.9 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 11.8, 12.3, 17.1,
(3aR, 3bS, 8aS, 9aR)-8-Hydroxymethyl-5,5-diisopropyl-2,2-dimethyloctahydro-1,3,4,9-tetraoxa-5-sila-cyclopenta[a]azulen-8-ol isopropylidene acetal (75) and 1,2,5,6-diisopropylidene-3-(ethenyl-diisopropylsilanyloxy)-D-glucose (74b). Sodium cyanoborohydride (40.6 mg, 0.646 mmol) was added to a solution of 74 (155 mg, 0.323 mmol), tributyltin chloride (5.3 mg, 0.016 mmol) and AIBN (10.6 mg, 0.065 mmol) in tert-butanol (20 mL). The mixture was refluxed for 48 h, the solution was filtered and the filtrate was concentrated at 30 °C (20 mmHg). The dry residue was extracted with ether (3 x 5 mL) and combined ethereal extracts were concentrated. Column chromatography (silica, petroleum ether : ether, 30 : 4) gave the title compounds 75 as a colorless oil (8.2 mg, 6%, less polar) and 74b as a colorless oil (116 mg, 90%, more polar).

Compound 75: $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 0.61$ (ddd, $J_1 = 15.2$ Hz, $J_2 = 6.4$ Hz, $J_3 = 2.7$ Hz, 1H), 1.80 (ddd, $J_1 = 13.8$ Hz, $J_2 = 6.3$ Hz, $J_3 = 3.7$ Hz, 1H), 2.08 (td $J_1 = 13.7$ Hz, $J_2 = 2.7$ Hz, 1H), 0.90-1.10 (m, 20H), 1.31 (s, 3H), 1.31 (s, 3H), 1.43 (s, 3H), 1.49 (s, 3H), 3.80 (d, $J = 8.6$ Hz, 1H), 3.90 (d, $J = 1.5$ Hz, 1H), 4.01 (d, $J = 8.7$ Hz, 1H), 4.34 (br s, 1H), 4.47 (d, $J = 3.6$ Hz, 1H), 5.88 (d, $J = 3.5$ Hz, 1H).

Compound 74b: $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 0.95-1.12$ (m, 14H), 1.30 (s, 3H), 1.32 (s, 3H), 1.40 (s, 3H), 1.49 (s, 3H), 3.96 (dd, $J_1 = 8.5$ Hz, $J_2 = 6.2$ Hz, 1H), 4.04 (dd, $J_1 = 8.0$ Hz, $J_2 = 2.7$ Hz, 1H), 4.11 (dd, $J_1 = 8.4$ Hz, $J_2 = 6.2$ Hz, 1H), 4.31 (dt, $J_2 = 7.9$ Hz, 1H).
Hz, J₁ = 6.2 Hz, 1H), 4.36 (d, J = 2.7 Hz, 1H), 4.41 (d, J = 3.6 Hz, 1H), 5.85-5.95 m, 2H), 6.05-6.19 (m, 2H).

(1-Bromoethenyl)iodomethyldimethylsilane (78), prepared according to General Procedure E from chloro(chloromethyl)dimethylsilane (12.2 mmol, 1.74 g). The volatile components were removed from the crude reaction product in vacuo and the residue was treated with a saturated solution of sodium iodide in anhydrous acetone (10 mL) at reflux for 20 h. Water (20 mL) was added, the mixture was extracted with petroleum ether (2 x 20 mL), and the combined organic extracts were dried (MgSO₄). Vacuum distillation gave the title compound 78 as a colorless oil (1.22 g, 33%), bp 105 – 110 ºC at 17 mmHg. ¹H NMR (400 MHz, CDCl₃): δ = 0.36 (s, 6H), 2.16 (s, 2 H), 6.30 (d, J = 2.1 Hz, 1H), 6.39 (d, J = 2.1 Hz, 1H). ¹³C NMR (100.6 MHz, CDCl₃): δ = -16.1, -3.5, 131.7, 134.8. Calcd for C₅H₁₀BrISi: C, 19.69; H, 3.30. Found: C, 20.69; H, 3.35.

(1-Bromoethenyl)-tri-n-butylstannane (79), prepared according to General Procedure A (with the exception of that a solution of Bu₃SnCl was added in ca 3-5 seconds and a solution of AcOH was not added) from tributyltin chloride (4.56 g, 14 mmol) as a colorless liquid (4.71 g, 85%), bp 108 – 109 ºC at 0.1 mmHg. ¹H NMR (300 MHz, CDCl₃): δ = 0.92 (t, J = 7.3 Hz, 9H), 1.06 (apparent t, J=8.1 Hz, 6H), 1.35 (sextet, J = 7.7 Hz), 1.50 – 1.70 (m, 6H), 6.13 (d, J = 1.9 Hz, 2H), 6.49 (d, J = 1.9 Hz). ¹³C NMR (75 MHz, CDCl₃): δ = 11.0, 13.9, 27.4, 28.9, 131.9, 137.6. Calcd for C₁₄H₂₉BrSn: C, 42.47; H, 7.38. Found: C, 42.83; H, 7.56.
6.4. Experimental details for Chapter 4

**General Procedure F: 2-Bromo-1-pent-1-en-3-yl propanoate (80a).** A solution of 51 (0.89 g, 5.4 mmol) and DMAP (0.79 g, 6.5 mmol) in anhydrous dichloromethane (5 mL) was treated with propionic anhydride (0.76 mL, 5.9 mmol) and the reaction mixture was kept for 3 h at rt. Ether (5 mL) and water (5 mL) were added, the layers were separated and the aqueous layer was extracted with ether (2 x 3 mL). The combined organic extracts were dried (MgSO₄) and concentrated. A petroleum ether : ether mixture (5 mL, 5 : 1) was added to the residual oil and the solution was filtered through a silica plug. Volatiles were removed at rt (20 mmHg) and the product 80a was obtained as a colorless oil (0.944 g, 80%). ¹H NMR (300 MHz, CDCl₃): δ = 0.88 (t, J = 7.4 Hz, 3H), 1.15 (t, J = 7.6 Hz, 3H), 1.68-1.82 (m, 2H), 2.36 (q, J = 7.6 Hz, 2H), 5.15 (t, J = 6.7 Hz, 1H), 5.61 (d, J = 1.9 Hz, 1H), 5.88 (dd, J₁ = 1.9 Hz, J₂ = 0.7 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 9.3, 25.8, 27.8, 77.7, 119.5, 131.6, 173.5.

**(Z)-4-Bromo-2-methyl-hept-4-enoic acid (80b)** LiN(SiMe₃)₂ (1.22 mL, 1M in THF) was added to a solution of 80a (181 mg, 0.814 mmol) and chlorotrimethylsilane (0.21 mL, 1.63 mmol) in anhydrous THF (2.1 mL) at -60 to -65 °C. The mixture was allowed to warm up to rt (in ca 1 h 30 min) and then was kept at rt for 1 h. 5% Aq HCl (5 mL) was added and the mixture was extracted with dichloromethane (2 x 5 mL). The combined organic extracts were concentrated at 30 °C (20 mmHg) and then treated with sat. aq NaHCO₃ (4 mL). The aqueous solution was extracted with hexanes (2 x 3 mL) to
remove non-acidic admixtures and filtered with charcoal (0.1g). The aqueous filtrate was acidified with 10% aq HCl and the cloudy mixture was extracted with dichloromethane (3 x 2 mL). The combined organic extracts were dried (MgSO₄) and concentrated at 40 °C (16 mmHg) to afford pure **80b** as a colorless oil (101 mg, 56%). ^1H NMR (300 MHz, CDCl₃): δ = 0.98 (t, J = 7.5 Hz, 3H), 1.17 (d, J = 7.0 Hz, 3H), 2.16 (apparent q, J = 7.5 Hz, 2H), 2.40-2.50 (m, 1H), 2.85 (ddd, J₁ = 13.2 Hz, J₂ = 6.8 Hz, J₃ = 0.9 Hz, 1H), 2.91 (dd, J₁ = 12.7 Hz, J₂ = 5.7 Hz, 1H), 5.73 (t, J = 6.8 Hz, 1H), 11.95 (br s, 1H). ^13C NMR (75 MHz, CDCl₃): δ = 13.1, 16.0, 25.0, 38.2, 44.8, 124.0, 133.3, 182.6.

**3-Bromo-2-methylbut-3-en-2-yl propanoate (81a)** was obtained from **10** (1.29 g, 7.81 mmol) according to General Procedure F (with exception the esterification was conducted for 48 h at 40 °C) as a colorless liquid (1.40 g, 80%). ^1H NMR (300 MHz, CDCl₃): δ = 1.09 (t, J = 7.6 Hz, 3H), 1.60 (s, 6H), 2.29 (q, J = 7.6 Hz, 2H), 5.55 (d, J = 2.7 Hz, 1H), 5.80 (d, J = 2.7 Hz, 1H). ^13C NMR (75 MHz, CDCl₃): δ = 9.2, 26.5, 28.5, 81.0, 116.6, 138.4, 173.1.

**General procedure G: Synthesis of 4-bromo-2,5-dimethyl-hex-4-enoic acid (81b).** A solution of tert-butylchlorodimethylsilane (273 mg, 1.81 mmol) and HMPA (1.2 mL) in anhydrous THF (1.8 mL) was added to a solution of **81a** (200 mg, 0.905 mmol) in THF (2.1 mL) at −70 °C. LiN(SiMe₃)₂ (1.36 mL, 1M in THF) was slowly added and the reaction mixture was stirred at −70 °C for 20 min and then allowed to warm up to rt (in ca 1 h 30 min). The mixture was stirred at rt for 2 h after which 5% aq HCl (5 mL) was
added and the mixture was extracted with dichloromethane (2 x 5 mL). The combined organic extracts were washed with 5% aq HCl (2 x 2 mL) to remove HMPA and then were concentrated at 30 °C (20 mmHg) and treated with sat. aq NaHCO₃ (4 mL). The aqueous solution was extracted with hexanes (2 x 3 mL) to remove non-acidic admixtures and filtered with charcoal (0.1g). The aqueous filtrate was acidified with 10% aq HCl and the cloudy mixture was extracted with dichloromethane (3 x 2 mL). The combined organic extracts were dried (MgSO₄) and concentrated at 40 °C (16 mmHg) which allowed for pure 81b as a colorless oil (93 mg, 47%).

**General Procedure H: Synthesis of 4-bromo-2,5-dimethyl-hex-4-enoic acid (81b).**

Trimethylsilyl triflate (0.26 mL, 1.45 mmol) was slowly added to a cooled (dry ice bath) solution of 81a (200 mg, 0.905 mmol) and triethylamine (0.50 mL, 3.62 mmol) in dichloromethane (0.7 mL). The reaction mixture was allowed to warm up and then was kept at rt for 48 h. 5% Aq HCl (5 mL) was added and the mixture was stirred for 1 h at rt. The layers were separated and the organic layer was extracted with dichloromethane (2 x 5 mL). The combined organic extracts were concentrated at 30 °C (20 mmHg) and treated with sat. aq NaHCO₃ (4 mL). The aqueous solution was extracted with hexanes (2 x 3 mL) to remove non-acidic admixtures and filtered with charcoal (0.1g). The aqueous filtrate was acidified with 10% aq HCl and the cloudy mixture was extracted with dichloromethane (3 x 2 mL). The combined organic extracts were dried (MgSO₄) and concentrated at 40 °C (16 mmHg) to afford pure 81b as a colorless oil (153 mg, 77%).

**1H NMR (300 MHz, CDCl₃):** δ = 1.19 (d, J = 6.9 Hz, 3H), 1.80 (s, 3H), 1.89 (s, 3H), 2.64
(dd, J₁ = 14.2 Hz, J₂ = 8.0 Hz, 1H), 2.85-3.00 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ = 16.1, 21.0, 25.8, 38.7, 40.6, 118.7, 133.3, 182.9.

2-Bromo-3-methylhepta-1,6-dien-3-yl propanoate (83a) was obtained from 22 (618 mg, 3.01 mmol) according to General Procedure F (with the exception that the esterification was conducted for 48 h at 40 °C) as a colorless liquid (630 mg, 80%). ¹H NMR (400 MHz, CDCl₃): δ = 1.14 (t, J = 7.6 Hz, 3H), 1.70 (s, 3H), 1.09-2.10 (m, 4H), 2.34 (qd, J₁ = 7.6 Hz, J₂ = 1.6 Hz, 2H), 4.98 (dd, J₁ = 10.4 Hz, J₂ = 1.5 Hz, 1H), 5.05 (dd, J₁ = 17.1 Hz, J₂ = 1.5 Hz, 1H), 5.66 (d, J = 2.6 Hz, 1H), 5.76-5.83 (m, 1H), 5.85 (d, J = 2.3 Hz, 1H). ¹³C NMR (100.6 MHz, CDCl₃): δ = 9.1, 22.6, 27.9, 28.3, 37.5, 83.2, 114.9, 117.9, 136.9, 137.6, 172.7. Anal. Calcd for C₁₁H₁₇BrO₂: C, 50.59; H, 6.56. Found: C, 50.46; H, 6.52.

4-Bromo-2,5-dimethyl-nona-4,8-dienoic acid (83b) (mixture (E)- and (Z)- products, Scheme 64) was prepared from 83a (500 mg, 1.91 mmol) according to General Procedure H. The diastereomeric ratio of the crude 83b (250 mg, 50%) was determined from integration of the allylic CH₃ ¹H NMR resonances (400 MHz, CDCl₃): δ = 1.80 (s, 0.42H) and δ = 1.88 (s, 0.58H). ¹H NMR (400 MHz, CDCl₃): δ = 1.21 (d, J = 6.3 Hz) and 1.20 (d, J = 7.0 Hz) (overl., 3H), 1.80 (s, 1.3H), 1.88 (s, 1.9H), 2.10-2.45 (m, 4.7H), 2.66 (dd, J₁ = 14.5 Hz, J₂ = 8.2 Hz, 1H), 2.85-2.93 (m, 1H), 3.00 (quintet, J = 6.1 Hz, 1H), 4.95-5.10 (m, 2H), 5.75-5.90 (m, 1H). ¹³C NMR (100.6 MHz, CDCl₃): δ = 15.7, 15.9,
2-Bromo-3-methylhepta-1,6-dien-3-yl acetate (84a) was obtained from 22 (500 mg, 2.45 mmol) according to General Procedure F (with the exception that the esterification was conducted with acetic anhydride for 48 h at 40 °C) as a colorless liquid (512 mg, 85%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.70$ (s, 3H), 1.90-1.96 (m, 1H), 2.02-2.05 (m, 3H), 2.06 (s, 3H), 4.99 (dq, $J_1 = 11.9$ Hz, $J_2 = 1.2$ Hz, 1H), 5.06 (dq, $J_1 = 15.5$ Hz, $J_2 = 1.6$ Hz, 1H), 5.66 (d, $J = 2.6$ Hz, 1H), 5.75-5.85 (m, 1H), 5.84 (d, $J = 2.6$ Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta = 21.8$, 22.6, 27.9, 37.5, 83.5, 114.9, 117.6, 136.7, 137.6, 169.3. Anal. Calcd for C$_{10}$H$_{15}$BrO$_2$: C, 48.60; H, 6.12. Found: C, 48.72; H, 6.25.

4-Bromo-5-methyl-nona-4,8-dienoic acid (84b) (mixture (E)- and (Z)- products, Scheme 64) was prepared from 84a (406 mg, 1.55 mmol) according to General Procedure H. The diastereomeric ratio of the crude 84b (284 mg, 70%) was determined from integration of the allylic CH$_3$ $^1$H NMR resonances (400 MHz, CDCl$_3$): $\delta = 1.80$ (s, 0.42H and $\delta = 1.91$ (s, 0.58H). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.80$ (s, 1.3H), 1.91 (s, 1.6H), 2.15-2.23 (m, 2H), 2.28-2.35 (m, 2H), 2.62-2.68 (m, 2H), 2.84 (br t, $J = 7.3$ Hz, 2H), 4.95-5.10 (m, 2H), 5.73-5.90 (m, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta = 18.6$, 23.4, 31.2, 32.2, 32.7, 32.9, 33.4, 33.9, 38.3, 114.9, 115.4, 119.7, 120.9, 135.3, 135.5, 137.4, 137.8, 179.1. Anal. Calcd for C$_{10}$H$_{15}$BrO$_2$: C, 48.60; H, 6.12. Found: C, 48.82; H, 6.17.
3-C-(1-bromoethenyl)-1,2:5,6-bis-O-(1-methylethylidene)-α-D-allofuranose propionate (85a) was obtained from 29b (500 mg, 1.39 mmol) according to General Procedure F (with the exception that the esterification was conducted for 48 h at 60 °C) as a colorless oil (570 mg, 97%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.18$ (t, J = 7.6 Hz, 3H), 1.34 (s, 6H), 1.45 (s, 3H), 1.53 (s, 3H), 2.39 (q, J = 7.5 Hz, 2H), 4.03 (dd, J$_1$ = 5.5 Hz, J$_2$ = 1.8 Hz, 2H), 4.19 (d, J = 6.2 Hz, 1H), 4.25 (q, J = 5.5 Hz, 1H), 5.19 (d, J = 3.9 Hz, 1H), 5.77 (d, J = 2.9 Hz, 1H), 5.87 (dd, J$_1$ = 2.9 Hz, J$_2$ = 0.6 Hz, 1H), 5.91 (d, J = 3.9 Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta = 9.2$, 26.8, 26.91, 26.94, 27.8, 66.3, 73.5, 81.6, 82.7, 85.6, 105.0, 109.3, 112.7, 120.3, 127.0, 172.2.

tert-Butyldimethylsilyl ester of (R)-4-Bromo-4-[(3aR,5S,6aR)-5-((R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-dihydro-furo[2,3-d][1,3]dioxol-(6Z)-ylidene]-2-methyl-butyric acid (85b). A solution of tert-butyldimethylsilyl triflate (0.12 mL, 0.502 mmol) in dichloromethane (1 mL) was added over 10 h (syringe pump) to a stirred solution of 85a (141 mg, 0.335 mmol) and triethylamine (0.23 mL, 1.67 mmol) in dichloromethane (1.1 mL) at rt. The mixture was stirred for 24 h at rt and the dichloromethane was then removed at 30 °C (20 mmHg). The residual oil was extracted with ethyl acetate (2 x 2 mL), the ethyl acetate was removed at 30 °C (20 mmHg) and the residual oil was subjected to column chromatography (silica, petroleum ether : ethyl acetate 4 : 1) to afford 85b as a colorless oil (61 mg, 34%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.19$ (s, 3H), 0.20 (s, 3H), 0.90 (s, 9H), 1.19 (d, J = 7.2 Hz, 3H), 1.30 (s, 3H), 1.40 (s,
9H), 2.48 (dd, J1 = 14.5 Hz, J2 = 4.5 Hz, 1H), 2.80-2.98 (m, 1H), 3.14 (dd, J1 = 14.6 Hz, J2 = 9.1 Hz, 1H), 3.83 (dd, J1 = 8.4 Hz, J2 = 6.3 Hz, 1H), 3.93 (dd, J1 = 13.3 Hz, J2 = 6.2 Hz, 1H), 4.06 (dd, J1 = 8.4 Hz, J2 = 6.2 Hz, 1H), 5.05 (d, J = 7.2 Hz, 1H), 5.08 (d, J = 4.4 Hz, 1H), 5.79 (d, J = 4.4 Hz, 1H) 13C NMR (100.6 MHz, CDCl3): δ = -4.7, -4.5, 17.7, 17.8, 25.6, 25.7, 26.5, 27.9, 27.8, 40.4, 42.3, 67.4, 77.9, 81.5, 83.9, 104.3, 110.3, 113.2, 126.9, 139.2, 175.4. NOE (500 MHz): irradiation of the CH2 protons (at 3.14 ppm) resulted in enhancement of the H4 proton in the carbohydrate ring (at 5.05 ppm).

Cesium salt of (R)-4-Bromo-4-[(3aR,5S,6aR)-5-((R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-dihydro-furo[2,3-d][1,3]dioxol-(6Z)-ylidene]-2-methyl-butyric acid (85c). The product 85b (61 mg, 0.11 mmol) was dissolved in anhydrous acetonitrile (0.5 mL) and dry cesium fluoride (17 mg, 0.11 mmol) was added. The mixture was stirred at 50 °C in a sealed tube for 24 h. Upon slow cooling, crystal formation was observed which were submitted for a single crystal X-ray analysis.

3-Bromo-1-(tert-butyldiphenylsilyloxy)-2-methyl-but-3-en-2-yl propanoate (86a) was obtained from 30b (419 mg, 1.0 mmol) according to General Procedure F (with the exception that esterification was conducted for 48 h at rt) as a colorless oil (404 mg, 86%). 1H NMR (400 MHz, CDCl3): δ = 0.87 (s, 9H), 1.15 (t, J = 7.6 Hz, 3H), 1.84 (s, 3H), 2.31 (dd, J1 = 7.7 Hz, J2 = 3.5 Hz, 1H), 2.35 (dd, J1 = 7.6 Hz, J2 = 3.5 Hz, 1H), 3.78 (d, J = 9.9 Hz, 1H), 3.87 (d, J = 9.9 Hz, 1H), 5.79 (d, J = 2.6 Hz, 1H), 5.97 (d, J = 2.6 Hz, 1H), 7.40-7.50 (m, 6H), 7.70-7.80 (m, 4H). 13C NMR (100.6 MHz, CDCl3): δ = 9.0, 19.4,

4-Bromo-6-(tert-butyldiphenylsilyloxy)-2,5-dimethyl-hex-4-enoic acids (86b+86c) (mixture (E)- and (Z)-products) was prepared from 86a (475 mg, 1.00 mmol) according to General Procedure H. The diastereomeric ratio of the crude 86b+86c (28 mg, 8%) was determined from integration of the allylic CH\textsubscript{3} \textsuperscript{1}H NMR resonances (400 MHz, CDCl\textsubscript{3}): \( \delta = 1.99 \) (s, 2.4H) and \( \delta = 1.94 \) (s, 0.6H). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 1.00-1.10 \) (m, 12H), 1.94 (s, 0.6H), 1.99 (s, 2.4H), 2.37 (dd, \( J_1 = 14.7 \) Hz, \( J_2 = 8.3 \) Hz, 1H), 2.52-2.63 (m, 1H), 2.75-2.83 (m, 1H), 4.14 (d, \( J = 11.9 \) Hz, 0.70H), 4.25 (d, \( J = 11.9 \) Hz, 0.70H), 4.40 (s, 0.34H), 7.35-7.55 (m, 6H), 7.60-7.70 (m, 4H).

3-Bromo-1-(tert-butyldiphenylsilyloxy)-2-methyl-but-3-en-2-yl acetate (87a) was obtained from 30b (419 mg, 1.0 mmol) according to General Procedure F (with exception the esterification was conducted with acetic anhydride) as a colorless oil (415 mg, 89%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 1.10 \) (s, 9H), 1.85 (s, 3H), 2.05 (s, 3H), 3.77 (d, \( J = 9.9 \) Hz, 1H), 3.88 (d, \( J = 9.9 \) Hz, 1H), 5.79 (d, \( J = 2.6 \) Hz, 1H), 5.97 (d, \( J = 2.6 \) Hz, 1H), 7.40-7.50 (m, 6H), 7.70-7.80 (m, 4H). \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}): \( \delta = 19.4, 20.5, 21.7, 26.8, 67.2, 83.4, 119.2, 127.8, 129.9, 133.01, 133.14, 134.4, 135.7, 169.2. \) Anal. Calcd for C_{23}H_{29}BrO_{3}Si: C, 59.86; H, 6.33. Found: C, 59.96; H, 6.40.
4-Bromo-6-(tert-butyldiphenylsilyloxy)-5-methyl-hex-4-enoic acids (87b+87c) (mixture (E)- and (Z)- products) was prepared from 87a (461 mg, 1.00 mmol) according to General Procedure H. The diastereomeric ratio of the crude 87b+87c (354 mg, 77%) was determined from integration of the -CH$_2$O- $^1$H NMR resonances (400 MHz, CDCl$_3$):

$\delta = 4.26$ (s, 0.8H) and $\delta = 4.42$ (s, 0.4H). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.12$ (s, 9H), 1.97 (s, 0.57H), 2.01 (s, 0.80H), 2.52 (t, $J = 7.8$ Hz, 0.80H), 2.63 (t, $J = 7.7$ Hz, 1.23H), 2.86 (t, $J = 7.7$ Hz, 0.40H), 4.26 (s, 0.80H), 4.42 (s, 0.40H), 7.35-7.50 (m, 6H), 7.70-7.80 (m, 4H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta = 19.2$, 26.82, 26.89, 32.1, 32.6, 33.1, 63.4, 68.0, 123.7, 133.2, 133.5, 134.8, 135.3, 135.5, 135.6.

(E)-4-Bromo-6-(tert-butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enoic acid, methyl ester (87d). The 87b+87c mixture was treated with an excess of ethereal diazomethane and the methyl esters thus obtained were subjected to column chromatography (silica, pentane : ether 10 : 1). The separation was incomplete, however ca 100 mg of essentially pure major (E)- ester 87d (the less polar fraction) was isolated as a colorless oil. The combined yield of esters was 336 mg (71%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.09$ (s, 9H), 1.99 (s, 3H), 2.46 (t, $J = 7.4$ Hz, 2H), 2.62 (t, $J = 7.6$ Hz, 2H), 3.63 (s, 3H), 4.24 (s, 2H), 7.40-7.50 (m, 6H), 7.70-7.80 (m, 4H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta = 19.3$, 26.8, 32.6, 33.1, 51.6, 63.4, 124.1, 127.7, 129.8, 133.3, 135.3, 135.6, 172.6. NOE (400 MHz): irradiation of the -CH$_2$O- protons (at 4.24 ppm) resulted in enhancement of the –CH$_2$-CH$_2$-COOMe protons (at 2.62 ppm) and vice versa.
2-Bromo-3-methylpenta-1,4-dien-3-yl propionate (88a) was obtained from 21 (450 mg, 2.5 mmol) according to General Procedure F (with the exception that the esterification was conducted at 40 °C for 48 h and the product was purified by silica chromatography with petroleum ether : ether (20 : 1) mixture as an eluant) as a colorless oil (465 mg, 78%). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.18 (t, $J$ = 7.6 Hz, 3H), 1.73 (s, 3H), 2.42 (q, $J$ = 7.6 Hz, 2H), 5.09 (m, $J$ = 0.7 Hz, 1H), 5.16 (br q, $J$ = 1.0 Hz, 1H), 5.69 (d, $J$ = 1.9 Hz, 1H), 5.70 (s, 1H), 5.96 (dd, $J_1$ = 1.8 Hz, $J_2$ = 1.1 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 9.2, 18.5, 27.9, 79.0, 115.6, 119.8, 129.9, 139.6, 172.9.

General Procedure I: 4-Bromo-2,5-dimethyl-hepta-4,6-dienoic acids and 6-bromo-2,5-dimethyl-hepta-4,6-dienoic acids mixture (88b+88c+88d). Anhydrous MnCl$_2$ (119 mg, 0.94 mmol) was stirred with anhydrous THF (4 mL) for 1 h at rt. A pink fine slurry was formed. LiN(SiMe$_3$)$_2$ (2.6 mL, 1M in THF) was slowly added and the resulting clear brown solution was stirred for 20 min at rt. The clear dark brown reaction mixture was cooled in a dry ice bath (no precipitate formation was observed) and a solution of 88a (200 mg, 0.86 mmol) in anhydrous THF (1 mL) was slowly added. The reaction mixture was allowed to warm up to rt and was transferred to a pressure tube. The reaction mixture was kept at 80 °C for 20 h and was then cooled to rt and transferred via a cannula to a 1M aq HCl (10 mL) under argon. (It is important to isolate the basic reaction mixture from oxygen prior to the neutralization step to suppress the oxidation of Mn$^{+2}$ to Mn$^{+4}$.) The pink reaction mixture was stirred for 10 min at rt and then was extracted with dichloromethane (3 x 4 mL). The organic extracts were dried (MgSO$_4$) and concentrated.
at rt (16 mmHg). The product mixture was obtained as a colorless oil (160 mg, 80%). The diastereomeric ratio of the resulting mixture of 88b+88c+88d was determined from integration selected $^1$H NMR resonances (Fig. 18.).

Fig. 18. Integration data for 88b+88c+88d mixture (300 MHz, CDCl$_3$)

![Diagram](image)

$^6$H $\delta = 6.75$
(dd, $J_1 = 17.1$ Hz, $J_2 = 10.9$ Hz, 0.83H)

$^6$H $\delta = 6.97$
(dd, $J_1 = 17.1$ Hz, $J_2 = 10.9$ Hz, 0.10H)

$^7$H $\delta = 5.95$
(d, $J = 2.3$ Hz, 0.07H)

$^1$H NMR (300 MHz, C$_6$D$_6$): $\delta = 1.15$-1.25 (4.0H), 1.89 (s, 1H), 2.03 (s, 2.4H), 2.75-3.10 (m, 4.5H), 3.67 (s, 2.6H), 3.69 (s, 2H), 5.10-5.30 (m, 2.8H), 5.95 (d, $J = 2.3$ Hz, 0.08H), 6.75 (dd, $J_1 = 17.1$ Hz, $J_2 = 10.9$ Hz, 1.0H), 6.97 (dd, $J_1 = 17.1$ Hz, $J_2 = 10.9$ Hz, 0.12H).

(E)-4-Bromo-2,5-dimethyl-hepta-4,6-dienoic acid, methyl ester (88e) The mixture of acids 88b+88c+88d (obtained from 0.86 mmol of 88a) was treated with an excess of ethereal diazomethane and the mixture of esters was separated by column chromatography (silica, petroleum ether : acetone 20 : 1) to afford pure 88e as a colorless liquid (the least polar fraction, 110 mg, 52%). $^1$H NMR (300 MHz, C$_6$D$_6$): $\delta = 1.01$ (d, $J = 6.9$ Hz, 3H), 1.90 (s, 3H), 2.58-2.70 (m, 1H), 2.90-3.20 (m, 2H), 3.29 (s, 3H), 4.95 (dd, $J_1 = 10.9$ Hz, $J_2 = 0.9$ Hz, 1H), 5.08 (dd, $J_1 = 17.1$ Hz, $J_2 = 1.1$ Hz, 1H), 6.59 (dd, $J_1 =$
17.1 Hz, $J_2 = 10.9$ Hz, 1H). $^{13}$C NMR (75 MHz, C$_6$D$_6$): $\delta = 16.6, 19.6, 39.4, 41.2, 51.7, 115.8, 128.15, 133.4, 135.3, 175.7$. NOe (500 MHz): irradiation of the $-\text{CH}=\text{CH}_2$ proton (at 5.08 ppm) resulted in enhancement of the $-\text{CH}_2$- protons (at 2.58-2.70 ppm) while irradiation of allylic methyl protons (at 1.90 ppm) resulted only in enhancement of the $-\text{CH}=\text{CH}_2$ proton (at 5.08 ppm).

2-Bromo-3-methylpenta-1,4-dien-3-yl ester of N-trifluoroacetyl proline (89a).

Diisopropylcarbodiimide (0.37 mL) was slowly added to a solution of 21 (322 mg, 1.82 mmol), N-trifluoroacetylproline$^{106}$ (500 mg, 2.37 mmol) and DMAP (22.3 mg, 0.182 mmol) in dichloromethane (2.5 mL) at rt. The reaction mixture was stirred for 16 h at rt, water (2 mL) was added and the mixture was filtered. The aqueous layer was extracted with ethyl acetate (2 x 5 mL) and the combined organic extracts were dried (MgSO$_4$) and concentrated. The residue was dissolved in a petroleum ether : ethylacetate mixture (5 : 1, 5 mL) and filtered through a silica plug. The plug was washed with the same solvent mixture and the combined filtrates were concentrated at 50 °C (20 mmHg). The title product was obtained as a diastereomeric mixture (540 mg, 80%). $^1$H NMR (300 MHz, CHCl$_3$): $\delta = 1.18-1.30$ (m, 2.4H), 1.71 (s, 3H), 1.78 (s, 3.1H), 2.00-2.20 (m, 9.7H), 3.50-3.85 (m, 5H), 4.55 (dd, $J_1 = 12.3$ Hz, $J_2 = 6.5$ Hz, 2H), 4.60-4.71 (m, 0.49H), 5.31 (ddd, $J_1 = 10.8$ Hz, $J_2 = 7.9$ Hz, $J_3 = 0.5$ Hz, 2H), 5.36 (d, $J = 3.7$ Hz, 1H), 5.41 (d, $J = 3.7$ Hz, 1H), 5.65 (dd, $J_1 = 6.2$ Hz, $J_2 = 2.7$ Hz, 1.4H), 5.67 (dd, $J_1 = 4.5$ Hz, $J_2 = 3.1$ Hz, 0.4H), 5.92 (dd, $J_1 = 2.6$ Hz, $J_2 = 2.3$ Hz, 2H), 5.95-6.12 (m, 2H).
2-(2-Bromo-3-methyl-penta-2,4-dienyl)-1-(trifluoroacetyl)-pyrrolidine-2-carboxylic acids and 2-(4-Bromo-3-methyl-penta-2,4-dienyl)-1-(trifluoroacetyl)-pyrrolidine-2-carboxylic acids mixture (89b+89c+89d) were obtained according to the General procedure I from 89a (540 mg, 1.46 mmol) as a colorless oil (486 mg, 90%). The diastereomeric ratio of the 88b+88c+88d mixture was determined from integration of selected $^1$H NMR resonances (Fig. 19).

Fig. 19. Integration data for 89b+89c+89d mixture (300 MHz, CDCl$_3$)

![Chemical Structures](image.png)

$^6$H $\delta = 6.63$ (dd, $J_1 = 17.0$ Hz, $J_2 = 10.9$ Hz, 0.56H)

$^6$H $\delta = 7.01$ (dd, $J_1 = 17.3$ Hz, $J_2 = 10.9$ Hz, 0.12H)

$^7$H $\delta = 5.82$ (d, $J = 2.0$ Hz, 0.35H)

2-((E)-2-Bromo-3-methyl-penta-2,4-dienyl)-1-(trifluoroacetyl)-pyrrolidine-2-carboxylic acid methyl ester (89e) and 2-((E)-4-bromo-3-methyl-penta-2,4-dienyl)-1-(trifluoroacetyl)-pyrrolidine-2-carboxylic acid methyl ester (89e) were obtained upon treatment of the previous crude product mixture with diazomethane followed by a chromatographic separation (silica, petroleum ether : ethylacetate, 6:1).
Fig. 20. Structures of methyl esters 89e and 89f

![Structures of methyl esters 89e and 89f](image)

Compound 89e (168 mg, 30%, less polar) $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 2.00-2.10 (m, 3H), 2.03 (s, 3H), 2.20-2.40 (m, 1H), 3.65-3.70 (m, 3H), 3.72 (s, 3H), 3.75-3.85 (m, 1H), 5.24 (d, $J = 11.5$ Hz, 1H), 5.38 (dd, $J_1 = 17.0$ Hz, $J_2 = 0.9$ Hz, 1H), 6.62 (dd, $J_1 = 17.0$ Hz, $J_2 = 10.9$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 19.6, 24.4, 33.8, 37.3, 48.6, 53.2, 71.0, 116.9, 116.5 (q, $^1J_{C-F}$= 277 Hz), 123.0, 132.8, 138.0, 155.9 (d, $^2J_{C-F}$ = 37 Hz), 172.5. NOe (500 MHz): irradiation of the –C=CH$_2$ proton (at 6.62 ppm) resulted in enhancement of the –CH$_2$- protons (at 2.20-2.40 ppm).

Compound 89f (121 mg, 22%, more polar, contaminated with ca 30% of 89e) $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.87 (s, 3H), 1.99-2.30 (m, 4H), 2.86 (dd, $J_1 = 15.4$ Hz, $J_2 = 8.0$ Hz, 1H), 3.30 (dd, $J_1 = 15.4$ Hz, $J_2 = 7.5$ Hz, 1H), 3.50-3.70 (m, 2H), 4.09 (s, 3H), 5.64 (d, $J = 2.0$ Hz, 1H), 5.95 (br t, $J = 7.7$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 14.7, 24.3, 31.9, 35.1, 48.9, 53.0, 70.6, 116.5 (q, $^1J_{C-F}$= 277 Hz), 117.0, 117.6, 128.2, 138.0, 172.6.

1-(1-Bromoethenyl)-4,4-dimethylcyclohex-2-enyl propionate (90a) was obtained from 24b (453 mg, 1.96 mmol) according to General Procedure F (with the exception that the
esterification was conducted at 40 °C for 19 h and the product was purified by silica chromatography (pentane : ether, 100:5)) as a colorless oil (423 mg, 75%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.98$ (s, 3H), 1.03 (s, 3H), 1.12 (t, $J = 7.5$ Hz, 3H), 1.49 (ddd, $J_1 = 12.5$ Hz, $J_2 = 9.1$ Hz, $J_3 = 3.3$ Hz, 1H), 1.57 (ddd, $J_1 = 12.5$ Hz, $J_2 = 9.1$ Hz, $J_3 = 3.3$ Hz, 1H), 1.88 (ddd, $J_1 = 13.5$ Hz, $J_2 = 9.1$ Hz, $J_3 = 3.5$ Hz, 1H), 2.08 (ddd, $J_1 = 13.4$ Hz, $J_2 = 9.2$ Hz, $J_3 = 3.5$ Hz, 1H), 2.25-2.40 (m, 2H), 5.64 (dd, $J_1 = 2.3$ Hz, $J_2 = 0.5$ Hz, 1H), 5.73 (d, $J = 10.2$ Hz, 1H), 5.84 (dd, $J_1 = 2.3$ Hz, $J_2 = 0.5$ Hz, 1H), 6.11 (dd, $J_1 = 10.2$ Hz, $J_2 = 0.5$ Hz, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta = 9.0$, 28.1, 28.4, 28.7, 31.0, 32.2, 32.5, 80.7, 118.3, 122.9, 139.69, 143.7, 172.9. Anal. Calcd for C$_{13}$H$_{19}$BrO$_2$: C, 54.37; H, 6.67. Found: C, 54.53; H, 6.53.

Fig. 21 structure of 90b

4-Bromo-4-[4,4-dimethyl-cyclohex-2-en-ylidene]-2-methyl-butyric acids (90b+90c) were obtained according to General Procedure I from 90a (500 mg, 1.74 mmol) as a colorless oil (300 mg, 60%, 90 :10 mixture of (E)- (Z)- products). The diastereomeric ratio was determined from integration of the -C(Me$_2$)-CH=CH- $^1$H NMR resonances ($\delta = 5.61$ (d, $J = 10.2$ Hz, 0.9H) and $\delta = 5.68$ (d, $J = 10.1$ Hz, 0.1H)) and from integration of -
C(Me₂)-CH=CH- ¹H NMR resonances (δ = 6.21 (d, J = 10.1 Hz, 0.9H)) and δ = 6.41 (d, J = 10.1 Hz, 0.1H). (E)-product: ¹H NMR (400 MHz, CDCl₃): δ = 1.01 (s, 6H), 1.15 (d, J = 6.8 Hz, 3H), 1.51 (t, J = 6.6 Hz, 2H), 2.52 (t, J = 6.6 Hz, 2H), 2.75 (dd, J₁ = 13.6 Hz, J₂ = 7.1 Hz, 1H), 2.86-3.00 (m, 2H), 3.66 (s, 3H), 5.61 (d, J = 10.2 Hz, 1H), 6.21 (d, J = 10.1 Hz, 1H). ¹³C NMR (100.6 MHz, CDCl₃): δ = 14.2, 28.2, 28.4, 28.6, 32.1, 33.4, 36.4, 120.5, 122.7, 133.2, 141.3, 168.7. NOe (400 MHz): irradiation of the C(Me₂)–CH=CH- proton (at 6.21 ppm) resulted in enhancement of the –CH₂- protons (at 2.75 ppm and 2.86-3.00 ppm).

1-(1-Bromoethenyl)-4,4-dimethylcyclohex-2-enyl acetate (91a) was obtained from 24b (500 mg, 2.15 mmol) according to General Procedure F (with the exception that the esterification was conducted at 40 °C for 19 h and the product was purified by silica chromatography (pentane : ether, 100:5)) as a colorless oil (507 mg, 86%). ¹H NMR (300 MHz, CDCl₃): δ = 0.97 (s, 3H), 1.03 (s, 3H), 1.47 (ddd, J₁ = 13.5 Hz, J₂ = 9.5 Hz, J₃ = 3.6 Hz, 1H), 1.57 (ddd, J₁ = 13.5 Hz, J₂ = 9.5 Hz, J₃ = 3.6 Hz, 1H), 1.88 (ddd, J₁ = 13.5 Hz, J₂ = 9.0 Hz, J₃ = 3.5 Hz, 1H), 2.03 (s, 3H), 2.06 (ddd, J₁ = 13.5 Hz, J₂ = 9.1 Hz, J₃ = 3.4 Hz, 1H), 5.63 (d, J = 2.3 Hz, 1H), 5.73 (d, J = 10.2 Hz, 1H), 5.83 (d, J = 2.3 Hz, 1H), 6.09 (d, J = 10.2 Hz, 1H). ¹³C NMR (100.6 MHz, CDCl₃): δ = 21.7, 28.4, 28.7, 31.0, 32.1, 32.5, 80.9, 118.3, 122.8, 136.5, 143.7, 169.4.

4-Bromo-4-[4,4-dimethyl-cyclohex-2-en-ylidene]-butyric acids (91b+91c)
were obtained according to General Procedure I from 91a (500 mg, 1.83 mmol) as a
colorless oil (350 mg, 70%, 80 : 20 mixture of (E)—(Z)—products). The diastereomeric ratio was determined from integration of the -C(Me₂)-CH=CH- ¹H NMR resonances (δ = 5.63 (d, J = 10.1 Hz, 0.8H) and δ = 5.68 (d, J = 10.1 Hz, 0.2H)) and from integration of the -C(Me₂)-CH=CH- ¹H NMR resonances (δ = 6.22 (d, J = 10.2 Hz, 0.8H)) and δ = 6.40 (d, J = 10.1 Hz, 0.2H)).

4-Bromo-4-[4,4-dimethyl-cyclohex-2-en-ylidene]-butyric acid methyl esters were obtained upon treatment of the mixture of 91b+91c obtained above with ethereal diazomethane. A chromatographic separation (silica, petroleum ether : ethyl acetate, 20:1) was unsuccessful providing a 80 : 20 mixture of methyl esters as a colorless oil (260 mg, 50%). (E)-Product: ¹H NMR (400 MHz, CDCl₃): δ = 1.02 (s, 6H), 1.52 (t, J = 6.6 Hz, 2H), 2.50 (t, J = 6.5 Hz, 2H), 2.60 (t, J = 7.7 Hz, 2H), 2.96 (t, J = 7.7 Hz, 2H), 3.68 (s, 3H), 5.63 (d, J = 10.1 Hz, 1H), 6.25 (d, J = 10.2 Hz, 1H). ¹³C NMR (100.6 MHz, CDCl₃): δ = 28.2, 28.4, 28.6, 32.1, 33.4, 36.4, 51.6, 120.5, 122.7, 133.2, 141.3, 172.8.

2-Bromopenta-1,4-dien-3-yl propionate (92a) was obtained from 25 (1.41 g, 8.65 mmol) according to General Procedure F (except that the product was purified by silica chromatography (petroleum ether : ether, 20:1)) as a colorless oil (2.13g, 81%). ¹H NMR (300 MHz, CDCl₃): δ = 1.15 (t, J = 7.6 Hz, 3H), 1.74 (ddd, J₁ = 6.6 Hz, J₂ = 1.6 Hz, J₃ = 0.6 Hz, 1H), 2.37 (q, J = 7.6 Hz, 2H), 5.51 (ddq, J₁ = 15.3 Hz, J₂ = 7.2 Hz, J₃ = 1.7 Hz, 1H), 5.60 (d, J = 2.0 Hz, 1H), 5.71 (br d, J = 7.2 Hz, 1H), 5.80-5.95 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ = 9.2, 27.9, 76.7, 117.4, 119.4, 130.4, 133.3, 173.0.
Fig. 22. Selected NMR integration data for 92b – 92c

(Z)-4-Bromo-2-methyl-hepta-4,6-dienoic acid and (E)-6-bromo-2-methyl-hepta-4,6-dienoic acid (92b+92c) were obtained according to the General Procedure H from 92a (300 mg, 1.37 mmol) as a colorless oil (258 mg, 86%, mixture of 92b and 92c in a 53 : 47 ratio). The diastereomeric ratio was determined from integration of selected $^1$H NMR resonances (Fig. 22). The (E) stereochemistry for 92c was determined from the $^3$J$_{HH}$ coupling constant value (16.6 Hz).

Fig. 23. Structures and selected NMR data for 92d and 92e

(Z)-4-Bromo-2-methyl-hepta-4,6-dienoic acid methyl ester (92d) and (E)-6-bromo-2-methyl-hepta-4,6-dienoic acid methyl ester (92e) were obtained upon treatment of the mixture of acids 92b+92c obtained above (258 mg, 1.10 mmol) with ethereal
diazomethane as a colorless oil (205 mg, 80%). A chromatographic separation (silica, petroleum ether : acetone, 20:1) was only marginally successful.

**92d:** colorless oil, R<sub>f</sub> = 0.328 (34 mg, 13%, a part of the leading fraction); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.16 (d, J = 6.9 Hz, 3H), 2.51 (dd, J<sub>1</sub> = 16.5 Hz, J<sub>2</sub> = 9.9 Hz, 1H), 2.84-2.98 (m, 2H), 3.69 (s, 3H), 5.26 (dd, J<sub>1</sub> = 10.2 Hz, J<sub>2</sub> = 1.5 Hz, 1H), 5.36 (dd, J<sub>1</sub> = 17.0 Hz, J<sub>2</sub> = 1.4 Hz, 1H), 6.32 (d, J = 9.9 Hz, 1H), 6.58 (dt, J<sub>1</sub> = 17.0 Hz, J<sub>2</sub> = 10.1 Hz, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 16.4, 38.3, 45.5, 52.0, 120.3, 126.5, 130.7, 134.4, 176.1. NOe (500 MHz): irradiation of 5H (at 6.32 ppm) resulted in enhancement of the 3H proton (at 2.51 and 2.84-2.98 ppm) (Fig. 23).

**92e:** colorless oil, R<sub>f</sub> = 0.313 (35 mg, 14%, the last part of the tailing fraction); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.18 (d, J = 6.9 Hz, 3H), 2.25-2.36 (m, 1H), 2.50-2.65 (m, 2H), 3.69 (s, 3H), 5.56 (d, J = 1.2 Hz, 1H), 5.73 (d, J = 1.3 Hz, 1H), 6.00 (dd, J<sub>1</sub> = 14.8 Hz, J<sub>2</sub> = 6.4 Hz, 1H), 6.08 (d, J = 14.6 Hz, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 16.9, 36.0, 39.4, 51.8, 118.9, 129.7, 130.6, 134.9, 176.4.

**2-Bromo-penta-1,4-dien-3-yl ester of N-trifluoroacetyl proline (93a).** Diisopropyl carbodiimide (0.37 mL) was slowly added to a solution of 25 (297 mg, 1.82 mmol), N-trifluoroacetylproline<sup>106</sup> (500 mg, 2.37 mmol) and DMAP (22.3 mg, 0.182 mmol) in dichloromethane (2.5 mL) at rt. The reaction mixture was stirred for 16 h at rt, water (2 mL) was added and the mixture was filtered. The aqueous layer was extracted with ethyl acetate (2 x 5 mL), and the combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography (silica, petroleum
ether: ethyl acetate, 4 : 1) to afford 93a as a colorless oil (530 mg, 82%, 1 : 1 diastereomeric mixture). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 2.00-2.50 (m, 5H), 3.65-3.86 (m, 2H), 4.67 (dd, $J_1 = 8.6$ Hz, $J_2 = 3.7$ Hz, 1H), 4.75-4.80 (m, 0.2H) 5.40-5.55 (m, 2.3H), 5.72 (d, $J = 2.2$ Hz, 1H), 5.73 (d, $J = 4.2$ Hz, 0.2H), 5.80 (br d, $J = 5.9$ Hz, 1H), 5.83-5.98 (m, 1.2H), 6.00-6.05 (m, 1H), 6.15-6-20 (m, 0.2H). $^{13}$C NMR (75 MHz, CHCl$_3$): $\delta$ = 21.3, 25.0, 28.5 31.6, 47.3 (q, $J_{CF} = 3.2$ Hz), 48.2, 59.5 (q, $J_{CF} = 3.2$ Hz), 60.3, 60.4, 77.9, 78.1, 78.3, 116.3 (q, $^1J_{CF} = 285$ Hz), 119.9, 120.6, 129.6, 132.3, 156.0 (d, $^2J_{CF} = 38$ Hz), 169.2.

Fig. 24. Selected NMR integration data for 93b – 93c

2-((Z)-2-Bromo-penta-2,4-dienyl)-1-(trifluoroacetyl)-pyrrolidine-2-carboxylic acid and 2-((E)-4-Bromo-penta-2,4-dienyl)-1-(trifluoroacetyl)-pyrrolidine-2-carboxylic acid (93b+93c) were obtained according to the General Procedure H from 93a (142 mg, 0.34 mmol) as a colorless oil (125 mg, 88%). The diastereomeric ratio of the 93b+93c mixture was determined from integration of selected $^1$H NMR resonances (Fig. 24).
2-((Z)-2-Bromo-penta-2,4-dienyl)-1-(trifluoroacetyl)-pyrrolidine-2-carboxylic acid methyl ester (93d) and 2-((E)-4-Bromo-penta-2,4-dienyl)-1-(trifluoroacetyl)-pyrrolidine-2-carboxylic acid methyl ester (93e) were obtained upon treatment of the mixture of acids 93b+93c (125 mg, 0.34 mmol) obtained above with ethereal diazomethane as a colorless oil (94 mg, 75%). A chromatographic separation (silica, petroleum ether : acetone, 10:1) was only marginally successful.

93d: colorless oil, Rf = 0.22 (28 mg, 19%, a part of the leading fraction); ¹H NMR (300 MHz, CDCl₃): δ = 2.00-2.20 (m, 3H), 2.40-2.55 (m, 1H), 3.15 (d, J = 15.2 Hz, 1H), 3.65-3.84 (m, 6H), 5.31 (dd, J₁ = 10.3 Hz, J₂ = 1.5 Hz, 1H), 5.39 (dd, J₁ = 16.9 Hz, J₂ = 1.5 Hz, 1H), 6.32 (d, J = 10.0 Hz, 1H), 6.59 (dt, J₁ = 17.0 Hz, J₂ = 10.1 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 24.3, 34.2, 42.2, 48.9, 53.2, 70.5, 116.1 (q, JCF = 287 Hz), 121.3, 134.2, 134.5, 155.9 (d, JCF = 37 Hz), 172.5. NOe (500 MHz): irradiation of ⁵H (at 6.32 ppm) resulted in enhancement of the ³H protons (at 3.15 ppm) (Fig. 25).

93e: colorless oil, Rf = 0.19 (24 mg, 16%, the last part of the tailing fraction); ¹H NMR (300 MHz, CDCl₃): δ = 2.05-2.20 (m, 3H), 2.16 (d, J = 6.4 Hz, 3H), 2.82 (dd, J₁ =
14.2 Hz, J₂ = 7.4 Hz, 1H), 3.29 (dd, J₁ = 14.2 Hz, J₂ = 7.7 Hz, 1H), 3.65-3.80 (m, 3H), 3.76 (s, 3H), 5.61 (d, J = 1.3 Hz, 1H), 5.76 (d, J = 0.6 Hz, 1H) 5.93 (dt, J₁ = 14.9 Hz, J₂ = 7.5 Hz, 1H), 6.11 (dd, J₁ = 14.7 Hz, J₂ = 0.7 Hz, 1H).

2-Bromo-4-methylpenta-1,4-dien-3-yl propionate (94a) was obtained from 27 (1.14 g, 7.96 mmol) according to General Procedure F (with exception that the product was purified by silica chromatography (petroleum ether : ether 20 : 1)) as a colorless oil (1.47 g, 80%). ¹H NMR (300 MHz, CDCl₃): δ = 1.18 (t, J = 7.6 Hz, 3H), 1.73 (s, 3H), 2.42 (q, J = 7.6 Hz, 2H), 5.05-5.10 (m, 1H), 5.15-5.17 (m, 1H), 5.69 (d, J = 1.9 Hz, 1H), 5.70 (s, 1H), 5.96 (dd, J₁ = 1.8 Hz, J₂ = 1.1 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ = 9.2, 18.4, 27.8, 79.0, 115.6, 119.8, 129.8, 139.6, 172.9.

Fig. 26 Selected NMR integration data for 94b – 94c

(Z)-4-Bromo-2,6-dimethyl-hepta-4,6-dienoic acid and (E)-6-Bromo-2,4-dimethyl-hepta-4,6-dienoic acid (94b+94c) were obtained according to General Procedure H from 94a (200 mg, 0.86 mmol) as a colorless oil (160 mg, 80%). The 56:44 diastereomeric
ratio of 94b and 94c was determined from integration of selected $^1$H NMR resonances (Fig. 26).

Fig. 27. Structures and selected NMR data for 93d and 93e

![Structures of 94d and 94e](image)

$94d$: colorless oil, $R_f = 0.28$ (69 mg, 43%, a part of the leading fraction); $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.16$ (d, $J = 6.9$ Hz, 3H), 1.95 (t, $J = 0.6$ Hz, 3H), 2.43-2.54 (m, 1H), 2.83-2.97 (m, 2H), 3.68 (s, 3H), 5.09 (apparent quintet, $J = 1.6$ Hz, 1H), 5.14 (apparent septet, $J = 0.9$ Hz, 1H), 6.26 (s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta =$ 16.3, 22.7, 38.3, 46.9, 51.9, 118.4, 122.7, 132.1, 140.4, 176.1. NOe (500 MHz): irradiation of $^5$H (at 6.26 ppm) resulted in enhancement of the $^3$H protons (at 2.83-2.97 ppm) and the methyl group (at 1.95 ppm) (Fig. 27).
**94e:** colorless oil, \( R_t = 0.25 \) (46 mg, 29%, the last part of the tailing fraction); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 1.14 \) (d, \( J = 6.9 \) Hz, 3H), 1.82 (d, \( J = 1.4 \) Hz, 3H), 2.13 (ddd, \( J_1 = 13.6 \) Hz, \( J_2 = 7.4 \) Hz, \( J_3 = 1.0 \) Hz, 1H), 2.44 (ddd, \( J_1 = 13.6 \) Hz, \( J_2 = 7.7 \) Hz, \( J_3 = 1.1 \) Hz, 1H), 2.68 (sextet, \( J = 7.0 \) Hz, 1H), 3.68 (s, 3H), 5.54 (t, \( J = 1.5 \) Hz, 1H), 5.67 (d, \( J = 1.5 \) Hz, 1H), 5.80 (apparent septet, \( J = 1.3 \) Hz, 1H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 16.9, 17.6, 38.0, 43.7, 51.8, 119.5, 127.5, 139.4, 176.0 \). NOe (500 MHz): irradiation of the methyl group (at 1.82 ppm) resulted in enhancement of the \( 7\)H protons (at 5.54 ppm) and \(^2\)H proton (at 2.68 ppm) (Fig. 27).

**2-Bromo-4-methylhexa-1,4-dien-3-yl propionate (95a)** was obtained from 26 (0.927 g, 5.94 mmol) according to General Procedure E (with exception that the product was purified from traces of the (Z) isomer by silica chromatography (petroleum ether : ether, 20 : 1)) as a colorless oil (0.844 g, 70%). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 1.15 \) (t, \( J = 7.6 \) Hz, 3H), 1.74 (ddd, \( J_1 = 6.6 \) Hz, \( J_2 = 1.6 \) Hz, \( J_3 = 0.6 \) Hz, 3H), 5.51 (qq, \( J_1 = 8.1 \) Hz, \( J_2 = 1.7 \) Hz, 1H), 5.60 (d, \( J = 2.0 \) Hz, 1H), 5.71 (d, \( J = 7.2 \) Hz, 1H), 5.80-5.94 (m, 2H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta = 9.2, 18.0, 27.9, 76.7, 118.8, 126.4, 131.4, 132.1, 173.0 \).

**1-(Trifluoroacetyl)-pyrrolidine-2-carboxylic acid 3-bromo-2-methylbut-3-en-2-yl ester 103.** Diisopropyl carbodiimide (2.64 g, 20.9 mmol) was added over 8h (syringe pump) to a solution 10 (3.0 g, 18.2 mmol), N-trifluoroacetyl proline\(^{106}\) (5.4 g, 24.4 mmol), and DMAP (0.22 g, 1.82 mmol) in dichloromethane (15 mL) at 45 °C. The
mixture was kept at 45 °C for 8 h (16 h total). Ethyl acetate (30 mL) was added, ammonia
gas was bubbled through the solution for 1 min and the solution was filtered. The filtrate
was concentrated and sonicated with a mixture of hexanes (60 mL) and ethyl acetate (20
mL). The liquid was decanted from the semisolid oil and the oil was again twice
sonicated with the mixture of hexanes (6 mL) and ethyl acetate (2 mL). The combined
organic extracts were filtered through a plug of silica (d=35 mm, l=50 mm). The filtrates
were concentrated which gave the product 103 as yellowish oil (4.16 g, 64%). \(^1\)H NMR
(300 MHz, CDCl\(_3\)): \(\delta = 1.62\) (s, 3H), 1.70 (s, 3H), 2.00-2.45 (m, 4H), 3.60-3.88 (m, 2H),
4.51 (t, J = 6.1 Hz, 1H), 5.61 (d, J = 2.8 Hz, 1H), 5.87 (d, J = 2.8 Hz, 1H). \(^{13}\)C NMR (75
MHz, CDCl\(_3\)): \(\delta = 24.9, 25.3, 26.7, 28.4, 47.3\) (q, \(^\text{5}_\text{J}_{\text{CF}} = 3.0\) Hz), 60.8, 82.6, 116.3 (q, \(^\text{1}_\text{J}_{\text{CF}} = 285\) Hz), 117.2, 137.2, 155.8 (q, \(^\text{2}_\text{J}_{\text{CF}} = 38\) Hz), 168.8.

2-(2-Bromo-3-methyl-but-2-en-1-yl)-1-(trifluoroacetyl)-pyrrolidine-2-carboxylic
acid (104) was prepared from 103 (1.48 g, 4.08 mmol) according to General Procedure I
(with the exception that the reaction mixture was kept at 60 °C for 18 h). The acid 104
was obtained as a pinkish powder (1.34 g, 92%) mp 162-163 °C, sufficiently clean
according to \(^1\)H and \(^{13}\)C NMR analysis for use without further purification. \(^1\)H NMR (400
MHz, CDCl\(_3\)): \(\delta = 1.79\) (s, 3H), 1.91 (s, 3H), 2.00-2.18(m, 3H), 2.32 (dt, J\(_1 = 13.0\) Hz, J\(_2 =
7.6\) Hz, 1H), 3.45 (d, J = 16.0 Hz, 1H), 3.58 (d, J = 16.0 Hz, 1H), 3.73 (dt, J\(_1 = 10.5\) Hz,
J\(_2 = 8.0\) Hz, 1H), 3.87 (quintet, J = 5.6 Hz, 1H). \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)): \(\delta = 21.4,\)
24.2, 25.7, 33.6, 36.9, 48.6, 70.4, 114.4, 116.3 (q, \(^\text{1}_\text{J}_{\text{CF}} = 285\) Hz), 136.7, 155.8 (q, \(^\text{2}_\text{J}_{\text{CF}} =
38\) Hz), 176.5.
2-(2-Bromo-3-methyl-but-2-en-1-yl)-pyrrolidine-2-carboxylic acid amide (105).

Diisopropylcarbodiimide was added to a slurry of 104 (1.10 g, 3.07 mmol) and HOBt (0.498 g, 3.69 mmol) in dichloromethane (10 mL) for 20 min at rt. The mixture was stirred for 24 h at rt and then ammonia gas was bubbled through the mixture for 5 min. The brownish fine slurry was stirred for 1 h at rt and water (10 mL) was added. The mixture was filtered through a sintered glass filter (porosity 4.5 –5.5), the layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried (MgSO₄) and concentrated at 30 °C (20 mmHg). The brownish semicrystalline oil was refluxed in a mixture of methanol (100 mL), water (6 mL) and K₂CO₃ (2.2 g) for 2 h.¹¹⁰ The reaction mixture was cooled to rt and the small amount of white crystalline solid was removed by filtration. The filtrate was dried (MgSO₄) and concentrated at 40 °C (20 mmHg). The brownish solid obtained was extracted with ether (2 x 10 mL), the combined extracts were concentrated at rt (20 mmHg) and the product was purified by column chromatography (silica, ethyl acetate).

The title product 105 was obtained as a colorless crystalline solid (0.843 g, 84%) mp 102-105 °C. ¹H NMR (400 MHz, CDCl₃): δ = 1.68-1.79 (m, 3H), 1.81 (s, 3H), 1.89 (s, 3H), 2.12-2.20 (m, 1H), 2.45 (br s, 1H), 2.90 (dt, J₁ = 10.2 Hz, J₂ = 6.1 Hz, 1H), 2.96 (d, J = 15.2 Hz, 1H), 3.02-3.12 (m, 1H), 3.23 (d, J = 15.2 Hz, 1H), 5.39 (br s, 1H). ¹³C NMR (100.6 MHz, CDCl₃): δ = 21.2, 25.7, 36.4, 43.8, 47.1, 70.3, 114.5, 117.4, 173.8.
N- Allyl-2-(2-Bromo-3-methyl-but-2-en-1-yl)-pyrrolidine-2-carboxylic acid amide (106). Allyl iodide (1.30 g, 7.70 mmol) was added to a slurry of 105 and K₂CO₃ (1.34 g) in anhydrous acetone (30 mL). The reaction mixture was stirred and refluxed for 48 h, cooled to rt and treated with water (5 mL). The aqueous layer was extracted with ether (3 x 15 mL), and the combined organic extracts were dried (MgSO₄) and concentrated at rt (20 mmHg). The residual oil was purified by column chromatography (silica, petroleum ether : ethylacetate, 1 : 1) to afford the title compound 106 as a colorless oil (739 mg, 76%). ¹H NMR (300 MHz, CDCl₃): δ = 1.65-1.85 (m, 2H), 1.87 (s, 3H), 1.91 (s, 3H), 1.98 (ddd, J₁ = 13.1 Hz, J₂ = 9.1 Hz, J₃ = 5.8 Hz, 1H), 2.13 (ddd, J₁ = 13.1 Hz, J₂ = 8.4 Hz, J₃ = 7.0 Hz, 1H), 2.70 (d, J = 15.8 Hz, 1H), 2.86 (q, J = 8.9 Hz, 1H), 3.15 (ddd, J₁ = 10.5 Hz, J₂ = 6.5 Hz, J₃ = 2.4 Hz, 1H), 3.42 (dt, J₁ = 5.9 Hz, J₂ = 1.4 Hz, 2H), 3.77 (d, J = 15.8 Hz, 1H), 5.11 (dq, J₁ = 10.2 Hz, J₂ = 1.6 Hz, 1H), 5.23 (dq, J₁ = 17.1 Hz, J₂ = 1.7 Hz, 1H), 5.80-6.00 (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ = 21.8, 22.9, 26.1, 36.2, 38.5, 51.1, 52.0, 71.9, 116.2, 117.3, 135.2, 136.8, 179.9.

7-Isopropylidene-6-methylene-hexahydro-indolizine-8a-carboxylic acid amide (107). A 2 neck round bottom flask (50 mL) equipped with a Schlenk tube and a reflux condenser with an argon bubbler was loaded with 106 (386 mg, 1.28 mmol), triphenylphosphine (67 mg, 0.26 mmol) and K₂CO₃ (1.06 g, 7.69 mmol) while palladium acetate (14.4 mg, 0.064 mmol) was placed in the Schlenk tube. The whole setup was evacuated to 0.1 mmHg and filled with argon (3 times). Anhydrous acetonitrile (20 mL)
was added to the flask, and the flask was immersed in a 100 °C oil bath. After the reaction mixture began to reflux, the contents of the Schlenk tube were added to the flask and reflux was continued for 48 h. The mixture was cooled to rt, filtered and concentrated in vacuo. Water (4 mL) and 1M aq HCl (3 mL) were added to the residue and the yellowish slurry was filtered. Solid K$_2$CO$_3$ (0.5 g) was added to the filtrate and the resulting white precipitate was filtered, washed with water (2 x 1 mL) and dried at 0.1 mmHg overnight to afford the title compound **107** as a white solid (217 mg, 77%) mp 146-148 °C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.60-1.75 (m, 3H), 1.81 (s, 3H), 1.86 (s, 3H), 2.00-2.20 (m, 1H), 2.47 (d, J = 14.1 Hz, 1H), 2.65-2.75 (m, 1H), 2.80 (d, J = 14.2 Hz, 1H), 2.90-3.02 (m, 1H), 3.21 (d, J = 14.6 Hz, 1H), 3.56 (d, J = 14.5 Hz, 1H), 4.90 (s, 1H), 5.06 (s, 1H), 5.79 (br s, 1H), 7.56 (br s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 21.6, 22.8, 23.3, 33.5, 37.6, 52.7, 54.6, 69.0, 113.0, 127.6, 130.2, 143.5, 180.1.

[(Z)-1-iodoprop-1-en-3-yl]-2-(2-Bromo-3-methyl-but-2-en-1-yl)-pyrrolidine-2-carboxylic acid amide (**111**). (Z)-3-bromo-1-iodopropene-1 ($^{113}$) (1.07 g, 4.37 mmol) was added to a slurry of **105** (0.57 g, 2.17 mmol), K$_2$CO$_3$ (0.90 g) and Bu$_4$NI (32 mg, 0.087 mmol) in anhydrous methylethylketone (4 mL). The reaction mixture was stirred and refluxed for 64 h, cooled to rt and treated with water (5 mL). The aqueous layer was extracted with ether (3 x 15 mL), and the combined organic extracts were dried (MgSO$_4$) and concentrated at rt (20 mmHg). The residual oil was purified by column chromatography (silica, petroleum ether : ethylacetate, 1 : 1) to afford the title compound **111** as a yellow crystals (650 mg, 70%) mp 110-111 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ =
1.70-1.85 (m, 2H), 1.88 (s, 3H), 1.91 (s, 3H), 2.00 (ddd, J₁ = 13.2 Hz, J₂ = 9.1 Hz, J₃ = 5.4 Hz, 1H), 2.12 (ddd, J₁ = 13.2 Hz, J₂ = 8.6 Hz, J₃ = 7.2 Hz, 1H), 2.77 (d, J = 15.8 Hz, 1H), 2.96 (dd, J₁ = 16.2 Hz, J₂ = 8.3 Hz, 1H), 3.08 (td, J₁ = 8.7 Hz, J₂ = 4.1 Hz, 1H), 3.46 (ddd, J₁ = 14.8 Hz, J₂ = 4.2 Hz, J₃ = 0.8 Hz, 1H), 3.63 (dd, J₁ = 13.8 Hz, J₂ = 4.9 Hz, 1H), 3.72 (d, J = 15.8 Hz, 1H), 5.64 (br s, 1H), 6.30-6.36 (m, 2H), 7.06 (br s, 1H). 

13C NMR (100.6 MHz, CDCl₃): δ = 21.6, 22.8, 25.9, 36.1, 38.5, 51.4, 53.2, 71.6, 83.1, 116.9, 135.1, 138.7, 179.1.

Propynyl-2-(2-Bromo-3-methyl-but-2-en-1-yl)-pyrrolidine-2-carboxylic acid amide (112). Palladium acetate (7.2 mg, 0.012 mmol) was added to a stirred mixture of compound 111 (103 mg, 0.24 mmol), N-tosyl-3-indolboronic acid (100 mg, 0.48 mmol), Ph₃P (12.6 mg, 0.048 mmol) and TBAF (0.48 mL, 1 M in THF) in THF (1 mL). The mixture was kept at rt for 24 h and THF was removed in vacuo. 3M aq HCl (3 mL) was added, the slurry was filtered and the aqueous filtrate was treated with K₂CO₃ until CO₂ evolution ceased. The reaction mixture was extracted with ethyl acetate (2 x 3 mL), organic extracts were dried (MgSO₄) and concentrated in vacuo. The residual oil was purified by column chromatography (silica, ethyl acetate) to afford the title compound 112 as a colorless oil (51 mg, 72%). 1H NMR (400 MHz, CDCl₃): δ = 1.70-1.82 (m, 2H), 1.85 (s, 3H), 1.89 (s, 3H), 1.99-2.12 (m, 2H), 2.22 (d, J = 2.4 Hz, 1H), 2.66 (d, J = 15.9 Hz, 1H), 3.00 (dd, J₁ = 16.4 Hz, J₂ = 7.9 Hz, 1H), 3.29 (td, J₁ = 8.4 Hz, J₂ = 4.0 Hz, 1H), 3.62 (dd, J₁ = 16.8 Hz, J₂ = 2.5 Hz, 1H), 3.71 (dd, J₁ = 16.9 Hz, J₂ = 2.4 Hz, 1H), 3.76 (d,
J = 15.9 Hz, 1H), 5.52 (br s, 1H), 7.25 (s, 1H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ = 21.5, 22.8, 25.8, 36.2, 38.0, 38.6, 51.4, 71.1, 71.7, 81.4, 116.4, 135.5, 179.2.

3-(1H-Indol-3-ylmethyl)-8a-[2-(1H-indol-3-yl)-3-methyl-but-2-enyl]-hexahydro-pyrrolo[1,2-a]pyrazin-1-one (115) Palladium acetate (7.2 mg, 0.012 mmol) was added to a stirred mixture of compound 111 (103 mg, 0.24 mmol), N-tosyl-3-indolboronic acid (100 mg, 0.48 mmol), Ph$_3$P (12.6 mg, 0.048 mmol) and K$_2$CO$_3$ (200 mg) in THF (1 mL) water (1 mL) mixture. The mixture was stirred at rt for 24 h and THF was removed in vacuo. 3M aq HCl (3 mL) was added, the slurry was filtered and the aqueous filtrate was treated with K$_2$CO$_3$ until CO$_2$ evolution ceased. The reaction mixture was extracted with ethylacetate (2 x 3 mL), organic extracts were dried (MgSO$_4$) and concentrated in vacuo. The residual oil was purified by column chromatography (silica, ethyl acetate : ethanol 4 : 1) to afford the title compound 112 as a colorless oil (32 mg, 30%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.60-1.70 (m, 2H), 1.78 (s, 3H), 1.84 (s, 3H), 1.90-2.05 (m, 3H), 2.30-2.45 (m, 2H), 2.69 (dd, $J_1$ = 16.3 Hz, $J_2$ = 8.3 Hz, 1H), 2.85-3.00 (m, 4H), 3.07 (d, $J$ = 14.7 Hz, 1H), 7.18 (br s, 1H), 7.45-7.56 (m, 6H), 7.67-7.80 (m, 4H). APT (100.6 MHz, CDCl$_3$): 21.3 (-), 23.1(+), 25.8(-), 33.4(+), 34.1(+), 37.5(+), 43.62(-), 43.66(-), 45.2(+), 50.47(+), 50.59(+), 52.4(+), 67.3(+), 116.7(+), 128.8(-), 129.0(-), 130.38(-), 130.48(-), 130.88(-), 130.97(-), 134.6 (+), 175.2 (+).
Chapter 7. References


177.


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*J. Comp. Chem.* **1993**, *14*, 1347-1363. The package was running on a two 2 GHz desktop
computers equipped with 1 Gb memory and 140 Gb hard drive each under Linux
operation system. The choice of HF6-31G* basis set was dictated by the SM5.42R
model used which at the moment of our calculations was only parameterized for the title
basis set.


49. A typical optimization took about 3 weeks on a desktop 2.4 GHz Pentium 4 computer
with 1 GB memory; this precluded the use of an MP2 correlation correction as well as
HF/DFT methods available within the GAMESOL package.

4501-4520.


53. Norris, P. (Youngstown State University), personal communication.


1384.
56. Of course, the $\alpha$-anomer would suffer increased steric crowding on the $\alpha$-face which might have eroded this high stereocontrol; unfortunately, no studies along these lines have been published.


81. The closely related 1-bromo-1-chloroethene was mentioned in the literature (see, for example: Havel, J. J.; Skell, P. S. J. Am. Chem. Soc. 1972, 94, 1792-1793; Agre, C. L.; Hilling, W. J. Am. Chem. Soc. 1952, 74, 3895-3899) but it readily polymerizes and has not found utility as a synthetic reagent. In contrast 1,1-dichloroethene is an inexpensive article of commerce and has found some synthetic utility: see, for example: Qian, M.; Negishi, E. Organic Process Research and Development 2003, 7, 412-417.


118. The title compound was described in the literature many times. Nevertheless, in our hands, most known methods gave the product contaminated with pyridine, acetic acid and other polar admixtures. The present method is a modification of the procedure described by Herscovici and Antonakis: Herscovici, J.; Antonakis, K. J. Chem. Soc. Chem. Commun. 1980, 561-562.


125. Ketone 39a was kindly provided by Dr. Peter Norris, Department of Chemistry, Youngstown State University.


