ÉTUDES POUR LA CONSTRUCTION DU SQUELETTE PICRASANE DES QUASSINOÏDES UTILISANT UNE STRATÉGIE DE DIELS-ALDER TANDEM À DIENE-TRANSMISSIBLE ET/OU UNE POLYCYCLISATION RADICALAIRE

PAR

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SUMMARY

The first chapter of this thesis describes the synthesis of compounds 82 and 83, precursors for a radical polycyclization reaction. The results of this radical polycyclization model are also described in detail.

The second chapter presents the initial route to diene-transmissive Diels-Alder precursors based upon an aldol condensation reaction as the key step for the introduction of chirality on the dienophile tether.

The third chapter explains a second route to tetracyclic quassinoid intermediates via a S$_{N}$2’ organocuprate displacement on an allylic acetate 112. The entire synthesis of the diene-transmissive Diels-alder precursors 137 and 138 are described.

Chapter four presents the results on the two diene-transmissive Diels-Alder reactions. The results of the transformation of the various tetracycles into suitable radical cyclization precursors are also discussed.

The fifth chapter describes two syntheses of chiral synthon 109 used for monocyanocuprate reactions (described in chapters 6 and 7). The synthesis of the racemic equivalent of 109 used in chapter 3 is also described.

Chapter six depicts the attempted synthesis of tetracyclic quassinoid intermediates starting from chiral (-)-quinic acid.

The seventh chapter details the second-generation synthesis of tetracyclic quassinoid intermediates via (-)-quinic acid. Their diene-transmissive Diels-Alder reaction, and the initial 6-exo-trig radical cyclizations based upon a $\alpha$-silyl radical on tetracycles 375 and 376 are also described. An attempted 5-exo-trig cyclization of monoselenoacetal 371 is described.
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Introduction

The Modern Paradigm of Organic Synthesis

In most publications today dedicated to total synthesis, one would find discussions on; the target molecule, the challenges it poses structurally, the synthetic strategy to be employed, the results, and any future work required. With the enormous variety of potential targets and the novel chemistry developed each day to fabricate them the modus operandi of the modern synthetic chemist remains essentially constant. For undoubtedly, the choice of target molecule is based upon two factors: the synthetic challenge and/or biological activity. The fervor over synthetically challenging and biologically active Taxol clearly demonstrates this point.¹ The continued drive for effective medicines and better living will undoubtedly push the advancement of science in organic chemistry in the future.

1.2 General features, biology, and synthesis of Quassinoids

The plant family Simaroubaceae is the most common source for the degraded triterpenoid natural products known as “quassinoids”.² A “quassinoid” refers the chemically related constituents of the Simaroubaceae family that form the bitter principles of the quassin group. Quassinoids are the quintessential target for the modern organic chemist, possessing both a potent biological activity and a complex molecular structure. Although a complete review of the structural features of quassinoids is too vast for this introduction, the vast majority of quassinoids possess a C20 picrasane skeleton (Figure.1).³
Many quassinoids possess a great variety of biological activities that have been documented elsewhere, and include antiviral, antimalarial, antineoplastic, and insect antifeedant properties. Recently reported biological activities will only increase the synthetic interest in this family of triterpenes.

Some commonly cited quassinoids are bruceantine, simalikalactone D, quassimarin, glucaurubolone and the parent compound quassin (Figure 2). Recently, both simalikalactone D and quassimarin, have been isolated from the plant family Leitneriaceae, a significant discovery since the family Simaroubaceae is not widely distributed. Bruceantine is a potent antileukemic agent, both simalikalactone D and quassimarin suppress KB (epidermoid carcinoma), A549 (lung carcinoma), HCT-8 (ileocecal carcinoma), CAKI-1 (renal cancer), MCF-7 (breast cancer), and SK-MEL-2 (melanoma) human tumor cell lines significantly in recent in vitro assays. Simalikalactone D is also an antimalarial agent 50 times more potent than quinine.
Figure 2. Some commonly cited quassinoids

With their impressive array of biological activities, and their complex, highly oxygenated frameworks, it is not surprising that a number of groups have reported synthetic efforts towards quassinoids. Despite this attention, few
efforts have resulted in total synthesis, attesting to the complexity of the target molecules. The Grieco group has been the most successful from the first total synthesis of racemic quassin in 1980,\textsuperscript{15} bruceantin in 1993,\textsuperscript{16} to the very recent synthesis of 5(R)- and 5(S)-polyandrane in 1999.\textsuperscript{17} Professor Grieco’s group has published the syntheses of a number of other quassinoids.\textsuperscript{18} Other successful efforts include those by Valenta,\textsuperscript{19} Watt,\textsuperscript{20} Hirota,\textsuperscript{21} and Shing’s most recent synthesis of (+)-quassin from (+)-carvone in 1998.\textsuperscript{22}

Since 1990, the research group of professor Spino has been interested in the synthesis of quassinoids. Their work has resulted in the publication of the stereoselective synthesis of an advanced tetracyclic quassinoid intermediates.\textsuperscript{23} The strategy is based upon a diene-transmissive [4+2] cycloaddition (Scheme 1). The advantage of this strategy is the generation of three rings and six stereocenters in a single step. The key diene-transmissive Diels-Alder reaction is also compatible with many functional groups, making it more attractive in the synthesis of complex molecules such as quassinoids.

\textbf{Scheme 1} Diene-transmissive Diels-Alder strategy.
1.3 The Diene-Transmissive Diels-Alder reaction

Despite the potential advantages of diene-transmissive Diels-Alder reaction, and the popularity of the Diels-Alder reaction in organic chemistry in general, the strategy has not been used to any large extent. Initially investigated by Tsuge and others, the diene-transmissive Diels-Alder reaction is defined as two sequential Diels-Alder cycloadditions of a cross-conjugated triene with a dienophile (Scheme 1).

Tsuge et al have used a diene-transmissive Diels-Alder reaction of bis(silyloxy) cross conjugated trienes with azodicarbonyl compounds to yield bicyclic heterocycles. While Saito and co-workers have used the diene-transmissive Diels-Alder cycloaddition to fabricate fused nitrogen and sulfur heterocycles from azatrienes and thioketones respectively. Finally Fallis et al have published work in 1999 towards oxygenated nor-steroid and triterpenoid skeletons based on this methodology (Scheme 2). The cross-conjugated triene 11 is generated during an interesting indium-mediated γ-pentadienylation of hemiacetal 9. Oxidation of the allylic alcohol 11 and in situ cycloaddition provided cycloadduct 13 resulting from an endo-boat transition state with the OMOM group adopting an equatorial position. Finally, an intermolecular Diels-Alder reaction furnishes the nor-triterpenoid 14 arising from an endo transition state on the less encumbered convex face of 13.
Scheme 2 Fallis’ use of the diene-transmissive Diels-Alder reaction

There are several potential problems that might limit the use of the diene transmissive Diels-Alder reaction, including the regioselectivity during the initial cycloaddition, the preparation of highly substituted trienes with geometric
integrity, and finally, difficulties in using acyclic trienes that might not be stable to the conditions of the Diels-Alder reaction.\textsuperscript{33} The successful development of just such a strategy for the synthesis of quassinoids by Spino’s group indicates such limitations can be overcome by careful planning. In compound 6 (Scheme 1) one diene is locked in a \textit{transoid} configuration and cannot partake in the initial cycloaddition. Secondly, the presence of the oxygen heteroatom effectively controls the regiochemistry during the initial inverse electron-demand cycloaddition with ethyl vinyl ether. Finally, the transmitted diene (compound 8) is locked in a \textit{cisoid} configuration, allowing the intramolecular cycloaddition to proceed in a predictable fashion based upon the substituents on the dienophile tether in the more stable chair-like \textit{endo} transition state.\textsuperscript{34} All of these modifications provide an effective route to the complex tetracyclic framework.

All that is required to provide the pentacyclic framework of bruceantin 1, or the picrasane skeleton of quassin 5 is transformation of the tetrasubstituted double bond (of 8) to the desired oxomethano bridge (for 1) or axial C8 methyl group (for 5) (Scheme 3). The explosion of free radical reactions in synthetic organic chemistry over the past 20 years provides plenty of potential for just such transformations.\textsuperscript{35}

\textbf{Scheme 3} Transformations required on the tetrasubstituted double bond
1.4 Carbon Centered Radicals in Organic Synthesis

The triphenyl methyl radical reported in 1900 by Gomberg is the first carbon radical on record.\textsuperscript{36} It took another eight decades before use of such radicals would be considered routine in the strategies of complex natural products in organic synthesis.\textsuperscript{37} Radical reactions possess a number of features that have made their employment fruitful. They include: 1) Carbon-centered radicals are highly reactive species that proceed under neutral and mild conditions which do not compromise high degrees of chemo, regio, or stereoselectivity. 2) Carbon-centered radicals generally add to double bonds with an early, reactant-like, transition state in an exothermic, irreversible manner. 3) The reactive nature of radicals coupled with a reaction medium free of counterions or aggregates makes them ideal for the formation of crowded bonds. 4) Carbon-centered radicals are unreactive towards both OH and NH groups rendering the use of protecting groups unnecessary. 5) Carbon radicals are not subject to β-elimination of OR or NR\textsubscript{2} groups as carbanions are. They are immune to capture by β-OR or β-NR\textsubscript{2} groups, and do not promote migration of β-H or β-CR\textsubscript{3} groups, as carbocations would. 6) The potential for tandem or cascade reactions for the formation of highly complex molecules in a single synthetic step is high.

A complete review of radical cyclizations would be inappropriate and many reviews on specific areas have already been published.\textsuperscript{38} Rather, focus will be given to processes capable of forming the five membered oxomethano ring. Fortunately, formation of five membered rings are faster than that of any other ring size.\textsuperscript{39} The 5-exo-trig cyclization proceeds with outstanding regioselectivity. Comparing the parent 5-hexenyl radical, the 5-exo-trig cyclization is 50 times faster than the 6-endo-trig (Figure 3).\textsuperscript{40}
Early on, it was discovered that the presence of a heteroatom at the 2 position of the hexenyl radical generally slowed the cyclization rate (compared to the all carbon analog)\textsuperscript{41} while a heteroatom at the position 3 accelerated it.\textsuperscript{42} With the development of the bromo acetal cyclizations of Stork\textsuperscript{43} and Ueno,\textsuperscript{44} this type of cyclization (heteroatom at position 3) has flourished in organic synthesis (Figure 4). Unfortunately, in the case of quassinoids the heteroatom is not allylic to the double bond but rather homoallylic, giving a situation with a heteroatom in position 2 (Figure 4, bottom).

**Figure 3** 5-hexenyl radical cyclization

![Diagram of 5-hexenyl radical cyclization](image)

The reaction proceeds with a 50:1 ratio of 5-exo to 6-endo products.
Figure 4. Heteroatom influence on 5-hexenyl radical cyclizations
In sharp contrast to the extensive use of cyclizations with a heteroatom in position 3, the position 2 analogue has remained relatively unexplored. Early work by Beckwith had investigated the relative reactivities of \( S_{\text{H}2} \) attack by tributyltin radicals for such an environment (\( R\text{CH}_2\text{OCH}_2X \)) with a position 2 or \( \alpha \) heteroatom (\( X = \text{PhSe, Cl, PhS} \)). Beckwith found \( \text{PhSe} > \text{Cl} > \text{PhS} \) to be the order of reactivity with relative rates of 4350:118:2.7 respectively. In another report, Beckwith et al indicated the slower cyclization rate could be due higher activation energies caused by delocalization of the radical onto the oxygen restricting the rotational freedom of the \( \sigma\text{-CO} \) bond. Despite the lower cyclization rates, Beckwith also showed hydrogen abstraction by \( \alpha\text{-alkoxy} \) radical was four times slower than the hexenyl radical at 298K.

Rawal et al in 1993 published the first substantive report of alkoxymethyl radical cyclizations for the synthesis of tetrahydrofurans and tetrahydropyrans. The synthesis of the reactive monoseleno acetals 15 was not a trivial problem, as initially reported by Beckwith. Rawal et al used a two step process to produce selenoacetals like 15. Rawal’s results indicated a highly effective regioselective cyclization of alkoxymethyl radicals (Scheme 4). Neither the 6\text{-endo}-trig cyclization was observed nor substantial amounts of reduced product acquired from abstraction of hydrogen by the alkoxymethyl radical. Rawal’s report showed the potential usefulness of these alkoxymethyl radicals in the synthesis of five membered rings like those found in bruceantin 1.
Another feature of carbon radical reactions is the potential for tandem reactions, forming a number of carbon-carbon bonds in complex structures in a

Scheme 4 Some alkoxy methyl radical cyclizations by Rawal et al.
single operation. In 1985, Curran et al employed a tandem radical cyclization strategy in the total synthesis of the linear triquinane hirsutene (Scheme 5). Many other examples of such processes are documented to date. Recently, large steroid frameworks have been synthesized from both linear tandem cascades and macrocyclization-transannular cascade reactions. Pattenden and co-workers successfully cyclized polyolefin selenyl ester 19 to polycycle 20 from consecutive 6-endo-trig modes of cyclizations (Scheme 6). Consecutive chair-like transition states can be used to explain the reported stereochemistry.

Scheme 5 Tandem radical cyclization of triquinane hirsutene.

Scheme 6 Cascade cyclization of phenoselenyl ester 19 to give polycycles
Pattenden has also reported a number of approaches to steroids from a macrocyclization-transannular strategy.\textsuperscript{54} Both \textit{trans} and \textit{cis} decalone systems \textsuperscript{22} and \textsuperscript{23} were formed from a 10-\textit{endo}-trig cyclization on an activated enone \textsuperscript{21}, followed by a 6-\textit{endo/exo}-trig transannular cyclization in good yield (Scheme 7). Subjecting a positional isomer \textsuperscript{24} to the same conditions yielded the \textit{trans} decalone \textsuperscript{23} and \textit{cis} 5,7-fused bicycle \textsuperscript{25} in a similar yield. From a judicial positioning of the double bond that will suffer the transannular cyclization, the type of fused bicycle could be controlled to some extent.\textsuperscript{55} The same group has also accomplished macrocyclizations of both 13 and 17 membered rings on activated enones.\textsuperscript{56}
Scheme 7 Tandem macro-transannular cyclization
Finally, Curran’s group reported the first triple transannular radical cyclization of macrocycle 26 (Scheme 8). The yield was low in this case and competing 1,5-hydrogen shifts were later shown to be the limiting factor. These results and those of Pattenden only emphasizes the progress made in this field.

Scheme 8  Triplet transannular radical cyclization
1.5 Project Outline

Our aim was the synthesis of both the tetracyclic and pentacyclic picrasane frameworks of quassinoids such as contained in bruceantin 1 and quassin 5. To this end, two different routes were employed. One involves a tandem radical cyclization starting with a 5-exo-trig alkoxyethyl radical, followed by a 10-endo-trig macrocyclization, and finally a 6-exo-trig transannulation (Scheme 9). The results from Rawal’s studies suggest the alkoxyethyl 5-exo-trig cyclization should function well. We anticipated the intermediate radical produced after the first 5-exo-trig cyclization should find the terminal alkene in close proximity owing to a favorable chair-like transition state (Scheme 9). The resulting radical is very similar to those reported by Pattenden and the desired 6-exo-trig annulation would give a pentacyclic structure found in many quassinoids.

Potential obstacles include the macrocyclization on an unactivated terminal double bond. The reported macrocyclizations by Pattenden and others58 involve terminal enones. The stereochemistry of the A/B, B/C, and B,D rings might also have to be addressed using this approach.
Scheme 9 Proposed radical polycyclization

The second approach involves a diene-transmissive Diels-Alder reaction to provide the tetracyclic quassinoid intermediate following a similar route taken by Noah Tu (Scheme 1). The major difference will be the placement of a hydroxyl group at C13 (picrasane numbering), that could be later transformed
into an alkoxymethyl or thiomethyl radical precursor (Scheme 10). As noted in previous work, the selectivity of the intramolecular Diels-Alder reaction will be controlled by the placement of chiral substituents on the dienophile tether. The intramolecular Diels-Alder reaction should proceed via the more stable *endo* chair-like transition state with the substituents adopting an equatorial position. With the stereochemical outcome controlled in this fashion, the tetracycle would then be converted to either an alkoxymethyl or a thiomethyl radical precursor. The alkoxymethyl radical cyclization will generate the bruceantin 1 framework, while the thiomethyl radical cyclization followed by reductive desulfurization will yield the C8 axial methyl group found in quassin 5.
Scheme 10 Diene-transmissive Diels-Alder, radical cyclization strategy
Results and Discussion

Chapter 1. Radical Polycyclization

The synthetic route to the target radical precursor 83 (Scheme 9, page 18) began with commercially available 1,4-cyclohexanedione mono-ethylene ketal 51. Reduction of 51 with sodium borohydride and subsequent protection with benzyl bromide (Scheme 11) provided benzyl ether 53 in 83 % yield. Treatment of the ketal with hydrochloric acid in refluxing THF furnished the desired ketone 54 in 94 % yield.

Scheme 11 Synthesis of ketone 54

In order to introduce unsaturation to the system, ketone 54 was initially treated with LDA followed by phenylselenyl chloride (Scheme 12). Oxidation and elimination of the selenide 55 gave a complex mixture of products in which the desired α, β-unsaturated ketone 57 was only a minor constituent. An alternative route using bromide and catalytic aluminum trichloride provided the α-bromo ketone 56, that gave the desired ketone 57 in 50% yield (for 2 steps) upon treatment with DBU in refluxing benzene. The bromination-elimination reaction of 57 gave bromoketone 58 78% yield.
The next required step was a 1,2-addition of vinyllithium onto ketone 58, followed by acetylation of the resulting alcohol to give the required acetate for coupling with the appropriate cuprate reagent (Scheme 13). Transmetallation of tetravinyltin with \( n \)-butyllithium followed by addition of 58 in ether at \(-78^\circ\text{C}\) resulted in a 1.5:1.0 mixture of diastereomeric alcohols 59 and approximately 15\% of product 60 resulting from a 1,4-addition. Use of cerium trichloride augmented the overall yield modestly. However product arising from 1,4-addition remained over 15\%. Changing the solvent from ether to THF while using cerium trichloride provided in 81 \% yield a 1:1 mixture of alcohols 59 in with no detectable amounts of 60 (Table 1).
Table 1 Addition of vinyllithium to bromoketone 58.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Additive</th>
<th>% Yield 59</th>
<th>% Yield 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et₂O</td>
<td>None</td>
<td>68</td>
<td>13</td>
</tr>
<tr>
<td>Et₂O</td>
<td>CeCl₃</td>
<td>68</td>
<td>17</td>
</tr>
<tr>
<td>THF</td>
<td>CeCl₃</td>
<td>81</td>
<td>0</td>
</tr>
</tbody>
</table>

Conversion of alcohol 59 to the corresponding acetate 11 proceeded in 83 % yield. The stage was now set for the $S_{N}^{2'}$ displacement of the allylic acetate with the Gilman-type cuprate 62 (Scheme 13). This step proceeded with complete regio- and chemoselectively to give triene 63 as a single diastereomer in 89 % yield. Metal-halogen exchange with $n$-butyllithium and quenching the resulting anion with dry DMF furnished aldehyde 64 in 74 % yield.
With the desired aldehyde now available, the ytterbium catalyzed inverse electron demand Diels-Alder reaction could now be performed.\textsuperscript{64} Accordingly, the aldehyde \textbf{64} was cleanly converted into a 1.0:1.6 mixture of inseparable cycloadducts (\textbf{65} and \textbf{66}) in 82\% yield (Scheme 14).

\textbf{Scheme 13} Cuprate S\textsubscript{N}2' displacement of allylic acetate \textbf{63}
All that remained to do was the removal of the benzyl protecting group and installation of the selenide precursor. Use of Raney-Ni reduced the terminal alkene while leaving the benzyl group intact. All other attempts to effect deprotection of the secondary alcohol resulted in decomposition products. These results may not be surprising in hindsight with the enol-ether diene being extremely sensitive to Lewis and Bronsted acids.

Due to these problems, the choice was made to deprotect the benzyl group directly after the cuprate reaction. Accordingly, treatment of $\text{63}$ with TMSI generated \textit{in situ} from sodium iodide and TMSCl yielded the desired alcohol $\text{67}$ in 49% yield. Following the reaction conditions depicted in Scheme 15, metal-halogen exchange using two equivalents of $n$-butyllithium resulted in only 26% yield of the desired aldehyde $\text{17}$ with most of the remaining product being starting material.
Scheme 15 Alternate route to deprotect the benzyl group.

All attempts to improve this result were unsuccessful. Despite the fact the reaction sequence worked well with the benzyl group, the problems encountered with it’s removal, and with the subsequent metal-halogen exchange reaction, prompted us to change it to a group that could be removed under milder more selective conditions.

The choice was made to use the tert-butyldiphenylsilyl (TBDPS) group in place of the benzyl. The same reaction sequence as described above was used en route to the selenide radical precursor. Protection of the starting alcohol and deprotection of the ketal 69 yielded ketone 70 in 97% yield from 51 (scheme 16). Bromination of 70 and elimination with DBU gave ketone 71 in a 62 % yield. Use of Meyer’s sulphinate provided a direct route to the α,β-unsaturated ketone in an excellent 93% yield. The simplicity of the protocol and improvement of the yield made this route much more attractive. The bromination-elimination reaction of 71 gave bromoketone 72 in 90% yield. In some instances dibromo ketone 73 was isolated as a secondary product (up to 30%), especially when the addition rate of Br₂ was too rapid, quite possibly due to the bulky TBDPS group sterically encumbering the double bond. However the dibromo ketone could be cleanly converted into the desired ketone 72 with sodium iodide and tin dichloride in nearly quantitative yield (Scheme 16).
Addition of vinyl lithium in the presence of cerium trichloride in THF to $\alpha,\beta$-unsaturated ketone 72 resulted in exclusive formation of alcohols 74 in 93% yield.
as a 1.4:1.0 mixture. Quenching the reaction mixture with acetic anhydride gave the two acetates 75 directly in 79% yield (Scheme 17). Displacement of the acetate with the organocuprate reagent 62 proceeded in nearly quantitative yield, as did the metal-halogen exchange reaction to give aldehyde 77. Removal of the silyl protecting group with hydrofluoric acid in a pyridine buffer procured alcohol 68 in 93% yield.69
Scheme 17 Formation of hetero Diels-Alder precursor 68
Once again the stage was set for the inverse electron demand Diels-Alder cycloaddition with ethyl vinyl ether. Accordingly the Diels-Alder reaction proceeded in a completely endo fashion to give a mixture of two diastereomers in an average of 83 to 97% yield (Figure 5). Placing a sample of the crude mixture through an analytical HPLC column indicated a 1.0:1.0 ratio of diastereomers. Analysis of the crude mixture by $^1$H NMR was complicated due to peak broadening likely caused by the ytterbium catalyst. The two cycloadducts could be separated by standard flash chromatography. At that point, it was difficult to know which cycloadduct possessed the correct relative stereochemistry at C14 so each was used separately in the subsequent reactions. Since then, it has been determined that the more polar cycloadduct of the Diels-Alder reaction possesses the correct sterochemistry at C14 (vide infra).

Figure 5 Hetero Diels-Alder reaction of aldehyde 68
Following the protocol of Rawal and co-workers, the (tributylstannyl)methyl unit was introduced with potassium hydride and $\text{ICH}_2\text{SnBu}_3$ (Scheme 18).\textsuperscript{70} The selenides $82/83$ were then fabricated from a metal-metal exchange reaction with $n$-butyllithium and quenching the resulting anion with diphenyldiselenide. The radical polycyclization could now be attempted.

The initial attempt, with a slow addition of tributyltin hydride and AIBN to a refluxing solution of selenide $83$ in benzene (0.015M) resulted in clean reduction to give the methyl ether in 81% isolated yield (Scheme 19). When the same conditions were attempted on the less polar selenide $82$, the tricycle $84$ was isolated in 74% yield.

Scheme 18 Formation of selenides $82/83$
Because of the fact selenide 83 resulted in reduced product all other attempts were made with higher dilution [0.006M] but again the methyl ether was isolated in high yield (65% or more), with no trace of a cyclized product. From the results with selenide 82, it is clear that the initial 5-exo-trig cyclization is possible and that its failure in the case of selenide 83 is likely due to simple conformational constrains. Likely, the alkoxy methyl radical is never in position near or above the enol ether exocyclic double bond. Simple MM2 calculations seem to confirm this hypothesis (Figure 6). In the case of the selenide 83 the radical generated would...
appear to rest on the exterior of the bicycle while in the other case the alkoxy methyl radical could approach the enol ether exocyclic double bond.

**Figure 6** Radicals generated by selenides 82 and 83

If the failure to cyclize for selenide 83 was a simple conformational problem, the addition of a methyl group to position C13 should produce a Thorpe-Ingold effect that might allow the 5-exo-trig cyclization to occur. To this
end oxidation of alcohol 79 with Dess-Martin’s periodinane in pyridine lead mainly to decomposition products. The trace amounts of ketone, which were formed, could not be successfully alkylated with methylmagnesiumbromide (Scheme 20). Further attempts were abandoned due to lack of material as well as unsatisfactory results obtained for selenide 82 (vide infra).

Scheme 20 Attempts to form tertiary alcohol 87

While the initial 5-exo-trig cyclization was successful in the case of selenide 82, the 10-endo-trig cyclization remained a challenge. Under a variety of conditions (see Table 2) the 10-endo-trig cyclization failed.
Table 2 Radical Cyclizations of Selenide 82

<table>
<thead>
<tr>
<th>Reactants</th>
<th>Initiator</th>
<th>Solvent</th>
<th>Concentration</th>
<th>Products % yield (SM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu₃SnH</td>
<td>AIBN</td>
<td>benzene</td>
<td>0.006 mM</td>
<td>74%</td>
</tr>
<tr>
<td>(TMS)₃SiH</td>
<td>AIBN</td>
<td>benzene</td>
<td>0.006 mM</td>
<td>18% (82)</td>
</tr>
<tr>
<td>(TMS)₃SiH</td>
<td>AIBN</td>
<td>benzene</td>
<td>0.004 mM</td>
<td>27% (49)</td>
</tr>
<tr>
<td>(Bu₃Sn)₂</td>
<td>hv</td>
<td>benzene</td>
<td>0.300 mM</td>
<td>(100)</td>
</tr>
<tr>
<td>None</td>
<td>(PhCO₂)₂</td>
<td>benzene</td>
<td>0.125 mM</td>
<td>decomposition</td>
</tr>
<tr>
<td>None</td>
<td>AIBN</td>
<td>benzene</td>
<td>0.006 mM</td>
<td>(100)</td>
</tr>
<tr>
<td>SmI₂</td>
<td>none</td>
<td>THF</td>
<td>0.011 mM</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

These results are nonetheless interesting and give clues as to what the solutions to the problem might be. It should be noted that the lone pair on the oxygen stabilizes the original alkoxy-methyl radical that is generated. That, according to frontier orbital theory, should increase the energy of the SOMO. This radical would be rendered “nucleophilic” and should react well with electron deficient alkenes (with low-lying LUMO’s). Interestingly, this radical reacted with the electron rich exocyclic enol ether in the 5- exo-trig cyclization. This point would appear to support the argument that the conformation rather than electronics are responsible for the failure of 82 to cyclize in the key 5- exo-trig cyclization. As a side note, very little reduced product was isolated using tin.
hydride on 83, once again indicating that the rate of cyclization is faster under the reaction conditions than rate of reduction.

Again, an oxygen lone pair stabilizes the radical generated by the first 5-exo-trig cyclization. This radical should be “nucleophilic” and possess a high energy SOMO (Figure 7). The terminal alkene has a lower energy LUMO than the previous enol ether and yet this 10-endo-trig cyclization fails. Could this be due to entropy as well, rather than enthalpy?

Figure 7 Radical generated after the 5-exo-trig cyclization

It is entirely conceivable that the alkene never approaches close enough to the alkoxyethylene radical to react with it. The stabilized high energy SOMO radical should also be less prone to hydrogen abstraction than a low-energy SOMO radical but only the tricyclic compound was isolated. Under the reaction conditions the rate of reduction was faster than the rate of 10-endo-trig cyclization. Using the “weaker hydride donor, (TMS)$_3$SiH also resulted in isolation of the tricycle rather than the pentacycle.$^{73}$
This fact demonstrates another problem with this system, the irreversible termination of the polycyclization by hydrogen abstraction. What appears to be required is to initiate and carry out to cyclization under “hydride free conditions”. Attempts to initiate the reaction photochemically and using hexabutylditin resulted only in starting material, as did using AIBN without any hydride present. In the cases using either benzoyl peroxide or samarium diiodide resulted in complex mixtures of products.

Neither the methyl ether 85 nor tricycle 84 were crystalline, so a single crystal X-ray analysis could not be used to confirm the relative stereochemistry of the two adducts. Assignments of the stereochemistry at C14 were made by proton NMR experiments. 2D COSY and NOSEY experiments were not conclusive at all, and instead simple coupling constants proved to be the most informative. In the ¹H NMR of tricycle 84, the proton on C13 is a doublet with a relatively small J value of 4.3 Hz whereas the same proton in compound 85 is a double of triplets with J values of 10.4 and 3.8 Hz. Simple models and minimized chem3D structures give vicinal dihedral angles of 85, 65 and 50 degrees in the case of tricycle 84 for the proton at C14 and protons as C11 with the proton at C13 respectively (see Figure 8). Using Karplus’s correlation this should give J values of 0, <1 and 4 Hz, which nicely matches the observed value of 4.3 Hz. In the case of methyl ether 85, the same analysis yielded dihedral angles of 180, 180, and 55 degrees, which should give J values of 10, 10 and 3 Hz respectively. Again this correlates very closely with the observed data of 10.4 and 3.8 Hz. Reversing the stereochemistry at C14 in each case and applying the same analysis yielded results that did not closely match the observed values nearly so well. All the evidence suggests these assignments are correct.
This route to quassinoids has plenty of potential, with only slight changes likely required before the polycyclization is successful. The major change would be to restrict the rotation of the alkyl chain containing the terminal alkene. Keeping the terminal alkene close to the generated radical should allow cyclization to take place. Carrying out the cyclizations under “hydride free conditions” would also improve the chances of success with this method. 

Figure 8 Dihedral angles for some protons of 84 and 85
Chapter 2. Aldol Condensation route to quassinoids

Despite the fact that the polycyclization of triene 82/83 was unsuccessful, the results were encouraging with respect to the initial 5-exo-trig cyclization. The question remained however, would the 5-exo-trig cyclization work on a tetracycle like compound 90 (Scheme 21)? As noted previously, conformation appeared to greatly influence the success of the cyclization, and in this case the double bond is no longer exocyclic, but endocyclic although the reaction is still a 5-exo-trig cyclization. Previous published results from Spino and Tu showed that a diene-transmissive Diels-Alder with chiral substituents on the side chain was a viable route to the tetracyclic framework common to many quassinoids. To this end target compound 90 could be constructed from an intermediate 74 used in the polycyclization sequence (Scheme 21).
Accordingly alcohol 74 was treated with ethyl vinyl ether in the presence of mercury (II) trifluoroacetate in the hopes of synthesizing allyl vinyl ether 91 from which aldehyde 92 could be procured from a Claisen rearrangement. Interestingly only the aldehyde was isolated, the system was sufficiently active to undergo the rearrangement at room temperature. As was observed in the
cuprate reaction, this rearrangement is completely regio and chemoselective. This fact indicates that the active conformer must be conformer $92_b$. Addition of triethylamine to the reaction mixture increased the circa $50\%$ yield to $88\%$ and gave a much cleaner reaction. (Scheme 22)

Scheme 22. Synthesis of aldehyde 92 by Claisen rearrangement

The stage was now set for the aldol reaction. Using Evan's methodology, the initial attempt resulted in only $10\%$ of aldol adduct 94 while $40\%$ of the starting aldehyde was recovered. The second attempt resulted in only $5\%$ yield of the aldol adduct and no starting material using the same conditions (Scheme 23). As a simple test to see if the reaction conditions were appropriate, the
reaction was carried out with benzaldehyde 95. The reaction worked well resulting in a 64% yield of adduct 96 and recovering an additional 34% of the starting oxazolidinone. Clearly the difficulties in the preceding reactions were due to the aldehyde. Two more unsuccessful attempts with aldehyde 92 confirmed the belief the aldehyde was the problem. Perhaps undetectable mercury salts left over from the previous reaction were the culprit, so the aldehyde was resubjected to flash chromatography to hopefully remove any impurities.

Scheme 23. Aldol condensation of aldehyde 92.

Finally the next attempt resulted in 80% of the desired aldol adduct 94. At first look, it appears the problem might have been mercury salts. As a
contingency plan, other routes were investigated to fabricate aldehyde 92 without the use of mercury, but none of them were nearly as efficient (Scheme 24).

Scheme 24 Alternate routes to aldehyde 92.

The result obtained in the aldol reaction proved difficult to reproduce, working only half of the time. Presumably, the difficulty in getting the aldehyde sufficiently
pure is responsible for the demure. Freshly distilling the solvent, dibutylboron triflate, triethylamine, and recrystallization of the oxazolidinone before each reaction could not guarantee success. The aldol reaction was never consistently reproducible.

The synthetic route required protection of the alcohol followed by reduction of the auxiliary then a metal halogen exchange reaction to give the aldehyde-alcohol 101 (Scheme 25).

Interestingly, results obtained in the protection of the alcohol in the aldol adduct proved to be very insightful as to the problems encountered in the aldol reaction. We initially opted for a MOM protecting group to allow selective removal of the silyl ether at a later stage. This group also has the advantage of showing few signals in the $^1$H NMR spectra. With this in mind, protection using P$_2$O$_5$ and dimethoxymethane resulted in isolation in 51% combined yield of two products that were later identified as furans 102 and 103. In fact, all other attempts to protect alcohol 94 resulted in unwanted products (Table 3).
The isolation of furans 102 and 103 was most informative. As noted in Table 3, use of Lewis acids resulted in an effective 5-exo-trig cyclization of the alcohol on the exocyclic double bond followed by a $S_{N}2'$ type expulsion of the OTBDPS group on the C13 carbon (Scheme 26).

**Table 3. Attempts at protecting alcohol 94**

<table>
<thead>
<tr>
<th>Reactants</th>
<th>Solvent</th>
<th>Products</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_2O_5$, (CH$_3$O)$_2$CH$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>102 and 103</td>
<td>51%</td>
</tr>
<tr>
<td>NEt$_3$, MOMCl$^{80}$</td>
<td>CH$_2$Cl$_2$</td>
<td>Unknown, lose of TBDPS</td>
<td>-</td>
</tr>
<tr>
<td>NEt$_3$, MeOTf$^{81}$</td>
<td>CH$_2$Cl$_2$</td>
<td>102 and 103</td>
<td>74%</td>
</tr>
<tr>
<td>Mel, NaH</td>
<td>THF/ DMF</td>
<td>Unknown</td>
<td>-</td>
</tr>
<tr>
<td>Mel, imidazole</td>
<td>DMF</td>
<td>Decomposition</td>
<td>0%</td>
</tr>
<tr>
<td>Me$_3$OB$_4$ $^{82}$</td>
<td>CH$_2$Cl$_2$</td>
<td>102 and 103</td>
<td>Not purified</td>
</tr>
<tr>
<td>CH$_2$CN$_2$, SiO$_2$ $^{83}$</td>
<td>Et$_2$O</td>
<td>94</td>
<td>85%</td>
</tr>
<tr>
<td>BnBr, KH</td>
<td>THF</td>
<td>Decomposition</td>
<td>0%</td>
</tr>
</tbody>
</table>
This realization helps explain the ease with which the aldol adduct decomposes. In fact, furans 102 and 103 were detected in the decomposition mixtures obtained in the various protection reactions attempted. The aldol reaction required the use of dibutylborontriflate, and any excess reagent, in the presence of aldol adduct 94, could initiate such a process. Even in the few cases where products were isolated that were unidentified, the OTBDPS group was not present (entry 2). Perhaps the conditions with the greatest chance of success were CH$_2$N$_2$ and silica gel, but unfortunately this resulted in recovery of starting material.

It should be noted that in the previous synthesis completed by Noah Tu, the system was very similar except it lacked the OTBDPS group. In that case the alcohol could be effectively protected with TBDMSOTf and triethylamine, but it is highly doubtful that under these conditions there would have been success in our case. In any event installing a TBDMS protecting group would require the differentiation of the two silyl protecting groups at the end of the synthesis.

Other options remained, including reduction of the auxiliary in compound 94 directly to the alcohol. To this end alcohol 94 was treated with LAH, resulting in a mixture of products. A second, and somewhat more risky and intriguing option was to use Furans 102 and 103 as the protected form of the alcohol, continue the sequence until the appropriate time, and then open the furans 104 under acidic conditions to give a new product 105 as protected alcohol (Scheme 26 Formation of furans 102 and 103)
This option was never fully investigated (*vide infra*) but treatment of alcohol 94 in presence of acid and alcohol suggests it might be possible.

In the final analysis, the lack of reproducibility of the aldol reaction, and the difficulties thereafter, lead to the abandonment of this route. Clearly having alcohols placed in positions C3 and C13 were causing unforeseen and serious problems. A slightly less complex tether, with a methyl group in the appropriate position should still be able to differentiate the face of attack during the

**Scheme 27** Potential route to use 102/103 as a protected alcohol
intramolecular Diels-Alder reaction (Scheme 28). The goal of the present project was to test the viability of making the C8-C13 oxomethano bridge on a tetracycle such as 106, regardless of the substitution on the ring A. The route that was envisioned to make a simpler compound like 107 was an SN2’ organocuprate displacement of allylic acetate 75 with a chiral chain 108. With the new route planned, work began on the synthesis of chiral synthon 109 and testing of the organocuprate reaction.

Scheme 28 Revised route to tetracyclic selenide 106
Chapter 3. Tetracycle synthesis via organocuprate sequence

Before work began in earnest on this route, a number of strategic changes were made with respect to protecting groups. The results during the aldol sequence demonstrated some of the shortcomings of the TBDPS group. It was decided that a group that was more robust and yet easy to remove under a number of conditions would be used. The choice was made that a $\rho$-methoxybenzyl (PMB) would be adequate. This would also allow the use of a TBS group on the chiral chain, another group that is easy to install and remove. Not only might the PMB be more sturdy and easy to remove but also during the diene-transmissive Diels-Alder reaction might give a better ratio of products. As noted in the chapter 1 the benzyl group gave a ratio of products at C14 of 1:1.5, while previously unpublished results from Eric Fillion gave a 4:1 ratio in favor of the undesired product when using a TBDPS (Scheme 29). The tert-butyldiphenylsilyl group adopting an equatorial position, in which the two phenyl groups effective block the $\alpha$-face of the molecule, can explain this result.
Scheme 29 Hetero Diels-Alder results with TBDPS protecting group

To test the viability of the cuprate reaction silyl ether 74 was deprotected with TBAF to give diol 110. This diol was then mono-protected with PMBCl in 52% yield, and the resulting alcohol 111 transformed into allylic acetate 112 under standard conditions in 95% yield (Scheme 30).
Allylic acetate 112 was then subjected to a Gilman-type cuprate to yield the desired coupled product as a single geometric regioisomer in 82% yield. (Scheme 31) The alkylithium used in this reaction was acquired from a metal-halogen exchange reaction with tert-butyllithium, and iodoalkane 113 in ethyl ether.85
These results were extremely encouraging, so work began on fabrication of a chiral chain to replace iodide 113, as well as bringing along a large quantity of allylic acetate 112. Accordingly, alcohol 52 was protected under standard conditions with PMBCl to give protected alcohol 115 in 96% yield (Scheme 32). Removal of the ketal with PPTS in acetone yielded ketone 116 in 92% yield. Unsaturation was introduced to the system using Meyer’s sulphinate methodology. Finally, bromination and elimination gave bromoketone 118 that successfully underwent 1,2-addition with vinyllithium. Treatment with acetic anhydride gave the desired acetate 112. Allylic acetate could be obtained in 6 steps from alcohol 52 in 51% overall yield.
Scheme 32. Synthesis of allylic acetate 112

52 R = H

115 R = PMB

KH, PMBCl
THF, r.t.
96%

1) KH, PhS(O)OMe
THF, 0°C
2) Na₂CO₃, toluene,
reflux, 82%

Br₂, NEt₃,
ClCH₂CH₂Cl
0°C, 92%

n-BuLi,
(CH₂=CH)₄Sn
THF, -78 to 0°C
90%

Ac₂O, NEt₃,
DMAP
CH₂Cl₂, r.t.
82%

111

112
The yield for the initial Gilman-type cuprate reaction was excellent, however, from the viewpoint of the number of equivalents of chiral chain required, the reaction had to be optimized. The initial reaction used 2.0 eq of cuprate to 1.0 eq of acetate, with the cuprate requiring 2.0 eq of alkyllithium chain. Clearly 4.0 eq of chiral chain for every equivalent of acetate is not economical. Fortunately, a host of potential cuprate reagents have been developed to specifically deal with this challenge.\textsuperscript{87} This was also of importance due to the fact that there was some difficulty in the synthesis of such a chiral chain (\textit{vide infra}). Once a sufficient quantity of chiral chain 109 (Scheme 28, page 48) was acquired, the same Gilman-type coupling conditions were applied and a similar result was obtained (entry 2, Table 4). Reducing the equivalents of CuI to 1.5 marginally reduced the yield, however 3 equivalents was still too high (entry 3). The initial break came with the use of copper cyanide that reduced the required number of equivalents of achiral chain 119 to 1.4 and gave a 81% yield with the remaining product being starting material (entry 4).
Table 4: Reaction conditions for the cuprate addition reaction on acetate 112.

<table>
<thead>
<tr>
<th>#</th>
<th>Cuprate (eq)</th>
<th>Alkyl lithium used (eq)</th>
<th>Temp (°C) of 112 Addition</th>
<th>Solvent</th>
<th>Final Rxn Temp. (°C)</th>
<th>Product % yield (SM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuI (2.0)</td>
<td>119 (4.0)</td>
<td>0</td>
<td>Et₂O</td>
<td>0</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>CuI (2.0)</td>
<td>120 (4.0)</td>
<td>0</td>
<td>Et₂O</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>CuI (1.5)</td>
<td>120 (3.0)</td>
<td>0</td>
<td>Et₂O</td>
<td>0</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>CuCN (1.4)</td>
<td>119 (1.4)</td>
<td>-78</td>
<td>Et₂O/ THF</td>
<td>5</td>
<td>81, (19)</td>
</tr>
<tr>
<td>5</td>
<td>CuCN (1.4)</td>
<td>120 (1.4)</td>
<td>-78</td>
<td>Et₂O/ THF</td>
<td>0</td>
<td>36, (64)</td>
</tr>
<tr>
<td>6</td>
<td>CuCN(2-th)</td>
<td>nBuLi (1.5)</td>
<td>-78</td>
<td>Et₂O</td>
<td>-40</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>CuCN(2-th)</td>
<td>120 (1.5)</td>
<td>-78</td>
<td>Et₂O</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>CuI-LiI (1.3)</td>
<td>120 (2.6)</td>
<td>-30</td>
<td>Et₂O/ THF</td>
<td>r.t.</td>
<td>0, (100)</td>
</tr>
<tr>
<td>9</td>
<td>CuCN (1.3)</td>
<td>120 (2.6)</td>
<td>-45</td>
<td>Et₂O</td>
<td>-10</td>
<td>36</td>
</tr>
<tr>
<td>10</td>
<td>CuCN (1.4)</td>
<td>nBuLi (1.4)</td>
<td>-78</td>
<td>THF</td>
<td>r.t.</td>
<td>50, (36)</td>
</tr>
<tr>
<td>11</td>
<td>CuCN-LiI (1.4)</td>
<td>nBuLi (1.4)</td>
<td>-70</td>
<td>THF</td>
<td>r.t.</td>
<td>0, (100)</td>
</tr>
<tr>
<td>12</td>
<td>CuCN(1.4)</td>
<td>120 (1.4)</td>
<td>-78</td>
<td>Et₂O/ THF</td>
<td>-60</td>
<td>30, 41&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>CuCN(1.4)</td>
<td>120 (1.4)</td>
<td>-78</td>
<td>Et₂O/ THF</td>
<td>-20</td>
<td>32, (63)</td>
</tr>
<tr>
<td>14</td>
<td>CuCN(1.4)</td>
<td>120 (1.4)</td>
<td>-78</td>
<td>Et₂O/ THF</td>
<td>0</td>
<td>51, (42)</td>
</tr>
<tr>
<td>15</td>
<td>CuCN(2-th)</td>
<td>120 (1.4)</td>
<td>-78</td>
<td>Et₂O/ THF</td>
<td>r.t.</td>
<td>44, 23&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>16</td>
<td>CuCN(1.5)</td>
<td>120 (1.5)</td>
<td>-78</td>
<td>Et₂O/ THF</td>
<td>5</td>
<td>74</td>
</tr>
<tr>
<td>17</td>
<td>CuCN(1.5)</td>
<td>120 (1.5)</td>
<td>-50</td>
<td>Et₂O/ THF</td>
<td>0</td>
<td>92</td>
</tr>
</tbody>
</table>

Notes: Max temperature(1) r.t. (2) -78°C (3) 0°C; (a) addition of thiienyl group, (b) addition of tert-butyl group, (c) isolation of alcohols
Attempts to reproduce this result with the chiral alkyllithium 120 were unsuccessful. Generally, a small amount of desired product was obtained with the remainder being starting material (entry 5). Use of the 2-thienyl group as a non-transferable “dummy” ligand has become popular and is known to augment the reactivity of cyanocuprates.88 A simple test using n-butyllithium as the chain with the thienylcyanocuprate gave quantitative conversion at low temperature (entry 6). Under the same conditions using chiral alkyllithium 120, the results were disappointing (entry 7). Over half the isolated product was starting material and 20% of the isolated product arose from the transfer of the “non-transferable dummy” thienyl ligand. This result suggested that perhaps the problem was related with the formation of the chiral alkyllithium 120. One more attempt with a higher order cyanocuprate (entry 8) resulted in only 36% yield of desired product and provided a valuable clue as to the potential problem. A secondary product isolated from the reaction mixture was determined to be alcohol 122 (Figure 9).

![122](image)

**Figure 9.** The secondary product 122

The chiral alkyllithium 120 is generated from the metal-halogen exchange reaction between chiral iodoalkane 109 and 2.2 equivalents of tert-butyllithium (Scheme 31).85 To assure that all the tert-butyllithium has been consumed, the reaction mixture is warmed from -78°C to room temperature. This allows the second equivalent of tert-butyllithium to destroy the generated tert-butylliodide while the remaining 0.2 equivalents of tert-butyllithium are quenched by the ether solvent itself. Thereby allowing only the generated chiral alkyllithium to be present in the solution. At the elevated temperature an intramolecular rearrangement is possible to give alcohol 122 (Scheme 33). It is interesting to note that in the case of alkyllithium 113 no rearrangement was noted and the yield for the cuprate reaction was excellent (entry 4). Perhaps this is due to the
fact that the addition of a methyl group provides an added gauche interaction that brings the carbanion closer to the silyl group in the case of chiral alkyllithium 120. While in the case of alkyllithium 119 the most stable zig-zag conformation places the carbanion far from the silyl group.

Scheme 33. Formation of alcohol 122

Clearly, if the alkyllithium 120 undergoes such a migration, it is unavailable during the cuprate reaction in it’s desired form. Keeping this in mind, the number of equivalents of tert-butyllithium was reduced to 2.0 and the exchange reaction was kept at -78°C. Under these conditions (entry 12) 41% of the isolated product was formed from the displacement by tert-butyllithium. Obviously, during the metal-halogen exchange reaction, the elimination of the tert-butyliodide was not complete at -78°C, leaving tert-butyllithium in the solution.

From that point on, the metal-halogen exchange reaction was warmed to 0°C to allow for the mutual annihilation of both tert-butyllithium and tert-butyliodide. In fact, the observation that the reaction mixture changed from colourless to yellow and back to colourless again allowed us to know when this annihilation was complete. Using these conditions resulted in trace quantities (at most) of the alcohol 122 being visible in the reaction mixture.
With the certainty that all the challenges had been meet, the reaction was attempted again with the chiral alkyl lithium 120 (entries 13 and 14) only to yield 50% of the desired product with the remainder being starting material. These results were perplexing considering under the same conditions with alkyl lithium 119 an 81% yield was observed (entry 4). Careful analysis of the recovered starting material (of entries 4, 13, and 14) gave other clues as to what might be occurring. The starting acetates in cases 13 and 14 were a 1:1 mixture of diastereomers. While the remaining starting material after the reaction was essentially one diastereomer. In the case of the successful cyanocuprate reaction (entry 4) the starting material was a 8:2 ratio of diastereomers that gave and 8:2 ratio of desired product to starting material. This fact suggested that only one of the two diastereomers was reactive under the current reaction conditions.

A final attempt at augmenting the cuprate reactivity with a thienyl dummy ligand resulted in only 44% yield of desired product (entry 15). Under these conditions the acetate was also cleaved, as suggested by the isolation of alcohols 111. Use of additives such as lithium iodide to completely solublize the cuprate effectively killed the reaction, giving only starting material (entries 8 and 11).89

Fortunately the story was not yet complete. When the cyanocuprate was allowed to quickly warm to 0°C a black reaction mixture with 74% desired product resulted (entry 16) from a 1:1 mixture of diastereomeric acetates. Indeed, optimum conditions called for the addition of the acetate at temperatures of -50°C for a far shorter period then rapidly warming the reaction mixture to 0°C and keeping it at that temperature for hours (entry 17). Under such conditions reproducible yields over 90% could be obtained using only 1.5 equivalents of copper cyanide and alkyl lithium 120.

One can only speculate as to what is going on. It was clear though that during the reaction at -40°C, the reactive diastereomer had been consumed completely (tlc observation). The second diastereomer undergoes the cuprate addition at around 0°C, however, on numerous occasions the final temperature had reached zero and yet the reaction remained incomplete. In these cases it had taken many hours for the reaction to reach this temperature. Could a time
dependant (rather than temperature) decomposition of the cuprate species be the explanation for this observation?

In order to save time and expenses, the chiral chain was used in its racemic form for the rest of the synthesis. With all the problems regulated during the cuprate reaction, the remaining steps could be investigated. The initial investigations were made with compound 114 that lacked the required methyl group. The metal-halogen reaction and quenching with DMF gave aldehyde 123 in 77% yield, setting up the inverse-electron demand Diels-Alder reaction. As noted before, this reaction proceeded well resulting in a mixture of two diastereomers. Due to difficulties in removing the catalyst, the mixture was immediately subjected to treatment with TBAF to remove the silyl-protecting group. The overall yield for the two steps was 83% giving an inseparable mixture of two diastereomers (Scheme 34). In the case of compound 121 the metal halogen exchange reaction proceeded in 90 % yield. The Diels-Alder and deprotection reactions gave an overall yield of 72%
Oxidation of the alcohol and a Wadsworth-Emmons olefination were all that was required to set-up the intramolecular Diels-Alder reaction. All attempts to oxidize the primary alcohol resulted in other intriguing results (see Table 5).

**Scheme 34** Hetero Diels-Alder reaction on aldehydes 123/124
Table 5. Oxidation of Alcohols 126 and 128

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>126</td>
<td>Swern\textsuperscript{91}</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>126</td>
<td>PCC, MS, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>126</td>
<td>NIS, Bu\textsubscript{4}Ni\textsuperscript{92}</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>126</td>
<td>TPAP, NMO, MS\textsuperscript{93}</td>
<td>129 plus other</td>
</tr>
<tr>
<td>5</td>
<td>128</td>
<td>TPAP, NMO, MS</td>
<td>130 plus other</td>
</tr>
<tr>
<td>6</td>
<td>128</td>
<td>Ag\textsubscript{2}CO\textsubscript{3}/celite\textsuperscript{94}</td>
<td>Decomposition</td>
</tr>
<tr>
<td>7</td>
<td>128</td>
<td>Dess-Martin, py\textsuperscript{71}</td>
<td>130 plus other</td>
</tr>
</tbody>
</table>

During the TPAP oxidation of 128, the \textsuperscript{1}H NMR of the crude mixture displayed a clearly visible aldehyde peak. However any attempt to purify the aldehyde further resulted in a product that contained no signal in the aldehyde region. Passing the mixture through a short plug of silica gel and using the resulting mixture directly in the Wadsworth-Emmons olefination resulted in Diels-Alder precursor 131 in 16% yield from alcohol 128 (Scheme 35). Another product was also isolated from the reaction mixture. Analysis revealed it to be tetracycle 132, isolated in 30% yield from the starting alcohol 128.
Scheme 35 Oxidation-Olefination sequence of 128.

This was the first time such a hetero Diels-Alder reaction was observed in this system. Perhaps the metal catalysis used in the oxidation activated the aldehyde and allowed the Diels-Alder to proceed. In an attempt to reduce the amount of hetero Diels-Alder product observed other oxidations were attempted. Dess-Martin's periodinane was capable of oxidizing the primary alcohol. However the reaction was never quite complete and the aldehyde did require some purification. Proton NMR of the aldehyde after flash chromatography did appear to show the same hetero Diels-Alder impurity.

The low overall yield for the two step transformation 128 to 131 and the high yield of the undesired product required another route to the Diels-Alder precursor. Fortunately, a somewhat less elegant sequence had been fruitful. Protection of aldehyde 124 as an acetal and removal of the silyl-protecting group with TBAF yielded alcohol 134 in 87% yield for the two steps (Scheme 36). Oxidation with Dess-Martin's periodinane and Wadsworth-Emmons olefination on the crude aldehyde yielded α,β-unsaturated ester 136 in 80 % yield for the two steps. Simple deprotection of the acetal in the presence of PPTS and wet acetone yielded the desired Diels-Alder precursor 137. Deprotection of the PMB protecting group with DDQ gave a second Diels-Alder precursor 138. Overall the two precursors were prepared in 13 and 14 steps from alcohol 52 in 26% and 18% yield respectively.
1) ethylene glycol, PPTS, benzene, reflux
2) TBAF, THF, r.t
87% 2 steps

1) Dess-Martin
CH₂Cl₂, r.t.
2) NaH, MDEPA, 0°C,
80% 2 steps

PPTS, acetone water, reflux
92%

DDQ, CH₂Cl₂, H₂O
70%

Scheme 36. Synthesis of Diels-Alder precursors 137 and 138
Chapter 4. Transformation of tetracycles

Upon the successful completion of the two Diels-Alder precursors \textbf{137} and \textbf{138}, the key bond-forming step was attempted. It is known that the initial hetero Diels-Alder reaction proceeds with complete \textit{endo} selectivity to give an approximate 1.5:1.0 ratio of products (Figure 5, Chapter 1, page 30).\textsuperscript{96} Assuming complete facial selectivity during the intramolecular Diels-Alder reaction with the methyl group adopting an equatorial position in a \textit{endo}-chair-like transition state (\textit{endo}-TS\textsubscript{A} Scheme 37), we expect four tetracycles (\textbf{150}:\textbf{151}:\textbf{152}:\textbf{153}) to form in a 1.5:1:5:1:1 ratio, reflecting the 1.5:1 ratio of the initial hetero Diels-Alder reaction (Figure 10).

\textbf{Scheme 37} Four possible chair-like transition states
Figure 10 Four expected tetracycles during diene-transmissive DA reaction
Tetracycles 150 and 152, having the wrong C14 stereochemistry for quassinoids, could be used to probe the subsequent reactions that were envisioned as depicted in Scheme 38. Although the stereochemistry at C14 is not the correct one for quassinoid synthesis, the results from the radical cyclization would also be interesting with this system.

Scheme 38 Envisioned route for compounds 150/152

We envisioned using tetracycle 151, with the C13-α stereochemistry to prepare the thiomethylradical precursor 158 via a Mitsunobu reaction.97 Subsequent desulfurisation would procure the C8 axial methyl group present in a number of natural quassinoids (Scheme 39).
Finally tetracycle 153 which possess the correct relative stereochemistry everywhere would undergo the alkoxy methyl radical cyclization to give the C8-C13 oxomethano bridge of bruceantin and its homologues. (Scheme 40)

**Scheme 39** Envisioned route for tetracycle 151

Finally tetracycle 153 which possess the correct relative stereochemistry everywhere would undergo the alkoxy methyl radical cyclization to give the C8-C13 oxomethano bridge of bruceantin and its homologues. (Scheme 40)
Consequently, precursor **137** (Chapter 3) was exposed to ethyl vinyl ether in the presence of the Yb(FOD)$_3$ catalyst. After 6 days a mixture of 5 tetracycles was isolated in 92% combined yield. Only two of the tetracycles could be separated in pure form and, unfortunately, only a small amount of pure material was isolated. Analysis of the crude mixture by GC was unreliable due to peak overlapping. However, carefully analysis by $^1$H NMR (integration of the C6, C16 and methyl ester protons) of the isolated tetracyclic mixtures gave an approximate ratio of 3.7:2.3:1:4.4:1 for tetracycles **150:152:153:161:163**. Both **161** and **163** (Figure 11) arose from the *endo*-TS$_b$ where the C4-methyl is axial (Scheme 37) on intermediates **156** and **157** respectively (Figure 10). Apparently the intramolecular Diels-Alder reaction had not proceeded entirely as envisioned.

**Scheme 40** Destiny of tetracycle **153**.

![Scheme 40](image)

**Figure 11** Two unexpected tetracycles

159 from 153
R = protecting group

161 R = PMB
163 R = PMB
Tetracycles 150, 153, and 161 were confirmed by single crystal X-ray analysis, while tetracycle 152 and 163 were elucidated by \(^1\)H NMR analysis (vide infra). Reduction of the ester with lithium aluminum hydride gave the corresponding alcohols 164 (from 150), 165 (from 161), 166 (from 152), 167 (from 163), and 168 (from 153) in 80% yield, which could be separated by flash chromatography. Comparison of the \(^1\)H NMR of the 5 tetracycles proved to be informative. In one case, the C16 proton (δ 4.4) was a doublet of doublets (J=9 and 2 Hz) while the remaining 4 tetracycles showed triplets at δ 5.0 (J=7 Hz) for the same proton (Figure 12, 13 and 14).

Figure 12 \(^1\)H NMR spectra of tetracyclic alcohol 168
Figure 13 $^1$H NMR spectra of tetracycles 164 and 165.
tetracycle 166

Figure 14 $^1$H NMR spectra of tetracycles 166 and 167
The multiplicity of the C16 proton would soon become an extremely useful diagnostic tool in determining the relative stereochemistry at C7, C10, and C14 of other tetracyclic intermediates. Looking at the previously fabricated tetracycles by Noah Tu\textsuperscript{98} and Gang Liu\textsuperscript{99}, the tetracycles having the correct relative stereochemistry at C5, C7, C10 and C14 displayed a doublet of doublets for the C16 proton. The tetracycles epimeric at C14 always displayed a triplet for the C16 proton. This observation is based upon the conformation of the D ring after the diene-transmissive Diels-Alder reaction. The initial hetero Diels-Alder proceeds in an \textit{endo} fashion resulting in both the C14 and C16 protons being located on the same face of the tetracycle. The multiplicity of the C16 proton can then be used to determine the stereochemistry of the C14 proton (\textit{vide infra}).

This initial observation suggested that there was only one tetracycle present that contained the correct relative stereochemistry at C5, C7, C10, and C14. This was confirmed by a single crystal X-ray structure of tetracycle 168 (Figure 15).

\textbf{Figure 15} ORTEP Drawing of Tetracycle 168
The ORTEP drawing clearly shows the D ring adopting a chair conformation, with the C16 proton in the axial position. This proton would be expected to be a doublet of doublets with a large axial-axial (J=9 Hz) and a small axial-equatorial (J=2 Hz) coupling constants. Unfortunately, this tetracycle represented only 8% of the total isolated mixture.

Upon closer look at the $^1$H NMR of the 5 tetracycles (Figure 12, 13 and 14), it is interesting to note tetracycles 164, 165, 166 and 167 posses similarities and differences that makes their elucidation fairly easy. Tetracycles 164 and 165 are almost identical in the $\delta$ 4.00 to 3.00 region, and somewhat different in the aliphatic region, while tetracycles 166 and 167 are similar in the $\delta$ 4.00 to 3.00 region and different in the aliphatic region. At the same time, tetracycles 164 and 166 are similar in the aliphatic region as are tetracycles 165 and 167. This suggests that tetracycles 164 and 165 have the same relative stereochemistry at C13 as do tetracycles 166 and 167. The differences in the aliphatic region, in particular the shielded protons at ~0.75 ppm or 0.15 ppm and the doublet for the C17 carbon, suggest tetracycles 164 and 165 are epimeric at C4. Single crystal X-ray analysis confirmed this hypothesis. Derivatives of both 164 and 165 were crystalline from which X-ray crystal structure could be obtained. (Figure 16 and 17).
In each case, the ORTEP drawing shows the D ring in a twist boat conformation, with the C16 proton adopting a pseudo equatorial position. The observed triplet for these protons is consistent with the crystal structure. The isolation and elucidation of this tetracycle 165 was extremely important for its formation was not expected.
Figure 17 ORTEP Drawing of tetracycle 172 a derivative of 165.

These results also allowed the prediction of the absolute stereochemistry for tetracycles 166 and 167. Since no tetracycle emanating from intermediate 154 (Figure 10) had been elucidated yet one had to be tetracycle 152 or 162 (Scheme 41).
Since tetracycle 162 would be expected to be very similar to tetracycle 153 (and hence 168), tetracycle 162 can be dismissed with some confidence. The remaining two tetracycles 166 and 167 showed remarkable similarities between 4.00 ppm to 3.00 ppm in the $^1$H NMR spectra suggesting their stereochemistries at C13 was identical. The similarities in the aliphatic region between 164 and 166 seem to suggest that the C17 methyl group is equatorial in tetracycle 166. Likewise, the similarity between tetracycle 165 and 167 suggest that tetracycle 167 has the C17 methyl group in an axial position. Another conformation that this analysis is correct comes in the chemical shift and coupling constant for the C4 methyl group. Tetracycle 164 has an equatorial

**Scheme 41. Potential products of intermediate 154**
methyl group at $\delta$ 1.00 with $J = 6.5$ Hz while tetracycle 165 has an axial methyl at $\delta$ 0.95 with $J = 7.1$ Hz. In tetracycle 166 the methyl group can be found at $\delta$ 1.00 with a $J = 6.6$ Hz and in tetracycle 167, the methyl group is found at $\delta$ 0.96 and $J = 7.0$ Hz. When the methyl group is axial the coupling constant is somewhat larger and the protons slightly more shielded.

The low yield of tetracycle 153, the lack of formation of tetracycle 151 (Figure 10), and the isolation of tetracycles 161 and 163 indicated that the proposed endo-transition states (TS$_A$) were not preferred in the case for the precursors 156 and 157 (Scheme 42 and 43).

In each case it can be imagined that the ethoxy group (and part of the D ring) blocks the attack on the $\alpha$-face to some extent. In the case of intermediate 156, the PMB group could also block or destabilize attack on the $\alpha$-face. These two effects are obviously important enough in the case of intermediate 156 to give exclusively attack on the $\beta$-face although the methyl group must adopt an axial position. In the case of intermediate 157, the PMB group has a favorable influence blocking attack on the $\beta$-face to some extent. The influence of the ethoxy group (and D ring) and the axial methyl group (and PMB group) appear to be of similar energy because the yield of the two tetracycles 153 and 163 were essentially the same (Scheme 43).
Scheme 42 Transition states for intermediate 156

endo-TSA

endo-TSB

steric interactions, destabilizing

potentially destabilizing

151 not observed

161 only product
Scheme 43 Transition states for intermediate 157

**endo-TS**

- **endo-TSA**: Transition state A
- **endo-TSB**: Transition state B

Steric interactions, destabilizing

153:163 1:1

153

163
In the case of intermediates 154 and 155, no such interaction with the ethoxy group is possible in the TS\textsubscript{A} on the α-face. In these cases the intramolecular Diels-Alder reaction proceeded as expected. (Scheme 44).

Scheme 44 Transition states for intermediates 154 and 155

Clearly a 8% yield (from the tetracyclic mixture) of the tetracycle 153, and the absence of tetracycle 151, the two tetracycles most important for our study made this route unviable. One option was to remove the PMB group before the hetero Diels-Alder reaction in the hopes of alleviating this problem. The initial
Diels-Alder reaction with a C13-OH group was known to proceed in an 1.0:1:0 ratio and if the proposed intramolecular Diels-Alder now proceeded in the desired manner (Scheme 37), a final 1.0:1.0:1.0:1.0 ratio of tetracycles $200:201:202:203$ would be expected. Subjecting the precursor $138$ (Chapter 3) to ethyl vinyl ether gave a mixture of 5 tetracycles in a combined 84% yield. Once again, analysis of the crude mixture by GC or NMR was not reliable due to peak overlapping and-or peak broadening. However careful analysis of the isolated mixtures by $^1$H NMR gave an approximate ratio of 2.9:3.6:3.3:1.8:1 for tetracycles $200:201:202:203:213$ (Figure 10 and Scheme 45 and 46).

Scheme 45 Reversed selectivity in $endo$-$TS_A$ for intermediate 156
Removal of the PMB group completely reversed the selectivity for intermediate 156 in the intramolecular Diels-Alder reaction, giving tetracycle 201 as the single diastereomer (Scheme 45). This confirms that the PMB protecting group did indeed play a significant role in the formation of tetracycle 161 from 156 (see Scheme 42). The formation of tetracycle 201 was confirmed by a X-ray crystal structure (Figure 18). Tetracycle 201 has the desired stereochemistry at all carbons and is destined for the introduction of the C8 angular methyl group. Its formation as a major product was gratifying.

**Figure 18.** ORTEP drawing of 201

The ORTEP drawing once again shows the D ring adopting a chair conformation and, as mentioned previously, the proton at C16 displayed a doublet of doublets (J = 8 and 2 Hz) as would be expected for a axial proton.
Removal of the PMB group also influenced the transition state of the intramolecular Diels-Alder reaction from intermediate 157. The ratio of products arising from attack on the $\alpha$-face from 50:50 increased in the case of the PMB bearing precursor to 64:36 in this case (Scheme 46). The fact that this intermediate gave two products while intermediate 156 gave only one is somewhat perplexing and may involve subtle differences in conformation between the two transition states.

Scheme 46 Transition states for 157
In fact, intermediate 157 underwent the Diels-Alder reaction at a slower rate. During the isolation of the five tetracycles 200, 201, 202, 203, and 213, the some starting diene 157 (R=H) was isolated in pure form. Heating this compound in benzene overnight gave an approximate 2:1 mixture of tetracycles 203 and 213. In any event, the Diels-Alder reaction on the β-face remains competitive in this case. This fact will have to be addressed at a later stage if such a strategy will be used in a total synthesis.

Before the reduction-protection-deprotection sequence outlined in Scheme 40 was embarked upon, attempts were made to install the (tributylstannyl)methyl group on the free secondary alcohol of tetracycles 201, 202, 203 and 213 (Scheme 47). These tetracycles were not separable at this stage so mixtures were used. The steric environment of the tetracycles should be different and therefore the reactivity would be expected to be different. This difference in reaction rate could enable us to recover unreacted starting material in pure form for characterisation and thus could be viewed as beneficial. Under the conditions previously used, only starting material was isolated (Scheme 47). Even refluxing the mixture gave no detectable product. We feared the ester was responsible for this demeanor and thus decided to reduce it and protect the resulting alcohol.

**Scheme 47** Initial attempts at installation of (tributylstannyl)methyl unit.

Toward that end, protection of the free primary alcohol of tetracycles 164, 165, 166, 167, and 168 was undertaken. Initially, a trityl group was chosen with the hope of isolating crystalline products. Unfortunately, this protection was
never complete and the product was contaminated with unreacted tritylchloride. Protecting the alcohol as a methyl ether was the next option (Table 6), the yield in this case was unsatisfactory so a TBS group was finally opted for.

![Tetracycle Reaction Diagram]

Table 6 Attempts at protecting alcohols 164, 165, 166, 167, and 168.

<table>
<thead>
<tr>
<th>Tetracycle</th>
<th>Conditions</th>
<th>Products</th>
<th>Product % Yield (SM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>164</td>
<td>TrCl, NEt&lt;sub&gt;3&lt;/sub&gt;, DMAP, CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>170</td>
<td>23% (40)</td>
</tr>
<tr>
<td>164</td>
<td>NaH, MeI, THF</td>
<td>164</td>
<td>(100)</td>
</tr>
<tr>
<td>164</td>
<td>KH, MeI, THF</td>
<td>171</td>
<td>29%</td>
</tr>
<tr>
<td>165</td>
<td>TBSCl, imidazole, CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>172</td>
<td>100%</td>
</tr>
<tr>
<td>166</td>
<td>TBSCl, imidazole, CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>173</td>
<td>80% (19)</td>
</tr>
<tr>
<td>167</td>
<td>TBSCl, imidazole, CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>174</td>
<td>74% (14)</td>
</tr>
<tr>
<td>168</td>
<td>TBSCl, imidazole, CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>175</td>
<td>89%</td>
</tr>
<tr>
<td>164</td>
<td>MeOTf, DTBMP, CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>171</td>
<td>91%</td>
</tr>
</tbody>
</table>

Fortunately, tetracycle 172 was crystalline and was used to acquire an X-ray crystal structure and thus confirm the stereochemistry of 165 (Figure 17 vide supra). Removal of the PMB group became the next challenge. Accordingly, treatment of tetracycle 171 with DDQ yielded the desired secondary alcohol in
only 36% (Table 7). Unfortunately, attempts on other tetracycles under these conditions did not yield significantly different results. Use of either hydrogenolysis\textsuperscript{100} or cerium ammonium nitrate\textsuperscript{101} (CAN) resulted in cleavage of the ethoxy acetal or the silyl ether. The low to moderate yield of the deprotection in the case of DDQ might also be due to cleavage of the ethoxy acetal as well. During the reaction the corresponding hydroquinone was formed which is somewhat acidic and in the presence of water could conceivably hydrolyze the acetal.

![Diagram](image)

Table 7. Deprotection of the PMB group on tetracycles 171, 172, 174, and 175

<table>
<thead>
<tr>
<th>Tetracycle</th>
<th>OPMB</th>
<th>Me</th>
<th>H</th>
<th>Conditions</th>
<th>Products</th>
<th>Product % Yield (SM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>171</td>
<td>β</td>
<td>α</td>
<td>α</td>
<td>DDQ</td>
<td>176</td>
<td>36%</td>
</tr>
<tr>
<td>171</td>
<td>β</td>
<td>α</td>
<td>α</td>
<td>H₂, Pd/C</td>
<td>176 + loss of OEt</td>
<td>48% + 17%</td>
</tr>
<tr>
<td>172</td>
<td>β</td>
<td>β</td>
<td>α</td>
<td>CAN</td>
<td>loss of OEt</td>
<td>-</td>
</tr>
<tr>
<td>172</td>
<td>β</td>
<td>β</td>
<td>α</td>
<td>H₂, Pd/C</td>
<td>loss of TBS</td>
<td>26% (34)</td>
</tr>
<tr>
<td>174</td>
<td>α</td>
<td>β</td>
<td>α</td>
<td>DDQ</td>
<td>178</td>
<td>36%</td>
</tr>
<tr>
<td>175</td>
<td>β</td>
<td>α</td>
<td>β</td>
<td>DDQ</td>
<td>179</td>
<td>50%</td>
</tr>
</tbody>
</table>

In a parallel route, a mixture of tetracycles 200, 201, and 202 was reduced with lithium aluminum hydride to give a mixture of diols (in a total of 71% yield).
Unfortunately, only diol 180 could be isolated pure via this route. Diol 180 was crystalline and allowed a single crystal X-ray analysis to be acquired confirming the stereochemistry of adduct 164 (Figure 16 vide supra). The inability to isolate the other diols in a pure form resulted in only the use of diol 180 in subsequent steps (Scheme 48). Monoprotection of the primary alcohol as a TBS ether provided tetracycle 181 in 48 % yield. A sample of tetracycle 181 was used to correlate its stereochemistry to that of other tetracycles. Protection as PMB ether and removal of the TBS silyl group gave alcohol 164. In order to acquire the other tetracycles (200, 201, 202, 203, 213) pure, their primary alcohol had to be protected as a TBS ether (215, 216, 217, 218, and 219 respectively). At this stage generally the products could be isolated pure, and then deprotection of the TBS group provided the various alcohols in a pure form.

Scheme 48 Monoprotection of diol 180 and correlation to alcohol 164
The stage was now set for the installation of the (tributylstannyl)methyl unit (Table 8). Under conditions that functioned well on other secondary and tertiary alcohols the yields were extremely low. A crown ether was required to remove the potassium counter ion from the alcoholate, in order to form any product. However under these conditions a significant quantity of the methyl ether was isolated along with the desired product.

Table 8. Installation of the (tributylstannyl)methyl group

<table>
<thead>
<tr>
<th>Tetracycle</th>
<th>Base</th>
<th>Additive</th>
<th>Solvent</th>
<th>Product</th>
<th>% Yield (SM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>178</td>
<td>NaH</td>
<td>-</td>
<td>THF</td>
<td>178</td>
<td>(100)</td>
</tr>
<tr>
<td>181</td>
<td>KH</td>
<td>-</td>
<td>THF</td>
<td>181</td>
<td>(66)</td>
</tr>
<tr>
<td>181</td>
<td>KH</td>
<td>-</td>
<td>DMF</td>
<td>181</td>
<td>(68)</td>
</tr>
<tr>
<td>181</td>
<td>KH</td>
<td>-</td>
<td>THF:HMPA</td>
<td>185</td>
<td>38% (50)</td>
</tr>
<tr>
<td>179</td>
<td>KH</td>
<td>-</td>
<td>HMPA</td>
<td>179</td>
<td>(84)</td>
</tr>
<tr>
<td>176</td>
<td>KH</td>
<td>18-C-6</td>
<td>THF</td>
<td>183 + 184</td>
<td>53%+ 21%</td>
</tr>
<tr>
<td>179</td>
<td>KH</td>
<td>18-C-6</td>
<td>THF</td>
<td>187 + 188</td>
<td>40%+ 35%(25)</td>
</tr>
</tbody>
</table>

Exchange of the tributylstannyl group for lithium and quenching the resulting anion with diphenyldiselenide should have provided the desired
monoselenoacetals (Table 9). The initial attempt gave only starting material, while two subsequent reactions resulted in a mixture of products.

Table 9 Formation of Monoselenoacetals 189, 190, and 191

<table>
<thead>
<tr>
<th>Tetracycle</th>
<th>% Selenide</th>
<th>Stannane (% Yield)</th>
<th>Methyl ether (% Yield)</th>
<th>Alcohol (% Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>185</td>
<td>0</td>
<td>185 (34)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>183</td>
<td>0</td>
<td>183 (30)</td>
<td>184 (29)</td>
<td>176 (7)</td>
</tr>
<tr>
<td>187</td>
<td>0</td>
<td>0</td>
<td>188 (13)</td>
<td>179 (75)</td>
</tr>
</tbody>
</table>

Unlike the model studies\textsuperscript{102} and literature precedents\textsuperscript{103} the formation of the monoselenoacetals was unsuccessful in these cases. Although unexpected, this result was not the most puzzling. Formation of the methyl ether suggests the initial metal-metal exchange reaction proceeded and the resulting alkoxymethyl anion was trapped with water rather than the diphenyldiselenide electrophile. On the other hand, the formation of the alcohol suggests something entirely different is occurring. One possibility is that the monoselenoacetal was not stable to the aqueous work-up and was hydrolyzed. However, this is unlikely as previous selenoacetals showed no signs of sensitivity to water.

The installation of the (tributylstannyl)methyl unit and its conversion into the monoselenoacetal was becoming a significant challenge. One possible solution was the install the (tributylstannyl)methyl unit before the hetero Diels-
Alder reaction when the system is less encumbered. Accordingly, the PMB ether 133 was deprotected under standard conditions to give allylic alcohol 219 in 34% yield (Scheme 49). Generation of the alcolholate and alkylation with Bu$_3$SnCH$_2$I yielded the desired (tributylstannyl)methyl ether 220 in only 54% yield. The yields for this two step process were similar to those obtained with the tetracycles (Tables 7 and 8). Lack of material and insignificant improvement in the yield led to abandonment of this route.

Scheme 49 Installation of (tributylstannyl)methyl group on 133

Attention now turned to other strategies for the formation of the desired monoselenoacetal. One strategy called for the quenching of an alcoholate with diazomethane followed by the addition of phenylselenylchloride to give the desired product (Scheme 52). Unfortunatel on model systems this reaction failed.

Scheme 50 Diazomethane route to selenoacetals
A second strategy was based upon a Pummerer methyl sulfoxide rearrangement (Scheme 51). A test, mixing phenylmethylselenoxide and acetic anhydride, did give this rearranged product.

Scheme 51 Pummerer rearrangement route

Pummerer rearrangement products are common in Swern oxidations so oxalyl chloride seemed to be an obvious choice as an activator. Table 10 summarizes our efforts using these conditions.
Table 10 Pummerer Rearrangement results

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Activator</th>
<th>Base</th>
<th>X</th>
<th>Reactants</th>
<th>% Product Yield (SM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>221</td>
<td>(CF₃CO)₂O</td>
<td>NEt₃</td>
<td>S</td>
<td>BF₃OEt</td>
<td>61%</td>
</tr>
<tr>
<td>221</td>
<td>(CF₃CO)₂O</td>
<td>NEt₃</td>
<td>Se</td>
<td>BF₃OEt</td>
<td>0% (~100)</td>
</tr>
<tr>
<td>221</td>
<td>oxalyl chloride</td>
<td>NEt₃</td>
<td>Se</td>
<td>none</td>
<td>0% (~100)</td>
</tr>
<tr>
<td>179</td>
<td>oxalyl chloride</td>
<td>none</td>
<td>Se</td>
<td>none</td>
<td>0% (~100)</td>
</tr>
<tr>
<td>179</td>
<td>TfOTf</td>
<td>DTBMP</td>
<td>Se</td>
<td>none</td>
<td>0% (~100)</td>
</tr>
</tbody>
</table>

The reaction of 221 with phenylmethylsulfoxide led to a good yield of the expected thioacetal. Unfortunately, sulfur was not a reliable precursor of the alkoxy methylene radical as we have demonstrated previously.¹⁰⁶ For unknown reasons, the same reaction with the selenoxide analog led only to recovery of starting material.

The third alternative was based upon Guindon's reagent, dimethylboron bromide.¹⁰⁷ This reagent is commonly used for the mild cleavage of acetals and ketals and produces an α-bromo ether as an intermediate (Scheme 52).¹⁰⁸ The α-bromo ether would be expected to be a radical precursor or could be transformed into a selenoacetal. In fact, this reagent has been used as a common route to transform methoxymethyl (MOM) ethers into methylthiomethyl (MTM) ethers. This route therefore appeared extremely attractive, particularly in a total synthesis, because the common protecting group MOM could be used as an indirect radical precursor.
In order to test this hypothesis a model was used. Accordingly, the MOM ether 225 was treated with Guindon’s reagent, followed by benzeneselenol and triethylamine (Scheme 53). Although this protocol is reported to work very well for phenylthiol, in the case of the more acidic benzeneselenol the yields were very low. A significant quantity of bis(phenylseleno)methane was isolated. The formation of this side product can be envisioned to arise from complexation of the borane on the monoselenoacetal and a nucleophilic substitution reaction.

**Scheme 52** Formation of α-bromo ethers from MOM ethers
A solution to this problem was the removal of the borane and solvent prior to adding the selenolate under high vacuum. This intermediate could be isolated, characterized and manipulated fairly easily. Radical cyclizations were attempted on this intermediate (vide infra), and also it did prove to be a gateway to the monoselenoacetals (Table 11).

Table 11 Formation of monoselenoacetals from α-bromo ethers

<table>
<thead>
<tr>
<th>Selenide</th>
<th>Base/Reducing Agent</th>
<th>Solvent</th>
<th>Product % Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhSeH</td>
<td>NEt₃</td>
<td>CH₂Cl₂</td>
<td>0</td>
</tr>
<tr>
<td>PhSeH</td>
<td>NaH</td>
<td>THF</td>
<td>62%</td>
</tr>
<tr>
<td>(PhSe)₂</td>
<td>LiBH₄</td>
<td>THF</td>
<td>not isolated</td>
</tr>
</tbody>
</table>
To generate the monoselenoacetals effectively, use of the benzeneselenolate rather than the selenol was important. Addition of the preformed selenolates into a solution of the α-bromo ether gave the desired product. The yields were never optimized, and it can be imagined that reducing agents other than LiBH₄ could be used to generate the selenolate. In the case of the reaction with LiBH₄ (entry 3), the initial tlc’s showed a great deal of desired acetal 226, overnight the desired product had disappeared likely due to the excess hydride reacting with 226. The stench and instability of benzeneselenol makes the use of diphenyldiselenide more attractive. The initial 62% yield is already comparable to the two step tin-selenide process.

During a total synthesis, transformation of the α-bromo ether into the monoselenoacetal would only be important if the α-bromo ether was not a suitable radical precursor or if further transformations were required before a radical cyclization was to be attempted. In our case the tetracycle would be ready for a cyclization immediately so an investigation was made to address the question of whether the α-bromo ether would be a suitable radical precursor. With this in mind, α-bromo ether 227 was subjected to standard radical cyclization conditions resulting in an interesting observation (Scheme 54).
Rather than isolating a mixture of cis and trans tricycles 228, a product arising from what could be viewed as a cationic process was isolated. This result was extremely interesting and suggested that the triphenyltinhydride acted as a Lewis acid. To investigate this further a series of cyclizations were attempted with various hydride donors and Lewis acids on α-bromo ether 227 (Table 12).

**Scheme 54** Radical cyclization of α-bromo ether 227
Table 12 Cyclization of α-bromo ether 227

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Hydride/Lewis Acid</th>
<th>Initiator</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>Ph₃SnH</td>
<td>AIBN</td>
<td>229</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>None</td>
<td>None</td>
<td>227</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>Ph₃SnH</td>
<td>None</td>
<td>229</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>(TMS)₃SiH</td>
<td>AIBN</td>
<td>229</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>Bu₃SnH</td>
<td>AIBN</td>
<td>230</td>
</tr>
<tr>
<td>6</td>
<td>SePh</td>
<td>Ph₃SnH</td>
<td>AIBN</td>
<td>230</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>Me₄Sn</td>
<td>None</td>
<td>227</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>AgOTf</td>
<td>None</td>
<td>Decomposition</td>
</tr>
<tr>
<td>9</td>
<td>Br</td>
<td>ZnCl₂</td>
<td>None</td>
<td>229 + others</td>
</tr>
<tr>
<td>10</td>
<td>OMe</td>
<td>ZnCl₂</td>
<td>None</td>
<td>229 + 225+ others</td>
</tr>
</tbody>
</table>

The results from this study were remarkable. Under the reaction conditions for radical cyclizations, the hydride donor and initiator were added slowly to a refluxing solution of α-bromo ether 227. To investigate if the heat alone was causing the cyclization an attempt was made in the absence of both hydride and initiator, resulting in no reaction (entry 2). Use of only triphenyltinhydride in the absence of AIBN gave cyclized product strongly implying a cationic process (entry 3). Using Chatgilialogu’s reagent (entry 4) also gave the tricycle suggesting it too acted as a Lewis acid. Interestingly, tributyltinhydride gave reduced product arising from a radical process (entry 5). The addition time and concentration of the reaction mixture was fast enough...
under these reaction condition to give mainly reduced product rather than the cis and trans tricycles. Use of the monoselenoacetal and triphenyltinhydride also gave a product formed from a radical process (entry 6). By the choice of the appropriate hydride donor, entry into both a radical or cationic cyclization can be envisioned. This flexibility is extremely important in complex molecules and total synthesis. An attempt was made using tetramethyltin but only starting material was obtained in this reaction (entry 7). It appears that the phenyl groups on tin are augmenting its Lewis acidity. Use of strong Lewis acids did give cyclized produces in some cases however the reaction were generally less clean than those with triphenyltin hydride.

Unsaturated sulphones undergo radical cyclizations when treated with samarium diiodide.\textsuperscript{109} Since their phenythioacetal precursors are generally easier to fabricate than the corresponding selenides and since thioacetals could be used as a protecting group during the synthesis this strategy could prove advantageous. Oxidation of the thioether would generate the radical precursor. With this in mind, Sophie Gagnon converted MOM ether 225 to sulphone 231.\textsuperscript{110} Unfortunately all attempts to cyclize the sulphone failed under the action of SmI\textsubscript{2} (Scheme 55).

Scheme 55 Sophie Gagnon’s results with samarium diiodide

Another strategy that was developed in parallel to the $\alpha$-bromo ether route was based upon a bromomethyldimethylsilyl radical precursor. Initially developed by Stork, this route gains access to the C8 angular methyl group.\textsuperscript{111} This route would also provide access to the oxomethano bridge and has the added advantage that the radical precursor is easy to install (Scheme 56).\textsuperscript{112}
Although now a 6-exo-trig cyclization, this process is still favored under Baldwin's rules.

**Scheme 56** Potential route with bromomethyldimethylsilyl precursor
Accordingly, alcohols 221 and 224 were converted into silyl ethers 232 and 233 under standard conditions in 83 and 81 % yield respectively (Scheme 57). Subjecting the silyl ethers to standard radical cyclization conditions yielded the TMS ethers in near quantitative yield. It is possible no cyclization took place due to severe steric interactions between the cycle and the methyl groups. Although this process was unsuccessful on the model, nothing could be said about its utility on a tetracyclic structure.

Scheme 57 Bromomethyldisilyl radical cyclizations on 232 and 233.

With an apparently excellent way to generate either an α-bromo ether or α-seleno ether, our attention returned to the tetracycles. Accordingly, tetracycle 176 was protected as a methoxymethyl ether under near neutral conditions in 66% yield based on recovered starting material (Scheme 58).113
Scheme 58 Introduction of MOM ether to 226

Treatment of 236 with dimethylboron bromide and triphenyltinhydride in order to induce a cationic cyclization yielded a mixture of products, none of which resembled the desired pentacycle. It was obvious from the $^1$H NMR that dimethylboron bromide had cleaved the ethoxy acetal of the D ring. This result was not completely unexpected, however we were hoping perhaps the less sterically encumbered MOM acetal would be cleaved preferentially. To circumvent this problem the ethoxy acetal could be simply converted to a lactone. In natural quassinoids a lactone is present so this operation has to be done during a total synthesis.

Following a protocol used in the total synthesis of quassin by Shing and co-workers, tetracycle 171 was subjected to mild hydrolysis and oxidation using Fetizon’s reagent ($\text{Ag}_2\text{CO}_3$ on celite). Unfortunately the major product isolated (<15% yield) from this reaction lacked the PMB ether and was not a lactol or lactone (Scheme 59).
Scheme 59 Initial attempts at formation of lactone D ring

At this point in time, very little material remained to test the radical cyclization. Use of a α-bromo ether still appeared to be best and shortest route. Therefore, tetracycle 216 was used in an attempt to convert the acetal into a lactone by in situ hydrolysis and oxidation using Jone’s reagent (Scheme 60). Complete decomposition resulted in this case.

Scheme 60 Second attempt at lactone D ring

The loss of both the PMB and TBS groups in the previous attempts indicated that perhaps success would be realized by using a more robust protecting group on the C13 secondary alcohol. The TBDPS was installed under standard conditions from alcohol 201 to give 237. Hydrolysis of the lactone ring
was attempted using acetic acid and water (Scheme 61). Oxidation of the crude lactol with Jone’s reagent yielded 17\% of the lactone 238 from the acetal. After the poor yield, not enough material was available to continue the sequence. Perhaps another oxidant would be more appropriate in this case.

Scheme 61 Two step approach to lactone D ring

With very little material remaining, one final cyclization was attempted. In this case tetracycle 202 (stereochemistry unknown at the time) was transformed into silyl ether 239 under standard conditions. Subjecting this material to stoichiometric tin hydride conditions gave a complex mixture of products. One of which resembled the reduced TMS ether. After flash chromatography, three polar products were recovered in 55\% yield (Scheme 62).
One of these resembled tetracycle 202 and was later confirmed to be so. The other two polar products were tetracyclic, similar, but distinctly different from tetracycle 202. In order to obtain pure samples, the two unknowns were protected as a TBS ether and characterized. One product obtained pure provided a high resolution mass spectra of C_{27}H_{46}O_{5}Si that corresponds exactly to that of tetracycle 216 (and 217) (scheme 60). However, the proton NMR indicated it was not tetracycle 217. If the radical cyclization had taken place one would have expected an exact mass of C_{28}H_{50}O_{5}Si. Careful examination of the ¹H NMR indicated that the chemical shifts and multiplicities of the C13, C16, and C7 had changed most significantly. This suggested that the tetrasubstituted double bond had migrated. The migration can be rationalized by a 1,5-H shift and subsequent reduction of the allylic radical at C9 (Scheme 63).
Reduction of the allylic radical will give two products that should be very
similar spectroscopically and this was the case. It is plausible that during the
reaction the methylene radical could never approach the double bond and cyclize
due to steric repulsion from the ring system. Approaching the allylic proton at
C14 is sterically more favorable allowing the possibility for a 1,5-H shift, and thus
producing a stabilized allylic radical whose formation should be favored. A
thorough characterization of the tetracycle could not be performed due to the
small quantities of material so this conclusion can only be considered as
speculation.

No material remained to further test any of the cyclizations. The
challenges during the installation of the (tributylstannyl)methyl unit provided a
host of other strategies that were not tested in a satisfactory manner. The fact
that the diene-transmissive Diels-Alder reaction was not sufficiently selective to
provide enough material with the correct relative stereochemistry proved to be the biggest limitation in the strategy. Isolation of only 8% or 14% of material with the correct relative stereochemistry made using this sequence unviable. Control of the initial hetero Diels-Alder reaction was clearly required in this case. Previous results by Gang Liu indicated that an acetonide based on a C12 and C13 diol effectively directed the face of attack during the initial hetero Diels-Alder reaction, giving a 9:1 ratio of products (Scheme 64).\textsuperscript{115}

![Scheme 64 Influence of acetonide at C12-C13 on hetero Diels-Alder reaction](image)

To this end the following strategy was adopted starting from commercially available quinic acid (Scheme 65). The acetonide should effectively direct the first Diels-Alder reaction and a combination of the equatorial methyl group and the acetonide itself should also control the intramolecular Diels-Alder reaction. The selectivity of this reaction should be excellent. All that would remain would be the differentiation of the C12 and C13 alcohols and assuming one being axial and the other equatorial this should be relatively routine operation. Following this route enough material should be available to test the various radical cyclizations.
Scheme 65 New strategy based upon (-)-quinic acid
Chapter 5. Synthesis of the chiral chain

The chiral chain 109 (Scheme 29, Chapter 2) was initially to be used in the synthesis of the afore mentioned tetracycles (Chapters 3 and 4) and was finally abandoned due to the difficulty in it’s procurement. However, the use of chiral (-)-quinic acid as a building block required a chiral chain for the quassinoid A ring.

The initial strategy for the formation of chiral synthon 109 was based upon Evan’s chiral enolate methodology.116 Initial attempts to alkylate enolate 250 with bromide 251 or ethylene oxide 252 gave only starting material. Using iodomethane as the electrophile gave the desired alkylated product. Clearly the alkylation would only be successful with a reactive electrophile. Thereafter, an attempt was made using oxazalidinone 254 with iodomethane as the electrophile. Oxazalidinone 254 already possesses the required halide and if the alkylation was successful, would save a number of synthetic steps in the synthesis of 109. Perhaps not surprisingly a cyclopropane 255 was obtained as the major product. (Scheme 66).
The first modicum of success arose using 256 and trapping the anion with MeI (Scheme 67). The yield was poor but the desired adduct was acquired. Optimized conditions using methyltriflate generated adduct 257 in a moderate 64% yield. The 6:1 ratio of the two separable diastereomers was far lower than the ratios reported in other cases with methyl iodide in the literature.116
Scheme 67 First successful alkylation

Regardless, enough material could be acquired to continue the sequence. Hydrolysis of the auxiliary and reduction of the resulting acid yielded the highly volatile alcohol that was immediately protected as a TBS silyl ether 258. The overall yield for the 3 steps was 41%. Hydroboration of the double bond gave alcohol 259 that was converted to the desired iodide 109 in 86% yield for the two steps. (Scheme 68)

Scheme 68 Synthesis of chiral iodide 109 first generation
A successful route to chiral synthon 109 had been accomplished, however the poor yield and ratio during the alkylation step made us doubt enough material could be acquired from this route in an expeditious fashion.

With this in mind, another approach was used, this time using allylbromide as the electrophile (Scheme 69). An oxidative cleavage of the terminal double bond and subsequent reduction would give the desired intermediate. In following with this strategy, oxazolidinone 260 was effectively alkylated with allyl bromide in 89% yield after separation as one diastereomer. The auxiliary was then removed, and the resulting acid reduced to alcohol that was protected with a TBS group. The overall yield for the three steps was 92%. Treatment of the alkene 262 with ozone followed by reduction with sodium borohydride gave alcohol 259 that was transformed as mentioned previously to give iodoalkane 109.

Scheme 69 Improved synthesis of chiral alcohol 259
Under optimum conditions, chiral synthon 109 could be fabricated in 8 linear steps from commercially available Norephidrine119 with an overall yield of 52%. The troubles with the cuprate addition (Chapter 3, page 55), and few steps that followed, made this effort extremely unattractive, when a simple racemic chain could be procured with relative ease. Starting from commercially available 3-methyl-3-buten-1-ol 263, protection of the alcohol as a benzyl ether, and hydroboration gave alcohol 264 in an overall quantitative yield. Protection of the newly formed alcohol and deprotection of the benzyl group followed by conversion to the iodide gave the desired racemic synthon in 5 steps with an overall yield of 95%. (Scheme 70)

Scheme 70 Racemic synthesis of iodide 109
It should be noted that enantioselective hydroborations are possible, however in general the e.e.’s in the case of terminal alkene are low.\textsuperscript{120}

The problem experienced with the alkylation of Evan’s oxazolidinone (\textit{vide supra}) coupled with results from a concurrent synthesis in our laboratories led to the discovery of a novel approach to build alpha-alkylated carbonyl compounds which proved applicable to the synthesis of iodide 109.\textsuperscript{121}

Addition of alkenyllithiums 271 and 272 to (+)-menthone 270 in the presence of cerium trichloride gave propargylic alcohols 273 and 274 in 94\% and 83 \% yields respectively after flash chromatography solely as the axial alcohols (Scheme 71). The slow addition of a solution of menthone to the reaction mixture was found to greatly increase ratio of the axial isomer. Reduction of propargylic alcohol 273 to allylic alcohol 275 with Red-Al gave the desired product in only 43\% with recovery of 51\% of diol 276 resulting from the cleavage of the TBS protecting group. The liability of the TBS group under the reaction conditions resulted in the change to the PMB group. Accordingly the reduction proceeded cleanly to give allylic alcohol 277 in 97 \% yield. In some cases, trace quantities of allene 279 could be isolated, arising from elimination of 278. The propensity of alkoxyde 278 to eliminate to form allene 279 is a function of temperature and reaction time.
Treatment of the allylic alcohol 277 with \( n \)-butyllithium and quenching the alcohohlate with methyl chloroformate gave the carbonate in quantitative yield (Scheme 72). The crude carbonate was then subjected to a dimethylcuprate to give 280 in 99% yield as a single diastereomer.
Scheme 72 Key cuprate $S_{N}2'$ displacement on allylic carbonate

In an attempt to acquire a crystal structure of 280 the PMB protecting group was removed with DDQ to give alcohol 281 in 95% yield. Unfortunately the free alcohol was an oil. However, protection with the tert-butyldiphenylsilyl ether gave a crystalline product 282 from which a single crystal X-ray analysis could be acquired (Scheme 73).

Scheme 73 Synthesis of crystalline TBDPS ether 282

Interestingly the ORTEP diagram (see figure 19) shows the auxiliary adopting a chair conformation with both the isopropyl and methyl group in an axial position. This observation is presumably due to $A^{1,3}$ strain.
Oxidative cleavage of the trisubstituted double bond, then immediate treatment with sodium borohydride gave alcohol 283 in 93% yield. This alcohol was then converted into Mosher’s esters to confirm the high degree of enantiomeric excess. In this case the e.e. was determined to be around 99%. Alcohol 283 was protected as a silyl ether then the PMB ether was removed under standard conditions to give alcohol 259 that was later converted into the iodide as mentioned previously (Scheme 74).

**Figure 19** ORTEP drawing of 282.
Scheme 74 End-game of menthone sequence
Using this methodology, synthon 109 could be acquired from 4-butyn-1-ol in 8 steps in and overall yield of 52%. Sadly three of the steps are protections and deprotections that somewhat diminish the elegance of the route. Regardless, the key step of the sequence gives one diastereomer in quantitative yield on large-scale.

The cleavage of the TBS group in the reduction step using Red-Al, was somewhat bothersome, even though success had been achieved with the PMB protecting group. In order to avoid the Red-Al reduction step, a brief investigation was made for the addition of vinylolithiums to menthone. Previous results\textsuperscript{123} showed \textit{trans} propenyllithium could be added to menthone in high yield (99%). Accordingly, attempts to fabricate \textit{trans} vinylhalides from alkynes 272 with DIBAL\textsuperscript{124} and catachol borane\textsuperscript{125} gave synthetically unviable results. The yields were low and in the case of DIBAL the \textit{cis} isomer was isolated along with a host of other products. These two routes also failed the Lewis acid test; any group that would be cleaved during the Red-Al reduction would likely be removed under these reaction conditions as well. A solution was found in the use of Swartz’s reagent\textsuperscript{126} generated \textit{in situ} with Cp\textsubscript{2}ZrCl\textsubscript{2} and Superhydride.\textsuperscript{127} Quenching with either NBS or I\textsubscript{2} gave the desired \textit{trans} vinylhalides in high yield. (Table 13)

![Reaction Diagram]

Table 13 Formation of vinylhalides from 272

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Electrophile</th>
<th>Yield</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIBAL-H</td>
<td>I\textsubscript{2}</td>
<td>14%</td>
<td>(\textit{cis}), X=I</td>
</tr>
<tr>
<td>catachol borane</td>
<td>I\textsubscript{2}</td>
<td>29%</td>
<td>(\textit{trans}), X=I</td>
</tr>
<tr>
<td>Swartz’s reagent</td>
<td>I\textsubscript{2}</td>
<td>87%</td>
<td>(\textit{trans}), X=I</td>
</tr>
<tr>
<td>Swartz’s reagent</td>
<td>NBS</td>
<td>79%</td>
<td>(\textit{trans}), X=Br</td>
</tr>
</tbody>
</table>

Interestingly, the addition of the \textit{trans} vinylolithiums to menthone did not prove to be general. In most attempts, a fair quantity of menthone and terminal
alkene was recovered from the crude product. In all likelihood the more basic vinylolithiums were enolizing the menthone. The best results were found with the addition at -100°C of the vinylolithium formed from the corresponding vinylbromide. (Table 14). Clearly more work needs to be done to optimize the reaction.

![Chemical structure](image)

**Table 14** Addition of vinylolithiums to (+)-menthone

<table>
<thead>
<tr>
<th>X</th>
<th>Solvent</th>
<th>Alkylithium</th>
<th>Temperature</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>THF</td>
<td>t-BuLi</td>
<td>-78°C</td>
<td>49%</td>
</tr>
<tr>
<td>I</td>
<td>Et₂O</td>
<td>t-BuLi, CeCl₃</td>
<td>-78°C</td>
<td>20%</td>
</tr>
<tr>
<td>Br</td>
<td>THF:Et₂O</td>
<td>t-BuLi⁺</td>
<td>-100°C</td>
<td>70%</td>
</tr>
<tr>
<td>I</td>
<td>Hexane</td>
<td>n-BuLi⁺</td>
<td>-78°C</td>
<td>42%</td>
</tr>
<tr>
<td>I</td>
<td>Benzene</td>
<td>n-BuLi⁺</td>
<td>0°C</td>
<td>58%</td>
</tr>
</tbody>
</table>

It should be noted that in each case the only addition product was determined to be the axial alcohol. This two-step process should allow a variety of protecting groups to be used, that might not otherwise survive the reduction with Red-Al.

In the final analysis the menthorne methodology was used to provide a large quantity of chiral iodide **109** required in the (-)-quinic acid route to quassinoids (*vide infra*).
Chapter 6. (-)-Quinic acid route to quassinoids

Readily available (-)-quinic acid\textsuperscript{128} was the chiral starting material used in the synthesis of target compound \textbf{240} (Scheme 67, Chapter 4). Following literature protocols, treatment with TsOH and a mixture of benzene and cyclopentanone provided the known lactone \textbf{301}\textsuperscript{129} (Scheme 75). A cyclopentylidene ketal was chosen as the protecting group for the C12 and C13 hydroxyls because it is known that this ketal is easier to deprotect than the corresponding acetonide.\textsuperscript{130} Reduction of the lactone and oxidative cleavage of the resulting triol gave ketone \textbf{302} in 88\% yield.\textsuperscript{131} Mesylation and \textit{in situ} elimination of the secondary alcohol provided $\alpha,\beta$-unsaturated ketone \textbf{303} in 86\%. 
Scheme 75 Early transformations of (-)-quinic acid

Bromination and elimination of $\alpha,\beta$-unsaturated ketone 303 provided bromo-ketone 304 in 65% yield. Addition of vinyl lithium to bromo-ketone 304 in the presence of cerium trichloride proceeded in a stereoselective manner providing essentially one alcohol 305 in 74% yield. The $\beta$-face of bromo-ketone 304 is effectively blocked by the cyclopentylidene protecting group. Acetylation of 305 afforded allylic acetate 306 in quantitative yield (Scheme 76).
The procurement of allylic acetate 306 set the stage for its S$_{n}$2$'$ copper mediated displacement reaction by chiral synthon 109 (Scheme 77). Following the previously optimized reaction conditions (*vide supra*), the reaction proceeded in very low <15% yield. Unlike the previous system, the low yield was accompanied with recovery of very little acetate 306.

**Scheme 76** Formation of allylic acetate 306
Once again, optimization of this key step was required. In order to preserve 109, \( n \)-butyllithium was used as a surrogate alkyl lithium during the optimization process. In a recent report\textsuperscript{133}, the “sangrail” of organocuprates was disclosed, containing a dummy ligand with a silicon atom in the \( \beta \)-position that was non-transferable and greatly augmented the reactivity of the copper species. Acetate 306 was subjected to the \( S_N2' \) displacement reaction with this new reagent (Table 15).
Table 15  Optimization of cuprate reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Copper</th>
<th>Solvent</th>
<th>Product (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuI</td>
<td>Et₂O</td>
<td>308:309 (92)¹</td>
</tr>
<tr>
<td>2</td>
<td>CuCN²</td>
<td>Et₂O</td>
<td>308:309³</td>
</tr>
<tr>
<td>3</td>
<td>CuI</td>
<td>THF</td>
<td>308, trace 309 (100)¹</td>
</tr>
<tr>
<td>4</td>
<td>CuCN</td>
<td>THF</td>
<td>308, trace 309 (84)¹</td>
</tr>
<tr>
<td>5</td>
<td>CuI</td>
<td>Et₂O : THF</td>
<td>308 (75)</td>
</tr>
</tbody>
</table>

Notes: (1) crude yield, (2) no TMSCH₂Li used (3) no yield reported

Interestingly, and for the first time, the regioselectivity of the reaction was compromised with the use of the more reactive ligand. This lower regioselectivity was solvent dependent. Using diethyl ether, the major product was 309, while changing to THF yielded only trace quantities of this unwanted product. Conventional wisdom would suggest that in diethyl ether the reactive organocuprate is the dimer [LiCuR₂]₂ while in THF a monomeric species is present.¹³⁴ To accomplish the desired metal halogen exchange reaction with chiral synthon 109 depicted in Scheme 79, diethyl ether is required as the solvent. A mixture of THF and diethyl ether (entry 5) yielded exclusively product 308 in an isolated 75% yield.

Applying these conditions to allylic acetate 306 and using chiral synthon 109 (Scheme 77) provided 307 in 62% yield. This product was found to be extremely unstable. Metal-halogen exchange of 307 and quenching with DMF provided the desired aldehyde 310 in only 14% yield. Lowering the temperature
to -100°C and quenching the reaction after 60 seconds provided 310 in 71%. This reaction was not reproducible and generally decomposition resulted. Use of magnesium in place of n-butyllithium was unsuccessful in this case. Finally a palladium (0) carbonylation\textsuperscript{35} reaction was attempted to provide ester 311 (Scheme 78). Under these conditions only starting material was isolated.

Scheme 78 Metal-halogen exchange and palladium carbonylation reaction

Subjecting aldehyde 310 to ethyl vinyl ether in the presence of ytterbium resulted in decomposition of the starting material. The instability of both 307 and 310 became a serious problem. The likely cause was the cyclopentylidene protecting group, all attempts at removing it after the cuprate reaction resulted in decomposition (Scheme 79).
Scheme 79 Attempted deprotection of diol 307

The lack of stability of the various products effectively halted this synthesis. Unfortunately, the system with the cyclopentylidene ketal was far inferior to that of the acetonide as demonstrated by Gang Liu.\textsuperscript{136} In fact, the allylic acetate 306 underwent autoxidation upon standing at 5°C in the refrigerator (Scheme 80). The polar compound with a characteristic OH bend in the IR spectra was confirmed to be the hydroperoxide by its transformation into a TBS silyl ether and subsequent characterization.

Scheme 80 Autoxidation of 306
In order to alleviate the problem of the instability of the intermediates, it was decided to use two different protecting groups on the C12 and C13 diol. Perhaps this would also be sufficient to control the selectivity of the hetero Diels-Alder reaction. Regardless of the conformation, one of the two groups should be able to block the β-face of the molecule during the hetero Diels-Alder reaction (Scheme 81). Another advantage is that the C13 hydroxyl could be selectively deprotected afterwards and no differentiation of the diol would be required.

**Scheme 81** New approach for hetero Diels-Alder reaction
Chapter 7. Second generation (−)-quinic acid approach to quassinoids.

The final ascent to tetracyclic intermediate 320 (Figure 20) began with the lactonization of (-)-quinic acid and the selective benzylation of the equatorial hydroxyl following the protocol of Hanessian and co-workers, to give 321 (Scheme 82). With the C12 alcohol selectively protected, the choice of protecting group for the C13 hydroxyl could be made.

![Figure 20 Target intermediate](image)

Three potential choices were PMB, TBDPS, or a MOM group. The MOM group provided direct access to α-bromo ethers although the rest of the chemistry had not yet been developed with this group making it somewhat risky. Both the PMB and TBDPS had been used before, however, installation of the PMB on lactone 321 proved to be difficult, and the TBDPS ether was ultimately chosen. Mono-protection of the secondary alcohol proceeded in 78% yield accompanied by 22% of starting material. Reduction of the lactone and treatment of the triol with sodium periodate afforded β-hydroxy ketone 323 in 75% yield. Mesylation and in situ elimination provided α,β- ketone 324 in 93% yield. Conversion to the vinyl bromide 325 proceeded in 94% yield. 1,2-Addition of vinylolithium to bromo
ketone 325 and quenching with acetic anhydride provided allylic acetate 326 as a single diastereomer in 83% yield (Scheme 82).

**Scheme 82** Synthesis of allylic acetate 326
Allylic acetate 326 suffered an S\textsubscript{n}2' displacement with a monocyanocuprate reagent based upon chiral synthon 109 to afford 327 as a single geometric regioisomer in 96% yield. Metal-halogen exchange and treatment with DMF furnished \(\alpha,\beta\)-unsaturated aldehyde 328 in 80% yield (Scheme 83). The high yields and stability of compounds 326, 327, and 328 seem to suggest the rigid cyclopentylidene-protecting group was the source of the problems in the previous sequence (Scheme 77 and 78, Chapter 6). Transformation of aldehyde 328 to acetal 329 proceeded smoothly in near quantitative yield.

Scheme 83 Cuprate and metal-halogen exchange reaction on 326
To secure knowledge of the outcome of the first hetero Diels-Alder reaction, aldehyde 328 was subjected to ethyl vinyl ether in the presence of the ytterbium catalyst. Analysis of the crude $^1$H NMR provided an approximate ratio of 2:1. After separation of the two products it was determined that the more polar adduct was the major product during the reaction. Previous results suggested that the more polar adduct possessed the desired stereochemistry at C14. However, this stereochemistry could not yet be confirmed.

The next step was the selective deprotection of the primary TBS ether in the presence of the secondary allylic TBDPS ether. Use of PPTS in ethanol is commonly used for just such a transformation. In this case, deprotection of both the acetal and TBS ether resulted in low yield. Another possibility was the treatment of the silyl ether in a methanolic, carbon tetrachloride solution with ultrasound. Again, deprotection of both the TBS and acetal protecting groups resulted. One final attempt was made to protect aldehyde 328 as an acetal and deprotect the silyl ether in a single operation (Scheme 84). Unfortunately only the aldehyde-alcohol 333 was isolated in 64% yield.

![Scheme 84 Attempted simultaneous protection-deprotection sequence on 328](image)

Due to time constraints, it was decided to deprotect the primary alcohol using TBAF after formation of acetal 329. The less robust TBS ether was located on a primary alcohol compared to the large TBDPS group, located on a secondary alcohol. So, some selectively should be expected. Using 1 equivalent of fluoride in a dilute solution of 329 yielded 58% of alcohol 330 and 40% of diol 331(Scheme 85).
The synthesis was continued with alcohol 330. Oxidation of the primary alcohol employing Dess-Martin’s periodinane and Wadsworth-Emmons olefination on the crude aldehyde provided $\alpha,\beta$-unsaturated ester 332 in 66% yield for the two steps (Scheme 86).

Although the ratio of 2:1 was known for the hetero Diels-Alder reaction when a TBDPS ether was present on the C13 hydroxyl, the ratio was not known for the free alcohol. Before a commitment would be made on a large scale, a
test was to be made without the silyl-protecting group. Treatment of α,β-unsaturated ester 332 with TBAF yielded a surprising mixture of products. The fluoride anion was sufficiently basic enough (and the TBDPS ether encumbered enough) to allow the abstraction of the proton γ to the ester functionality (Scheme 87).

![Scheme 87](image)

**Scheme 87 γ-Enolate formation with fluoride anion on 332**

Both the recovered silyl ether and the free alcohol showed a mixture of α,β and α,γ - unsaturated esters. Epimerization of the methyl group was likely and this result rendered this approach useless in a synthetic sense. The mixture could be used to calculate the ratio of the first Diels-Alder reaction however. Deprotection of the acetal on the mixture of free alcohols provided aldehydes, in 92% yield. Submitting the mixture to the Diels-Alder reaction conditions yielded a complex mixture of products. It appeared two tetracycles were visible in equal proportions, however, difficulty in the isolation made this observation tenuous.

Rather than optimize the deprotection of the TBDPS ether, we decided to transform all of 332 to a suitable diene-transmissive Diels-Alder precursor. Diol 331 would also be transformed into a Diels-Alder precursor lacking a C13 protecting group and undergo the Diels-Alder reaction.

Accordingly, transacetalization of 332 provided aldehyde 335 in 92% yield that was immediately subjected to the diene-transmissive Diels-Alder reaction (Scheme 88). After five days an inseparable mixture of tetracycles 336 was
isolated in 82% yield. Again, neither GC mass spectra or $^1$H NMR proved reliable for determining the ratio of products for the Diels-Alder reaction. In order to determine the ratio and separate the tetracycles, the TBDPS group was removed. After heating a solution of 336 and TBAF to reflux, a 3:1 ratio of tetracycles 337:338 was isolated in 94% combined yield.
Scheme 88 Diene-transmissive Diels-Alder reaction

PPTS, H₂O, acetone, reflux, 92%

Yb(FOD)₃, 82%

TBAF, THF, reflux, 94%

332 → 335

336 + 337
Unfortunately, the major diastereomer was the undesired C14 epimer, indicating that the original hypothesis about the hetero Diels-Alder stereochemistry was incorrect. The favored face of attack was the β-face perhaps due to the TBDPS group adopting an empeding conformation (see 335β in Scheme 89). The resulting dienes underwent an intramolecular Diels-Alder reaction via endo transition states (TS337 and TS338) with the chiral tether adopting in a chair-like conformation in which the methyl group is in an equatorial position (Scheme 91). Unlike the previous diene-transmissive Diels-Alder reactions, TS337 appeared to be the sole reaction pathway (for that diastereomer). With the C12 and C13 protected alcohols blocking the β-face this result was expected. What might be trace quantities of another tetracycle appeared to be visible by 1H NMR.

Analysis of the 1H NMR spectra helped determine the relative stereochemistries of the two products. As noted in section F, the multiplicity and chemical shift of the C16 proton was diagnostic. In tetracycle 337, this proton was a triplet, suggesting the D ring is in a twist boat. Tetracycle 338 possesses a doublet of doublets for the C16 proton, suggesting the C5, C7, C10, and C14 stereochemistry represented that of the natural quassinoid family. A detailed two-dimensional NMR study was completed on the TBDPS derivative of tetracycle 338. The main nOe enhancements between the Hα-Hb, and Hc-Hd, and a total lack of enhancement between Hb-Hc, and Hb-Hd confirmed the conclusion 338 has the α stereochemistry at C14 (Figure 21). If tetracycle 338 had possessed the desired stereochemistry at C14, we would have expected to see a clear nOe enhancement between Hb-Hc and Hb-Hd. Based on precedents and the known stereochemistry of 338, we could state with confidence that 337 possesses the correct relative stereochemistry.
Scheme 89 Possible TS for diene-transmissive Diels-Alder reaction
Figure 21 Proposed stereochemistry for tetracycle 338

With the successful procurement of 337, the remaining strategy called for installation of a monoselenoacetal at C13 and a radical precursor suitable for providing the C8 axial methyl group. The small amount of material acquired in the synthesis of 337 required that both these functionalities be provided in an expeditious fashion.

We returned to a simpler model system to investigate a number of new potential strategies for the radical cyclization. The first was based upon Barton esters formed from O-acyl derivatives of thiohydroxamic acids (Scheme 90). 140

![Scheme 90](image)

**Scheme 90** Generation of alkoxy methyl radical from a Barton ester.

From literature accounts, the most effective methods to fabricate Barton esters is through the corresponding acid or acid chloride. 140 To this end, attempts
were made to alkylate, alcohol 224 with $\alpha$-halo ester 341 and $\alpha$-halo acid 342 (Scheme 91). All attempts with the $\alpha$-halo ester resulted in failure. Use of the $\alpha$-halo acid did produce the desired product 344 as an inseparable mixture with 342. The inability to secure 344 pure and time constraints ultimately shelved this strategy.

![Scheme 91 Attempts to fabricate Barton ester precursors](image)

The second novel route was based upon Eschenmoser's salt 350 as an entry to monoselenoacetals. Treatment of alcoholate 351 with Eschenmoser's salt would provide the mixed aminal 352. Quaternization with iodomethane would be provide an excellent leaving group that could be displaced with benzeneselenolate to give the desired monoselenoacetal 354 (Scheme 92).
Accordingly, alcohol 224 was treated with sodium hydride or \textit{n}-butyllithium then quenched with Eschenmoser’s salt, providing the O,N acetal 345 that was never isolated, but rather treated \textit{in situ} with iodomethane. The salt 346 could be isolated in over 75% yield. Treatment of the salt at reflux with lithium benzeneselenolate provided the desired acetal in 63% yield while recovering 17% of the starting alcohol 224 (Scheme 93). The benzeneselenolate was generated from super hydride and diphenyldiselenide in THF.\textsuperscript{141} A similar reaction using K-Selectride and diphenyldiselenide in the presence of 18-crown-6 (needed to solublize the mixture) resulted in 34% yield of 226 while recovering 50% of the starting alcohol 224.
This route proved to be most effective, although unoptimized. It should be noted that generating the selenolate from diphenyldiselenide resulted in only products 226 and 224 with no trace of the O,N-acetal 345. Interestingly heating a solution of 346 to reflux in THF yielded an unknown that spectroscopically resembled 348 (Scheme 94). This compound was stable to flash chromatography, which is somewhat surprising.\textsuperscript{142} Compound 348 failed to cyclize under standard radical cyclization conditions (Ph\textsubscript{3}SnH or Bu\textsubscript{3}SnH, AIBN, benzene reflux), yielding only starting material. However it suggests another route into α-halo ethers which can be transformed into the desired monoselenoacetals or other species.
With an efficient route available for the formation of monoselenoacetics, application to the tetracyclic structures was attempted. Addition of sodium hydride to tetracycle 338 followed by Eschenmoser’s salt and in situ quarternization with iodomethane provided the desired ammonium salt. Displacement with the appropriate selenolates generated the desired monoselenoacetal and other products (Table 16).

**Table 16** Preparation of monoselenoacetics

<table>
<thead>
<tr>
<th>Selenide</th>
<th>Reducing Agent</th>
<th>% yield 361</th>
<th>% yield 362</th>
<th>% yield 363</th>
<th>% yield 338</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhSeSePh</td>
<td>Super hydride</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td>60</td>
</tr>
<tr>
<td>PhSeH</td>
<td>NaH</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>45</td>
</tr>
</tbody>
</table>

361 $R = CH_2SePh, R_1 = Me$
362 $R = CH_2OCH_2SePh, R_1 = Me$
363 $R = H, R_1 = H$
Selenoacetal 361 was isolated in a maximum of only 5% yield in the two cases. The major product in each case was recovered alcohol 338 with a further 10% yield of a product formed from cleavage of the methyl ester. Selenolates are known to cleave methyl ester in a S_N_2 fashion.\textsuperscript{143} Besides the low yield, the second surprise was the formation of what appears to be the benzeneselenomethyl derivative 362. Unequivocal confirmation of this structure could not be made because an exact mass on the parent ion could not be obtained. Clearly though, both the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra indicated an extra methylene and phenyl group. The high yield of recovered starting material might suggest the initial formation of the O,N acetal and the corresponding salt was not complete. However, in the first example, the salt was isolated in 50% yield while only 30% of the starting material 338 was recovered. This result suggests the displacement by the selenolate caused the decomposition of the O,N acetal into starting alcohol 338. Whether this result is caused by the instability of the monoselenoacetal or a different reaction pathway has yet to be determined (Scheme 95).

\textbf{Scheme 95} Possible mechanism for lack of 361 formation
One thing is certain, on the tetracycle, this approach did not yield the desired monoselenoacetals in a synthetically useful yield. Perhaps the presence of the C12 protected alcohol contributed to the demur. To test this hypothesis the small remaining quantity of tetracycle 203 (Scheme 96) was subjected to the same experimental protocol. Under these conditions 19% yield of the desired tetracycle 371 was isolated alongside 24% of the starting tetracycle 203.

![Scheme 96 Installation of monoselenoacetal on the tetracycle](image)

Again, the yield was not fantastic, however, enough material was isolated to attempt the cyclization. The lack of a bulky C12 group could be considered to contribute to the modest improvement in the yield. In this case, none of the benzeneselenomethyl compound corresponding to 363 was isolated.

With a manageable quantity (10mg) of the monoselenoacetal 371 available the final radical cyclization was attempted. Heating the selenide 371 to reflux in the presence of AIBN and (TMS)₃SiH in a dilute solution of benzene afforded a complex mixture of products (Scheme 97).
Scheme 97 Radical cyclization of 371

After separation a mixed fraction (0.5mg) did appear to contain the desired pentacyclic compound 372. Unfortunately, the small quantity and purity of the sample limited the characterization that could be performed. Analysis by GC mass spectra showed the major component did contain the correct mass. A larger scale reaction would have to be attempted in order to determine the ratio of pentacyclic products and fully characterize 372. The remaining products in the reaction mixture appeared to be tetracyclic, however complex $^1$H NMR spectra made characterization difficult.

As noted in previous section (vide supra), the main challenge was the installation of the monoselenoacetal on the tetracycle. One final attempt was made to transform tetracycle 337 into selenoacetal 373 using the Eschenmoser salt methodology (Scheme 98). In this case we opted for a stronger base to form the desired alcohoholate that in turn might give more of the desired O,N acetal. Unfortunately this resulted in complete decomposition.
Scheme 98 Last attempt to form monoselenoacetal 373

With this result, our attention then returned to the bromomethyldimethylsilyl group as a radical precursor. The ease of installation and the possibility of transforming the cyclic siloxane intermediate into either the C8 axial methyl group or the oxomethano bridge added to its appeal (Scheme 99).

Scheme 99 Siloxane route to both oxomethano bridge and axial methyl functionalities.

Accordingly both tetracycles 337 and 338 were transformed into silyl ethers 375 and 376 in 78% and 87% yield respectively (Scheme 100). Subjecting silyl ether 376 to radical cyclization conditions cleanly yielded the TMS silyl ether in quantitative yield.
Scheme 100 Introduction of bromomethylsilyl group.

It can be imagined that the generated radical of 376 can never reach the tetracyclic double bond due to 1,3-diaxial steric interactions between the TMS radical and protons on both the C and D rings (Figure 22). The failure for this compound to undergo a cyclization could be blamed on conformational limitations.

Figure 22 Potential conformation of a radical generated from 376

Despite obtaining only reduced product in the case of 376, confidence for a successful cyclization remained for tetracycle 375. The same steric restrictions would not be present because the generated radical should be able to approach the double bond from over the D-ring. Syringe pump addition of tributyltin hydride and AIBN to a refluxing solution of 375 yielded a mixture of products.
The mixture was immediately treated with TBAF to cleave both the O-Si and C-Si bonds of the cyclic siloxane (Scheme 101). A total of 5 tetracyclic products were visible by \(^1\text{H}\) NMR, three of which could be isolated pure.

![Scheme 101 Radical cyclization of 375](image)

**Scheme 101** Radical cyclization of 375

The major constituent of the mixture in 43% yield was alcohol 337 formed from the cleavage of the TMS ether after simple reduction by the hydride. The two other products (380 and 381) isolated in a sufficiently pure form were both tetracyclic and possessed the same molecular weight as alcohol 337. Each lacked an axial methyl signal by both \(^1\text{H}\) and \(^{13}\text{C}\) NMR and represented 10% and 9% yield respectively. The clear difference in a number of chemical shifts and the lack of the axial methyl group suggests that the double bond had migrated during the radical cyclization. This result can be rationalized by a [1,5]-hydrogen shift to form an allylic radical (Scheme 102). Reduction of the allylic radical at C9 on each face of the molecule would provide 380 and 381.
The remaining two products from the mixture represented a combined yield of 11%. The $^1$H NMR of the mixture does appear to show a singlet representative of an axial methyl group. Until each product can be elucidated this result remains speculation.

The results of this cyclization demand further comment. The majority of product is attributed to simple reduction of the stabilized $\alpha$-silyl radical. The 6-exo-trig (or 7-endo-trig) cyclization is slower than the rate of reduction. In all probability, this can be attributed to the fact that the large TMS group has difficulty approaching the double bond (Figure 23). The two “extra” methyl groups on the silicon greatly increase the size of this group when compared to...

**Scheme 102** [1,5]-Hydrogen shift of the $\alpha$-silyl radical
the small alkoxy methyl radical generated from monoselenoacetals. There are reports of [1,5]-hydrogen transfer reaction being more rapid than both 6-exo-trig transannular\textsuperscript{144} and 5-exo-trig\textsuperscript{145} cyclizations. So perhaps this result should not be surprising considering the generated radical would be a stable allylic radical. These two results suggest the $\alpha$-silyl radical has troubles approaching the double bond without undergoing unwanted reactions.

\textbf{Figure 23} Potential conformation of the 375 generated radical

Unfortunately, this strategy did not produce the axial methyl group in high yield. Significant challenges remain to be overcome if this strategy is to be used in a total synthesis. Installation of monoselenoacetals remains a problem, although potential routes do remain to be investigated. The bromomethylidemethylsilyl route appears to be a dead end on this complex structure.
Conclusion

> A highly effective route to radical polycyclization precursors 82 and 83 was developed. The successful 5-exo-trig cyclization of 82 of an alkoxymethyl radical on a electron rich enol ether double bond provided evidence of an alkoxymethyl radical’s potential utility for the formation of the oxomethano bridge found in some quassinoids. The lack of success of the 10-endo-trig cyclization in the case of 82 indicated either we needed to restrict further the conformation of the alkene tether or activate the double bond for such a cyclization to be successful. Further development is required on this system.

> A potential new route for synthesis of cis and trans furans was discovered based upon a S_N_2’ type displacement of activated allylic alcohols by a hydroxyl group.

> A high yielding S_N_2’ monocyanocuprate reaction was optimized using allylic acetate 112. The optimized conditions were applied to other allylic acetates to provide several adducts which were used in the synthesis of tetracyclic quassinoid intermediates.

> The diene-transmissive Diels-Alder reactions successfully provided tetracyclic quassinoid intermediates. The hetero Diels-Alder reaction proceeded in an endo fashion giving a ratio of epimers at C14 dependent upon the protecting group(s) used on the C13 hydroxyl group. The presence of a protected alcohol at C12 also influenced this ratio at C14. The intramolecular Diels-Alder reaction proceeded via a chair-like endo transition state but was dependent on the stereochemistry at C14. The propensity for this intramolecular Diels-Alder reaction to proceed via the undesired β-face, in the case of the desired C14 epimer, was dependent upon the stereochemistry of the C13 alcohol and the nature of the protecting group used on that alcohol. The presence of a C12 protected alcohol favored attack on the desired α-face.

> Two new routes to monoselenoacetals were developed. One based upon α-bromo ethers formed from the dimethylboron bromide cleavage of MOM
ethers. The second is based on the S\textsubscript{N}2 displacement of a N-quaternized O,N mixed acetals.

> A new cationic cyclization was discovered based upon \(\alpha\)-bromo ethers utilizing triphenyltin hydride as a weak Lewis acid. This interesting result also allows radical cyclizations to be performed from the same \(\alpha\)-bromo ethers.

> The installation of monoselenoacetals was difficult on the tetracycles, probably requiring their introduction at an earlier stage (before the diene-transmissive Diels-Alder reaction). The MOM ether could probably be used as a precursor if the acetal on the D ring had been transformed into a lactone before hand.

> Finally the use of the bromomethyldimethylsilyl group on the C13 alcohol as a radical precursor is not suitable (under the present conditions) as a route to either a C8 axial methyl group or a C13-C8 oxomethanobridge. The 6-exo-trig cyclization fails due to steric encumberance and potentially a 1,5-hydrogen shift.
EXPERIMENTAL

General Remarks

All the reactions were carried out under a neutral atmosphere of nitrogen or argon. The solvents were dried and distilled prior to use. Ethyl ether, toluene, and benzene were dried over metallic sodium using benzophenone as an indicator, while THF was dried over both sodium and potassium using the same indicator. Dichloromethane, carbon tetrachloride, 1,2-dichloroethane, triethylamine, pyridine, acetonitrile, and diisopropylamine were distilled over calcium hydride. Hexanes and DMF were purchased anhydrous from Aldrich and used directly from the bottle, except during reaction in which DMF was the electrophile. In these cases DMF was distilled prior to use over calcium hydride under high vacuum (mechanical pump < 1.0 mmHg). Ethyl vinyl ether was distilled prior to use without a drying agent. Cerium trichloride was purchased in hydrated form and dried at 200°C under high vacuum over night prior to use. All alkyllithium solutions were titrated at -78°C with menthol and THF using 1,10-phenanthroline as the indicator.

The solvents were removed under reduced pressure (water pump) using a Büchi R-114 rotoevaporator, with a bath temperature around 30°C. Thin layer chromatography was performed using 0.25 mm Silica Gel 60 F$_{254}$ (EM Science-Merck) and flash chromatography using silica gel Kieselgel 60 (230-400 mesh ASTM).

All the proton nuclear magnetic resonance ($^1$H NMR) and carbon-13 nuclear magnetic resonance ($^{13}$C NMR) spectra were determined on a Brüker AC-300 ($^1$H: 300 MHz, $^{13}$C: 75 MHz). Deuterated chloroform was the solvent of choice for NMR spectra with a $^1$H reference of 7.26 ppm and $^{13}$C reference of 77.0 ppm. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. The $^1$H splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; and ABQ, AB quartet.

The infrared spectra (IR) were determined on a Perkin-Elmer 1600 Fourier transform spectrometer. The IR spectra were determined neat, unless otherwise stated. The melting points were performed on a Mettler Toledo model 62. High and low resolution Mass spectra (HRMS and LRMS) were obtained with a micromass spectrometer ZAB-1F model VG.
Alcohol 52

![Structure of Alcohol 52]

To a cooled 0°C solution of ketone 51 (22.1 g, 141 mmole) and methanol was added portionwise sodium borohydride (5.35 g, 141 mmole). The reaction was stirred for 3 hours before being brought to a pH 7 from the addition of 1N HCl. The mixture was partitioned between dichloromethane and brine, and the aqueous extracted with CH₂Cl₂ (x3). The aqueous layer was then concentrated until a precipitate began to form and this layer was extracted again with CH₂Cl₂ (x4). The combined organics were dried over MgSO₄, filtered and concentrated. The crude (22.69 g) residue was co-evaporated with benzene and used without further purification.

**Yield:** 100% **¹H NMR** (CDCl₃, 300MHz): δ 3.85 (s, 4H), 3.67-3.66 (m, 1H), 2.67 (bs, 1H), 1.80-1.68 (m, 4H), 1.61-1.43 (m, 4H). **¹³C NMR** (CDCl₃, 75 MHz): δ 108.2 (s), 67.7 (d), 64.0 (t), 31.7 (t), 31.4 (t). **LRMS** (m/z (relative intensity)): 158 (M⁺, 10), 99 (100). **HRMS** calculated for C₈H₁₄O₃: 158.0943 found: 158.0937

Benzyl ether 53

![Structure of Benzyl Ether 53]

To an oil free suspension of KH (10.19 g, 254 mmole) in THF (400 mL) was added a solution of alcohol 52 (16.4 g, 102 mmole) in THF (50 mL) via cannula at 0°C. After hydrogen evolution had ceased the mixture was warmed to room temperature and the reaction stirred for 3 hours further. Benzyl bromide (18.1 mL, 152 mmole) was added neat and the reaction stirred overnight. The reaction was quenched with saturated aqueous NH₄Cl, and the product extracted with CH₂Cl₂ (x4). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. Purification by flash chromatography (9:1 to 3:1 hexanes: ethyl acetate) yielded 20.8 g of ketal 53 as a clear yellow oil.

**Yield:** 83% **¹H NMR** (CDCl₃, 300MHz): δ 7.34-7.26 (m, 5H), 4.53 (s, 2H), 3.94-3.92 (m, 4H), 3.56-3.50 (m, 1H), 1.89-1.79 (m, 6H), 1.58-1.53 (m, 2H). **¹³C NMR** (CDCl₃, 75 MHz): δ 139.0 (s), 128.2 (d), 127.3 (d), 108.4 (s), 74.0 (d), 69.8 (t), 64.2 (t), 31.2 (t), 28.5 (t). **IR** (film, cm⁻¹): 3030, 2949, 2876, 1370, 1103. **LRMS** (m/z (relative intensity)): 248 (M⁺, 5), 99 (100), 86 (98). **HRMS** calculated for C₁₅H₂₀O₃: 248.1412 found: 248.1408.
Ketone 54

A mixture of ketal 53 (10.0 g, 40.3 mmole), THF (290 mL), and 1N HCl (96 mL) was heated to reflux for 5 hours. The mixture was cooled, then neutralized by the addition of saturated aqueous NaHCO₃ and extracted with dichloromethane (x3). The combined organics were washed with brine, dried over MgSO₄, filtered, and concentrated. The product was purified by flash chromatography (5:1 to 3:1 hexanes: ethyl acetate) yielded 7.70 g of ketone 54.

Yield: 94%  

³¹H NMR (CDCl₃, 300MHz): δ 7.37-7.28 (m, 5H), 4.59 (s, 2H), 3.83-3.79 (m, 1H), 2.67-2.56 (m, 2H), 2.30-2.22 (m, 2H), 2.19-2.09 (m, 2H), 2.00-1.89 (m, 2H).  

¹³C NMR (CDCl₃, 75 MHz): δ 211.0 (s), 138.4 (s), 128.3 (d), 127.4 (d), 127.3 (d), 72.1 (d), 70.1 (t), 37.1 (t), 30.3 (t).  

IR (film, cm⁻¹): 3031, 2941, 2886, 1716, 1103.  

LRMS (m/z (relative intensity)): 204 (M⁺, 7), 91 (100).  

HRMS calculated for C₁₃H₁₆O₂: 204.1150 found: 204.1152.

α-Bromoketone 56

To a cooled 0°C solution of ketone 54 (8.34g, 40.8 mmole) aluminum trichloride (82 mg, 0.61 mmole) and ethyl ether (120 mL) was added bromine (2.3 mL, 44.9 mmole) dropwise. The mixture was stirred at 0°C for 1 hour before gradually warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NaHCO₃. The layers were separated and the aqueous extracted with ethyl ether (x3). Crude bromoketone 56 was procured after treatment with MgSO₄, filtration and concentration. Purification by flash chromatography (10:1 to 3:1 hexanes: ethyl acetate) gave 8.24 g of bromoketone 56 as a clear yellow oil and 2.09 g of starting material 54 (25%).

Yield: 71%  

³¹H NMR (CDCl₃, 300MHz): δ 7.40-7.31 (m, 5H), 4.82 (dd, J= 10.1, 5.5 Hz, 1H), 4.62 (s, 2H), 3.99-3.94 (m, 1H), 2.79-2.67 (m, 2H), 2.39-2.29 (m, 1H), 2.24-2.14 (m, 1H), 2.05-1.97 (m, 1H).  

¹³C NMR (CDCl₃, 75 MHz): δ 201.5 (s), 137.8 (s), 128.4 (d), 127.6 (d), 127.3 (d), 72.3 (d), 70.4 (t), 51.3 (d), 42.2 (t), 35.1 (t), 30.6 (t).  

IR (film, cm⁻¹): 3031, 2947, 2870, 1726, 1454, 1095.  

LRMS (m/z (relative intensity)): 202 (M⁺-HBr, 28), 91 (100).  

HRMS calculated for C₁₃H₁₅O₂Br: 282.0255 found: 282.0251.
Enone 57.

\[ \text{O} \quad \text{O} \quad \text{Bn} \]

A mixture of bromoketone 56 (6.31 g, 22.3 mmole), DBU (4.0 mL, 26.7 mmole) and benzene (160 mL) was heated to reflux for 1.5 hours, before being filtered. The filtrate was brought to a pH of 7 with the addition of 1N HCl. The aqueous layer was extracted with ethyl ether (x3), and the combined organics dried over MgSO\(_4\), filtered and concentrated. Flash chromatography eluenting with a 6:1 to 3:1 mixture of hexanes:ethyl acetate yielded 3.18 g of ketone 57.

Yield: 70 % ¹H NMR (CDCl\(_3\), 300MHz): \( \delta \) 7.38 (m, 5H), 7.00-6.96 (m, J= 10.4 Hz, 1H), 5.99 (dt, J= 10.6, 1.2 Hz, 1H), 4.29-4.23 (m, 1H), 2.65-2.56 (m, 1H), 2.39-2.27 (m, 2H), 2.11-1.98 (m, 1H). ¹³C NMR (CDCl\(_3\), 75 MHz): \( \delta \) 198.6 (s), 150.4 (d), 137.7 (s), 129.6 (d), 128.4 (d), 127.8 (d), 127.6 (d), 127.3 (d), 72.4 (d), 70.9 (t), 35.2 (t), 29.1 (t). IR (film, cm\(^{-1}\)): 3031, 2954, 2870, 1693, 1454, 1201, 1093. LRMS (m/z (relative intensity)): 203 (MH\(^+\), 48), 220 (MNH\(_4^+\), 38), 91 (100). HRMS calculated for C\(_{13}\)H\(_{15}\)O\(_2\) (MH\(^+\)): 203.1072 found: 203.1077

Vinyl bromide 58

\[ \text{O} \quad \text{O} \quad \text{Bn} \quad \text{Br} \]

To a solution of ketone 57 (6.64 g, 32.8 mmole) in carbon tetrachloride (60mL) was added over 1 hour a solution of bromide (5.25 g, 32.8 mmole) in carbon tetrachloride (60 mL) at 0°C. Once complete the mixture was stirred for 45 minutes further at 0°C before a solution of triethylamine (5.64 g, 55.7 mmole) in carbon tetrachloride (30 mL) was added over 20 minutes. The reaction mixture was stirred for 20 minutes and filtered. The filtrate was washed with 1N HCl and saturated aqueous NaHCO\(_3\). The aqueous layers were extracted with ether and combined organics then dried over MgSO\(_4\), filtered and concentrated. Purification by flash chromatography using a 6:1 mixture of hexanes: ethyl acetate gave 7.23 g of bromoketone 58.

Yield: 78 % ¹H NMR (CDCl\(_3\), 300MHz): \( \delta \) 7.45 (dd, J= 13.0, 1.2 Hz, 1H), 7.39-7.32 (m, 5H), 4.64 (s, 2H), 4.29-4.24 (m, 1H), 2.84 (ddd, J= 16.8, 5.6, 4.5 Hz, 1H), 2.53-2.32 (m, 2H), 2.18-2.08 (m, 1H). ¹³C NMR (CDCl\(_3\), 75 MHz): \( \delta \) 190.4 (s), 150.5 (d), 137.2 (s), 128.5 (d), 128.0 (d), 127.7 (d), 125.0 (s), 73.6 (d), 71.1 (t), 34.7 (t), 29.0 (t). IR (film, cm\(^{-1}\)): 3066, 2959, 2871, 1703, 1454, 1317, 1096.
**LRMS** (m/z (relative intensity)): 280 (M⁺, 5), 282 (M⁺, 5), 201 (M⁺-Br, 40), 175 (100). **HRMS** calculated for C₁₃H₁₃BrO₂: 280.0099 found: 280.0107.

**Alcohols 59.**

![Alcohol Structure](image)

To a cooled 0°C solution of tetravinyltin (701 mg, 3.09 mmole) in THF (40 mL) was added [1.56M] n-butyllithium (7.21 mL, 11.2 mmole). After 30 minutes at 0°C the ice bath was removed and the mixture stirred for 1 hour further. This solution was then added via cannula to a cooled -78°C suspension of CeCl₃ (6.32 g, 16.9 mmole) and ketone 58 (1.58 g, 5.62 mmole) in THF (80 mL). The reaction mixture was stirred for 2 hours at -78°C before being quenched with saturated aqueous NH₄Cl. The layers were separated (a portion of 1 N HCl was added for clarification) and the aqueous layer extracted with ethyl ether (x4). The organics were then washed (brine), dried over MgSO₄, filtered and concentrated. Flash chromatography eluenting with 6:1 mixture of hexanes:ethyl acetate gave 1.41 g of alcohols 59 as a 1:1 mixture of two diastereomers.

**Yield:** 81% less polar isomer

**¹H NMR** (CDCl₃, 300MHz): δ 7.36-7.27 (m, 5H), 6.38 (d, J= 3.6 Hz, 1H), 5.80 (dd, J= 17.3, 10.6 Hz, 1H), 5.33 (dd, J= 17.1, 0.7 Hz, 1H), 5.24 (dd, J= 10.6, 0.7 Hz, 1H), 4.58 (ABQ, J= 13.6 Hz, 2H), 3.95-3.90 (m, 1H), 2.30 (bs, 1H), 2.20-2.12 (m, 1H), 1.97-1.79 (m, 3H). **¹³C NMR** (CDCl₃, 75 MHz): δ 141.0 (d), 138.0 (s), 132.7 (d), 132.6 (s), 128.3 (d), 127.5 (d), 114.9 (t), 74.2 (s), 73.1 (d), 70.4 (t), 33.2 (t), 24.7 (t). More polar isomer

**¹H NMR** (CDCl₃, 300MHz): δ 7.36-7.29 (m, 5H), 6.36 (d, J= 3.1 Hz, 1H), 5.90 (dd, J= 17.2, 10.7 Hz, 1H), 5.36 (d, J= 17.2 Hz, 1H), 5.27 (d, J= 10.7 Hz, 1H), 4.57 (s, 2H), 4.06-4.02 (m, 1H), 2.35 (s, 1H), 2.16-2.04 (m, 2H), 1.91-1.73 (m, 2H). **¹³C NMR** (CDCl₃, 75 MHz): δ 140.9 (d), 137.9 (s), 133.2 (d), 132.8 (s), 128.4 (d), 127.7 (d), 115.7 (t), 74.7 (s), 74.3 (d), 70.5 (t), 34.1 (t), 25.7 (t). **IR** (film, cm⁻¹): 3571, 3030, 2949, 2863, 1453, 1089. **LRMS** (m/z (relative intensity)): 229 (M⁺-Br, 50), 91 (100). **HRMS** calculated for C₁₅H₁₇O₂Br: 308.0412 found: 308.0405.
Acetates 61.

To a stirred solution of alcohol 59 (1.89 g, 5.39 mmole) and dichloromethane (20 mL) was added acetic anhydride (1.02 mL, 10.8 mmole), triethylamine (2.26 mL, 16.2 mmole) and DMAP (132 mg, 1.08 mmole) at room temperature. The mixture was stirred at room temperature for 3 days gradually becoming deep reddish-brown. The mixture was washed with 1 N HCl, and saturated aqueous NaHCO₃. The aqueous layer were then extracted with ethyl ether (x3), the combined organics dried over MgSO₄, filtered and concentrated. Purification by flash chromatography using a 8:1 to 4:1 hexanes:ethyl acetate mixture yielded 2.29 g of acetates 61 as a pale yellow oil.

Yield: 83 % less polar isomer ¹H NMR (CDCl₃, 300MHz): δ 7.36-7.28 (m, 5H), 6.45 (d, J= 4.5 Hz, 1H), 5.95 (dd, J= 10.8, 17.3 Hz, 1H), 5.30 (d, J= 10.8 Hz, 1H), 5.28 (d, J= 17.5 Hz, 1H), 4.59 (s, 2H), 3.88 (q, J= 4.3 Hz, 1H), 2.93-2.83 (m, 1H), 2.09 (s, 3H), 2.07-1.81 (m, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 169.1 (s), 138.3 (s), 136.3 (d), 132.9 (d), 128.4 (d), 127.7 (d), 116.4 (t), 82.4 (s), 71.4 (d), 70.4 (t), 28.5 (t), 24.9 (t), 22.0 (q). more polar isomer ¹H NMR (CDCl₃, 300MHz): δ 7.36-7.30 (m, 5H), 6.45 (d, J= 3.5, 2.3 Hz, 1H), 5.90 (dd, J= 17.3, 10.7 Hz, 1H), 5.38 (d, J= 17.2 Hz, 1H), 5.33 (d, J= 10.7 Hz, 1H), 4.58 (ABQ, J= 22.1 Hz, 2H), 4.17 (dd, J= 2.3, 5.4, 9.8 Hz, 1H), 2.63 (m, J= 3.2, 12.9 Hz, 1H), 2.14-2.03 (m, 2H), 2.09 (s, 3H), 1.80-1.68 (m, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 168.9 (s), 137.8 (s), 136.6 (d), 135.0 (d), 128.3 (d), 127.5 (d), 116.7 (t), 82.2 (s), 74.5 (d), 70.3 (t), 30.5 (t), 26.5 (t), 21.9 (q). IR (film, cm⁻¹): 3030, 2937, 2870, 1745, 1366, 1236, 1094, 1068. LRMS (m/z (relative intensity)): 368 (MNH₄⁺, 25), 308 (MNH₄⁺-AcOH, 25), 291 (M⁺-AcOH, 25), 211 (100). HRMS calculated for C₁₇H₂₃NO₃Br (MNH₄⁺): 368.0861 found: 368.0857.

Bromide 63

To a suspension of Mg (319 mg, 13.1 mmole) in ethyl ether (20 mL) was added 1-bromo-5-propene (1.82 g, 12.2 mmole) dropwise, resulting in a refluxing mixture. The reaction was kept at reflux for 4 hours, until all the magnesium was
consumed. The Grignard reagent was cooled and added via cannula to a suspension of copper (1) iodide (868 mg, 4.56 mmole) in ethyl ether (32 mL) at 0°C. After 15 minutes at 0°C a solution of acetate 61 (800 mg, 2.28 mmole) in ethyl ether (8 mL) was added via cannula. The resulting mixture was stirred for 1 hour at 0°C then quenched by the addition of saturated aqueous NH₄Cl. The product was extracted with ethyl ether (x3), dried over MgSO₄, filtered, and concentrated. The crude residue was purified by flash chromatography (9:1 hexanes: ethyl acetate) to provide 737 mg of 63 as a slightly yellow coloured liquid.

**Yield: 89 %**  
**¹H NMR** (CDCl₃, 300MHz): δ 7.36-7.27 (m, 5H), 6.32 (d, J=3.8 Hz, 1H), 5.98 (t, J= 7.5 Hz, 1H), 5.80 (ddt, J= 17.0, 10.2, 6.7 Hz, 1H), 5.04-4.92 (m, 2H), 4.59 (s, 2H), 4.10-4.06 (m, 1H), 2.65-2.60 (m, 1H), 2.37-2.28 (m, 1H), 2.19-1.91 (m, 5H), 1.87-1.77 (m, 1H), 1.47-1.38 (m, 4H).  
**¹³C NMR** (CDCl₃, 75 MHz): δ 138.7 (d), 138.3 (s), 133.2 (d), 131.5 (s), 130.6 (d), 128.3 (d), 127.6 (d), 114.4 (t), 73.9 (d), 70.2 (t), 33.5 (t), 28.6 (t), 28.0 (t), 27.8 (t), 23.0 (t).

**Aldehyde 64**

![Chemical Structure of Aldehyde 64](attachment:image.png)

To a cooled -78°C solution of vinylbromide 63 (507 mg, 1.40 mmole) in THF (13 mL) was added [1.56M] n-butyllithium (1.80 mL, 2.80 mmole). After 30 minutes DMF (800 µL, 10.3 mmole) was added at -78°C and the reaction stirred for 5 hour further before being quenched with saturated aqueous NH₄Cl. The layers were separated and the product extracted with ethyl ether (x3). The combined organics were dried over MgSO₄, filtered and concentrated. The crude aldehyde was purified by flash chromatography (15:1 hexanes:ethyl acetate) to provide 320 mg of aldehyde 64 as a faintly yellow coloured oil.

**Yield: 74 %**  
**¹H NMR** (CDCl₃, 300MHz): δ 9.56 (s, 1H), 7.38-7.30 (m, 5H), 6.69 (t, J= 7.5 Hz, 1H), 6.55 (d, J= 2.9 Hz, 1H), 5.80 (ddt, J= 17.0, 10.2, 6.7 Hz, 1H), 5.02-4.92 (m, 2H), 4.67 (ABQ, J= 18.4 Hz, 2H), 4.28-4.26 (m, 1H), 2.62 (m, 1H), 2.19-2.04 (m, 6H), 1.75-1.68 (m, 1H), 1.45-1.39 (m, 4H).  
**¹³C NMR** (CDCl₃, 75 MHz): δ 193.7 (d), 148.6 (d), 138.7 (d), 137.9 (s), 131.7 (d), 128.4 (d), 127.7 (s), 127.6 (d), 114.2 (t), 73.3 (d), 70.6 (t), 33.5 (t), 28.5 (t), 27.9 (t), 27.7 (t), 22.8 (t).
Diels-Alder adducts 65 and 66.

To a stirred solution of aldehyde 64 (307 mg, 0.990 mmole) and ethyl vinyl ether (4.6 mL) was added Yb(fod)$_3$ (127 mg, 0.120 mmole) at room temperature. The reaction mixture was stirred for 1 day before a solution of brine was added. This mixture was stirred for about 1 hour then separated and the product extracted with ethyl ether (x3), dried over MgSO$_4$, filtered and concentrated. The crude mixture was purified by flash chromatography (15:1 mixture of hexanes: ethyl acetate) to provide 308 mg of cycloadducts as an approximate 1:1 mixture of inseparable diastereomers.

**Yield:** 81% mixture of two isomers

**$^1$H NMR** (CDCl$_3$, 300MHz): $\delta$ 7.35-7.24 (m, 5H), isomer 6.44 (d, J= 2.1 Hz, 1H), 1 isomer 6.39 (d, J= 1.9 Hz, 1H), 5.80 (ddt, J= 17.0, 10.3, 6.6 Hz, 1H), 5.34-5.26 (m, 1H), 5.03-4.91 (m, 2H), 4.85-4.81 (m, 1H), 1 isomer 4.67 (d, J= 11.4 Hz, 1H), 1 isomer 4.64 (d, J= 12.1 Hz, 1H), 1 isomer 4.47 (d, J= 11.4 Hz, 1H), 1 isomer 4.42 (d, J= 12.2 Hz, 1H), 4.01-3.91 (m, 1H), 1 isomer 3.64-3.61 (m, 1H), 3.61-3.53 (m, 1H), 1 isomer 3.20-3.12 (m, 1H), 1 isomer 2.64 (dt, J= 14.3, 3.5 Hz, 1H), 2.54-1.94 (m, 7H), 1.83-1.74 (m, 1H), 1.63-1.52 (m, 1H), 1.44-1.29 (m, 5H), 1.26 (t, J= 7.1 Hz, 3H). Mixture of two isomers

**$^{13}$C NMR** (CDCl$_3$, 75 MHz): $\delta$ 138.9 (d), 138.6 (s), 136.7 (d), 136.4 (d), 134.3 (s), 133.9 (s), 128.4 (d), 128.2 (d), 127.8 (d), 127.6 (d), 127.3 (d), 122.3 (d), 121.5 (d), 116.8 (s), 116.2 (s), 114.2 (s), 100.1 (d), 99.9 (d), 82.5 (d), 74.1 (d), 73.7 (d), 71.0 (t), 70.5 (t), 64.5 (t), 64.4 (t), 39.9 (d), 38.8 (d), 33.7 (t), 33.5 (t), 30.9 (t), 30.1 (t), 29.4 (t), 28.5 (t), 27.7 (t), 27.6 (t), 27.4 (t), 25.4 (t), 21.3 (t), 15.2 (q)

**Alcohol 68:**

To a solution of pyridine (1.76 mL, 21.8 mmole) and acetonitrile (5 mL) was added 48% aqueous HF (634 µL, 17.5 mmole) at room temperature. This mixture
was stirred for 30 minutes before a solution of silyl ether 77 (981 mg, 2.14 mmole) in acetonitrile (10 mL) was added. The reaction was stirred at room temperature overnight. The following day water was added and the product extracted with ethyl ether (x3). The combined organics were dried over MgSO₄, filtered, and concentrated. Flash chromatography using a 3:1 to 1:1 hexanes:ethyl acetate mixture yielded 440 mg of alcohol 68 as a clear pale yellow coloured oil.

**Yield: 93%**

**¹H NMR (CDCl₃, 300MHz):** δ 9.50 (s, 1H), 6.63 (t, J= 7.4 Hz, 1H), 6.45 (d, J= 2.9 Hz, 1H), 5.75 (ddt, J= 17.0, 10.3, 6.7 Hz, 1H), 4.99-4.88 (m, 2H), 4.53-4.48 (m, 1H), 2.99 (bs, 1H), 2.57 (dt, J= 15.4, 4.9 Hz, 1H), 2.21-1.98 (m, 6H), 1.63-1.51 (m, 1H), 1.44-1.34 (m, 4H).

**¹³C NMR (CDCl₃, 75 MHz):** δ 194.0 (d), 150.7 (d), 138.7 (d), 137.4 (s), 131.8 (d), 127.6 (s), 114.3 (t), 66.8 (d), 33.5 (t), 31.0 (t), 28.5 (t), 27.9 (t), 22.8 (t).

**IR (film, cm⁻¹):** 3413, 2924, 2853, 1695, 1436, 1039, 910.

**LRMS (m/z (relative intensity)):** 220 (M⁺, 8), 41 (100), 55 (58), 91 (53), 109 (50).

**HRMS calculated for C₁₄H₂₀O₂:** 220.1463 found: 220.1465

**Ketal 69:**

![Ketal 69](image)

To a solution of alcohol 52 (5.00 g, 31.6 mmole), imidazole (5.38 g, 79.0 mmole) in DMF (20mL) was added TBDPSCI (9.86 mL, 37.9 mmole) at room temperature. The mixture was stirred at room temperature for 4 hours before being poured into hexane (30mL). The layers were separated and the DMF layer washed with hexanes (2x30mL) and ethyl ether (30mL). The combined hexanes-ethyl ether was washed with brine, dried over MgSO₄, filtered and concentrated. The crude residue was purified by flash chromatography eluting with 9:1 hexanes:ethyl acetate to give 12.5g of ketal 69 as a pale yellow oil.

**Yield: 100%**

**¹H NMR (CDCl₃, 300MHz):** δ 7.73-7.65 (m, 4H), 7.45-7.34 (m, 6H), 3.98-3.85 (m, 5H), 1.97-1.88 (m, 2H), 1.71-1.63 (m, 4H), 1.51-1.43 (m, 2H), 1.06 (s, 9H).

**¹³C NMR (CDCl₃, 75 MHz):** δ 135.7 (d), 134.8 (d), 134.5 (s), 129.5 (d), 127.6 (d), 127.4 (d), 108.6 (s), 68.4 (d), 64.1 (t), 31.7 (t), 30.8 (t), 26.9 (q), 19.2 (s).

**IR (film, cm⁻¹):** 3446, 3070, 2955, 2856, 2346, 1959, 1890, 1824, 1589, 1472, 1427, 1376, 1234, 1104, 1036, 703.

**LRMS (m/z (relative intensity)):** 339 (M⁺ - C₄H₉, 10), 199 (100), 200 (25).

**HRMS calculated for C₂₀H₂₃O₃Si (M⁺ - C₄H₉):** 339.1416 found: 339.1412
Ketone 70:

A mixture of ketal 69 (12.5g, 31.6 mmole), THF (226mL), and 1N HCl (75mL) was heated to reflux for 3 hours. The mixture was cooled, then neutralized by the addition of saturated aqueous NaHCO₃ and extracted with dichloromethane (x3). The combined organics were washed with brine, dried over MgSO₄, filtered, and concentrated. The product was crystallized from the addition of petroleum ether. Three crystallizations yielded 10.8 g of ketone 70 as a white solid.

Yield: 97% ¹H NMR (CDCl₃, 300MHz): δ 7.69-7.67 (m, 4H), 7.45-7.36 (m, 6H), 4.16-4.13 (m, J= 2.6Hz, 1H), 2.79-2.69 (m, 2H), 2.25-2.17 (dt, J= 14.4, 5.3 Hz, 2H), 1.99-1.93 (m, 2H), 1.83-1.78 (m, 2H), 1.09 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz): δ 211.5 (s), 135.6 (d), 133.8 (s), 129.7 (d), 127.6 (d), 66.9 (d), 36.9 (t), 33.7 (t), 26.9 (q), 19.2 (s). IR (film, cm⁻¹): 3069, 2954, 2857, 1716, 1427, 1108, 1043 703. LRMS (m/z (relative intensity)): 295 (M⁺ - C₄H₉, 92), 199 (100). HRMS calculated for C₁₈H₁₉O₂Si (M⁺ - C₄H₉): 295.1154 found: 295.1151. Melting point: 106.0°C

α,β-Unsaturated ketone 71 (from ketone 70):

To a solution of ketone 70 (10.59g, 30.0 mmole), PhSO₂Me (4.70g, 30.0 mmole) in THF (70mL) was added oil free suspension of KH (3.01g, 75.2 mmole) in THF (60mL) via cannula at room temperature. The mixture was stirred at room temperature for 30 minutes before being concentrated to dryness. The residue was partitioned between dichloromethane (100mL) and 0.5M H₃PO₄ (50mL). The layers were then separated and the aqueous extracted with dichloromethane (2x70mL). The combined organics were then dried over MgSO₄, filtered, and concentrated. The crude residue was taken up in toluene (300mL) and Na₂CO₃ (15.9g, 150 mmole) was added. The suspension was heated to reflux for 30 minutes, cooled, filtered through celite and concentrated. Purification by flash chromatography using 20:1 to 9:1 hexanes:ethyl acetate gave 9.80g (93%) of ketone 71 as a yellow liquid.

Yield: 93% ¹H NMR (CDCl₃, 300MHz): δ 7.72-7.67 (m, 4H), 7.48-7.38 (m, 6H), 6.78 (dd, J= 10.2, 2.5 Hz, 1H), 5.86 (d, J= 10.2 Hz, 1H), 4.52-4.47 (m, 1H), 2.52 (dt, J= 16.4, 4.5 Hz, 1H), 2.25-2.17 (m, 1H), 2.15-2.03 (m, 2H), 1.08 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz): δ 198.8 (s), 153.1 (d), 135.7 (d), 133.3 (s), 129.9 (d), 127.6 (d), 66.9 (d), 36.9 (t), 33.7 (t), 26.9 (q), 19.2 (s).
129.5 (d), 128.7 (d), 127.7 (d), 67.5 (d), 35.2 (t), 32.5 (t), 26.8 (q), 19.0 (s). \textbf{IR} (film, cm\textsuperscript{-1}): 3446, 3056, 2953, 2861, 2359, 1959, 1891, 1824, 1684, 1472, 1420, 1378, 1104. \textbf{LRMS} (m/z (relative intensity)): 293 (M\textsuperscript{+} - C\textsubscript{4}H\textsubscript{9}, 65), 199 (100). \textbf{HRMS} calculated for C\textsubscript{18}H\textsubscript{17}O\textsubscript{2}Si (M\textsuperscript{+} - C\textsubscript{4}H\textsubscript{9}): 293.0998 found: 293.0996

**Bromoketone 72 and dibromoketone 73:**

![Chemical structure]

To a solution of ketone 72 (19.0 g, 54.3 mmole) in carbon tetrachloride (500 mL) was added over 1 hour a solution of bromine (8.25 g, 51.6 mmole) in carbon tetrachloride (100 mL) at 0°C. Once complete the mixture was stirred for 45 minutes further at 0°C before a solution of triethylamine (9.89 g, 97.8 mmole) in carbon tetrachloride (100 mL) was added over 20 minutes. The reaction mixture was stirred for 20 minutes and filtered. The filtrate was washed with 1N HCl and saturated aqueous NaHCO\textsubscript{3}. The aqueous layers were extracted with ether and combined organics then dried over MgSO\textsubscript{4}, filtered and concentrated. Purification by flash chromatography using a 20:1 to 8:1 mixture of hexanes: ethyl acetate gave 21.0 g of bromoketone 72 as a white solid, and trace amounts of dibromoketone 73. **Yield:** 90\% \textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 300MHz): \(\delta\) 7.68-7.65 (m, 4H), 7.48-7.38 (m, 6H), 7.20 (d, J= 3.1 Hz , 1H), 4.48 (dt, J= 6.4, 3.1 Hz, 1H), 2.76 (dt, J= 16.7, 5.0 Hz, 1H), 2.33 (dt, J= 16.4, 8.2 Hz, 1H), 2.13-2.06 (m, 2H), 1.08 (s, 9H). \textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 75 MHz): \(\delta\) 190.6 (s), 153.1 (d), 135.7 (d), 132.9 (s), 130.2 (d), 127.9 (d), 124.1 (s), 68.8 (d), 34.7 (t), 32.4 (t), 26.8 (q), 19.1 (s). \textbf{IR} (film, cm\textsuperscript{-1}): 3060, 2955, 2857, 1699, 1427, 1106, 703. \textbf{LRMS} (m/z (relative intensity)): 373 (M\textsuperscript{+} - C\textsubscript{4}H\textsubscript{9}, 50), 371 (M\textsuperscript{+} - C\textsubscript{4}H\textsubscript{9}, 48), 199 (100), 213 (45). \textbf{HRMS} calculated for C\textsubscript{18}H\textsubscript{16}BrO\textsubscript{2}Si (M\textsuperscript{+} - C\textsubscript{4}H\textsubscript{9}): 371.0103 found: 371.0098. **Melting Point:** 78.2 °C. **Dibromoketone 73:** \textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 300MHz): \(\delta\) 7.69-7.67 (m, 4H), 7.50-7.40 (m, 6H), 7.30 (bs, 1H), 4.78-4.73 (m, 1H), 4.56 (t, J= 4.0 Hz, 1H), 2.46-2.38 (m, 2H), 1.11 (s, 9H). \textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 75 MHz): \(\delta\) 183.6 (s), 153.7 (d), 135.6 (d), 132.6 (s), 130.2 (d), 127.9 (d), 67.7 (d), 44.2 (d), 40.9 (t), 26.8 (q), 19.0 (s). \textbf{IR} (film, cm\textsuperscript{-1}): 3384, 3066, 2943, 2851,1964, 1892, 1820, 1702, 1594, 1466, 1425, 1353, 1312, 1179, 1107. \textbf{LRMS} (m/z (relative intensity)): 451 (M\textsuperscript{+} - C\textsubscript{4}H\textsubscript{9}, 28), 199 (100), 290 (80). \textbf{HRMS} calculated for C\textsubscript{18}H\textsubscript{15}O\textsubscript{2}SiBr\textsubscript{2} (M\textsuperscript{+} - C\textsubscript{4}H\textsubscript{9}): 448.9208 found: 448.9202

**Bromoketone 72 (from dibromoketone 73):**

A mixture of dibromoketone 73 (1.90 g, 3.75 mmole), sodium iodide (2.26 g, 15.1 mmole), tin dichloride (2.26 g, 11.9 mmole), water (6 mL) and THF (30 mL) was stirred to solution and brought to reflux. Before 1 hour had passed tlc indicated
reaction completion. The mixture was cooled and brine was added. After extraction with ethyl ether (x3), drying over MgSO$_4$, filtration and concentration the crude product was passed through a short plug of SiO$_2$ (9:1 hexanes: ethyl acetate) to give 1.50g (93%) of bromoketone.

**Allylic alcohol 74:**

![Image of allylic alcohol 74]

To a cooled 0°C solution of tetravinyltin (320mg, 1.41 mmole) in THF (20mL) was added [1.08M] $n$-butyllithium (4.73mL, 5.11 mmole). After 30 minutes at 0°C the ice bath was removed and the mixture stirred for 1 hour further. This solution was then added via cannula to a cooled -78°C suspension of CeCl$_3$ (2.86g, 7.67 mmole) and ketone 72 (1.10g, 2.55 mmole) in THF (40mL). The reaction mixture was stirred for 4 hours at -78°C before being quenched with saturated aqueous NH$_4$Cl. The layers were separated (a portion of 1 N HCl was added for clarification) and the aqueous layer extracted with ethyl ether (x4). The organics were then washed (brine), dried over MgSO$_4$, filtered and concentrated. Flash chromatography eluenting with 9:1 mixture of hexanes:ethyl acetate gave 447mg of a less polar alcohol and 646mg of a more polar alcohol.

**Yield:** 93% **Less polar isomer** $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.73-7.65 (m, 4H), 7.46-7.35 (m, 6H), 6.12 (d, J= 3.6 Hz, 1H), 5.72 (dd, J= 17.1, 10.6 Hz, 1H), 5.26 (d, J= 17.1 Hz, 1H), 5.17 (d, J= 10.6 Hz, 1H), 4.15 (q, 1H), 2.18-2.10 (m, 1H), 1.83-1.67 (m, 2H), 1.06 (s, 9H). **$^{13}$C NMR** (CDCl$_3$, 75 MHz): $\delta$ 141.2 (d), 135.7 (d), 135.4 (d), 133.7 (s), 131.1 (s), 129.7 (d), 127.6 (d), 114.9 (t), 74.1 (s), 68.3 (d), 33.0 (t), 28.2 (t), 26.9 (q), 19.1 (s). **More polar isomer** $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.72-7.64 (m, 4H), 7.47-7.35 (m, 6H), 6.10 (d, J= 3.1 Hz, 1H), 5.88 (dd, J= 17.3, 10.6 Hz, 1H), 5.35 (d, J= 17.2 Hz, 1H), 5.27 (d, J= 10.6 Hz, 1H), 4.29-4.23 (m, 1H), 2.07-2.01 (m, 1H), 1.87-1.80 (m, 1H), 1.77-1.70 (m, 2H), 1.06 (s, 9H). **$^{13}$C NMR** (CDCl$_3$, 75 MHz): $\delta$ 141.0 (d), 135.9 (d), 135.7 (d), 133.7 (s), 129.8 (d), 127.6 (d), 115.3 (t), 74.4 (s), 69.1 (d), 34.1 (t), 29.0 (t), 26.8 (q), 19.1 (s). **IR** (film, cm$^{-1}$): 3548, 3435, 3066, 2953, 2861, 1630, 1589, 1471, 1425, 1364, 1323, 1076. **LRMS** (m/z (relative intensity)): 399 (M$^+$ - C$_3$H$_9$, 5), 199 (100), 200 (41). **HRMS** calculated for C$_{20}$H$_{20}$O$_2$SiBr (M$^+$ - C$_4$H$_9$): 399.0416 found: 399.0424
Allylic acetate 75:

\[
\text{AcO} \quad \text{OTBDPS} \quad \begin{array}{c}
\text{Br} \\
\end{array}
\]

To a stirred solution of alcohol 74 (1.86g, 4.07 mmole) and dichloromethane (8mL) was added acetic anhydride (767 µl, 8.14 mmole), triethylamine (1.70mL, 12.2 mmole) and DMAP (99.4mg, 0.81 mmole) at room temperature. The mixture was stirred at room temperature for 4 days gradually becoming deep red-dark brown. The mixture was washed with 1 N HCl, and saturated aqueous NaHCO\textsubscript{3}. The aqueous layer was then extracted with ethyl ether (x3), the combined organics dried over MgSO\textsubscript{4}, filtered and concentrated. Purification by flash chromatography using a 15:1 hexanes:ethyl acetate mixture yielded 1.85g of acetate as a pale yellow oil.

**Yield:** 91%  
**Less polar acetate**  
\[\text{\textsuperscript{1}H NMR (CDCl}_3, 300MHz):} \]  
\[\delta \] 7.72-7.65 (m, 4H), 7.46-7.35 (m, 6H), 6.10 (d, J= 4.5 Hz, 1H), 5.87 (dd, J= 10.8, 17.4 Hz, 1H), 5.23 (d, J= 10.8 Hz, 1H), 5.17 (d, J= 17.4 Hz, 1H), 4.10 (q, J= 4.3 Hz, 1H), 3.00 (dt, J= 11.7, 3.2 Hz, 1H), 2.12 (s, 3H), 1.97-1.89 (m, 1H), 1.82-1.62 (m, 2H), 1.07 (s, 9H).  
\[\text{\textsuperscript{13}C NMR (CDCl}_3, 75 MHz):} \]  
\[\delta \] 168.9 (s), 136.4 (d), 135.8 (d), 135.7 (d), 135.2 (d), 133.7 (s), 129.7 (d), 127.6 (d), 116.3 (t), 82.3 (s), 66.7 (d), 28.2 (t), 28.0 (t), 26.8 (q), 22.0 (q), 19.1 (s).  

**More polar acetate**  
\[\text{\textsuperscript{1}H NMR (CDCl}_3, 300MHz):} \]  
\[\delta \] 7.69-7.63 (m, 4H), 7.45-7.34 (m, 6H), 6.25 (d, J= 2.5 Hz, 1H), 5.88 (dd, J= 17.3, 10.7 Hz, 1H), 5.37 (d, J= 16.8 Hz, 1H), 5.33 (d, J= 10.4 Hz, 1H), 4.42-4.38 (m, 1H), 2.43 (dt, J= 13.2, 3.8 Hz, 1H), 2.03 (s, 3H), 2.00-1.92 (m, 1H), 1.81-1.69 (m, 2H), 1.05 (s, 9H).  
\[\text{\textsuperscript{13}C NMR (CDCl}_3, 75 MHz):} \]  
\[\delta \] 169.1 (s), 137.9 (d), 136.7 (d), 135.7 (d), 133.4 (s), 129.8 (d), 127.7 (d), 127.6 (d), 124.4 (s), 116.6 (t), 82.4 (s), 69.5 (d), 30.6 (t), 29.8 (t), 26.8 (q), 21.9 (q), 19.1 (s).  
\[\text{IR (film, cm}^{-1}): \] 3056, 2943, 2851, 1743, 1635, 1471, 1425, 1364, 1235, 1087, 984.  
\[\text{LRMS (m/z (relative intensity)):} \] 441 (M+ - C\textsubscript{4}H\textsubscript{9}, 18), 443 (M+ - C\textsubscript{4}H\textsubscript{9}, 16), 241 (100), 199 (70).  
\[\text{HRMS calculated for C\textsubscript{22}H\textsubscript{22}O\textsubscript{3}BrSi (M+ - C\textsubscript{4}H\textsubscript{9}):} \] 441.0521 found: 441.0529

Allylic acetate 75 (from ketone 72): The acetate could be acquired directly from the ketone 72 as follows:

To a cooled 0°C solution of tetravinyltin (464µl, 2.55 mmole) in THF (30 mL) was added [1.00M] n-butyllithium (9.30 mL, 9.30 mmole). After 2.5 hours at 0°C this solution was added via cannula to a cooled -78°C suspension of CeCl\textsubscript{3} (5.19 g, 13.9 mmole) and ketone (1.99 g, 4.64 mmole) in THF (70 mL). The reaction mixture was stirred for 5 hours at -78°C before being quenched with acetic anhydride (10 mL) and warmed to room temperature. After 30 minutes saturated aqueous NH\textsubscript{4}Cl was added and the layers were separated. The aqueous layer
extracted with ethyl ether (x4), and the organics was washed with brine, dried over MgSO$_4$, filtered and concentrated. Flash chromatography eluenting with 15:1 mixture of hexanes:ethyl acetate gave 786 mg of a less polar acetate and 1049 mg of a more polar acetate. (79% yield for the two acetates).

**Vinylbromide 76:**

To a suspension of Mg (336 mg, 13.8 mmole) in ethyl ether (28 mL) was added 1-bromo-5-propene (2.07 g, 13.9 mmole) dropwise, resulting in a refluxing mixture. The reaction was kept at reflux for 3 hours, until all the magnesium was consumed. The Grignard reagent was cooled and added via cannula to a suspension of copper (1) iodide (968 mg, 5.08 mmole) in ethyl ether (24 mL) at 0°C. After 25 minutes at 0°C a solution of acetate 75 (1.269g, 2.54 mmole) in ethyl ether (8 mL) was added via cannula. The resulting mixture was stirred for 1 hour at 0°C then quenched by the addition of saturated aqueous NH$_4$Cl. The product was extracted with ethyl ether (x3), dried over MgSO$_4$, filtered, and concentrated. The crude residue was purified by flash chromatography (100% Hexanes to 25:1 hexanes: ethyl acetate) to provide 1.24 g of 76 as a slightly yellow coloured liquid.

**Yield:** 96% ¹H NMR (CDCl$_3$, 300MHz): $\delta$ 7.69-7.65 (m, 4H), 7.46-7.35 (m, 6H), 6.09 (d, J= 3.7 Hz, 1H), 5.92 (t, J= 7.4 Hz, 1H), 5.79 (ddt, J= 17.0, 10.2, 6.7 Hz, 1H), 5.03-4.92 (m, 2H), 4.33-4.28 (m, 1H), 2.61 (dt, J= 14.9, 5.9 Hz, 1H), 2.23-2.01 (m, 4H), 1.76-1.69 (m, 2H), 1.45-1.37 (m, 4H), 1.06 (s, 9H). ¹³C NMR (CDCl$_3$, 75 MHz): $\delta$ 138.8 (d), 135.8 (d), 134.0 (s), 133.9 (s), 133.7 (d), 132.6 (d), 131.7 (s), 129.7 (d), 127.7 (d), 126.1 (s), 114.4 (t), 69.0 (d), 33.6 (t), 31.5 (t), 28.7 (t), 28.6 (t), 27.9 (t), 26.9 (q), 23.0 (t), 19.2 (s). IR (film, cm$^{-1}$): 3070, 2930, 2856, 1427, 1105. LRMS (m/z (relative intensity)): 451 (M$^+$ - C$_4$H$_9$, 6), 453 (M$^+$ - C$_4$H$_9$, 6), 199 (100), 200 (23). HRMS calculated for C$_{29}$H$_{37}$OBrSi: 508.1797 found: 508.1793
Aldehyde 77:

To a cooled -78°C solution of vinylbromide 76 (1.10 g, 2.17 mmole) in THF (28 mL) was added [2.00M] n-butylithium (2.17 mL, 4.34 mmole). After 20 minutes DMF (1.26 mL, 16.3 mmole) was added at -78°C and the reaction stirred for 1 hour further before being quenched with saturated aqueous NH₄Cl. The layers were separated and the product extracted with ethyl ether (x3). The combined organics were dried over MgSO₄, filtered and concentrated. The crude aldehyde was purified by flash chromatography (100% hexanes to 15:1 hexanes:ethyl acetate) to provide 977 mg of aldehyde 77 as a faintly yellow coloured oil.

Yield: 98% ¹H NMR (CDCl₃, 300MHz): δ 9.42 (s, 1H), 7.71-7.67 (m, 4H), 7.47-7.37 (m, 6H), 6.64 (t, J= 7.3 Hz, 1H), 6.32 (d, J= 2.9 Hz, 1H), 5.78 (ddt, J= 16.9, 10.2, 6.7 Hz, 1H), 5.01-4.91 (m, 2H), 4.54-4.48 (m, 1H), 2.55 (dt, J= 15.5, 4.9 Hz, 1H), 2.13-1.99 (m, 4H), 1.85-1.77 (m, 1H), 1.73-1.61 (m, 1H), 1.43-1.36 (m, 4H), 1.08 (s, 9H).¹³C NMR (CDCl₃, 75 MHz): δ 193.9 (d), 151.8 (d), 138.8 (d), 137.1 (s), 135.7 (d), 133.7 (s), 131.3 (d), 129.9 (d), 127.7 (d), 114.3 (t), 68.4 (d), 33.6 (t), 31.2 (t), 28.6 (t), 27.9 (t), 26.8 (q), 22.9 (t), 19.1 (s). IR (film, cm⁻¹): 3069, 2932, 2857, 1696, 1427, 1107. LRMS (m/z (relative intensity)): 458 (M⁺, 8), 401 (M⁺ - C₄H₉, 25), 199 (100), 241 (95), 86 (49). HRMS calculated for C₃₀H₃₈O₂Si: 458.2641 found: 458.2650

Cycloadducts 78 and 79:

To a stirred solution of aldehyde 68 (410 mg, 1.86 mmole) and ethyl vinyl ether (10 mL) was added Yb(FOD)₃ (296 mg, 0.279 mmole) at room temperature. The reaction mixture was stirred for 5 days before a solution of brine was added. This mixture was stirred for about 1 hour then separated and the product extracted with ethyl ether (x3), dried over MgSO₄, filtered and concentrated. The
crude mixture was purified by flash chroma tography (using 9:1 to 3:1 mixture of hexanes: ethyl acetate) to provide 320 mg of a 78 and 210 mg of 79.

**Yield:** 97% adduct 78

1H NMR (C₆D₆, 300MHz): δ 6.55 (d, J = 2.1 Hz, 1H), 5.75 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.37 (dt, J = 7.4, 2.2 Hz, 1H), 5.05-4.95 (m, 2H), 4.69 (dd, J = 5.4, 2.9 Hz, 1H), 3.82-3.72 (m, 2H), 3.28 (dq, J = 9.5, 7.0 Hz, 1H), 2.52-2.44 (bt, 1H), 2.40-2.33 (m, 1H), 2.21-2.17 (m, 1H), 2.06-1.87 (m, 4H), 1.85-1.77 (m, 2H), 1.48-1.37 (m, 1H), 1.36-1.28 (m, 4H), 1.23-1.07 (m, 2H), 1.03 (t, J = 7.0 Hz, 3H).

13C NMR (C₆D₆, 75 MHz): δ 139.0 (d), 136.5 (d), 135.9 (s), 121.5 (d), 117.8 (s), 114.5 (t), 96.7 (d), 69.3 (d), 63.8 (t), 38.0 (d), 34.0 (t), 33.1 (t), 31.3 (t), 29.7 (t), 28.8 (t), 27.6 (t), 22.3 (t), 14.9 (q).

IR (film, cm⁻¹): 3415, 3076, 2923, 1641, 1446, 1138, 1051, 907. LRMS (m/z (relative intensity)): 292 (M⁺, 58), 91 (100), 84 (95), 129 (80), 117 (79), 131 (75), 133 (74). HRMS calculated for C18H28O3: 292.2038 found: 292.2032

**Stannanes 80 and 81:**

To an oil free suspension of KH (38.3 mg, 0.955 mmole) in THF (2 mL) was added a solution of alcohol 78 (111.7 mg, 0.382 mmole) in THF (5 mL) via cannula at room temperature. The resulting orange solution was stirred for almost 2 hours at room temperature before a solution of Bu₃SnCH₂I (306 mg, 0.710 mmole) in THF (5 mL) was added via cannula. The reaction mixture was stirred overnight at room temperature before being quenched with brine. The layers were separated and the product extracted with ethyl ether (x3). After drying over MgSO₄, filtration and concentration the crude product was purified by flash chromatography (25:1 Hexanes: Ethyl acetate) to give 190.1 mg of stannane 80 as a clear colourless oil. Stannane 81 was obtained in the same way from alcohol 79.
Yield: 84%  **Stannane 80**

**¹H NMR (C₆D₆, 300MHz):** δ 6.59 (d, J= 1.8 Hz, 1H), 5.76 (ddt, J= 17.0, 10.2, 6.7 Hz, 1H), 5.40 (dt, 7.4, 1.2 Hz, 1H), 4.99 (ddd, 17.0, 10.2, 1.7 Hz, 2H), 4.76 (dd, J= 8.1, 1.8 Hz, 1H), 3.96 (dq, J= 9.4, 7.1 Hz, 1H), 3.83 (ABQ, J= 9.4 Hz, 1H), 3.41 (dq, J= 9.4, 7.1 Hz, 1H), 3.34 (ABQ, J= 9.4 Hz, 1H), 3.07 (bs, 1H), 2.45-2.14 (m, 6H), 2.09-1.93 (m, 4H), 1.78-1.72 (m, 2H), 1.67-1.54 (m, 6H), 1.42-1.31 (m, 10H), 1.24-1.18 (m, 2H), 1.12 (t, J= 7.0 Hz, 3H), 0.98-0.92 (m, 12H).

**¹³C NMR (C₆D₆, 75 MHz):** δ 139.1 (d), 137.1 (d), 135.6 (s), 121.1 (d), 116.7 (s), 114.5 (t), 100.4 (d), 79.6 (d), 64.1 (t), 59.1 (t), 39.3 (d), 34.1 (t), 31.5 (t), 29.8 (t), 29.7 (t), 28.9 (t), 28.2 (t), 27.8 (t), 27.5 (t), 27.3 (t), 23.0 (t), 21.8 (t), 15.5 (q), 14.0 (q), 9.4 (t).

**Stannane 81**

**¹H NMR (C₆D₆, 300MHz):** δ 6.65 (d, J= 2.0 Hz, 1H), 5.76 (ddt, J= 17.0, 6.7, 10.1 Hz, 1H), 5.41 (dt, J= 7.4, 2.0 Hz, 1H), 5.07-4.97 (m, 2H), 4.76 (dd, J= 9.3, 1.7 Hz, 1H), 4.01-3.89 (m, 2H), 3.46 (ABQ, J= 19.5 Hz, 1H), 3.36 (dq, J= 9.4, 7.1 Hz, 1H), 2.83 (dt, J= 10.3, 3.8 Hz, 1H), 2.66-2.56 (m, 2H), 2.43-2.34 (m, 1H), 2.30-2.23 (m, 1H), 2.07-1.82 (m, 6H), 1.78-1.50 (m, 8H), 1.47-1.15 (m, 11H), 1.10 (t, J= 7.1 Hz, 3H), 1.05-0.89 (m, 13H).

**¹³C NMR (C₆D₆, 75 MHz):** δ 139.0 (d), 137.0 (d), 135.0 (s), 122.1 (d), 117.3 (s), 114.6 (t), 100.4 (d), 87.7 (d), 64.3 (t), 59.2 (t), 40.4 (d), 34.2 (t), 34.0 (t), 29.7 (t), 29.6 (t), 28.8 (t), 28.0 (t), 27.7 (t), 25.9 (t), 15.4 (q), 14.0 (q), 9.2 (t, J= 160 Hz).

**IR (film, cm⁻¹):** 2954, 2925, 2869, 1459, 1136, 1068.  **LRMS (m/z (relative intensity)):** 596 (M⁺, 3), 539 (M⁺ - C₄H₉, 30), 235 (100), 291 (91), 179 (80), 233 (73), 177 (70), 289 (69).  **HRMS** calculated for C₃₃H₅₆O₃Sn: 596.3251 found: 596.3265.

**Selenides 82 and 83:**

To a cooled -78°C solution of stannane 80 (141 mg, 0.238 mmole) in THF (4 mL) was added [2.0 M] n-butyllithium (179 µl, 0.357 mmole). The solution was stirred at -78°C for 20 minutes before a solution of diphenyldiselenide (111.4 mg, 0.357 mmole) in THF (1 mL) was added via cannula. The resulting yellow solution was stirred at -78°C for 3 hours before being quenched with brine. The product was extracted with ethyl ether (x2), dried over MgSO₄, filtered and concentrated. Purification by flash chromatography eluenting with 100% hexanes to 25:1 hexanes:ethyl acetate yielded 83.8 mg of selenide as a yellow coloured oil. **Selenide 83** was obtained in the same way from stannane 81.
Yield: 76% Selenide 82 $^1$H NMR (C$_6$D$_6$, 300MHz): $\delta$ 7.57-7.53 (m, 2H), 6.99-6.92 (m, 3H), 6.63 (s, 1H), 5.75 (dt, J= 7.4, 2.1 Hz, 1H), 5.05-4.91 (m, 4H), 4.75-4.72 (m, 1H), 3.89 (dq, J= 9.4, 7.1 Hz, 1H), 3.56 (bs, 1H), 3.40 (dq, J= 9.4, 7.1 Hz, 1H), 2.31-2.04 (m 4H), 2.01-1.86 (m, 6H), 1.71-1.64 (m, 1H), 1.36-1.28 (m, 4H), 1.11 (t, J= 7.1 Hz, 3H). $^{13}$C NMR (C$_6$D$_6$, 75 MHz): $\delta$ 139.0 (d), 137.6 (d), 134.9 (s), 132.5 (d), 129.3 (d), 126.9 (d), 121.6 (d), 116.2 (s), 114.5 (t), 100.3 (d), 74.1 (d), 70.7 (t), 64.0 (t), 38.6 (d), 34.0 (t), 31.3 (t), 29.7 (t), 28.9 (t), 27.9 (t), 27.1 (t), 21.9 (t), 15.4 (q).

Selenide 83 $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.59-7.56 (m, 2H), 7.29-7.24 (m, 3H), 6.46 (d, J= 1.8Hz, 1H), 5.80 (ddt, J= 17.0, 10.2, 6.7 Hz, 1H), 5.38 (d, J=9.8Hz, 1H), 5.29 (d, J= 9.8 Hz, 1H), 5.28-5.24 (m, 1H), 5.02-4.96 (m, 2H), 4.90 (dd, J= 9.6, 2.0 Hz, 1H), 3.92 (dq, J= 9.5, 7.1 Hz, 1H), 3.64-3.51 (m, 2H), 2.57 (dt, J= 16.7, 5.7 Hz, 1H), 2.50-2.42 (m, 1H), 2.30 (ddd, J= 13.1, 5.3, 2.1 Hz, 1H), 2.10-2.01 (m, 4H), 1.59-1.50 (m, 1H), 1.49-1.26 (m, 7H), 1.24 (t, J=7.1 Hz, 3H). IR (film, cm$^{-1}$): 3056, 2923, 1641, 1435, 1133, 1066. LRMS (m/z (relative intensity)): 462 (M$^+$, 3), 91 (100), 171 (65). HRMS calculated for C$_{25}$H$_{34}$O$_3$Se: 462.1673 found: 462.1669

General Procedure for radical cyclizations:

To a refluxing solution of the selenide in benzene was added a solution of tributyltin hydride, AIBN in benzene via syringe pump over approximately 14 hours. Removal of solvent in vacuo yielded a crude residue that was purified by flash chromatography using a 15:1 to 9:1 hexanes: ethyl acetate mixture.

Tricycle 84 and methyl ether 85

See ‘general procedure for radical cyclization’. Selenide (42 mg, 0.091 mmole) in benzene (10 mL), (24.5 $\mu$l, 0.091 mmole); tributyltin hydride (24.5 $\mu$l, 0.091 mmole) AIBN (3.8 mg, 0.023 mmole) in benzene (5 mL). Yielding 20.7 mg of 84 as the major product as a clear colourless oil.

Yield: 20.7 mg, 74% Tricycle 84 $^1$H NMR (Tol-d$_8$, 300MHz): $\delta$ 5.76 (ddt, J= 17.0, 10.2, 6.7 Hz, 1H), 5.07-4.97 (m, 2H), 4.66 (dt, J= 7.1, 2.5 Hz, 1H), 4.29 (d, J= 7.7 Hz, 1H), 4.15 (dd, J= 9.9, 2.9 Hz, 1H), 3.99 (dq, J= 9.4, 7.1 Hz, 1H), 3.82 (d, J= 4.3 Hz, 1H), 3.72 (s, 2H), 3.61 (d, J= 7.7 Hz, 1H), 3.41 (dq, J= 9.4, 7.1 Hz, 1H), 2.39 (dd, J= 15.4, 6.7 Hz, 1H), 2.21-2.17 (m, 1H), 2.02-1.92 (m, 2H), 1.90-
To a stirred solution of alcohol 74 (1.74 g, 3.80 mmole), ethyl vinyl ether (50 mL) and triethylamine (1 mL) was added mercury (II) trifluoroacetate (1.62g, 3.80 mmole) at room temperature. The mixture was stirred a total of three days before the solvent was removed \textit{in vacuo}. The residue was taken up in ethyl ether, washed with 10% aqueous KOH, and saturated aqueous NaHCO₃, dried over MgSO₄, filtered and concentrated. Purification by flash chromatography using a 15:1 to 9:1 mixture of hexanes: ethyl acetate yielded 1.61g of aldehyde 92.

\textbf{Yield: 88\%} ¹H NMR (CDCl₃, 300MHz): δ 9.79 (s, 1H), 7.72-7.68 (m, 4H), 7.48-7.38 (m, 6H), 6.16 (d, J= 3.7 Hz, 1H), 5.87 (t, J= 7.2 Hz, 1H), 4.37-4.31 (m, 1H), 2.70-2.63 (m, 1H), 2.60-2.56 (m, 2H), 2.49-2.42 (m, 2H), 2.26-2.21 (m, 1H), 1.80-1.74 (m, 2H), 1.09 (s, 9H). ¹³C NMR (CDCl₃, 75 MHz): δ 201.2 (d), 135.7 (d), 134.6 (d), 133.8 (s), 132.9 (s), 129.7 (d), 129.6 (d), 127.6 (d), 125.4 (s), 68.8 (d), 43.2 (t), 31.5 (t), 26.8 (q), 22.9 (t), 20.6 (t), 19.1 (s). LRMS (m/z (relative intensity)): 425 (M⁺, 25), 199 (100). HRMS calculated for C₂₂H₂₂O₂BrSi (M⁺ - C₄H₉): 425.0572 found: 425.0575
Aldol adduct 94:

\[
\text{HO} \buildrel \text{Br} \over{\longrightarrow} \ \text{N} \bigcap \Phi
\]

To a cooled -78°C solution of oxazolidinone (157 mg, 0.672 mmole) in dichloromethane (5 mL) was added dibutylborontriflate (212 mg, 194 µl, 0.773 mmole). After 15 minutes triethylamine (122 µl, 0.874 mmole) was added dropwise resulting in a suspension. The mixture was stirred for 15 minutes before being warmed to 0°C and stirred for 30 minutes further. The now yellow solution was cooled to -78°C and a solution of aldehyde 92 (316 mg, 0.653 mmole) in dichloromethane (5mL + 2mL rinse) was added dropwise. The reaction was stirred for 15 minutes then warmed to 0°C and stirred for 1.5 hours further. Phosphate buffer 7.2 pH (6 mL) was added at 0°C followed by a mixture of buffer/H₂O₂/MeOH (3mL/3mL/4mL). The mixture was allowed to warm temperature and stirred for 30 minutes further. The aldol adduct was extracted with dichloromethane (x3), dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography eluting with a 9:1 to 3:1 mixture of hexanes: ethyl acetate gave 385 mg of aldol adduct as a white amorphous solid. Yield: 82%.

\(^1\)H NMR (CDCl₃, 300MHz): δ 7.67-7.65 (m, 4H), 7.45-7.35 (m, 9H), 7.31-7.28 (m, 2H), 6.10 (d, J= 3.6 Hz, 1H), 5.92 (t, J= 7.3 Hz, 1H), 5.68 (dd, J= 7.2, 3.0 Hz, 1H), 4.78 (dquintet, J= 6.8, 3.0 Hz, 1H), 4.33-4.28 (m, 1H), 3.76-3.69 (m, 1H), 2.96 (bs, 1H), 2.70-2.61 (m, 1H), 2.35-2.18 (m, 3H), 1.74-1.62 (m, 3H), 1.58-1.42 (m, 1H), 1.24 (d, J= 7.0 Hz, 3H), 1.05 (d, J= 2.1 Hz, 9H), 0.88 (dd, J= 6.6, 1.5 Hz, 3H). \(^13\)C NMR (CDCl₃, 75 MHz): δ 177.2 (s), 152.5 (s), 135.6 (d), 133.9 (d), 133.7 (s), 133.0 (s), 132.3 (s), 131.4 (d), 129.6 (d), 128.7 (d), 127.6 (d), 125.8 (s), 125.5 (d), 78.8 (d), 70.6 (d), 68.9 (d), 54.6 (d), 42.2 (d), 33.2 (t), 31.4 (t), 26.8 (q), 24.4 (t), 22.9 (t), 19.1 (s), 14.3 (q), 10.3 (q). LRMS (m/z (relative intensity)): 658 (M⁺ - C₆H₅, 5), 660 (M⁺ - C₆H₅, 5), 380 (100), 460 (78), 462 (70), 216 (63), 440 (50), 442 (50). HRMS calculated for C₃₅H₃₇NO₅SiBr (M⁺ - C₄H₅): 658.1624 found: 658.1609
Alcohol 99:

To a stirred solution of alcohol 94 (81 mg, 0.113 mmole) and methanol (5 mL) was added TsOH (1 mg) at room temperature. After 2 days the solvent was removed in vacuo and the residue purified by flash chromatography (3:1 hexanes:ethyl acetate) yielding 17 mg of methyl ether 99 and recovering 9 mg of starting alcohol 94. 

**Yield 31%**

**¹H NMR** (CDCl₃, 300MHz): δ 7.46-7.35 (m, 3H), 7.32-7.29 (m, 2H), 6.32 (d, J= 3.7 Hz, 1H), 5.98 (t, J= 7.5Hz, 1H), 5.70 (d, J= 7.2Hz, 1H), 4.80 (quintet, J= 6.8 Hz, 1H), 3.97-3.94 (m, 1H), 3.91-3.86 (m, 1H), 3.78-3.70 (m, 1H), 3.38 (s, 3H), 2.99 (bs, 1H), 2.73-2.60 (m, 1H), 2.40-2.17 (m, 1H), 2.00-1.90 (m, 1H), 1.78-1.65 (m, 2H), 1.57-1.45 (m, 1H), 1.25 (d, J= 7.0 Hz, 3H), 0.89 (d, J= 6.6 Hz, 3H).  

**¹³C NMR** (CDCl₃, 75 MHz): δ 177.4 (s), 152.5 (s), 133.1 (s), 132.1 (d), 130.7 (d), 128.7 (d), 127.2 (s), 125.5 (d), 78.9 (d), 76.0 (s), 70.7 (d), 56.0 (d), 54.6 (q), 42.2 (d), 33.2 (t), 27.6 (t), 24.4 (t), 22.9 (t), 14.3 (q), 10.3 (q).  

**LRMS** (m/z (relative intensity)): 459 (M⁺ - MeOH, 5), 461 (M⁺ - MeOH, 5), 441 (M⁺ - CH₄O, 10), 443 (M⁺ - CH₄O, 10), 185 (100), 134 (80), 107 (65).  

**HRMS** calculated for C₂₃H₂₆O₄NBr (M⁺-CH₄O): 459.1045 found: 459.0712

Furans 102 and 103:

To a cooled 0°C solution of aldol adduct 94 (100.7 mg, 0.140 mmole), methyl triflate (17 µL, 0.148 mmole), and dichloromethane (5 mL) was added triethylamine (21µL, 0.154 mmole). The mixture was gradually warmed to room temperature and stirred overnight. The following morning tlc indicated the reaction was not yet complete. Accordingly another 17 µL of methyltriflate was
added, and 15 minutes later tlc indicated reaction completion. The mixture was quenched with saturated aqueous NH₄Cl, and the product extracted with dichloromethane (x3). Drying over MgSO₄, filtration, and evaporation yielded a crude residue that was purified by flash chromatography (15:1 to 9:1 Hexanes: Ethyl acetate) to give 12.3 mg of **102**, 21.8 mg of **103**, and 13.3 mg of a mixture of the two (total yield 74%).

**“trans” isomer 102**

**¹H NMR** (CDCl₃, 300MHz): δ 7.45-7.30 (m, 5H), 5.94 (dt, J= 9.9, 1.6 Hz, 1H), 5.75 (dt, 9.7, 3.9 Hz, 1H), 5.65 (d, J= 7.2 Hz, 1H), 4.86-4.83 (m, 1H), 4.77 (quintet, J= 6.8 Hz, 1H), 4.18 (q, J= 6.8 Hz, 1H), 3.95 (quintet, J= 6.9 Hz, 1H), 2.45-2.34 (m, 1H), 2.29-2.07 (m, 5H), 1.76-1.56 (m, 2H), 1.31 (d, J= 6.9 Hz, 3H), 0.89 (d, J= 6.6 Hz, 3H)

**¹³C NMR** (CDCl₃, 75 MHz): δ 174.7 (s), 135.3 (s), 133.1 (s), 129.6 (d), 128.7 (d), 128.1 (d), 125.5 (d), 114.2 (s), 80.7 (d), 79.9 (s), 78.8 (d), 54.9 (d), 42.7 (d), 29.8 (t), 29.6 (t), 23.1 (t), 22.4 (t), 14.3 (q), 13.6 (q).

**LRMS** (m/z [relative intensity]): 459 (M⁺, 10), 461 (M⁺, 10), 118 (100), 184 (63), 134 (62), 178 (58), 259 (53).

**HRMS** calculated for C₂₃H₂₆NO₄Br: 459.1045 found: 459.1035.

**“cis” isomer 103**

**¹H NMR** (CDCl₃, 300MHz): δ 7.45-7.30 (m, 5H), 5.93 (dt, J= 9.7, 1.7 Hz, 1H), 5.73 (dt, J= 9.7, 4.0 Hz, 1H), 5.67 (d, J= 7.1 Hz, 1H), 4.90 (dd, J= 9.5, 6.0 Hz, 1H), 4.77 (quintet, J= 6.8 Hz, 1H), 4.32-4.25 (m, 1H), 4.03 (quintet, J= 6.9 Hz, 1H), 2.45-2.33 (m, 1H), 2.26-2.07 (m, 5H), 1.91-1.78 (m, 1H), 1.72-1.61 (m, 1H), 1.28 (d, J= 6.9 Hz, 3H), 0.89 (d, J= 6.6 Hz, 3H).

**¹³C NMR** (CDCl₃, 75 MHz): δ 175.0 (s), 136.3 (s), 133.3 (s), 129.6 (d), 128.7 (d), 128.1 (d), 125.6 (d), 113.7 (s), 81.5 (d), 80.7 (d), 78.9 (d), 55.1 (d), 42.2 (d), 30.7 (t), 23.2 (t), 22.4 (t), 14.4 (q), 13.7 (q).

**LRMS** (m/z [relative intensity]): 459 (M⁺, 27), 461 (M⁺, 27), 118 (100), 134 (65), 380 (50).

**HRMS** calculated for C₂₃H₂₆NO₄Br: 459.1045 found: 459.1035

**Iodide 109:**

To a cooled 0°C solution of alcohol **259** (4.17 g, 19.1 mmole), in ethyl ether (113 mL) and acetonitrile (38 mL) was added triphenylphosphine (5.51 g, 20.0 mmole). Once the triphenylphosphine had dissolved, imidazole (1.43 g, 21.0 mmole) was added at 0°C. Iodine (4.85 g, 19.1 mmole) was added portion wise at 0°C once the imidazole had entered solution. The resulting orange suspension was stirred at 0°C for a total of 1.5 hours before pentane (175 mL) was added. The suspension was filtered through celite and the filtrate washed once with 5% aqueous Na₂S₂O₃, dried over MgSO₄, filtrated and concentrated. Flash chromatography using a 25:1 mixture of hexanes: ethyl acetate provided 5.96 g of iodide **109** as a clear colourless liquid.
Yield: 95 % \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300MHz): \(\delta\) 3.49-3.39 (m, J= 9.9, 9.5 Hz, 2H), 3.32-3.16 (m, J= 5.9 Hz, 2H), 2.04-1.94 (m, 1H), 1.77-1.55 (m, 2H), 0.89 (s, 9H), 0.88 (d, J= 5.9 Hz, 3H), 0.04 (s, 6H) \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): \(\delta\) 67.3 (t), 37.5 (t), 36.6 (d), 25.9 (q), 18.3 (s), 15.9 (t), 5.2 (t), -5.4 (q). IR (film, cm\textsuperscript{-1}): 2955, 2856, 1471, 1255, 1093, 836, 775. LRMS (m/z (relative intensity)): 215 (100), 185 (80), 271 (M – C\textsubscript{4}H\textsubscript{9}, 70). HRMS calculated for C\textsubscript{7}H\textsubscript{16}OSi (C\textsubscript{11}H\textsubscript{25}OSi-C\textsubscript{4}H\textsubscript{9}): 271.0015 found: 271.0017

[\alpha]\textsubscript{D}: -10.0 (c = 2.05, CH\textsubscript{2}Cl\textsubscript{2}) (from Evan’s route)

\textbf{Allylic alcohol 111:}

\[
\begin{align*}
\text{HO} & \quad \text{OPMB} \\
\text{Br} & \\
\text{C=C} & \quad \text{(C=O)}
\end{align*}
\]

To a cooled 0°C solution of tetravinyltin (3.53 mL, 19.4 mmole) in THF (485 mL) was added n-BuLi (37 mL, 70.5 mmole). After 15 minutes the reaction mixture was warmed to room temperature and stirred for 45 minutes before being cooled to -78°C. A solution of ketone 118 (10.97 g, 35.3 mmole) in THF (50 mL, + 15 mL rinse) was then added via cannula. The reaction was stirred at -78°C for a total of 1.5 hours before being quenched with saturated aqueous NH\textsubscript{4}Cl. The mixture was extracted with ethyl ether (x3) and the organics washed with brine, dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo. The crude alcohol was purified by flash chromatography using hexanes:ethyl acetate (3:1) as the eluent to give 10.8 g of a clear colourless oil. This alcohol is a 1:1 mixture of two inseparable isomers.

Yield: 90 % \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300MHz): \(\delta\) 7.26 (d, J= 7.6 Hz, 2H), 6.88 (d, J= 7.6 Hz, 2H), 6.35 (d, J= 3.6 Hz, 1H), 5.79 (dd, J= 17.2, 10.6 Hz, 1H), 5.33 (d, J= 17.2 Hz, 1H), 5.23 (d, J= 10.6 Hz, 1H), 4.50 (AB Quartet, J= 12.7 Hz, 2H), 3.92-3.88 (m, 1H), 3.80 (s, 3H), 2.27 (s, 1H), 2.18-2.10 (m, 1H), 1.92-1.78 (m, 3H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): \(\delta\) 159.1 (s), 141.0 (d), 132.8 (d), 132.4 (s), 129.9 (s), 129.1 (d), 114.9 (t), 113.7 (d), 74.1 (s), 72.7 (d), 70.0 (t), 55.1 (q), 33.2 (t), 24.6 (t) IR (film, cm\textsuperscript{-1}): 3455, 2950, 1612, 1513, 1302, 1247, 1174, 1076, 967, 821. LRMS (m/z (relative intensity)): 338 (M\textsuperscript{+}, 5), 340 (M\textsuperscript{+}, 5), 137(75), 136(80), 121(100). HRMS calculated for C\textsubscript{16}H\textsubscript{19}O\textsubscript{3} Br: 338.0517 found: 338.0513
Allylic acetate 112:

![Allylic acetate structure](image)

To a solution of alcohol 111 (10.78 g, 31.8 mmole), triethylamine (13.3 mL, 95.4 mmole), acetic anhydride (6 mL, 63.6 mmole) in dichloromethane (40 mL) was added DMAP (777 mg, 6.36 mmole) at room temperature. The mixture was stirred at room temperature for 4 days before being washed with 1N HCl and saturated aqueous NaHCO₃. The aqueous layers were extracted with ethyl ether (x3). The combined organics were then washed with brine, dried over MgSO₄, filtered and concentrated. Purification by flash chromatography eluenting with 6:1 hexanes: ethyl acetate yielded 10.01 g of two diastereomers as a slightly pale yellow oil.

**Yield:** 82% ¹H NMR (CDCl₃, 300MHz): δ  7.25 (d, J= 8.6 Hz, 2H), 6.88 (d, J= 8.6 Hz, 2H), 6.42 (d, J= 1.1 Hz, 1H), 5.89 (dd, J= 17.3, 10.7, 1H), 5.37 (d, J= 18.8 Hz, 1H), 5.32 (d, J= 10.9 Hz, 1H), 4.50 (AB Quartet, J= 13.5 Hz, 2H), 4.17-4.10 (m, 1H), 3.80 (s, 3H), 2.68-2.58 (m, 1H), 2.22-2.20 (m, 2H), 2.08 (s, 3H), 1.77-1.65 (m, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 169.1 (s), 159.1 (s), 136.5 (d), 135.1 (d), 129.8 (s), 129.2 (d), 125.2 (s), 116.7 (t), 113.7 (d), 82.5 (s), 74.2 (d), 70.1 (t), 55.1 (q), 30.4 (t), 26.5 (t), 21.8 (q). **Other isomer** ¹H NMR (CDCl₃, 300MHz): δ 7.28 (d, J= 8.6 Hz, 2H), 6.88 (d, J= 8.6 Hz, 2H), 6.43 (d, J= 4.5 Hz, 1H), 5.94 (dd, J= 17.3, 10.9 Hz, 1H), 5.29 (d, J= 10.3 Hz, 1H), 5.25 (d, J= 17.0 Hz, 1H), 4.51 (s, 2H), 3.86 (q, J= 4.4 Hz, 1H), 3.80 (s, 3H), 2.86 (dt, J= 11.8, 3.4, 1H), 2.09 (s, 3H), 2.06-1.99 (m, 1H), 1.92-1.89 (m, 1H), 1.85-1.79 (m, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 168.9 (s), 159.0 (s), 136.2 (d), 132.9 (d), 130.2 (s), 129.1 (d), 128.9 (s), 116.2 (t), 113.6 (d), 82.2 (s), 70.9 (d), 69.9 (t), 55.1 (q), 28.3 (t), 24.7 (t), 21.8 (q). IR (film, cm⁻¹): 2935, 1744, 1612, 1513, 1366, 1245, 1068, 1034, 821 LRMS (m/z (relative intensity)): 321 (M- C₂H₃O₂, 10), 323 (M- C₂H₃O₂, 10), 184 (40), 121 (100). HRMS calculated for C₁₆H₁₈O₂Br (M- C₂H₃O₂): 321.0490 found: 321.0485

Ketal 115:

![Ketal structure](image)

To an oil free suspension of KH (3.04 g, 75.8 mmole) in THF (200 mL) was added a solution of alcohol 52 (10.0 g, 63.2 mmole) in THF (50 mL + 20 mL
rinse) via cannula at 0°C. After hydrogen evolution had ceased (1 hour) a solution of PMBCl (10.4 g, 66.4 mmole) and THF (20 mL + 10 mL rinse) was added via cannula. The ice bath was removed and the reaction stirred overnight. The reaction was quenched with saturated aqueous NH₄Cl, and the product extracted with ether (3x80 mL). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. Purification by flash chromatography (3:1 to 1:1 hexanes: ethyl acetate) yielded 16.9g of ketal 115 as a clear yellow oil.

**Yield:** 96 %

**¹H NMR** (CDCl₃, 300MHz): δ 7.26 (d, J= 8.6 Hz, 2H), 6.86 (d, J= 8.6 Hz, 2H), 4.45 (s, 2H), 3.92 (s, 4H), 3.78 (s, 3H), 3.52-3.47 (m, 1H), 1.86-1.75 (m, 6H), 1.56-1.53 (m, 2H). **¹³C NMR** (CDCl₃, 75 MHz): δ 158.9 (s), 131.0 (s), 128.8 (d), 113.6 (d), 108.4 (s), 73.7 (d), 69.4 (t), 64.2 (t), 55.1 (q), 31.2 (t), 28.5 (t).

**IR** (film, cm⁻¹): 3011, 2943, 2877, 1611, 1513, 1247, 1103. **LRMS** (m/z (relative intensity)): 278 (M⁺, 10), 86 (100), 121 (90), 99 (90), 142 (65). **HRMS** calculated for C₁₆H₂₂O₄: 278.1518 found: 278.1515

**Ketone 116:**

A solution of ketal 115 (15.28 g, 54.9 mmole) and PPTS (4.1g, 16.5 mmole) in wet acetone (550 mL) was heated to reflux for 5.5 hours. The mixture was cooled and the solvent removed in vacuo. The residue was taken up in ethyl ether and washed with saturated aqueous NaHCO₃, and brine, then dried over MgSO₄. Flash chromatography using a 3:1 to 1:1 mixture of hexanes: ethyl acetate procured 11.89g of ketone 116 as a white solid.

**Yield:** 92% 

**¹H NMR** (CDCl₃, 300MHz): δ 7.29 (d, J= 8.6 Hz, 2H), 6.90 (d, J= 8.6 Hz, 2H), 4.53 (s, 2H), 3.81 (s, 3H), 3.82-3.78 (m, 1H), 2.67-2.56 (m, 2H), 2.31-2.22 (m, 2H), 2.17-2.10 (m, 2H), 2.00-1.91 (m, 2H). **¹³C NMR** (CDCl₃, 75 MHz): δ 211.2 (s), 159.0 (s), 130.4 (s), 128.9 (d), 113.7 (d), 71.8 (d), 69.8 (t), 55.1 (q), 37.1 (t), 30.4 (t). **IR** (CHCl₃, cm⁻¹): 3011, 2953, 2870, 1708, 1612, 1513, 1248 **LRMS** (m/z (relative intensity)): 234 (M⁺, 35), 121(100). **HRMS** calculated for C₁₄H₁₈O₃: 234.1256 found: 234.1259. **Melting Point:** 34.9°C
**α,β- Unsaturated ketone 117:**

![Chemical Structure](attachment:image.png)

A stirred suspension of oil free KH (4.08 g, 101.7 mmole) in THF (45 mL + 5mL rinse) was added via cannula to a solution of ketone 116 (9.53 g, 40.6 mmole), PhS(O)OMe (6.35 g, 40.6 mmole) in THF (135 mL) at 0°C. The ice bath was then removed and the reaction stirred for one hour further. The solvent was removed in vacuo and the residue partitioned between 0.5M H₃PO₄ (50 mL) and dichloromethane (90 mL). The aqueous layer was extracted with dichloromethane (80 mLx6) and the combined organics were washed (brine), dried over MgSO₄, filtered and concentrated. The crude residue was taken up in toluene (400 mL) and Na₂CO₃ (21.5 g, 203 mmole) was added. The suspension was heated to reflux for 30 minutes before being cooled and filtered through celite and concentrated. The crude residue was purified by flash chromatography eluting with a 3:1 hexanes: ethyl acetate mixture to give 7.80 g of ketone 117 as a clear slightly yellow coloured oil.

**Yield:** 82 %

**¹H NMR** (CDCl₃, 300MHz): δ 7.29 (d, J= 8.6 Hz, 2H), 6.96 (d, J= 10.3 Hz, 1H), 6.90 (d, J= 8.6 Hz, 2H), 5.98 (d, J= 10.3 Hz, 1H), 4.58 (AB quartet, J= 11.4, 5.9 Hz, 2H), 4.27-4.21 (m, 1H), 3.81 (s, 3H), 3.51 (t), 2.89 (t).

**¹³C NMR** (CDCl₃, 75 MHz): δ 198.5 (s), 159.2 (s), 150.6 (d), 129.5 (s), 129.3 (d), 129.2 (d), 113.8 (d), 71.9 (d), 70.4 (t), 55.1 (q), 35.1 (t), 28.9 (t).

**IR** (film, cm⁻¹): 2999, 2955, 2836, 1681, 1613, 1514, 1249, 1087

**LRMS** (m/z (relative intensity)): 232 (M⁺, 40), 122 (60), 121(100).

**HRMS** calculated for C₁₄H₁₆O₃: 232.1099 found: 232.1094

**Bromoketone 118:**

![Chemical Structure](attachment:image.png)

To a cooled 0°C solution of ketone 117 (7.80 g, 33.5 mmole) in 1,2-dichloroethane (305 mL) was added a solution of Br₂ (1.63 mL, 31.9 mmole) in 1,2-dichloroethane (70 mL) over a 1.5 hour period using an addition funnel. After 30 minutes further at 0°C a solution of triethylamine (8.42 mL, 60.4 mmole) in 1,2-dichloroethane (60 mL) was added over 30 minutes to the reaction mixture. The reaction was stirred for 30 minutes further at 0°C before being filtered through a pad of celite. The filtrate was washed with 1N HCl and saturated
aqueous NaHCO₃ and the aqueous layers extracted with dichloromethane (x2). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated to dryness. The crude product was purified by flash chromatography eluting with a 3:1 to 1:1 mixture of hexanes:ethyl acetate to give 9.58 g of 118 as a white solid.

**Yield:** 92 %

**¹H NMR** (CDCl₃, 300MHz): δ 7.42 (d, J= 3.5 Hz, 1H), 7.28 (d, J= 8.6 Hz, 2H), 6.90 (d, J= 8.6 Hz, 2H), 4.57 (s, 2H), 4.27-4.22 (m, 1H), 3.81 (s, 3H), 2.83 (dm, J= 16.8, 10.7 Hz, 1H), 2.47 (m, J= 16.8, 11.7 Hz, 1H), 2.37-2.28 (m, 1H), 2.16-2.04 (m, 1H).

**¹³C NMR** (CDCl₃, 75 MHz): δ 190.4 (s), 159.3 (s), 150.7 (d), 132.0 (s), 129.3 (d), 124.8 (s), 113.9 (d), 73.2 (d), 70.7 (t), 55.2 (q), 34.6 (t), 29.0 (t).

**IR** (film, cm⁻¹): 2955, 1697, 1611, 1513, 1463, 1318, 1249, 1174, 1032, 1000, 817. **LRMS** (m/z (relative intensity)): 310 (M⁺, 8), 136(27), 121(100). **HRMS** calculated for C₁₄H₁₅O₃Br: 310.0204 found: 310.0195. **Melting Point:** 62.7°C

**Vinylbromide 121:**

![Vinylbromide 121](image)

To a cooled -78°C solution of alkyl iodide 109 (4.51 g, 13.7 mmole) in Et₂O (126 mL) was added a [1.31M] solution of tert-butyllithium (20.9 mL, 27.4 mmole) fairly rapidly. After 5 minutes this solution was warmed to 0°C and stirred for 30 minutes before being cooled to -78°C (upon warming the solution becomes yellow only to fade to near colourless after 30 minutes). This cooled solution was then added via cannula to a stirred suspension of CuCN (1.22 g, 13.7 mmole) in THF (103 mL) at -68°C. This suspension was stirred for 1 hour further before a solution of acetate 112 (3.48 g, 9.13 mmole) in THF (70 mL) was added via cannula at -50°C. The reaction mixture was gradually warmed to 0°C over the next 2 hours and stirred further at 0°C before being quenched with a 9:1 solution of saturated aqueous NH₄Cl: concentrated NH₄OH. The mixture was extracted with ethyl ether (x3), washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography using 15:1 hexanes: ethyl acetate to give 4.43 g of 121 as a colourless oil.

**Yield:** 92 %

**¹H NMR** (CDCl₃, 300MHz): δ 7.27 (d, J= 8.6 Hz, 2H), 6.88 (d, J= 8.6 Hz, 2H), 6.31 (d, J= 3.7 Hz, 1H), 5.97 (t, J= 7.4 Hz, 1H), 4.51 (s, 2H), 4.08-4.03 (m, 1H), 3.80 (s, 3H), 3.39 (ddd, J= 9.8, 6.5, 6.0 Hz, 2H), 2.66-2.59 (m, 1H), 2.36-2.31 (m, 1H), 2.16-2.09 (m, 2H), 1.98-1.89 (m, 1H), 1.84-1.77 (m, 1H), 1.61-1.52 (m, 1H), 1.46-1.37 (m, 3H), 1.09-1.02 (m, 1H), 0.89 (s, 9H), 0.86 (d, J= 6.7
Hz, 3H), 0.03 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 159.1 (s), 133.2 (d), 131.4 (s), 130.7 (d), 130.3 (s), 129.2 (d), 127.3 (s), 113.7 (d), 73.6 (d), 69.9 (t), 68.2 (t), 51.2 (q), 35.6 (d), 32.8 (t), 28.3 (t), 28.0 (t), 26.6 (t), 25.8 (q), 23.0 (t), 18.2 (s), 16.6 (q), -5.4 (q). IR (film, cm$^{-1}$): 2952, 2855, 1612, 1513, 1462, 1248, 1089, 1038, 835. LRMS (m/z (relative intensity)): 465 (M – C$_4$H$_9$, 5), 467 (M – C$_4$H$_9$, 5), 122 (50), 74 (50), 121 (100). HRMS calculated for C$_{23}$H$_{34}$O$_3$SiBr (M – C$_4$H$_9$): 465.1460 found: 465.1470

α,β- Unsaturated aldehyde 124:

NOTE: During larger scale reactions (i.e. for 3.35 g, 6.40 mmole) of vinylbromides, the starting material was usually divided into equal portions of ~500mg each and done in series and purified together.

To a solution of vinylbromide 121 (518 mg, 0.99 mmole) in THF (20 mL) was added a [1.98M] solution of n-butyllithium (600 µL, 1.19 mmole) at -78°C, producing a yellow solution. After 15 minutes at -78°C, DMF (230 µL, 2.97 mmole) was added giving a clear colourless solution. The mixture was stirred another 20 minutes further before being quenched with saturated aqueous NH$_4$Cl. The layers were separated and the aqueous extracted with ethyl ether (x3), dried over MgSO$_4$, filtered, and concentrated in vacuo. The combined residues was purified by flash chromatography using 9:1 hexane:ethyl acetate as the eluent, providing 2.73 g of aldehyde 124 as a clear colourless oil.

Yield: 90% $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 9.55 (s, 1H), 7.29 (d, J= 8.6 Hz, 2H), 6.89 (d, J= 8.6 Hz, 2H), 6.68 (t, J= 7.4 Hz, 1H), 6.52 (d, J= 2.8 Hz, 1H), 4.60 (AB Quartet, J= 18.2 Hz, 2H), 4.28-4.23 (m, 1H), 3.80 (s, 3H), 3.43 (dd, J= 9.8, 5.9 Hz, 1H), 3.35 (dd, J=9.8, 6.5 Hz, 1H), 2.63 (dt, J= 15.3, 4.8 Hz, 1H), 2.22-2.05 (m, 4H), 1.73-1.54 (m, 2H), 1.48-1.34 (m, 3H), 1.12-1.02 (m, 1H), 0.89 (s, 9H), 0.86 (d, J= 6.7 Hz, 3H), 0.03 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHZ): $\delta$ 193.8 (d), 159.3 (s), 148.8 (d), 138.0 (s), 131.8 (d), 130.1 (s), 129.3 (d), 127.8 (s), 113.8 (d), 73.0 (d), 70.4 (t), 68.2 (t), 55.2 (q), 35.6 (d), 32.9 (t), 28.5 (t), 27.8 (t), 26.6 (t), 25.9 (q), 22.9 (t), 18.3 (s), 16.6 (q), -5.3 (q). IR (film, cm$^{-1}$): 2953, 2855, 1612, 1513, 1248, 1090, 836. LRMS (m/z (relative intensity)): 415 (M – C$_4$H$_9$, 3), 122 (50), 74 (54), 121 (100). HRMS calculated for C$_{24}$H$_{35}$O$_4$Si (M – C$_4$H$_9$): 415.2304 found: 415.2313
Cycloadduct 127:

A solution of aldehyde 124 (2.96 g, 6.26 mmole), Yb(fod)$_3$, and ethyl vinyl ether (70 mL) was stirred at room temperature for 2 days. Ethyl ether and water was added and the mixture stirred vigorously for 30 minutes. The layers were separated and the aqueous washed with ethyl ether. The organics were dried over MgSO$_4$, filtered and concentrated. Flash chromatography (9:1 hexanes:ethyl acetate) yielded 2.79 g of cycloadduct 127.

Yield: 86% two isomers

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.29-7.25 (m, 2H), 6.89-6.84 (m, 2H), 6.43-6.38 (m, J= 1.6 Hz, 1H), 5.32-5.28 (m, 1H), 4.87 (bs, 2H), 4.64-4.55 (m, 2H), 4.44-4.35 (m, 2H), 4.00 (bs, 1H), 3.80 (s, 3H), 3.62 (bs, 1H), 3.45-3.40 (m, J= 6.0 Hz, 1H), 3.36-3.31 (m, J= 6.7 Hz, 1H), 2.69-2.52 (m, 1H), 2.40-2.35 (m, 1H), 2.18-1.92 (m, 6H), 1.40-1.25 (m, 8H), 1.19-1.25 (m, 1H), 0.89 (s, 9H), 0.85 (d, J= 6.6 Hz, 3H), 0.03 (s, 6H). IR (film, cm$^{-1}$): 2940, 2852, 1621, 1513, 1464, 1346, 1248, 1135, 1077, 841. LRMS (m/z (relative intensity)): 544 (M$^+$, 5), 121 (100), 74 (50), 441 (10). HRMS calculated for C$_{32}$H$_{52}$O$_5$Si: 544.3584 found: 544.3592

Cycloadduct 128:

To a solution of silyl ether 127 (2.79 g, 5.12 mmole) and THF (55 mL) was added TBAF (6.2 mL, 6.2 mmole) at room temperature. After 8 hours ethyl ether was added and the solution washed with saturated aqueous NH$_4$Cl (x3), dried over MgSO$_4$, filtered and concentrated. Flash chromatography using 1:1 hexanes:ethyl acetate yielded 1.98 g of alcohol 128.
**Yield:** 90% Mixture of two isomers $^1H$ NMR (acetone d-6, 300MHz): $\delta$ 7.28 (d, J= 8.6 Hz, 2H), 6.88 (d, J= 8.6 Hz, 2H), one isomer 6.35 (d, J= 1.8 Hz, 1H), one isomer 6.30 (d, J= 1.2 Hz, 1H), 5.32-5.25 (m, 1H), 4.84-4.79 (m, 1H), one isomer 4.61 (d, J= 11.3 Hz, 1H), one isomer 4.55 (d, J= 11.3 Hz, 1H), one isomer 4.41 (d, J= 11.3 Hz, 1H), one isomer 4.33 (d, J= 11.3 Hz, 1H), 3.90-3.81 (m, 1H), 3.77 (s, 3H), 3.68-3.65 (m, 1H), 3.59-3.47 (m, 1H), 3.45-3.26 (m, 2H), one isomer 3.16-3.09 (m, 1H), one isomer 2.66 (dt, J= 14.3, 3.5 Hz, 1H), 2.54-2.47 (m, 1H), 2.41-2.20 (m, 3H), 2.16-1.93 (m, 3H), 1.78-1.71 (m, 1H), 1.55-1.30 (m, 5H), 1.20-1.06 (m, 1H), one isomer 1.16 (t, J= 7.1 Hz, 3H), one isomer 1.15 (t, J= 7.1 Hz, 3H), 0.87 (d, J= 6.6 Hz, 3H). Two isomers $^{13}C$ NMR (acetone d-6, 75 MHz): $\delta$ 170.6 (s), 137.6 (d), 136.1 (s), 135.6 (s), 132.6 (s), 132.5 (s), 130.6 (d), 123.2 (d), 122.3 (d), 118.2 (s), 117.9 (s), 114.9 (d), 101.4 (d), 101.2 (d), 83.2 (d), 75.3 (d), 71.3 (t), 68.4 (t), 65.1 (t), 55.9 (q), 41.2 (d), 39.9 (d), 37.1 (d), 34.8 (t), 34.2 (t), 32.2 (t), 31.4 (t), 29.2 (t), 28.9 (t), 28.7 (t), 26.7 (t), 22.6 (t), 17.7 (q), 16.1 (q). IR (film, cm$^{-1}$): 3458, 2929, 2862, 1643, 1612, 1513, 1442, 1301, 1248, 1132, 821. LRMS (m/z (relative intensity)): 430 (M$^+$, 3), 121 (100), 122 (43). HRMS calculated for C$_{26}$H$_{38}$O$_5$: 430.2719 found: 430.2726

**Cycloadduct 132:**

To a suspension of alcohol 128 (256 mg, 0.594 mmole), NMO (105 mg, 0.892 mmole), molecular sieves (297 mg) and dichloromethane (3.0 mL) was added TPAP (14 mg, 0.042 mmole) at room temperature. After 15 minutes tlc showed no starting material and the solvent was removed in vacuo. The crude mixture was quickly passed through a plug of silica gel using 3:1 hexanes:ethyl acetate as the solvent providing 174 mg of aldehyde 130 colourless aldehyde which was used immediately in the next step.

To a suspension of NaH (17.2 mg, 0.432 mmole) and THF (500 µL) at 0°C was added MDEPA (80 µL, 0.432 mmole). After 1 hour this solution was added via cannula (500 µL rinse) to a stirred solution of aldehyde 130 and THF (1 mL) at 0°C. The ice bath was removed and the reaction mixture stirred overnight. The mixture was quenched with saturated aqueous NH$_4$Cl, extracted with ethyl ether (x3), dried over MgSO$_4$, filtered and concentrated. Flash chromatography (6:1
hexanes:ethyl acetate) provided 60.4 mg of cycloadduct 132 as a mixture of isomers.

**Yield:** 30% MAJOR ISOMER

**1H NMR** (acetone d-6, 300MHz): $\delta$ 7.24 (d, J= 8.6 Hz, 2H), 6.88 (d, J= 8.6 Hz, 2H), 5.29-5.26 (m, 1H), 4.91 (t, J= 7.1 Hz, 1H), 4.56 (d, J= 11.5 Hz, 1H), 4.37 (d, J= 11.5 Hz, 1H), 3.87-3.79 (m, 1H), 3.76 (s, 3H), 3.71-3.68 (m, 1H), 3.58-3.39 (m, 1H), 2.74 (t, J= 9.4 Hz, 1H), 2.70-2.00 (m, 6H), 1.99-1.90 (m, 1H), 1.87-1.74 (m, 2H), 1.72-1.56 (m, 3H), 1.52-1.41 (m, 1H), 1.34-1.22 (m, 1H), 1.14 (t, J= 7.1 Hz, 3H), 1.10-1.01 (m, 1H), 0.97 (d, J= 6.5 Hz, 3H)

**13C NMR** (acetone d-6, 75 MHz): $\delta$ 160.6 (s), 133.0 (s), 132.8 (s), 130.5 (d), 128.4 (s), 114.9 (d), 99.9 (d), 90.7 (d), 80.9 (d), 74.5 (d), 71.2 (t), 63.8 (t), 56.0 (q), 42.8 (d), 38.5 (d), 37.2 (d), 35.0 (t), 31.4 (t), 29.3 (t), 26.7 (t), 26.5 (t), 22.0 (t), 19.5 (q), 16.2 (q).

**LRMS** (m/z (relative intensity)): 428 (M$^+$, 1), 382 (M$^+$ - C$_2$H$_6$O, 4), 261 (M$^+$ - C$_2$H$_6$O - C$_8$H$_9$O, 13), 121 (100). **HRMS** calculated for C$_{26}$H$_{36}$O$_5$: 428.2563 found: 428.2569

**Acetal 133:**

![Acetal 133](image)

A solution of aldehyde 124 (5.15 g, 10.9 mmole), PPTS (547 mg, 2.18 mmole), and ethylene glycol (6.07 mL, 109 mmole) in benzene (140 mL) was heated to reflux for 6 hours. The solvent was removed in vacuo and the residue taken up in Et$_2$O. The etheric layer was washed with saturated aqueous NaHCO$_3$, and brine. The combined aqueous layers were extracted once with ethyl ether. The organics were then dried over MgSO$_4$, filtered and concentrated to give 5.71 g of acetal 133 as an oil. The crude acetal was used in the next step without further purification.

**Yield:** ~100 %

**1H NMR** (CDCl$_3$, 300MHz): $\delta$ 7.28 (d, 8.6 Hz, 2H), 6.86 (d, J= 8.6 Hz, 2H), 6.21 (d, J= 2.9 Hz, 1H), 5.69 (t, J= 7.2 Hz, 1H), 5.55 (s, 1H), 4.54 (s, 2H), 4.12-4.07 (m, 1H), 4.04-3.99 (m, 2H), 3.97-3.92 (m, 2H), 3.80 (s, 3H), 3.43 (dd, J= 9.7 Hz, 1H), 3.33 (dd, J= 9.7, 6.6 Hz, 1H), 2.56 (dt, J= 15.4, 5.5 Hz, 1H), 2.22-2.07 (m, 3H), 2.04-1.94 (m, 1H), 1.74-1.66 (m, 1H), 1.62-1.54 (m, 1H), 1.46-1.32 (m, 3H), 1.08-1.02 (m, 1H), 0.88 (s, 9H), 0.86 (d, J= 6.7 Hz, 3H), 0.03 (s, 6H). **13C NMR** (CDCl$_3$, 75 MHz): $\delta$ 158.9 (s), 135.2 (s), 131.4 (s), 130.7 (s), 129.0 (d), 126.9 (d), 126.4 (d), 113.6 (d), 101.2 (d), 72.5 (d), 69.6 (t), 68.1 (t), 64.7 (t), 55.0 (q), 35.5 (d), 32.8 (t), 28.2 (t), 26.8 (t), 25.8 (t and q), 22.8 (t), 18.2 (s), 16.6 (q), -5.4 (q). **IR** (film, cm$^{-1}$): 2953, 2856, 1612, 1513, 1463, 1248, 1090,
836, 775. **LRMS** (m/z (relative intensity)): 516 (M⁺, 2), 459 (M – C₄H₉, 8), 122 (61), 261 (65), 186 (70), 74 (75), 121 (100). **HRMS** calculated for C₂₆H₃₉O₅Si (M – C₄H₉): 459.2567 found: 459.2574

**Alcohol 134:**

\[
\text{HO} \quad \begin{array}{c}
\text{OPMB}
\end{array} \quad \begin{array}{c}
\text{O}
\end{array}
\]

TBAF (12.6 mL, 12.6 mmole) was added to a solution of acetal 133 (5.45 g, 10.5 mmole) in THF (105 mL) at room temperature. After 6 hours a 1:1 solution of ethyl acetate: ethyl ether was added to the mixture. The resulting mixture was washed with saturated aqueous NH₄Cl (x2), and the aqueous layer extracted once with ethyl acetate: ethyl ether 1:1. The combined organics were dried over MgSO₄, filtered and concentrated. The crude residue was purified by flash chromatography using a 3:1 to 1:1 mixture of hexanes:ethyl acetate as the eluent to give 3.66 g of alcohol 134 as a colourless oil.

**Yield:** 87 (2 steps) %

**¹H NMR** (CDCl₃, 300MHz): δ 7.28 (d, J=8.6 Hz, 2H), 6.86 (d, J= 8.6 Hz, 2H), 6.21 (d, J= 2.9 Hz, 1H), 5.68 (t, J= 7.2 Hz, 1H), 5.55 (s, 1H), 4.54 (s, 2H), 4.12-4.07 (m, 1H), 4.04-3.99 (m, 2H), 3.97 (m, 2H), 3.80 (m, 3H), 3.49 (dd, J= 9.5, 5.8 Hz, 1H), 3.41 (dd, J= 9.5, 6.4 Hz, 1H), 2.58 (dt, J= 15.3, 5.3 Hz, 1H), 2.23-2.09 (m, 3H), 2.01-1.94 (m, 1H), 1.74-1.59 (m, 2H), 1.49-1.35 (m, 3H), 1.17-1.08 (m, 1H), 0.91 (d, J= 6.7 Hz, 3H).

**¹³C NMR** (CDCl₃, 75 MHz): δ 158.9 (s), 135.2 (s), 131.4 (s), 130.6 (s), 129.1 (d), 126.7 (d), 126.5 (d), 113.6 (d), 101.2 (d), 72.4 (d), 69.6 (t), 67.9 (t), 64.7 (t), 55.1 (q), 35.5 (d), 32.7 (t), 28.1 (t), 26.7 (t), 22.8 (t), 16.4 (q).

**IR** (film, cm⁻¹): 3441, 2931, 1613, 1513, 1463, 1247, 1172, 1048, 821. **LRMS** (m/z (relative intensity)): 402 (M⁺, 1), 264 (45), 136 (50), 91 (55), 131 (60), 77 (60), 122 (90), 121 (100). **HRMS** calculated for C₂₄H₃₄O₅: 402.2406 found: 402.2397
Aldehyde 135:

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

To a stirred solution of alcohol 134 (3.02 g, 7.49 mmole) in dichloromethane (61 mL) at room temperature was added Dess-Martin periodinane (4.76 g, 11.2 mmole). After 1.5 hours ethyl ether (100 mL) was added to the reaction mixture, followed by a solution (100 mL) of Na$_2$S$_2$O$_3$ (25g) in saturated aqueous NaHCO$_3$. The mixture was stirred for 5 minutes until all the solids had entered solution. The layers were separated and the aqueous extracted with ethyl ether (x2). The etheric layer was washed with saturated aqueous NaHCO$_3$, water, then dried over MgSO$_4$, filtered and concentrated. Yielding 2.98 g, of aldehyde 135 as a clear colourless oil that was used in the next step without further purification.

**Yield: 99%**

$^1$H NMR (CDCl$_3$, 300MHz): \( \delta \) 9.61 (d, \( J=1.9 \) Hz, 1H), 7.28 (d, \( J=8.6 \) Hz, 2H), 6.87 (d, \( J=8.6 \) Hz, 2H), 6.23 (d, \( J=3.0 \) Hz, 1H), 5.66 (t, \( J=7.2 \) Hz, 1H), 5.53 (s, 1H), 4.54 (s, 2H), 4.13-4.07 (m, 1H), 4.04-3.99 (m, 2H), 3.97-3.92 (m, 2H), 3.80 (s, 3H), 2.62-2.53 (m, 1H), 2.37-2.31 (m, 1H), 2.22-2.12 (m, 3H), 2.01-1.93 (m, 1H), 1.76-1.62 (m, 2H), 1.50-1.34 (m, 3H), 1.09 (d, \( J=7.0 \) Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz): \( \delta \) 205.0 (d), 158.9 (s), 135.0 (s), 131.9 (s), 130.6 (s), 129.0 (d), 126.8 (d), 126.0 (d), 113.6 (d), 101.2 (d), 72.4 (d), 69.7 (t), 64.7 (t), 55.1 (q), 46.0 (d), 30.0 (t), 28.1 (t), 27.8 (t), 26.6 (t), 22.8 (t), 13.1 (q).

IR (film, cm$^{-1}$): 2934, 2861, 1722, 1613, 1513, 1462, 1247, 1058, 945, 821.

LRMS (m/z (relative intensity)): 400 (M$^+$, 1), 264 (35), 77 (58), 91 (61), 122 (63), 132 (70), 121 (100).

HRMS calculated for C$_{24}$H$_{32}$O$_5$: 400.2250  found: 400.2253

$\alpha,\beta$-Unsaturated ester 136:

\[
\begin{align*}
\text{OPMB} & \quad \text{O} \quad \text{O} \\
\text{MeO}_2\text{C} & \quad \text{O}
\end{align*}
\]

To a cooled 0°C suspension of NaH (389 mg, 9.74 mmole) in THF (40.5 mL) was added MDEPA (1.78 mL, 9.74 mmole). After 1.25 hours at 0°C this clear
colourless solution was added via cannula to a solution of aldehyde 135 (2.98 g, 7.49 mmole) in THF (37.5 mL) at 0°C. After 30 minutes at 0°C the reaction was quenched with saturated aqueous NH₄Cl and the layers separated. The mixture was extracted with ethyl ether (x3) and the combined organics dried over MgSO₄, filtered and concentrated. The crude residue was purified by flash chromatography eluting with a 3:1 mixture of hexanes:ethyl acetate yielding 2.72 g of 136 as a single isomer.

**Yield:** 80 %

**¹H NMR** (CDCl₃, 300MHz): δ 7.27 (d, J= 8.6 Hz, 2H), 6.89-6.81 (m, J= 8.6, 8.1 Hz, 3H), 6.21 (d, J= 3.0 Hz, 1H), 5.77 (d, J= 15.7 Hz, 1H), 5.65 (t, J= 7.1 Hz, 1H), 5.53 (s, 1H), 4.54 (s, 2H), 4.12-4.06 (m, 1H), 4.04-3.99 (m, 2H), 3.97-3.92 (m, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 2.59-2.52 (m, 1H), 2.32-2.27 (m, 1H), 2.22-2.10 (m, 3H), 2.00-1.94 (m, 1H), 1.74-1.66 (m, 1H), 1.39-1.36 (m, 4H), 1.03 (d, J= 6.7 Hz, 3H).

**¹³C NMR** (CDCl₃, 75 MHz): δ 167.1 (s), 158.9 (s), 154.5 (d), 135.1 (s), 131.6 (s), 130.6 (s), 129.0 (d), 126.6 (d), 126.3 (d), 119.2 (d), 113.6 (d), 101.2 (d), 72.4 (d), 69.6 (t), 64.7 (t), 55.0 (q), 51.2 (q), 36.3 (d), 35.6 (t), 28.1 (t), 27.8 (t), 26.9 (t), 22.8 (t), 19.2 (q).

**IR** (film, cm⁻¹): 2932, 2869, 1712, 1655, 1612, 1513, 1248, 1172, 1057, 822. **LRMS** (m/z (relative intensity)): 456 (M⁺, 15), 320 (30), 77 (55), 91 (60), 122 (80), 121 (100). **HRMS** calculated for C₂₇H₃₆O₆: 456.2512 found: 456.2509

**Aldehyde-ester 137:**

A solution of acetal 136 (2.67 g, 5.84 mmole), PPTS (440 mg, 1.75 mmole), and wet acetone (117 mL) was heated to reflux for 3 hours. The solvent was removed in vacuo and the residue taken up in ethyl ether (200 mL) and washed with saturated aqueous NaHCO₃ (60 mL) and brine (60 mL). The combined aqueous layers were back extracted once with ether. The combined organics were dried over MgSO₄, filtered and concentrated. Purification by flash chromatography (3:1 Hexanes: ethyl acetate) yielded 2.23 g of aldehyde 137 as a colourless oil.

**Yield:** 92 %

**¹H NMR** (CDCl₃, 300MHz): δ 9.53 (s, 1H), 7.29 (d, J= 8.6 Hz, 2H), 6.89 (d, J= 8.6 Hz, 2H), 6.84 (dd, J= 15.7, 8.0 Hz, 1H), 6.66 (t, J= 7.3 Hz, 1H), 6.53 (d, J= 2.8 Hz, 1H), 5.77 (d, J= 15.6 Hz, 1H), 4.59 (ABQ, J= 18.4 Hz, 2H), 4.28-4.22 (m, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 2.65-2.57 (m, 1H), 2.31-2.26 (m, 1H), 2.20-2.02 (m, 4H), 1.72-1.60 (m, 1H), 1.44-1.37 (m, 4H), 1.03 (d, J= 6.7 Hz, 3H). **¹³C NMR** (CDCl₃, 75 MHz): δ 193.7 (d), 167.1 (s), 159.2 (s), 154.5 (d),
149.2 (d), 137.7 (s), 131.1 (d), 129.9 (s), 129.2 (d), 127.9 (s), 119.2 (d), 113.7 (d), 72.8 (d), 70.3 (t), 55.1 (q), 51.2 (q), 36.3 (d), 35.5 (t), 28.0 (t), 27.7 (t), 26.7 (t), 22.8 (t), 19.2 (q). IR (film, cm\(^{-1}\)): 2932, 2857, 1722, 1694, 1656, 1612, 1513, 1435, 1248, 1072, 822. LRMS (m/z (relative intensity)): 412 (M\(^+\), 3), 122 (100), 121 (75), 77 (73), 276 (20). HRMS calculated for C\(_{25}\)H\(_{32}\)O\(_5\): 412.2250 found: 412.2247

**Alcohol-aldehyde 138:**

![Chemical structure of alcohol-aldehyde 138](image)

To a cooled 0°C biphasic mixture of PMB ether 137 (744 mg, 1.80 mmole), dichloromethane (15 mL) and water (830 µL) was added DDQ (532 mg, 2.34 mmole) resulting in a deep green coloured mixture. The mixture was stirred for 2.5 hrs at which time the colour had become orange and tlc indicated reaction completion. The mixture was poured into a separatory funnel containing dichloromethane and saturated aqueous NaHCO\(_3\). The mixture was vigorously shaken and the layers separated. After extraction with dichloromethane (x3), a brine wash, drying over MgSO\(_4\), filtration and concentration *in vacuo*, the crude product was purified by flash chromatography (3:1 to 1:1 hexanes: ethyl acetate) yielded 367 mg of aldehyde 138 as a colourless oil.

**Yield:** 70 % ¹\(^1\)H NMR (CDCl\(_3\), 300MHz): \(\delta\) 9.53 (s, 1H), 6.83 (dd, J= 15.7, 8.0 Hz, 1H), 6.65 (t, J= 7.3 Hz, 1H), 6.48 (d, J= 2.9 Hz, 1H), 5.75 (d, J= 15.7 Hz, 1H), 4.57-4.51 (m, 1H), 3.70 (s, 3H), 2.56 (dt, J= 15.4, 4.9 Hz, 1H), 2.32-2.02 (m, 6H), 1.58 (dt, J= 12.3, 4.4 Hz, 1H), 1.43-1.33 (m, 4H), 1.02 (d, J= 6.7 Hz, 3H). ¹³C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 193.9 (d), 167.3 (s), 154.7 (d), 150.8 (d), 137.5 (s), 131.4 (d), 127.7 (s), 119.2 (d), 66.9 (d), 51.4 (q), 36.5 (d), 35.6 (t), 31.2 (t), 28.1 (t), 26.7 (t), 22.9 (t), 19.3 (q). IR (film, cm\(^{-1}\)): 3426, 2930, 2858, 1719, 1694, 1436, 1274, 1199, 1035, 870. LRMS (m/z (relative intensity)): 292 (M\(^+\), 1), 261 (M\(^+\)-CH\(_3\)O, 10), 133 (100), 77 (60), 95 (60). HRMS calculated for C\(_{17}\)H\(_{24}\)O\(_4\): 292.1674 found: 292.1664. HRMS calculated for C\(_{16}\)H\(_{21}\)O\(_3\) (M\(^+\)-CH\(_3\)O): 261.1491 found: 261.1479
Tetracycle 150.

To a stirred solution of aldehyde 137 (617 mg, 1.5 mmole) and ethyl vinyl ether (15 mL) was added Yb(FOD)$_3$ (237 mg, 0.22 mmole) at room temperature. After six days ethyl ether and water were added and the mixture stirred vigorously for thirty minutes. The layers were separated and the organics dried over MgSO$_4$, filtered, and concentrated. Purification by flash chromatography (6:1 hexanes:ethyl acetate) yielded 202 mg of tetracycle 150, 116 mg of tetracycle 152, 50 mg of tetracycle 153, 244 mg of tetracycle 161, and 54 mg of tetracycle 163 for an overall yield of 92%. Only tetracycles 150 and 152 could be isolated in a pure enough form for characterization.

**Yield:** 30%  $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.24 (d, J=8.6 Hz, 2H), 6.84 (d, J=8.6 Hz, 2H), 4.95 (t, J=7.3 Hz, 1H), 4.55 (d, J=11.9 Hz, 1H), 4.36 (d, J=11.9 Hz, 1H) 4.32 (m, 1H), 3.79 (s, 3H), 3.81-3.66 (m, 1H), 3.63 (s, 3H), 3.61-3.58 (m, 1H), 3.46 (dq, J=9.8, 7.0 Hz, 1H), 2.88 (dd, J=9.1, 6.5 Hz 1H), 2.37-2.32 (m, 1H), 2.17-2.04 (m, 3H), 1.96-1.88 (m, 2H), 1.76-1.62 (m, 3H), 1.59-1.47 (m, 2H), 1.36-1.20 (m, 4H), 1.19 (t, J=7.0 Hz, 3H), 1.04-0.92 (m, H), 0.89 (d, J=6.4 Hz, 3H).  

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 176.1 (s), 158.9 (s), 130.9 (s), 130.0 (s), 129.1 (d), 128.6 (s), 113.4 (d), 98.1 (d), 72.1 (d), 69.8 (t), 65.3 (d), 62.5 (t), 55.1 (q), 51.2 (q), 49.7 (d), 47.8 (d), 39.5 (d), 35.7 (t), 34.1 (d), 30.7 (t), 28.7 (t), 25.7 (t), 25.3 (t), 20.2 (t), 20.0 (q), 15.1 (q).  

**IR** (film, cm$^{-1}$): 2927, 1739, 1611, 1512, 1247, 1060, 1033, 1008

Tetracycle 152
**Yield:** 18% \( ^1 \text{H NMR} \) (CDCl\(_3\), 300MHz): \( \delta \) 7.24 (d, J= 8.6 Hz, 2H), 6.85 (d, J= 8.6Hz, 2H), 4.93 (t, J= 7.2 Hz, 1H), 4.60 (d, J= 11.2 Hz, 1H), 4.35 (d, J= 11.2 Hz, 1H), 4.29-4.26 (m, 1H), 3.82-3.70 (m, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.46 (dq, J= 9.8, J= 7.0 Hz, 1H), 3.09 (ddd, J= 11.8, 8.8, 3.1 Hz, 1H), 2.87 (dd, J= 8.8, 6.3 Hz, 1H), 2.58 (ddd, J= 13.6, 7.1, 4.2 Hz, 1H), 2.35-2.28 (m, 2H), 2.21-2.14 (m, 1H), 2.10-2.05 (m, 1H), 1.92-1.88 (m, 1H), 1.76-1.72 (m, 1H), 1.68-1.60 (m, 2H), 1.57-1.50 (m, 1H), 1.34-1.20 (m, 4H), 1.19 (t, J=7.1 Hz, 3H), 1.14-0.93 (m, 2H), 0.90 (d, J= 6.3 Hz, 3H) \( ^{13} \text{C NMR} \) (CDCl\(_3\), 75 MHz): \( \delta \) 175.6 (s), 159.1 (s), 130.9 (s), 130.6 (s), 129.9 (s), 129.3 (dx2), 113.7 (dx2), 97.6 (d), 79.7 (d), 70.2 (t), 65.1 (d), 62.8 (t), 55.3 (q), 51.5 (q), 50.0 (d), 48.0 (d), 39.9 (d), 39.0 (d), 36.0 (d), 35.7 (t), 33.3 (t), 29.0 (t), 27.3 (t), 25.8 (t), 25.1 (t), 20.2 (q), 15.3 (q)

**General procedure for the reduction of tetracycles**

To a cooled 0°C solution of tetracycles (1.0 eq.) in THF (0.09M) was added a (1.0M) THF solution of lithium aluminum hydride (2.6 eq). The mixture was warmed to room temperature and stirred for four hours. The mixture was cooled to 0°C and quenched with 2N NaOH. The resulting white suspension was filtered, and washed with THF. The was filtrate dried over MgSO\(_4\), filtered and concentrated. Flash chromatography (6:1 to 3:1 hexanes:ethyl acetate) yielded the various tetracycles.

**Tetracycle 164**

See `General procedure for the reduction of tetracycles`. Tetracycle 150 (200 mg, 0.412 mmole), LiAlH\(_4\) (1.6 mL, 1.6 mmole), THF (5 mL). Yielding 140 mg of tetracycle 164.

**Yield:** 74% \( ^1 \text{H NMR} \) (CDCl\(_3\), 300MHz): \( \delta \) 7.24 (d, J= 8.6 Hz, 2H), 6.85 (d, J= 8.6 Hz, 2H), 5.06 (t, J= 7.2 Hz, 1H), 4.55 (d, J= 11.8 Hz, 1H), 4.46-4.45 (m, 1H), 4.35 (d, J= 11.8 Hz, 1H), 3.84-3.74 (m, 1H), 3.80 (s, 3H), 3.71-3.67 (m, 1H), 3.63-3.60 (m, 1H), 3.57-3.42 (m, 2H), 3.24-3.16 (m, 1H), 2.41-2.35 (m, 1H), 2.22-2.07 (m,
3H), 2.05-1.92 (m, 3H), 1.89-1.61 (m, 4H), 1.48-1.24 (m, 3H), 1.20 (t, J= 7.1 Hz, 3H), 1.16-1.03 (m, 1H), 1.00 (d, J= 6.5 Hz, 3H), 0.97-0.88 (m, 1H), 0.11 (dt, J= 10.6, 5.0 Hz, 1H)

**Tetracycle 165**

See `General procedure for the reduction of tetracycles`. A mixture of tetracycles 153, 161, 163 (186 mg, 0.384 mmole), LiAlH₄ (32 mg, 0.844 mmole), THF (4 mL). Yielded 51.3 mg of pure 165, 29.3 mg of pure 167, 45 mg of pure 168 and 34.2 mg of a mixture of the three, overall yield 80%.

**¹H NMR** (CDCl₃, 300MHz): δ 7.24 (d, J= 8.6 Hz, 2H), 6.86 (d, J= 8.6 Hz, 2H), 5.02 (t, J= 7.3 Hz, 1H), 4.55 (d, J= 11.9 Hz, 1H), 4.43-4.42 (m, 1H), 4.35 (d, J= 11.9 Hz, 1H), 3.84-3.74 (m, 1H), 3.79 (s, 3H), 3.68-3.60 (m, 2H), 3.48 (dq, J= 9.8, 7.0 Hz, 1H), 3.29 (dd, J= 11.1, 2.6 Hz, 1H), 2.36-2.31 (m, 1H), 2.17-1.89 (m, 9H), 1.76 (dt, J= 13.8, 7.8 Hz, 1H), 1.57-1.39 (m 5H), 1.21 (t, J= 7.0 Hz, 3H), 1.09-0.98 (m, 1H), 0.95 (d, J= 7.1 Hz, 3H), 0.78-0.72 (m, 1H)

**Tetracycle 166**

See `General procedure for the reduction of tetracycles`. A mixture of tetracycles 161 and 152 (293.5 mg, 0.605 mmole), LiAlH₄ (1.2 mL, 1.2 mmole), THF (7 mL). Yielded 63 mg of pure 166, 149.4 mg of pure 165, and 8mg of a mixture of the two, overall yield 80%.

**¹H NMR** (CDCl₃, 300MHz): δ 7.25 (d, J= 8.6 Hz, 2H), 6.87 (d, J= 8.6 Hz, 2H), 5.02 (t, J= 7.2 Hz, 1H), 4.61 (d, J= 11.2 Hz, 1H), 4.41 (m, 1H), 4.35 (d, J= 11.2
Hz, 1H), 3.85-3.74 (m, 1H), 3.80 (s, 3H), 3.59-3.52 (m, 1H), 3.47 (dq, J = 9.7, 7.1 Hz, 1H), 3.22-3.17 (m, 1H), 3.07 (ddd, J = 11.7, 8.7, 3.1 Hz, 1H), 2.62 (ddd, J = 13.6, 7.2, 4.2 Hz, 1H), 2.32-2.13 (m, 4H), 2.08-2.01 (m, 1H), 1.88-1.84 (m, 1H), 1.76-1.67 (m, 2H), 1.61-1.54 (m, 1H), 1.51-1.22 (m, 4H), 1.21 (t, J = 7.1 Hz, 3H), 1.17-1.04 (m, 2H), 1.00 (d, J = 6.6 Hz, 3H), 1.23 (dt, J = 10.6, 5.0 Hz, 1H)

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.25 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.00 (t, J = 7.3 Hz, 1H), 4.60 (d, J = 11.2 Hz, 1H), 4.37-4.33 (m, 2H), 3.84-3.74 (m, 1H), 3.79 (s, 3H), 3.68-3.61 (m, 1H), 3.49 (dq, J = 9.8, 7.0 Hz, 1H), 3.24 (dd, J = 11.2, 2.6 Hz, 1H), 3.08 (dd, J = 11.6, 8.5, 3.1 Hz, 1H), 2.59 (ddd, J = 13.5, 7.0, 4.0 Hz, 1H), 2.35-2.10 (m, 4H), 2.07-1.96 (m, 2H), 1.90-1.81 (m, 2H), 1.57-1.40 (m, 5H), 1.21 (t, J = 7.1 Hz, 3H), 1.17-0.99 (m, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.73-0.66 (m, 1H).

Tetracycle 167

See procedure under Tetracycle 165 for an example.

$^1$C NMR (CDCl$_3$, 75 MHz): $\delta$ 159.0 (s), 130.9 (s), 130.6 (s), 129.3 (d), 128.5 (s), 113.7 (d), 97.5 (d), 79.7 (d), 70.3 (t), 69.6 (t), 66.9 (t), 63.0 (t), 55.2 (q), 47.0 (d), 43.6 (d), 40.0 (d), 38.4 (d), 36.4 (d), 35.9 (t), 33.5 (t), 28.8 (t), 27.1 (t), 25.9 (t), 24.8 (t), 20.2 (q), 15.1 (q)

Tetracycle 168

See procedure under Tetracycle 165 for an example
\[ ^1 \text{H NMR} \,(C_6H_6, 300MHz): \delta \ 7.24 \,(d, \ J= 8.6 \text{ Hz}, \ 2H), \ 6.78 \,(d, \ J= 8.6 \text{ Hz}, \ 2H), \ 4.52 \,(d, \ J= 11.4 \text{ Hz}, \ 1H), \ 4.44 \,(dd, \ J= 9.6, 2.1 \text{ Hz}, \ 1H), \ 4.23 \,(d, \ J= 11.4 \text{ Hz}, \ 1H), \ 4.07\-4.02 \,(m, \ 1H), \ 3.90 \,(dd, \ J= 9.4, 3.0 \text{ Hz}, \ 1H), \ 3.87 \,(dq, \ J= 9.3, 7.0 \text{ Hz}, \ 1H), \ 3.67\-3.66 \,(m, \ 1H), \ 3.32 \,(dq, \ J= 9.3, 7.0 \text{ Hz}, \ 1H), \ 3.28 \,(s, \ 3H), \ 3.01 \,(ddd, \ J= 11.5, 8.3, 3.2 \text{ Hz}, \ 1H), \ 2.95 \,(bs, \ 1H), \ 2.63 \,(ddd, \ J= 12.6, 4.8, 2.1 \text{ Hz}, \ 1H), \ 2.36 \,(m, \ 1H), \ 2.00\-1.93 \,(m, \ 1H), \ 1.83\-1.78 \,(m, \ 3H), \ 1.66\-1.61 \,(m, \ 2H), \ 1.59\-1.26 \,(m, \ 5H), \ 1.25 \,(s, \ 3H), \ 1.24\-1.00 \,(m, \ 3H), \ 1.06 \,(d, \ J= 7.0 \text{ Hz}, \ 3H), \ 0.79\-0.70 \,(m, \ 1H)\]

\[ ^13 \text{C NMR} \,(acetone \ d-6, \ 75 MHz): \delta \ 160.6 \,(s), \ 135.2 \,(s), \ 132.8 \,(s), \ 130.6 \,(d), \ 129.2 \,(s), \ 114.9 \,(d), \ 103.1 \,(d), \ 82.0 \,(d), \ 74.1 \,(d), \ 71.4 \,(t), \ 64.9 \,(t), \ 63.6 \,(t), \ 56.0 \,(q), \ 49.7 \,(d), \ 47.9 \,(d), \ 45.8 \,(d), \ 43.1 \,(d), \ 40.4 \,(t), \ 38.5 \,(t), \ 35.2 \,(d), \ 30.1 \,(t), \ 28.3 \,(t), \ 27.9 \,(t), \ 27.0 \,(t), \ 24.4 \,(q), \ 16.2 \,(q)\]

\[ \text{IR} \,(\text{CHCl}_3, \ cm^{-1}): \ 3506, \ 3008, \ 2927, \ 2857, \ 1612, \ 1513, \ 1380, \ 1066, \ 1035. \]

\[ \text{LRMS} \,(m/z \,(\text{relative intensity})): \ 456 \,(M^+, \ 5), \ 121 \,(100), \ 122 \,(89), \ 289 \,(80), \ 149 \,(63), \ 73 \,(58), \ 410 \,(20). \]

\[ \text{HRMS} \,\text{calculated for} \ C_{28}H_{40}O_5: \ 456.2876 \,\text{found:} \ 456.2868. \]

\[ \text{Melting point:} \ 131.4^\circ C\]

**Tetracycle 171**

![Diagram](image_url)

To a cooled 0°C solution of tetracycle 164 (47.7 mg, 0.104 mmole), DTBMP (86 mg, 0.416 mmole) and dichloromethane (1 mL) was added MeOTf (24 µL, 0.208 mmole). The clear solution was stirred at 0°C for a few hours before being warmed to room temperature and stirred overnight. The resulting heterogeneous mixture was quenched with methanol. Dichloromethane and saturated aqueous NaHCO\textsubscript{3} were added, the layers separated, and the product extracted with dichloromethane (x2). The combined organics were dried over MgSO\textsubscript{4}, filtered and concentrated. Flash chromatography (15:1 to 9:1 to 3:1 to 1:1 hexanes:ethyl acetate) yielded 44.7 mg of tetracycle 171 and 1.8 mg (4%) of tetracycle 164.

**Yield: 91%**

\[ ^1 \text{H NMR} \,(CDCl_3, 300MHz): \delta \ 7.25 \,(d, \ J= 8.6 \text{ Hz}, \ 2H), \ 6.85 \,(d, \ J= 8.6 \text{ Hz}, \ 2H), \ 5.03 \,(d, \ J= 7.1 \text{ Hz}, \ 1H), \ 4.55 \,(d, \ J= 7.1 \text{ Hz}, \ 1H), \ 4.36 \,(d, \ J= 11.9 \text{ Hz}, \ 1H), \ 4.23\-4.21 \,(m, \ 1H), \ 3.83\-3.72 \,(m, \ 1H), \ 3.79 \,(s, \ 3H), \ 3.60\-3.57 \,(m, \ 1H), \ 3.52\-3.42 \,(m, \ 2H), \ 3.24 \,(s, \ 3H), \ 3.11 \,(dd, \ J= 7.3, 9.2 \text{ Hz}, \ 1H), \ 2.31\-2.26 \,(m, \ 1H), \ 2.19\-1.90 \,(m, \ 6H), \ 1.75\-1.62 \,(m, \ 4H), \ 1.45\-1.21 \,(m, \ 4H), \ 1.19 \,(t, \ J= 7.1 \text{ Hz}, \ 3H), \ 1.08\-0.99 \,(m, \ 1H), \ 0.94 \,(d, \ J= 6.5 \text{ Hz}, \ 3H), \ 0.78 \,(dt, \ J= 10.5, 3.6 \text{ Hz}, \ 1H). \]

\[ ^13 \text{C NMR} \,(CDCl_3, 75 MHz): \delta \ 158.9 \,(s), \ 131.1 \,(s), \ 130.6 \,(s), \ 129.2 \,(d), \ 128.9 \,(s), \ 113.5 \,(d), \]

192
General procedure for the protection of the tetracycles as a TBS ether.

To a stirred solution of tetracycle (1.0 eq), imidazole (1.5 eq), and dichloromethane (0.1M) was added TBSCI (1.3 eq). After stirring overnight water and dichloromethane was added. The layers were separated, the aqueous extracted with dichloromethane (x2), the organics washed with brine, dried over MgSO₄, filtered and concentrated. Purification by flash chromatography (9:1 to 3:1 to 1:1 hexanes:ethyl acetate) yielded the silyl ethers 172, 173, and 175.

Tetracycle 172

See ‘General procedure for the protection of tetracycles as a TBS ether’. Tetracycle 165 (149 mg, 0.327 mmole), imidazole (33.4 mg, 0.49 mmole), TBSCI (64.1 mg, 0.425 mmole), dichloromethane (3 mL). Yielding 186 mg of 172.

Yield: 100% ¹H NMR (CDCl₃, 300MHz): δ 7.24 (d, J= 8.6 Hz, 2H), 6.85 (d, J= 8.6 Hz, 2H), 4.97 (t, J= 7.2 Hz, 1H), 4.54 (d, J= 11.9 Hz, 1H), 4.36 (d, J= 11.9 Hz, 1H), 4.21-4.19 (m, 1H), 3.87 (dd, J= 9.5, 4.4 Hz, 1H), 3.79 (s, 3H), 3.76 (dq, J= 9.9, 7.1 Hz, 1H), 3.58-3.56 (m, 1H), 3.48 (dq, J= 9.9, 7.1 Hz, 1H), 3.23 (t, J= 9.5 Hz, 1H), 2.25-2.20 (m, 1H), 2.12-1.88 (m, 9H), 1.66 (dt, J= 13.7, 7.3 Hz, 1H), 1.51 (bs, 3H), 1.47-1.33 (m, 2H), 1.19 (t, J= 7.1 Hz, 3H), 1.15-1.07 (m, 1H), 0.92 (d, J= 7.1 Hz, 3H), 0.87 (s, 9H), 0.01 (d, J= 2.2 Hz, 6H). ¹³C NMR (CDCl₃, 75 MHz): δ 158.9 (s), 131.1 (s), 129.5 (s), 129.3 (d), 113.6 (d), 98.1 (d), 72.3 (d), 69.9 (t), 66.8 (d), 64.3 (t), 62.5 (t), 55.3 (q), 43.6 (d), 43.4 (d), 34.2 (d), 33.8 (d), 33.2 (t), 33.1 (d), 30.9 (t), 30.2 (t), 25.9 (q), 25.5 (t), 20.9 (t), 20.2 (t), 18.2 (s), 15.4 (q), 13.4 (q), -5.2 (q). IR (film, cm⁻¹): 3007, 2929, 2856, 1612, 1513, 1249, 1059, 1036. LRMS (m/z (relative intensity)): 524 (M⁺ - C₂H₆O, 15), 74 (100), 403 (93), 122 (55), 303 (40), 449 (40). HRMS calculated for C_{32}H_{48}O₄Si (M⁺ - C₂H₆O): 524.3322 found: 524.3318. Melting Point: 221.8°C
Tetracycle 173

See 'General procedure for the protection of tetracycles as a TBS ether'.
Tetracycle 166 (62.6 mg, 0.137 mmole), imidazole (14.0 mg, 0.206 mmole),
TBSCI (26.9 mg, 0.178 mmole), dichloromethane (1 mL). Yielded 62.9 mg of 173
and 12 mg (19%) of tetracycle 166.

Yield: 80%

$^1$H NMR (C$_6$D$_6$, 300MHz): $\delta$ 7.26 (d, J= 8.7 Hz, 2H), 6.81 (d, J= 8.7
Hz, 2H), 5.02 (t, J= 7.1 Hz, 1H), 4.57 (d, J= 11.5 Hz, 1H), 4.41 (bs, 1H), 4.26 (d,
J= 11.5 Hz, 1H), 4.02 (dd, J= 9.6, 4.1 Hz, 1H), 3.92-3.76 (m, 2H), 3.38 (dq, J=
9.7, 7.1 Hz, 1H), 3.29 (s, 3H), 3.10-3.02 (m, 1H), 2.83 (ddd, J= 13.4, 7.3, 4.4 Hz,
1H), 2.55-2.52 (m, 1H), 2.32-2.27 (m, 1H), 2.11-2.05 (m, 2H), 1.88-0.97 (m,
12H), 1.14 (t, J= 7.1 Hz, 3H), 1.05 (d, J= 5.9 Hz, 3H), 0.99 (s, 9H), 0.09 (d, J= 1.3
Hz, 6H).

$^{13}$C NMR (C$_6$D$_6$, 75 MHz): $\delta$ 159.6 (s), 132.6 (s), 131.7 (s), 129.6 (s),
129.3 (d), 128.6 (d), 114.0 (d), 98.0 (d), 80.3 (d), 70.3 (t), 66.8 (d), 64.3 (t), 62.9
(t), 54.7 (q), 46.0 (d), 43.4 (d), 41.0 (d), 38.5 (d), 37.1 (t), 36.8 (d), 34.5 (t), 29.6
(t), 27.6 (t), 26.3 (q), 25.1 (t), 21.1 (q), 18.7 (s), 15.5 (q), -5.0 (q), -5.1 (q)

Tetracycle 175

See 'General procedure for the protection of tetracycles as a TBS ether'.
Tetracycle 168 (42.5 mg, 0.093 mmole), imidazole (12 mg, 0.176 mmole), TBSCI
(17 mg, 0.179 mmole), dichloromethane (1 mL). Yielding 47.4 mg of 175.

Yield: 89%

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.25 (d, J= 8.6 Hz, 2H), 6.86 (d, J= 8.6
Hz, 2H), 4.61-4.55 (m, 2H), 4.37 (d, J= 11.0 Hz, 1H), 3.94 (dq, J= 9.7, 7.1 Hz,
1H), 3.87-3.76 (m, 3H), 3.79 (s, 3H), 3.56 (dq, J= 9.7, 7.0 Hz, 1H), 3.15-3.07 (m, 1H), 2.45 (ddd, J= 12.3, 5.0, 2.0 Hz, 1H), 2.34 (m, 1H), 2.13-1.92 (m, 5H), 1.73-1.62 (m, 5H), 1.40-1.10 (m, 4H), 1.23 (t, J= 7.0 Hz, 3H), 1.03-0.80 (m, 1H), 0.92 (d, J= 5.9 Hz, 3H), 0.88 (s, 9H), 0.04 (d, J= 1.8 Hz, 6H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) : $\delta$ 159.0 (s), 133.7 (s), 130.8 (s), 129.2 (d), 127.8 (s), 113.7 (d), 101.7 (d), 81.2 (d), 70.7 (t), 70.6 (d), 64.2 (t), 62.1 (t), 55.2 (q), 48.7 (d), 46.7 (d), 44.2 (d), 41.8 (d), 39.3 (t), 37.0 (t), 33.5 (d), 28.5 (t), 27.0 (t), 26.6 (t), 25.8 (t), 25.8 (q), 23.4 (q), 18.1 (s), 15.2 (q), -5.4 (q).

LRMS (m/z (relative intensity)) : 570 (M$^+$, 1), 513 (M$^+$ - C$_4$H$_9$, 10), 73 (100), 121 (80), 403 (25).

HRMS calculated for C$_{30}$H$_{45}$O$_5$Si (M$^+$ - C$_4$H$_9$): 513.3036 found: 513.3042

General procedure for the removal of the PMB group from the tetracycles

To a cooled 0°C solution of tetracycle (1.0 eq), dichloromethane:H$_2$O (18:1, 0.13M) was added DDQ (1.3 eq.). After 0.5 to 2 hours dichloromethane and saturated aqueous NaHCO$_3$ were added. The aqueous layer was extracted with dichloromethane (x3), and the organics dried over MgSO$_4$, filtered and concentrated. Flash chromatography (9:1 to 1:1 hexanes:ethyl acetate) yielded tetracycles 176 and 179.

Tetracycle 176

See `General procedure for removal of PMB group from the tetracycles`. Tetracycle 171 (29.1 mg, 0.062 mmole), dichloromethane (520 µL), H$_2$O (30 µL), DDQ (17 mg, 0.074 mmole), reaction time 2 hours. Yielding 7.9 mg of 176 as a clear colourless film.

**Yield: 36%** $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 5.07 (t, J= 6.9Hz, 1H), 4.21-4.18 (m, 1H), 3.90 (m, 1H), 3.77 (dq, J= 9.7, 7.1 Hz, 1H), 3.52-3.42 (m, 2H), 3.24 (s, 3H), 3.14 (dd, J= 9.2, 7.0 Hz, 1H), 2.32-2.27 (m, 1H), 2.20-2.03 (m, 4H), 1.99-1.90 (m, 2H), 1.78-1.68 (m, 3H), 1.63-1.44 (m, 2H), 1.39-1.23 (m, 3H), 1.19 (t, J= 7.1 Hz, 3H), 1.08-1.00 (m, 1H), 0.95 (d, J= 6.4Hz, 3H), 0.81 (dt, J= 9.5, 3.8 Hz, 1H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) : $\delta$ 130.0 (s), 128.8 (s), 97.7 (d), 74.4 (t), 66.8 (d), 66.3 (d), 62.7 (t), 58.9 (q), 47.1 (d), 41.2 (d), 40.9 (d), 38.1 (d), 36.5 (t), 34.2 (d), 30.9 (t), 29.2 (t), 28.8 (t), 26.3 (t), 20.5 (q), 19.2 (t), 15.3 (q). IR (film, cm$^{-1}$): 3448,
2921, 1447, 1380, 1338, 1115, 1061, 1010, 958. LRMS (m/z (relative intensity)): 350 (M\(^+\), 1), 304 (M\(^+\)-C\(_2\)H\(_6\)O, 100), 332 (M\(^+\)-H\(_2\)O, 5), 241 (80). HRMS calculated for C\(_{21}\)H\(_{32}\)O\(_3\) (M\(^+\)-H\(_2\)O): 332.2351 found: 332.2356

**Tetracycle 179**

![Tetracycle 179](image)

See `General procedure for removal of PMB group from the tetracycles`. Tetracycle 175 (45.9 mg, 0.080 mmole), dichloromethane (670 µL), H\(_2\)O (35 µL), ethanol (35 µL), DDQ (27 mg, 0.12 mmole), reaction time 0.5 hours, yielding 18.0 mg of 179 as a colourless film.

**Yield:** 50% \(^1\)H NMR (CDCl\(_3\), 300MHz): \(\delta\) 4.58 (dd, J= 9.6, 2.2 Hz, 1H), 3.93 (dq, J= 9.7, 7.1 Hz, 1H), 3.86-3.76 (m, 3H), 3.56 (dq, J= 9.7, 7.1 Hz, 1H), 3.40-3.33 (m, 1H), 2.38 (ddd, J= 12.4, 5.0, 2.2 Hz, 1H), 2.21-2.16 (m, 1H), 2.12-2.06 (m, 1H), 1.98-1.84 (m, 3H), 1.75-1.59 (m, 5H), 1.52-1.33 (m, 3H), 1.22 (t, J= 7.0 Hz, 3H), 1.21-1.10 (m, 1H), 1.04-0.80 (m, 2H), 0.91 (d, J= 6.1, 3H), 0.89 (s, 9H), 0.04 (d, J=2.1 Hz, 6H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 133.9 (s), 127.4 (s), 101.7 (d), 74.2 (d), 70.6 (d), 64.2 (t), 62.1 (t), 48.8 (d), 46.8 (d), 44.2 (d), 43.7 (d), 39.0 (t), 37.0 (t), 33.5 (d), 31.6 (t), 28.6 (t), 26.7 (t), 25.9 (q), 25.8 (t), 23.4 (q), 18.1 (s), 15.3 (q), -5.4 (q). LRMS (m/z (relative intensity)): 450 (M\(^+\), 3), 74 (100), 375 (50), 393 (45), 347 (45), 255 (43). HRMS calculated for C\(_{26}\)H\(_{46}\)O\(_4\)Si: 450.3165 found: 450.3160

**Tetracycle 180**

![Tetracycle 180](image)
See `General procedure for the reduction of tetracycles (page 186)`. Mixture of tetracycles 200, 201, 202 (213 mg, 0.584 mmole), THF (8 mL), (1.0M) LiAlH₄ (1.5 mL, 1.5 mmole), reaction time 4 hours, yielded 88.7 mg of tetracycle 180 as a white solid, and 50.8 mg (26%) of a mixture of other tetracyclic diols.

**Yield:** 45% 

**¹H NMR** (CDCl₃, 300MHz): \(\delta\) 5.11 (t, J= 7.1 Hz, 1H), 4.45 (m, 1H), 3.97-3.94 (m, 1H), 3.79 (dq, J= 9.7, 7.1 Hz, 1H), 3.58-3.51 (m, 1H), 3.47 (dq, J= 9.6, 7.0 Hz, 1H), 3.23-3.19 (m, 1H), 2.40-2.35 (m, 1H), 2.23-1.89 (m, 6H), 1.78-1.49 (m, 5H), 1.45-1.35 (m, 1H), 1.33-1.12 (m, 2H), 1.20 (t, J= 7.1 Hz, 3H), 1.08-0.88 (m, 1H), 1.01 (d, J= 6.5 Hz, 3H), 0.14 (dt, J= 10.6, 5.0 Hz, 1H).  

**¹³C NMR** (CDCl₃, 75 MHz): \(\delta\) 130.8, 129.0, 97.8, 70.0, 67.0, 66.0, 63.1, 47.0, 43.6, 40.2, 38.4, 36.1, 34.6, 30.8, 29.2, 28.7, 25.9, 20.3, 19.3, 15.2.  

**LRMS** (m/z (relative intensity)): 336 (M⁺, 3), 319 (M⁺-H₂O, 8), 290 (100), 242 (95), 241 (72), 84 (63).  

**HRMS** calculated for C₂₀H₃₂O₄: 336.2300 found: 336.2296

**Tetracycle 182**

[Diagram of Tetracycle 182]

To an oil free suspension of KH (1.8 mg, 0.045 mmole) and THF (300 µL), was added a solution of tetracycle 181 (10.1 mg, 0.022 mmole) and THF (400 µL) via cannula. After H₂ evolution had ceased, PMBCl (6 µL, 0.045 mmole) was added. The reaction was stirred at room temperature for 3 hours before saturated aqueous NH₄Cl was added. The aqueous layer was extracted with Et₂O (x3), dried over MgSO₄, filtered and concentrated. Purification by flash chromatography (15:1 to 6:1 hexanes:ethyl acetate) yielded 10.5 mg of tetracycle 182.

**Yield:** 82%  

**¹H NMR** (CDCl₃, 300MHz): \(\delta\) 7.25 (d, J= 8.0 Hz, 2H), 6.85 (d, J= 8.6 Hz, 2H), 5.01 (t, J= 7.1 Hz, 1H), 4.55 (d, J= 12.2 Hz, 1H), 4.36 (d, J= 11.9 Hz, 1H), 4.20 (bm, 1H), 3.80 (s, 3H), 3.76 (dq, J= 9.9, 7.1 Hz, 1H), 3.65 (dd, J= 9.6, 4.0 Hz, 1H), 3.59-3.56 (m, 1H), 3.51-3.42 (m, 2H), 2.31-2.26 (m, 1H), 2.14-1.88 (m, 6H), 1.77-1.61 (m, 5H), 1.46-1.14 (m, 4H), 1.19 (t, J= 7.1 Hz, 3H), 1.06-0.98 (m, 1H), 0.94 (d, J= 6.5 Hz, 3H), 0.85 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H)

**Tetracycle 183**
A solution of tetracycle 176 (17.2 mg, 0.049 mmole), 18-crown-6 (17 mg, 0.064 mmole) and THF (500 µL + 500 µL rinse), was added via cannula to an oil free suspension of KH (6 mg, 0.148 mmole) and THF (500 µL) at room temperature. After H₂ evolution had ceased a solution of ICH₂SnBu₃ (31.6 mg, 0.073 mmole) and THF (500 µL) was added via cannula. After 4 hours the resulting suspension was cooled to 0°C and quenched with saturated aqueous NH₄Cl, the layers were separated and the aqueous extracted with ethyl ether (x3). The organics were dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography (hexane to 25:1 to 15:1 to 9:1 to 3:1 to 1:1 hexanes:ethyl acetate) yielded 18.0 mg of stannane 183 and 3.8 mg of methyl ether 184.

**Yield:** 53% ¹H NMR (CDCl₃, 300MHz): δ 5.02 (t, J= 7.1 Hz, 1H), 4.17 (m, 1H), 3.86-3.72 (m, 2H), 3.51-3.44 (m, 3H), 3.28-3.27 (m, 1H), 3.25 (s, 3H), 3.09 (dd, J= 9.1, 7.5 Hz, 1H), 2.29-2.12 (m, 3H), 2.01-1.76 (m, 4H), 1.71-1.57 (m,4H), 1.54-1.42 (m, 6H), 1.39-1.24 (m, 9H), 1.19 (t, J= 7.1 Hz, 3H), 1.09-1.01 (m, 1H), 0.94 (d, J= 6.5 Hz, 3H), 0.91-0.82 (m, 15H), 0.80-0.72 (m, 2H).  IR (film, cm⁻¹): 2919, 1455, 1377, 1118, 1064, 1016, 952.  LRMS (m/z (relative intensity)): 654 (M⁺, 2), 597 (M⁺-C₄H₉, 15), 291 (100), 75 (73), 551 (50).  HRMS calculated for C₃₀H₅₃O₄Sn (M⁺-C₄H₉): 597.2966 found: 597.2972

**Tetracycle 200**

To a stirred solution of aldehyde 138 (408 mg, 1.4 mmole) and ethyl vinyl ether (14 mL) was added Yb(FOD)₃ (222 mg, 0.21 mmole) at room temperature. After six days ethyl ether and water were added and the mixture stirred vigorously for thirty minutes. The layers were separated and the organics dried over MgSO₄,
filtered, and concentrated. Purification by flash chromatography (3:1 hexanes:ethyl acetate) yielded 100 mg of tetracycle 200, 122 mg of tetracycle 201, 111 mg of tetracycle 202, 59 mg of tetracycle 203, and 36 mg of tetracycle 213 for an overall yield of 84%.

Yield: 23% 1H NMR (CDCl₃, 300MHz): δ 5.00 (t, J=7.1 Hz, 1H), 4.33-4.29 (m, 1H), 3.92 (dt, J=4.1, 1.6 Hz, 1H), 3.78 (dq, J=9.8, 7.1 Hz, 1H), 3.63 (s, 3H), 3.46 (dq, J=9.8, 7.1 Hz, 1H), 2.90 (dd, J=9.0, 6.4 Hz, 1H), 2.39-2.33 (m, 1H), 2.17-2.13 (m, 1H), 2.08-1.92 (m, 3H), 1.77-1.63 (m, 4H), 1.55 (dt overlapped with m, J=13.8, 7.2 Hz, 2H), 1.33-1.18 (m, 3H), 1.19 (t, J=7.1Hz, 3H), 1.00-0.92 (m, 1H), 0.89 (d, J=6.3Hz, 3H). 13C NMR (CDCl₃, 75 MHz): δ 175.2 (s), 129.4 (s), 98.5 (d), 66.0 (d), 63.0 (t), 51.0 (q), 50.0 (d), 48.1 (d), 39.7 (d), 39.1 (d), 36.0 (t), 34.6 (d), 31.3 (t), 29.6 (t), 28.9 (t), 26.0 (t), 20.4 (q), 19.8 (t), 15.5 (q). IR (film, cm⁻¹): 3499, 2927, 2853, 1738, 1434, 1370, 1281, 1151, 1060, 1012, 755. LRMS (m/z (relative intensity) chemical ionization NH₃): 301(100), 318 (70), 300 (55), 319 (48), 363 (M⁺-H, 5). HRMS calculated for C₂₁H₃₁O₅ (M-H): 363.2171 found: 363.2180

Tetracycle 201

![Image of Tetracycle 201](image)

Yield: 29% 1H NMR (CDCl₃, 300MHz): δ 4.61 (dd, J=8.2, 2.3Hz, 1H), 4.03-4.01 (m, 1H), 3.88-3.86 ( m, 1H), 3.84 (dq, J=9.5, 7.1Hz, 1H), 3.66 (s, 3H), 3.44 (dq, J=9.5, 7.0Hz, 1H), 2.73 (dd, J=11.5, 7.1Hz, 1H), 2.50-2.47 (m, 1H), 2.28-2.20 (m, 2H), 2.15-2.07 (m, 1H), 1.99-1.69 (m, 5H), 1.65-1.44 (m, 4H), 1.38-1.20 (m, 2H), 1.17 (t, J=7.1Hz, 3H), 1.12-1.02 (m, 1H), 0.85 (d, J=6.5 Hz,3H). 13C NMR (CDCl₃, 75 MHz): δ 174.3 (s), 133.0 (s), 123.3 (s), 100.2 (d), 69.8 (d), 66.6 (d), 63.1 (t), 51.1 (q), 49.6 (d), 43.5 (d), 39.6 (d), 38.8 (d), 36.3 (t), 32.3 (t), 29.0 (t), 26.4 (t), 21.5 (t), 20.6 (q), 15.0 (q)

Tetracycle 202
Yield: 26% ¹H NMR (CDCl₃, 300MHz): δ 4.96 (t, J=7.2 Hz, 1H), 4.31-4.28 (m, 1H), 3.80 (dq, J=9.8, 7.1 Hz, 1H), 3.64 (s, 3H), 3.49 (dq, J= 9.8, 7.1Hz, 1H), 3.35 (ddd, J= 11.9, 8.4, 3.5 Hz, 1H), 2.89 (dd, J= 8.9, 6.3 Hz, 1H), 2.55 (ddd, J= 4.2, 7.1, 6.4 Hz, 1H), 2.31-2.26 (m, 1H), 2.17-2.09 (m, 2H), 2.00-1.89 (m, 2H), 1.77-1.61 ( m, 4H), 1.51 (m, 2H), 1.34-1.21 (m, 2H), 1.20 (t, J= 7.1 Hz, 3H), 1.19-1.08 (m, 1H), 1.00-0.94 (m, 1H), 0.90 (d, J= 6.4Hz, 3H)

Tetracycle 202B

To a suspension of tetracycle 202 (16 mg, 0.043 mmole), MOM-ON (16.0 mg, 0.103 mmole), NaOAc (6 mg, 0.072 mmole), and THF (500 µL) was added a solution of AgOTf (24.0 mg, 0.094 mmole) and THF (500 µL) rapidly via cannula. A suspension formed immediately, after 10 minutes the mixture was quenched with toluene and brine. The organics were washed with 1 N HCl, saturated aqueous NaHCO₃, dried over MgSO₄, filtered and concentrated. Purification by flash chromatography yielded 1.6 mg of tetracycle 202B and 6.4 mg of tetracycle 202 (24%)

Yield: % ¹H NMR (CDCl₃, 300MHz): δ 4.95 (t, J= 7.2Hz, 1H), 4.77 (d, J= 6.9 Hz, 1H), 4.59 (d, J= 6.9 Hz, 1H), 4.32-4.29 (m, 1H), 3.80 (dq, J= 9.8, 7.1 Hz, 1H), 3.63 (s, 3H), 3.47 (dq, J= 9.8, 7.1 Hz, 1H), 3.37 (s, 3H), 3.31-3.23 (m, 1H), 2.88 (dd, J= 8.9, 6.4 Hz, 1H), 2.54 (ddd, J= 13.5, 7.1, 4.3 Hz, 1H), 2.31-2.26 (m, 2H), 2.16-2.04 (m, 2H), 1.93-1.90 (m, 1H), 1.76-1.57 (m, 3H), 1.35-1.19 (m, 3H), 1.20 (t, J= 7.1 Hz, 3H), 1.17-1.08 (m, 1H), 0.99-0.94 (m, 1H), 0.90 (d, J= 6.4 Hz, 3H)
IR (film, cm⁻¹): 2927, 2359, 1739, 1366, 1150, 1106, 1039. LRMS (m/z (relative intensity)): 346 (M – C₂H₄O₂, 100), 282 (91), 212(68), 241(50), 300(50), 406 (M⁺, 2). HRMS calculated for C₂3H₃₄O₆: 406.2355 found: 406.2363

Tetracycle 203

Yield: 14% ¹H NMR (CDCl₃, 300MHz): δ 4.50 (dd, J = 9.7, 1.8Hz, 1H), 3.84-3.77 (m, 2H), 3.65 (s, 3H), 3.47-3.39 (m, 2H), 2.67 (dd, J = 11.9, 7.2Hz, 1H), 2.36-2.29 (m, 1H), 2.15-2.00 (m, 4H), 1.96-1.76 (m, 3H), 1.67-1.58 (m, 3H), 1.50-1.21 (m, 4H), 1.17 (t, J=7.1Hz, 3H), 1.02-0.89 (m, 1H), 0.83 (d, J=6.1 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 173.4 (s), 132.8 (s), 124.6 (s), 101.5 (d), 73.3 (d), 69.4 (d), 63.7 (t), 50.9 (q), 49.0 (d), 44.3 (d), 43.0 (d), 41.9 (d), 39.9 (d), 37.6 (t), 36.5 (t), 31.2 (t), 29.2 (t), 26.7 (t), 20.6 (q), 15.0 (q). Melting point: 159.4°C (yellow-white solid)

Tetracycle 213 (enantiomer shown)

Yield: 8% ¹H NMR (CDCl₃, 300MHz): δ 4.95 (t, J = 7.2 Hz, 1H), 4.28-4.25 (m, 1H), 3.75 (dq, J= 9.8, 7.1 Hz, 1H), 3.66 (s, 3H), 3.46 (dq, J= 9.8, 7.1 Hz, 1H), 3.45-3.36 (m, 1H), 2.91 (t, J= 8.4 Hz, 1H), 2.49 (ddd, J = 13.6, 6.8, 4.2 Hz, 1H), 2.37-2.30 (m, 1H), 2.16-2.05 (m, 2H), 2.02-1.77 (m, 4H), 1.69-1.58 (m, 4H), 1.56-1.42 (m, 4H), 1.28-1.23 (m, 1H), 1.19 (t, J= 7.1 Hz, 3H), 0.92 (d, J= 7.1 Hz, 3H)
General procedure for the protection of C13 alcohol of tetracycles as a TBS ether

To a stirred solution of tetracycle (1.0 eq.), imidazole (2.5 eq.), and dichloromethane (0.54 M) was added TBSCl (1.3 eq.). The mixture was stirred overnight and quenched with H₂O and dichloromethane. The aqueous layer was extracted with dichloromethane (x2), and the organics washed with brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (15:1 to 6:1 to 1:1 hexanes:ethyl acetate) yielded the tetracycles as silyl ether. This method was used to convert tetracycles 200, 201, 202, 203 and 213 into tetracycles 215, 216, 217, 218, and 219 respectively.

Tetracycle 215

See `General procedure for the protection of the C13 alcohol of tetracycles as a TBS ether`. Tetracycle 200 (183.5 mg, 0.503 mmole), imidazole (51.4 mg, 0.754 mmole), TBSCI (98.6 mg, 0.654 mmole), dichloromethane (5 mL). Yielded 100 mg of 215 and 110 mg of 200 (60%)

Yield: 40% ¹H NMR (C₆D₆, 300MHz): δ 5.06 (t, J= 7.3 Hz, 1H), 4.45-4.42 (m, 1H), 3.92 (dq, J= 9.7, 7.1 Hz, 1H), 3.73-3.71 (m, 1H), 3.45 (dq, J= 9.7, 7.0 Hz, 1H), 3.48 (s, 3H), 2.93 (dd, J=8.9, 6.1 Hz, 1H), 2.38-2.19 (m, 2H), 2.01-1.92 (m, 1H) 1.89-1.81 (m, 2H), 1.79-1.71 (m, 2H), 1.62-1.52 (m, 2H), 1.48-1.44 (m, 1H), 1.38-1.32 (m, 2H), 1.17 (t, J=7.1 Hz, 3H), 1.13-0.97 (m, 3H) 0.91 (d, J=9.8Hz, 3H), 0.90 (s, 9H), 0.88-0.81 (m, 1H), 0.00 (s, 3H), -0.01 (s, 3H). ¹³C NMR (C₆D₆, 75 MHz): δ 175.3 (s), 129.7 (s), 98.8 (d), 67.5 (d), 66.2 (d), 63.0 (t), 51.1 (q), 50.1 (d), 48.3 (d), 39.7 (d), 39.1 (d), 36.1 (t), 35.2 (t), 30.5 (t), 29.2 (t), 26.1 (q) 20.5 (q), 18.4 (s), 15.6 (q), -4.3 (q), -4.6 (q). IR (film, cm⁻¹): 2928, 2855, 1738, 1462, 1370, 1251, 1105, 1008, 835. LRMS (m/z (relative intensity)): 74 (100), 189(90), 432 (M⁺-C₂H₅O, 70) 375(60), 300 (50). HRMS calculated for C₂₅H₄₀O₄Si (M-C₂H₅O): 432.2696 found: 432.2688

Tetracycle 216
See `General procedure for the protection of the C13 alcohol of tetracycles as a TBS ether`. A mixture of 200, 201, 202, and 213 (289.5 mg, 0.794 mmole), imidazole (135 mg, 1.98 mmole), TBSCl (156 mg, 1.03 mmole), and dichloromethane (1.5 mL). Yielded: 103.3 mg of pure 216, 145 mg of pure 217, and 74.3 mg of a mixture of 215 and 219. Overall yield of 85%.

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 4.55-4.51 (m, 1H), 3.93-3.92 (m, 1H), 3.84-3.79 (m, 2H), 3.67 (s, 3H), 3.46 (dq, $J=9.7$, 7.1 Hz, 1H), 2.67 (dd, $J=12.2$, 7.0 Hz, 1H), 2.29-2.26 (m, 2H), 2.13-2.08 (m, 1H), 1.79-1.56 (m, 8H), 1.41-1.40 (m, 2H), 1.26-1.23 (m, 2H), 1.19 (t, $J=7.1$ Hz, 3H), 1.04-1.00 (m, 1H), 0.86 (s, 9H), 0.85 (d, $J=5.9$ Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

Tetracycle 217

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 175.7 (s), 130.4 (s), 129.8 (s), 97.6 (d), 73.8 (d), 65.0 (d), 62.8 (t), 51.4 (q), 49.8 (d), 48.0 (d), 39.8 (d), 39.0 (d), 38.1 (d), 35.7 (t), 33.4 (t), 32.2 (t), 28.9 (t), 25.8 (q), 25.1 (t), 20.2 (q), 18.0 (s), 15.3 (q), -4.0 (q), -4.6 (q).

Tetracycle 218

See tetracycle 216 for details.

$^1$H NMR (CDCl$_3$, 200MHz): $\delta$ 4.93 (t, $J=7.1$Hz, 1H), 4.29-4.25 (m, 1H), 3.78 (dq, $J=9.8$, 7.1 Hz, 1H), 3.62 (s, 3H), 2.86 (dd, $J=8.9$, 6.4 Hz, 1H), 2.46 (ddd, $J=7.2$, 7.1, 4.3 Hz, 1H), 2.22-2.07 (m, 3H), 1.91-1.81 (m, 2H), 1.75-1.61 (m, 5H), 1.32-1.23 (m, 2H), 1.20 (t, $J=7.1$ Hz, 3H), 0.89 (d, $J=6.8$ Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).
See `General procedure for the protection of the C13 alcohol of tetracycles as a TBS ether`. A mixture of 201, 202, 203, and 213 (260.4 mg, 0.714 mmole), imidazole (122 mg, 1.79 mmole), TBSCl (140 mg, 0.93 mmole), and dichloromethane (1.3 mL). Yielded: 33 mg of pure 217, 102 mg of pure 218, 49.6 mg of pure 219, and 123.6 mg of a mixture of 216 and 218. Overall yield of 90%

\[ \text{\textsuperscript{1}H NMR (CDCl}_3, 300MHz): \delta 4.49 (dd, J= 9.7, 2.1 Hz, 1H), 3.85-3.79 (m, 2H), 3.67 (s, 3H), 3.46 (dq, J= 9.5, 7.1 Hz, 1H), 3.43-3.30 (m, 1H), 2.69 (dd, J= 12.0, 7.3 Hz, 1H), 2.28-2.23 (m, 1H), 2.17-2.06 (m, 3H), 2.04-1.97 (m, 1H), 1.84-1.77 (m, 2H), 1.68-1.59 (m, 2H), 1.56 (bs, 2H), 1.49-1.28 (m, 2H), 1.27-1.20 (m, 2H), 1.19 (t, J= 7.1 Hz, 3H), 1.03-1.02 (m, 1H), 0.88 (s, 9H), 0.87 (d, J= 6.0 Hz, 3H), 0.05 (s, 6H). \]

\[ \text{\textsuperscript{13}C NMR (CDCl}_3, 75 MHz): \delta 173.4 (s), 132.6 (s), 125.1 (s), 101.8 (d), 74.3 (d), 69.4 (d), 63.7 (t), 50.9 (q), 49.0 (d), 44.3 (d), 43.5 (d), 41.9 (d), 39.9 (d), 37.6 (t), 36.5 (t), 31.7 (t), 29.3 (t), 26.8 (t), 26.7 (t), 25.8 (q), 20.7 (q), 17.9 (s), 15.0 (q), -4.2 (q), -4.7 (q) \]

Tetracycle 219

See tetracycle 218 for details

\[ \text{\textsuperscript{1}H NMR (CDCl}_3, 300MHz): \delta 4.93 (t, J= 7.2 Hz, 1H), 4.28-4.25 (m, 1H), 3.76 (dq, J= 9.7, 7.1 Hz, 1H), 3.66 (s, 3H), 3.45 (dq, J= 9.7, 7.1 Hz, 1H), 3.44-3.34 (m, 1H), 2.89 (t, J= 8.6 Hz, 1H), 2.43-2.27 (m, 2H), 2.18-2.07 (m, 1H), 2.05-1.82 (m, 6H), 1.70-1.55 (m, 3H), 1.51-1.44 (m, 3H), 1.20 (t, J= 7.1 Hz, 3H), 1.14-1.08 (m, 1H), 0.91 (d, J= 7.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) \]

Tetracycle 219B
See ‘General procedure for the reduction of tetracycles (page 186)’. Tetracycle 215 (75.6 mg, 0.158 mmole), LiAlH₄ (410 µL, 0.410 mmole), THF (2.2 mL). Yielding 51.1 mg of 219B and 6.8 mg of 219C.

**Yield:** 71% ¹H NMR (CDCl₃, 300MHz): δ 5.05 (t, J= 7.3 Hz, 1H), 4.43 (m, 1H), 3.95 (t, J= 4.0 Hz, 1H), 3.78 (dq, J= 9.8, 7.1 Hz, 1H), 3.53 (dd, J= 10.8, 10.4 Hz, 1H), 3.46 (dq, J= 9.8, 7.1 Hz, 1H), 3.19 (dd, J= 11.2, 2.3 Hz, 1H), 2.31-2.26 (m, 1H), 2.20-2.09 (m, 2H), 1.98-1.24 (m, 12H), 1.20 (t, J= 7.1 Hz, 3H), 1.17-1.06 (m, 1H), 0.99 (d, J= 6.5 Hz, 3H), 0.97-0.90 (m, 1H), 0.86 (s, 9H), 0.10 (dt, J= 10.7, 5.0 Hz, 1H), 0.03 (d, J= 2.1 Hz, 6H). ¹³C NMR (CDCl₃, 75 MHz): δ 130.6 (s), 129.0 (s), 98.2 (d), 70.3 (d), 67.0 (t), 66.6 (d), 63.0 (t), 47.0 (d), 43.4 (d), 40.0 (d), 38.4 (d), 36.1 (t), 35.2 (d), 31.4 (t), 30.0 (t), 28.7 (t), 25.9 (q), 20.2 (q), 19.7 (t), 18.1 (s), 15.1 (q), -4.5 (q), -4.7 (q). IR (film, cm⁻¹): 3548, 2927, 2854, 1460, 1384, 1253, 1103, 1061, 1004, 832. LRMS (m/z (relative intensity)): 450 (M⁺, 5), 404 (M⁺ - C₂H₆O, 100), 347 (95), 75 (90). HRMS calculated for C₂₆H₄₆O₄Si: 450.3165 found: 450.3174. HRMS calculated for C₂₄H₄₀O₃Si (M⁺ - C₂H₆O): 404.2747 found: 404.2757

**Tetracycle 219C**

Yield: 8% ¹H NMR (CDCl₃, 300MHz): δ 4.68 (dd, J= 9.2, 2.9 Hz, 1H), 3.95-3.85 (m, 4H), 3.76 (bs, 1H), 3.55 (dq, J= 9.5, 7.1 Hz, 1H), 2.31-2.01 (m, 4H), 1.90-1.60 (m, 9H), 1.59-1.52 (m, 4H), 1.45-1.39 (m, 1H), 1.23 (t, J= 7.1 Hz, 3H), 0.87 (d, J= 7.3 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H).
Tetracycle 219D

To a cooled 0°C solution of tetracycle 219B (51.1 mg, 0.113 mmole), DTBMP (93 mg, 0.452 mmole) and dichloromethane (1 mL) was added MeOTf (26 µL, 0.226 mmole). The clear solution was stirred at 0°C for a 15 minutes before being warmed to room temperature and stirred overnight. The resulting heterogeneous mixture was quenched with methanol. Dichloromethane and saturated aqueous NaHCO$_3$ were added, the layers separated, and the product extracted with dichloromethane (x2). The combined organics were dried over MgSO$_4$, filtered and concentrated. Flash chromatography (15:1 hexanes:ethyl acetate) yielded 42.1 mg of tetracycle 219D.

**Yield: 80%**

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 5.02 (t, J= 7.2 Hz, 1H), 4.20-4.18 (m, 1H), 3.94-3.92 (m,1H), 3.77 (dq, J= 7.1, 9.9 Hz, 1H), 3.54-3.43 (m, 2H), 3.24 (s, 3H), 3.09 (dd, J= 9.2, 7.3 Hz, 1H), 2.22-2.12 (m, 3H), 1.95-1.82 (m, 3H), 1.80-1.65 (m, 4H), 1.53-1.40 (m, 2H), 1.36-1.21 (m, 3H), 1.20 (t, J= 7.1 Hz, 3H), 1.07-0.99 (m, 1H), 0.94 (d, J= 6.4 Hz, 3H), 0.86 (s, 9H), 0.76 (dt, J= 10.5, 3.7 Hz, 1H), 0.03 (d, J= 1.7 Hz, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 130.3 (s), 128.7 (s), 98.3 (d), 74.7 (t), 67.2 (d), 66.9 (d), 62.6 (t), 58.9 (q), 47.3 (d), 41.2 (d), 40.8 (d), 38.1 (d), 36.7 (t), 34.8 (d), 31.6 (t), 30.2 (t), 29.0 (t), 26.5 (t), 26.0 (q), 20.6 (q), 19.8 (t), 18.2 (s), 15.3 (q), -4.4 (q), -4.6. IR (film, cm$^{-1}$): 2927, 2855, 1461, 1384, 1253, 1118, 1065, 1015, 832. LRMS (m/z (relative intensity)): 464 (M$^+$, 4), 418 (M$^+$-C$_2$H$_6$O, 100), 74 (98), 361 (68). HRMS calculated for C$_{27}$H$_{48}$O$_4$Si: 464.3322 found: 464.3312. HRMS calculated for C$_{25}$H$_{42}$O$_3$Si(M$^+$-C$_2$H$_6$O): 418.2903 found: 418.2895

MOM acetal 225.

To a stirred solution of alcohol 224 (420 mg, 2.75 mmole) and dimethoxymethane (14 mL) was added LiBr (240 mg, 2.76 mmole) and TsOH (53 mg, 0.28 mmole). After two days both water and ethyl ether were added, the
layer were separated and the aqueous extracted with ethyl ether (x3). The organics were dried over MgSO₄, filtered and concentrated. Purification by flash chromatography (15:1 hexanes:ethyl acetate) yielded 461 mg of 225 as a clear colourless oil.

**Yield:** 85% ¹H NMR (CDCl₃, 300MHz): δ 4.70 (ABQ, J= 9.6 Hz, 2H), 3.85-3.77 (m, 1H), 3.37 (s, 3H), 2.21-2.14 (m, 2H), 1.98-1.85 (m, 7H), 1.69-1.50 (m, 5H). ¹³C NMR (CDCl₃, 75 MHz): δ 127.6 (s), 125.1 (s), 94.5 (t), 72.5 (d), 55.0 (q), 36.9 (t), 30.1 (t), 29.7 (t), 28.7 (t), 28.6 (t), 22.9 (t), 22.8 (t). IR (film, cm⁻¹): 2926, 2832, 1441, 1150, 1104, 1055, 1036. LRMS (m/z (relative intensity)): 196 (M⁺, 3), 134 (100), 135 (95), 91 (85), 79 (70). HRMS calculated for C₁₂H₂₀O₂: 196.1463 found: 196.1459

**Bromohydrin 227.**

To a cooled -78°C solution of MOM ether 225 (75 mg, 0.382 mmole) and dichloromethane was added (1.33M) Me₂BBr (373 µL, 0.5 mmole). The mixture was stirred at -78°C for one hour then the system was placed under high vacuum. The bath was removed and the temperature slowly brought to room temperature. The resulting 93 mg of 227 an orange-brown oil was then used without further purification.

**Yield:** 100% ¹H NMR (CDCl₃, 300MHz): δ 5.79 (s, 2H), 4.04-3.95 (m, 1H), 2.24-2.17 (m, 2H), 1.99-1.83 (m, 7H), 1.73-1.50 (m, 5H). ¹³C NMR (CDCl₃, 75 MHz): δ 127.8 (s), 124.5 (s), 75.9 (d), 74.8 (t), 35.3 (t), 30.0 (t), 29.6 (t), 28.1 (t), 27.1 (t), 22.7 (t). IR (film, cm⁻¹): 2925, 2831, 1442, 1103, 1056, 1029

**Cyclic ether 229.**

To a refluxing solution of crude bromohydrin 227 (1.0 eq) and benzene (0.017M) was added Ph₃SnH (1.3 eq) in benzene (0.14M) via syringe pump over ten hours. The solvent was removed and the crude mixture purified by flash chromatography (25:1 hexanes:ethyl acetate) yielding 229 as a volatile colourless oil.

**Yield:** 54% ¹H NMR (CDCl₃, 300MHz): δ 5.35-5.31 (m, 1H), 4.45 (t, J= 5.0 Hz, 1H), 3.83 (d, J= 6.6 Hz, 1H), 3.47 (d, J= 6.6 Hz, 1H), 2.52-2.43 (m, 1H), 2.07 (dd, J= 14.4, 6.3 Hz, 1H), 1.97-1.81 (m, 2H), 1.78-1.50 (m, 6H), 1.40 (dt, J= 12.6, 6.5
Hz, 1H), 1.30-1.22 (m, 1H). **13C NMR** (CDCl₃, 75 MHz): δ 141.3 (s), 117.7 (d), 77.8 (t), 77.3 (d), 44.6 (t), 44.3 (s), 33.9 (t), 30.8 (t), 28.7 (t), 25.2 (t), 21.2 (t).

**LRMS** (m/z (relative intensity)): 164 (M⁺, 3), 134 (100). **HRMS** calculated for C₁₁H₁₆O: 164.1201 found: 164.1205

**Tetracycle 236**

To a suspension of tetracycle 176 (35 mg, 0.10 mmole), MOM-ON (35.3 mg, 0.227 mmole), NaOAc (12 mg, 0.143 mmole), and THF (910 µL) was added a solution of AgOTf (49.7 mg, 0.193 mmole) and THF (820 µL) rapidly via cannula. A suspension formed immediately, after one hour the mixture was quenched with toluene and brine. The organics were washed with 1 N HCl, saturated aqueous NaHCO₃, dried over MgSO₄, filtered and concentrated. Purification by flash chromatography yielded 19.8 mg of tetracycle 236 and 8.5 mg of tetracycle 176 (24%)

**Yield:** 56% **1H NMR** (CDCl₃, 300MHz): δ 5.06 (t, J= 7.0 Hz, 1H), 4.71 (d, J= 6.9 Hz, 1H), 4.58 (d, J= 6.9 Hz, 1H), 4.23 (m, 1H), 3.85-3.82 (m, 1H), 3.77 (dq, J= 9.8, 7.1 Hz, 1H), 3.52-3.41 (m, 2H), 3.36 (s, 3H), 3.24 (s, 3H), 3.12 (dd, J= 9.3, 7.2 Hz, 1H), 2.35-2.30 (m 1H), 2.20-1.90 (m, 6H), 1.77-1.55 (m, 4H), 1.52-1.46 (m, 1H), 1.37-1.22 (m, 3H), 1.19 (t, J= 7.1 Hz, 3H), 1.08-0.99 (m, 1H), 0.94 (d, J= 6.5 Hz, 3H), 0.80 (dt, J= 10.5, 3.7 Hz, 1H). **13C NMR** (CDCl₃, 75 MHz): δ 130.4 (s), 129.1 (s), 97.8 (d), 95.1 (t), 74.5 (t), 71.2 (d), 66.9 (d), 62.5 (t), 58.9 (q), 55.5 (q), 47.1 (d), 41.2 (d), 40.8 (d), 38.1 (d), 36.6 (t), 33.7 (d), 30.9 (t), 28.9 (t), 26.6 (t), 26.4 (t), 20.6 (q), 20.1 (t), 15.3 (q). **IR** (film, cm⁻¹): 2923, 1448, 1382, 1336, 1117, 1101, 1042, 1013. **LRMS** (m/z (relative intensity)): 394 (M⁺, 4), 286 (100), 287 (70), 303 (65). **HRMS** calculated for C₂₃H₃₈O₅: 394.2719 found: 394.2709
Alcohol 259:

To a cooled 0°C mixture of crude silylether 284 (10 g, 29.6 mmole), water (15 mL), and dichloromethane (245 mL) was added DDQ (8.7 g, 38.5 mmole) portionwise. After 1.5 hours the deep green mixture had turned orange and tlc showed no starting material. The mixture was poured into a mixture of saturated aqueous NaHCO₃ and dichloromethane. Extraction (x4), washing with brine, drying over MgSO₄, filtration and evaporation gave a crude residue that was purified by flash chromatography (Toluene, then 15:1 to 6:1 to 3:1 hexanes: ethyl acetate). A total of 5.49 g of alcohol 259 was procured (85% for 2 steps).

Yield: 82% 

1H NMR (CDCl₃, 300MHz): δ 3.73-3.60 (m, 2H), 3.54 (dd, J= 4.5, 10.0 Hz, 1H), 3.42 (dd, J= 7.2, 10.0 Hz, 1H), 2.70 (bs, 1H), 1.81-1.75 (m, 1H), 1.62-1.54 (m, 2H), 0.90 (s, 9H), 0.89 (d, J= 5.4 Hz, 3H), 0.07 (s, 6H)

13C NMR (CDCl₃, 75 MHz): δ 68.6 (t), 60.9 (t), 33.8 (d), 25.8 (q), 18.3 (s), 17.2 (q), -5.5 (q).

IR (film, cm⁻¹): 3346, 2955, 2857, 1471, 1388, 1255, 1093, 1056, 1006, 836.

LRMS (m/z (relative intensity)): 74 (100), 105 (90), 161 (M-C₄H₉, 13)

HRMS calculated for C₁₁H₂₇O₂Si (M+H): 219.1780 found: 219.1777

Alcohol 259 (racemic series):

A suspension of benzyl ether 266 (5.04 g, 16.3 mmole), 10% Pd/C (2.5 g) and ethyl acetate (100 mL) was stirred under a H₂ atmosphere for 1 day at room temperature. The suspension was then filtered through a pad of celite (rinsing with ethyl acetate), evaporation of the filtrate yielded 3.50 g (100%) of alcohol 259.

Alcohol 259 (from oxazolidinone alkylation):

Ozone was bubbled through a cooled -78°C solution of alkene 262 (2.67 g, 12.4 mmole) in dichloromethane (100 mL). The flow of ozone was continued until the solution became blue. Nitrogen was then bubbled through the solution to remove the excess ozone (flow of N₂ was continued for a total of 15 minutes after the loss of the blue colour). The solvent was then removed in vacuo yielding the crude ozonide: 

1H NMR (CDCl₃, 300MHz): δ 5.25-5.22 (m, J= 5.0, 5.2 Hz, 1H), 5.19 (d, J= 2.3 Hz, 1H), 5.04 (d, J= 2.1 Hz, 1H), 3.48-3.40 (m, 2H), 1.93-1.81 (m, 2H), 1.61-1.51 (m, 2H), 0.97-0.93 (m, J= 6.5, 5.7 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H) 

13C NMR (CDCl₃, 75 MHz): δ 103.2 (d), 103.0 (d), 93.9 (t), 93.8 (t), 67.8 (t), 67.7 (t), 34.7 (t), 34.6 (t), 25.8 (q), 18.2 (s), 16.9 (q), 16.8 (q), -5.5 (q).

IR (film, cm⁻¹): 2943, 2882, 2738, 1728, 1471, 1390, 1255, 1098, 1056, 836.

LRMS (m/z (relative intensity)): (M⁺ – CHO) 159 (50), 74(100). 

HRMS calculated for C₁₁H₂₅O₃Si (M⁺ – CHO): 205.0896 found: 205.0901
The residue was then dissolved in methanol (45 mL) and cooled to 0°C at which time sodium borohydride (1.98 g, 52.3 mmole) was added portionwise. The mixture was warmed to room temperature and stirred overnight. The following day water (45 mL) and ethyl ether (80 mL) were added. The resulting aqueous phase was extracted with ether (2x20 mL) and the combined organics washed with brine (25 mL), dried over MgSO₄, filtered and concentrated. Flash chromatography eluenting with 6:1 to 3:1 mixture of hexanes: ethyl acetate yielded 2.24 g of alcohol 259 as a clear faintly pale yellow liquid.

**Adduct 261:**

![Adduct 261](image)

To a stirred solution of NaN(TMS)₂ (27.4 mL, 27.4 mmole) in THF (65 mL) was added a solution of 260 (5.80g, 24.9 mmole) in THF (15mL + 10mL rinse) via cannula at -78°C. This reaction was stirred for 0.5 hours before a solution of allylbromide (6.5mL, 74.7 mmole) in THF (10 mL) was added via cannula at -78°C. The reaction mixture was stirred at -78°C for 1 hour then gradually warmed to -45°C and kept at this temperature until reaction completion (generally 1.5 hours). The reaction was quenched with saturated aqueous NH₄Cl, and the mixture extracted with dichloromethane (x2). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography eluenting with 15:1 hexanes:ethyl acetate to give 6.03 g of 261 as a white solid.

**Yield:** 89 % ¹H NMR (CDCl₃, 300MHz): δ 7.45-7.29 (m, 5H), 5.80 (ddt, J= 7.0, 10.1, 17.1 Hz, 1H), 5.66 (d, J= 7.3 Hz, 1H), 5.09-5.01 (m, 2H), 4.78 (q, J= 6.8 Hz, 1H), 3.88 (sextet, J= 6.8 Hz, 1H), 2.49 (quintet, J= 6.8 Hz, 1H), 2.21 (quintet, J= 7.0 Hz, 1H), 1.19 (d, J= 6.8 Hz, 3H), 0.86 (d, J= 6.6 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 176.2 (s), 152.6 (s), 135.1 (d), 133.3 (s), 128.6 (d), 125.5 (d), 117.0 (t), 78.6 (d), 54.7 (d), 37.8 (t), 37.0 (d), 16.4 (q), 14.6 (q). IR (film, cm⁻¹): 3036, 2974, 2933, 1774, 1697, 1369, 1343, 1194. LRMS (m/z (relative intensity)): 273 (M⁺, 40), 107(45), 134(48), 118(100). HRMS calculated for C₁₆H₁₉O₃N: 273.1365 found: 273.1371. [α]D: +40.5 (c 1.99, C₂H₂).
Silyl ether 262:

A solution of 30% H$_2$O$_2$ (11.4 mL, 101 mmole) was added to a cooled 0°C solution of 261 (6.90 g, 25.2 mmole) in THF (96 mL) and H$_2$O (32 mL). Shortly thereafter a solution of LiOH (2.11 g, 50.4 mmole) in H$_2$O (16 mL) was added to the reaction mixture. The mixture was stirred at 0°C for 1.5 hours before a solution of 1.5N Na$_2$SO$_3$ (74 mL, 111 mmole) was added slowly to quench the excess H$_2$O$_2$. The THF was removed in vacuo, and the aqueous layer extracted with dichloromethane (x3). The aqueous layer was then acidified with 1N HCl and extracted with ethyl ether (x3). The etheric layer was dried over MgSO$_4$, filtered and concentrated giving 2.77 g of the crude acid as a green-yellow oil. This acid was used without further purification in the next step.

**Yield:** ~96 %

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 5.76 (ddt, J= 7.0, 10.1, 17.0 Hz, 1H), 5.12-5.04 (m, 2H), 2.56 (sextet, J= 6.8 Hz, 1H), 2.44 (quintet, J= 6.8 Hz, 1H), 2.21 (quintet, J= 7.0 Hz, 1H), 1.19 (d, J= 6.9 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 182.9 (s), 135.0 (d), 117.1 (t), 39.1 (d), 37.4 (t), 16.2 (q). IR (film, cm$^{-1}$): 3081, 2980, 2940, 1709, 1463, 1418, 1286, 1246, 1212, 918. LRMS (m/z (relative intensity)): 114 (M$^+$, 26), 99 (42), 69(100). HRMS calculated for C$_6$H$_{10}$O$_2$: 114.0681 found: 114.0675. $\left[\alpha\right]_{D}$: +11.1 (c 2.09, CH$_2$Cl$_2$)

To a 1.0M solution of lithium aluminum hydride (31.5mL, 31.5 mmole) in Et$_2$O was added slowly via cannula a solution of acid (2.77 g, 24.2 mmole) in Et$_2$O (110 mL) at 0°C. The reaction mixture was stirred for 4 hours at 0°C before being SLOWLY quenched with H$_2$O (1.2 mL). Once complete, 2N NaOH (2.2 mL) and H$_2$O (3.6 mL) were added slowly. To this cloudy suspension was then added MgSO$_4$ and the mixture stirred overnight. The mixture was then filtered through a pad of celite and rinsed with Et$_2$O. The ether was then removed by distillation using a vigreux column giving 2.27 g of the crude alcohol as a clear slightly yellow coloured liquid.

**Yield:** ~94 %

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 5.81 (ddt, J= 7.1, 10.1, 17.1 Hz, 1H), 5.08-5.00 (m, 2H), 3.55-3.43 (m, 2H), 2.17 (quint, J= 6.8 Hz, 1H), 1.99-1.90 (m, 1H), 1.73 (sextet, J= 6.6 Hz, 1H), 1.33 (bs, 1H), 0.92 (d, J= 6.7 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 136.8 (d), 115.9 (t), 67.5 (t), 37.7 (t), 35.4 (d), 16.2 (q). IR (film, cm$^{-1}$): 3333, 3077, 2957, 2918, 2875, 1640, 1457, 1043, 992, 911. LRMS (m/z (relative intensity)): 100 (M$^+$, 1), 82 (M-H$_2$O, 35), 67 (100). HRMS calculated for C$_6$H$_{10}$ (M-H$_2$O): 82.0782 found: 82.0779. $\left[\alpha\right]_{D}$: -2.35 (c 2.18, CH$_2$Cl$_2$)

To a solution of alcohol (2.27 g, 22.7 mmole) and imidazole (3.86 g, 56.8 mmole) in dichloromethane (42 mL) was added TBSCI (4.28 g, 28.4 mmole) at room temperature. The reaction was stirred a total of 5 hours before water (40 mL)
and ethyl ether (80 mL) were added. The layers were separated and the organics washed with water (40 mL) and brine (40 mL). The combined aqueous layers were then extracted with ethyl ether (2x40 mL). After drying over MgSO$_4$ and filtration the organics were concentrated in vacuo. Flash chromatography eluting with a 25:1 to 6:1 hexanes: ethyl acetate mixture provided 4.96 g of silyl ether as a clear colourless oil.

**Yield:** 92% (overall from 261)

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 5.78 (ddt, J= 7.1, 10.0, 17.1 Hz, 1H), 5.30-4.97 (m, 2H), 3.41 (dt, J= 6.1, 9.7 Hz, 2H), 2.23-2.15 (m, 1H), 1.89-1.79 (m, 1H), 1.71-1.64 (m, 1H), 0.89 (s, 9H), 0.86 (d, J= 6.7 Hz, 3H), 0.03 (s, 6H) $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 137.3 (d), 115.7 (t), 67.7 (t), 35.7 (d), 25.9 (q), 18.4 (s), 16.4 (q), -5.4 (q). IR (film, cm$^{-1}$): 3077, 2956, 2929, 2857, 1641, 1471, 1255, 1094. LRMS (m/z (relative intensity)): 213 (M-H, 1), 157 (M-C$_4$H$_9$, 55), 75(100). HRMS calculated for C$_8$H$_{17}$OSi (M-C$_4$H$_9$): 157.1049 found: 157.1046

**IR**

$[^\alpha]_{D}$: -1.33 (c 1.88, CH$_2$Cl$_2$)

**Benzyl ether 264:**

To an oil free suspension of KH (3.07g, 76.5 mmole) and THF (12 mL) at 0°C was added a solution of alcohol 263 (6.0g, 69.6 mmole) and THF (96 mL) via cannula. After 15 minutes the ice bath was removed and the mixture was stirred 30 minutes further before being cooled again to 0°C. A solution of benzyl bromide (12.5g, 73.1 mmole) and THF (12 mL) was then added via cannula. After 15 minutes the ice bath was removed and the reaction mixture was left to stir overnight. The reaction was quenched with aqueous NH$_4$Cl, the product extracted with ethyl ether (x3), washed once (brine), dried over MgSO$_4$, filtered and concentrated. Purification by flash chromatography eluting with 25:1 to 10:1 Hexanes: ethyl acetate yielded 12.69g of benzyl ether 264 as a slightly yellow coloured liquid.

**Yield:** 100 %

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.35-7.27 (m, 5H), 4.79 (s, 1H), 4.74 (s, 1H), 4.53 (s, 2H), 3.58 (t, J= 6.9 Hz, 2H), 2.35 (t, J= 6.9 Hz, 2H), 1.75 (s, 3H) $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 142.7 (s), 138.4 (s), 128.2 (d), 127.6 (d), 127.4 (d), 111.4 (t), 72.8 (t), 68.6 (t), 37.7 (t), 22.6 (q). IR (film, cm$^{-1}$): 3071, 3030, 2936, 2856, 1649, 1453, 1103, 888. LRMS (m/z (relative intensity)): 91 (100), 175 (M$^+$ - 1, 6). HRMS calculated for C$_{12}$H$_{16}$O: 176.1201 found: 176.1196
Alcohol 265:

A solution of alkene 264 (12.7g, 69.6 mmole) in THF (72 mL) was added via cannula to a cooled 0°C [2.0M] solution of BH$_3$.SMe$_2$ (24 mL, 47.9 mmole). Once the addition was complete the ice bath was removed and the reaction mixture was stirred for 1 hour before being cooled again to 0°C. A solution of 2N NaOH (72 mL, 144 mmole) was then added SLOWLY followed by a 30% H$_2$O$_2$ (11.4g, 335 mmole). The reaction was then stirred overnight and partitioned between water and ethyl ether. The product was extracted with ethyl ether (x3), the combined organics dried over MgSO$_4$, filtered and concentrated. Purification by Kugelrohr distillation yielded 13.95 g of alcohol 265 as a clear colourless oil. Generally the crude product was pure by $^1$H NMR, and could be used without further purification.

Yield: 100% $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.38-7.28 (m, 5H), 4.52 (s, 2H), 3.63-3.40 (m, J= 6.5 Hz, 4H), 2.41 (bs, 1H), 1.85-1.77 (m, 1H), 1.75-1.53 (m, 2H), 0.92 (d, J= 6.8 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 137.9 (s), 128.3 (d), 127.6 (d), 72.9 (t), 68.5 (t), 67.8 (t), 33.8 (d and t), 17.0 (q). IR (film, cm$^{-1}$): 3405, 3030, 2926, 2869, 1453, 1365, 1096, 1028. LRMS (m/z (relative intensity)): 91 (100), 107 (70), 194 (M+, 4). HRMS calculated for C$_{12}$H$_{18}$O$_2$: 194.1307 found: 194.1311

Silyl ether 266:

To a solution of alcohol 265 (4.67g, 24.0 mmole), imidazole (2.45g, 36 mmole), and dichloromethane (45 mL) was added TBDMSCl (3.98g, 26.4 mmole). The resulting suspension was stirred overnight before both water (50 mL) and dichloromethane (100 mL) were added. The layers were separated and the organics washed with water and brine, dried over MgSO$_4$, filtered and concentrated. Purification by flash chromatography (15:1 Hexanes: Ethyl acetate) yielded 7.39g of silyl ether 266 as a clear colourless oil.

Yield: 100% $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.35-7.27 (m, 5H), 4.50 (s, 2H), 3.52 (t, J= 6.4 Hz, 2H), 3.42 (ddd, J= 9.8, 5.6, 15.3 Hz, 2H), 1.79-1.70 (m, 2H), 1.44-1.35 (m, 1H), 0.89 (d, J= 5.6 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 138.6 (s), 128.3 (d), 127.6 (d), 127.4 (d), 72.8 (t), 68.7 (t), 68.2 (t), 33.2 (t), 32.9 (d), 25.9 (q), 18.3 (s), 16.8 (q), -5.4 (q). IR (film, cm$^{-1}$):
3030, 2954, 2928, 2856, 1471, 1361, 1255, 1097, 836. LRMS (m/z (relative intensity)): 308 (M+, 1) 165 (100), 201 (50), 217 (40). HRMS calculated for C$_{18}$H$_{32}$O$_2$Si: 308.2171 found: 308.2177

**Alkyne 272:**

![PMBO-alkyne](https://example.com/alkyne.png)

To a stirred suspension of NaH (4.31 g, 108 mmole) in THF (400 mL) was added 4-butyn-1-ol (7.5 mL, 98.9 mmole) slowly at 0°C. Once complete the ice bath was removed and the mixture was stirred for 1 hour further. A solution of PMBBBr (19.9 g, 98.9 mmole) in THF (50 mL) was then added via cannula. The reaction was stirred overnight then quenched by the addition of aqueous NH$_4$Cl. The mixture was extracted with ethyl ether (x3), washed with brine, dried over MgSO$_4$, filtered and concentrated. Purification by flash chromatography (15:1 Hexanes: Ethyl acetate) yielded 14.82g, of alkyne 272 as a pale yellow liquid.

**Yield:** 86%

$^1$H NMR (CDCl$_3$, 300MHz): δ 7.27 (d, J= 8.4 Hz, 2H), 6.88 (d, J= 8.6 Hz, 2H), 4.49 (s, 2H), 3.80 (s, 3H), 3.57 (t, J= 7.0 Hz, 2H), 2.48 (dt, J= 7.0, 2.7 Hz, 2H), 1.98 (t, J= 2.7 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 159.1 (s), 129.9 (s), 129.2 (d), 113.7 (d), 81.2 (s), 72.4 (t), 69.2 (d), 67.7 (t), 55.0 (q), 19.7 (t). IR (film, cm$^{-1}$): 3291, 2863, 1613, 1513, 1248, 1098. LRMS (m/z (relative intensity)): 190 (M+, 10), 189 (M+ - H, 12), 121 (100). HRMS calculated for C$_{12}$H$_{14}$O$_2$: 190.0994 found: 190.0985

**Alcohol 273:**

![Alcohol 273](https://example.com/alcohol.png)

To a cooled -78°C solution of alkyne (10.75g, 58.3 mmole) in THF (120mL) was added a [2.0M] solution of n-butyllithium (16.4 mL, 32.7 mmole) and [1.55M] solution of n-butyllithium (16.5 mL, 25.6 mmole). The resulting solution was stirred for 1 hour then added via cannula slowly (over 30 minutes) to a stirred suspension of CeCl$_3$ (25.0g, 68.0 mmole) in THF (230mL) at -78°C. The resulting suspension was stirred for 1 hour at -78°C before a solution of (+) menthone (7.50 g, 48.6 mmole) in THF (100mL) was added via cannula (over 0.5 hour).
After another 3 hours at -78°C the reaction was quenched with the addition of saturated aqueous NH₄Cl. The layers were separated and the aqueous extracted with ethyl ether (x3). The combined organics were then washed (water then brine), dried over MgSO₄, filtered and concentrated. Flash chromatography (25:1 to 20:1 to 15:1 Hexanes:ethyl acetate) provided 15.4 g of axial alcohol as a yellow coloured liquid

**1H NMR** (CDCl₃, 300MHz): δ 3.69 (t, J= 7.1 Hz, 2H), 2.42 (t, J= 7.1 Hz, 2H), 1.94-1.88 (m, 1H), 1.75-1.70 (m, 2H), 1.46-1.25 (m, 7H), 0.94 (d, J= 7.0 Hz, 3H), 0.91 (d, J= 6.8 Hz, 3H), 0.89 (s, 9H), 0.85 (d, J= 6.6 Hz, 3H), 0.07 (s, 6H).  

**13C NMR** (CDCl₃, 75 MHz): δ 86.0 (s), 80.6 (s), 71.7 (s), 61.9 (t), 50.5 (d), 50.5 (t), 34.8 (t), 28.1 (d), 27.3 (d), 25.8 (q), 23.8 (q), 23.1 (t), 21.9 (q), 20.4 (t), 18.6 (q), 18.2 (s), -5.3 (q).  

**IR** (film, cm⁻¹): 3485, 2952, 2861, 1471, 1255, 1107, 943, 838, 776.  

**LRMS** (m/z (relative intensity)): 281 (M⁺ - C₄H₉, 5), 74 (100), 105 (60).  

**HRMS** calculated for C₁₆H₂₉O₂Si (M⁺ - C₄H₉): 281.1937 found: 281.1940  

[α]D:

**Alcohol 274:**

To a cooled -78°C solution of alkyne 272 (10.25 g, 53.9 mmole) in THF (110 mL) was added a [2.0M] solution of n-butyllithium (27mL, 54 mmole). The resulting solution was stirred for 1 hour then added via cannula slowly (over 20 minutes) to a stirred suspension of CeCl₃ (23.4g, 62.9 mmole) in THF (210 mL) at -78°C. The resulting suspension was stirred for 1.25 hours at -78°C before a solution of (+) menthone (6.92 g, 44.9 mmole) in THF (90 mL) was added via cannula (over 1.5 hours). After another 2 hours at -78°C the reaction was quenched with the addition of saturated aqueous NH₄Cl. The layers were separated and the aqueous extracted with ethyl ether (x3). The combined organics were then washed (water then brine), dried over MgSO₄, filtered and concentrated. Flash chromatography (6:1 Hexanes:ethyl acetate) provided 12.9g of axial alcohol 274 as a yellow coloured liquid.  

**Yield: 83% 274 1H NMR** (CDCl₃, 300MHz): δ 7.27 (d, J= 8.0 Hz, 2H), 6.88 (d, J= 8.6 Hz, 2H), 4.47 (s, 2H), 3.81 (s, 3H), 3.55 (t, J= 7.1 Hz, 2H), 2.51 (t, J= 7.1 Hz, 2H), 2.38 (dseptet, J= 6.9, 1.9 Hz, 1H), 1.92 (dt, J= 13.5, 2.9 Hz, 1H), 1.78-1.68 (m, 2H), 1.52-1.22 (m, 5H), 0.94 (d, J= 7.4 Hz, 3H), 0.92 (d, J= 7.4 Hz, 3H),
0.86 (d, J = 6.3 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 159.1 (s), 130.2 (s), 129.1 (d), 113.7 (d), 86.0 (s), 80.3 (s), 72.4 (t), 71.6 (s), 68.3 (t), 55.1 (q), 50.4 (d), 50.4 (t), 34.8 (t), 28.1 (d), 27.2 (d), 23.8 (q), 21.9 (q), 20.5 (t), 20.0 (t), 18.6 (q). IR (film, cm$^{-1}$): 3453. LRMS (m/z (relative intensity)): 344 (M$^+$, 10), 327 (100), 121 (100). HRMS calculated for C$_{22}$H$_{32}$O$_3$: 344.2351 found: 344.2359

**Allylic alcohol 275:**

![Allylic alcohol 275](image)

A solution of 65%w/w Red-Al (16.2 mL, 54.0 mmole) in THF (135 mL) was added via cannula to a cooled -78$^\circ$C solution of alcohol 273 (12.2 g, 36.0 mmole) in THF (65mL). Once complete the mixture was warmed to room temperature and stirred for a total of five days, at which time GC analysis indicated the total consumption of starting material. The mixture was quenched by the slow addition of ethyl alcohol. A solution of 1N HCl was added and the layers separated. The aqueous layer was extracted with ethyl ether (x3). The combined organic layers were then washed with both water and brine, dried over MgSO$_4$, filtered, and concentrated. Purification by flash chromatography (9:1 to 3:1 Hexanes: Ethyl acetate) yielded 5.33 g of allylic alcohol 275 as a clear colourless oil, and 4.28 g of diol 276 as a white solid.

**Yield: 43 %**

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 5.63 (dt, J = 15.6, 6.5 Hz, 1H), 5.50 (d, J = 15.6 Hz, 1H), 3.64 (t, J = 6.8 Hz, 2H), 2.27 (q, J = 6.7 Hz, 2H), 2.00-1.95 (m, 1H), 1.80-1.70 (m, 2H), 1.53-1.37 (m, 4H), 1.12-1.04 (m, 2H), 0.91-0.81 (m, 6H), 0.89 (s, 9H), 0.83 (d, J = 6.4 Hz, 3H), 0.05 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 140.3 (d), 123.5 (d), 76.0 (s), 63.1 (t), 49.5 (t), 35.9 (t), 35.1 (t), 27.9 (d), 26.7 (d), 25.9 (q), 23.8 (q), 22.2 (q), 20.8 (t), 18.5 (q), 18.3 (s), -5.3 (q). IR (film, cm$^{-1}$): 3478, 2953, 2858, 1471, 1385, 1255, 1102, 972, 836, 776. LRMS (m/z (relative intensity)): 283 (M$^+$ - C$_4$H$_9$, 10), 74 (100), 105 (80), 135 (68), 191 (56). HRMS calculated for C$_{16}$H$_{31}$O$_2$Si (M$^+$ - C$_4$H$_9$): 283.2093 found: 283.2095
Diol 276

Yield: 52\% \ H NMR (CDCl$_3$, 300MHz): $\delta$ 3.67 (t, J= 6.2 Hz, 2H), 2.93 (bs, 1H), 2.44 (t, J= 6.2Hz, 2H), 2.39-2.29 (m, 2H), 1.92 (dt, J= 13.5, 2.9 Hz, 1H), 1.74-1.64 (m, 2H), 1.49-1.42 (m, 1H), 1.40-1.32 (m, 2H), 1.30 (bs, 1H), 1.26-1.19 (m, 1H), 0.93 (d, J= 6.9Hz, 3H), 0.90 (d, J= 7.0 Hz, 3H), 0.83 (d, J= 6.3 Hz, 3H). \ C NMR (CDCl$_3$, 75 MHz): $\delta$ 86.9 (s), 80.3 (s), 71.7 (s), 61.0 (t), 50.5 (d), 50.3 (t), 34.8 (t), 28.2 (d), 27.2 (d), 23.9 (q), 23.0 (t), 21.9 (q), 20.5 (t), 18.6 (q). \ IR (film, cm$^{-1}$): 3382, 2949, 2869, 2235, 1455, 1045. \ LRMS (m/z (relative intensity)): 224 (M$^+$, 5), 84 (100), 86 (97), 139 (97), 179 (60). \ HRMS calculated for C$_{14}$H$_{24}$O$_2$: 224.1776 found: 224.1773. \ Melting point: 51.0°C

Allylic alcohol 277:

A solution of 65%w/w Red-Al (11.0 mL, 36.9 mmole) in THF (92 mL) was added via cannula to a cooled -78°C solution of alcohol 274 (8.47 g, 24.6 mmole) in THF (45 mL). Once complete the mixture was warmed to room temperature and stirred overnight. The next day the solution was heated to reflux for 3 hours then cooled and quenched by the slow addition of ethyl alcohol. A solution of 1N HCl was added and the layers separated. The aqueous layer was extracted with ethyl ether (x3). The combined organic layers were then washed with both water and brine, dried over MgSO$_4$, filtered, and concentrated. Purification by flash chromatography (9:1 Hexanes: Ethyl acetate) yielded 8.25 g (97\%) of allylic alcohol 277 as a clear colourless oil, and trace amounts of allene 279 as a colourless oil.
Yield: 70-97 %

^1^H NMR (CDCl$_3$, 300MHz): δ 7.26 (d, J= 8.6 Hz, 2H), 6.87 (d, J= 8.6 Hz, 2H), 5.65 (dt, J= 15.6, 6.6 Hz, 1H), 5.52 (d, J= 15.6 Hz, 1H), 4.44 (s, 2H), 3.80 (s, 3H), 3.49 (t, J= 6.8 Hz, 2H), 2.36 (q, J= 6.7 Hz, 2H), 1.96 (dseptet, J= 7.0, 1.9 Hz, 1H), 1.84-1.65 (m, 2H), 1.55-1.37 (m, 4H), 1.13-1.04 (m, 2H), 0.99-0.88 (m, 1H), 0.86-0.82 (m, 9H).

^1^3^C NMR (CDCl$_3$, 75 MHz): δ 159.0 (s), 140.2 (d), 130.5 (s), 129.1 (d), 123.2 (d), 113.6 (d), 76.0 (s), 72.4 (t), 69.8 (t), 55.1 (q), 49.4 (d, t), 35.0 (t), 32.7 (t), 27.7 (d), 26.7 (d), 23.8 (q), 22.2 (q), 20.8 (t), 18.5 (q).

IR (film, cm$^{-1}$): 3479, 1615, 1586. LRMS (m/z (relative intensity)): 328 (M$^+$ - H$_2$O, 15), 192 (100), 121 (85).

HRMS calculated for C$_{22}$H$_{32}$O$_2$: 328.2402 found: 328.2395.

[$\alpha$]$_D$: +19.1 (c = 1.653, CHCl$_3$).

**Allene 279**

^1^H NMR (CDCl$_3$, 300MHz): δ 7.26 (d, J= 8.6 Hz, 2H), 6.87 (d, J= 8.6 Hz, 2H), 5.05-5.02 (m, 1H), 4.45 (s, 2H), 3.80 (s, 3H), 3.50 (t, J= 7.1 Hz, 2H), 2.32-2.18 (m, 3H), 1.81-1.71 (m, 3H), 1.64-1.47 (m, 3H), 1.12-0.93 (m, 2H), 0.91 (d, J= 6.7 Hz, 2H), 0.90 (d, J= 6.4 Hz, 3H), 0.81 (d, J= 6.8 Hz, 3H).

^1^3^C NMR (CDCl$_3$, 75 MHz): δ 198.9 (s), 159.0 (s), 130.6 (s), 129.1 (d), 113.6 (d), 106.0 (s), 87.0 (d), 72.4 (t), 69.7 (t), 55.1 (q), 46.2 (d), 41.2 (t), 34.9 (t), 34.2 (d), 29.9 (t), 29.2 (d), 28.3 (t), 22.1 (q), 21.8 (q), 18.6 (q).

IR (film, cm$^{-1}$): 2950, 2866, 1962, 1612, 1513, 1456, 1247, 1099. LRMS (m/z (relative intensity)): 328 (M$^+$, 2), 123 (100), 121 (80), 285 (58).

HRMS calculated for C$_{22}$H$_{32}$O$_2$: 328.2402 found: 328.2395.

**Allylic alcohol 277 (directly from menthone):**

To a cooled (N$_2$, ethyl ether bath) solution of vinylbromide 287 (703 mg, 2.59 mmole), THF (9 mL), and ethyl ether (2.2 mL) was added a [1.7M] solution of tert-butyllithium (3.45mL, 5.86 mmole). After 70 minutes a solution of (+) menthone (333 mg, 2.16 mmole) and THF (4.3 mL) was added SLOWLY via cannula. Once complete the reaction mixture was allowed to gradually warm to room temperature. After 3.75 hours aqueous NH$_4$Cl was added, and the product extracted with ethyl ether (x3). Washing with brine, drying over MgSO$_4$, filtration and concentration yielded the crude alcohol. Purification as mentioned above provided 526mg (70%) of alcohol.

**Cuprate adduct 280:**

A solution of [2.0M] n-butyllithium (15.5 mL, 30.9 mmole) was added to a cooled -78°C solution of alcohol (8.24 g, 23.8 mmole) in THF (240 mL). This solution
was stirred at -78°C for 1 hour before methylchloroformate (2.76 mL, 35.7 mmole) was added quickly. The reaction was warmed over the next 2.25 hours to -10°C and quenched by the addition of saturated aqueous NH₄Cl. The carbonate was extracted with ethyl ether (x3), dried over MgSO₄, filtered and concentrated. The resulting yellow coloured carbonate was used in the next step without further purification.

**Yield:** 100 % ¹H NMR (CDCl₃, 300MHz): δ 7.25 (d, J= 8.6 Hz, 2H), 6.87 (d, J= 8.6 Hz, 2H), 5.78 (d, J= 16.0 Hz, 1H), 5.44 (dt, J= 16.0, 6.8 Hz, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 3.49 (t, J= 6.7 Hz, 2H), 2.69 (dt, J= 14.1, 2.7 Hz, 1H), 2.38 (q, J= 6.8 Hz, 2H), 2.15 (dquintet, J= 7.0, 1.8 Hz, 1H), 1.87-1.75 (m, 2H), 1.59-1.48 (m, 2H), 1.20-1.06 (m, 2H), 0.93-0.90 (m, 1H), 0.88 (d, J= 7.9 Hz, 3H), 0.87 (d, J= 6.8 Hz, 3H), 0.83 (d, J= 7.0 Hz, 3H). IR (film, cm⁻¹): 2953, 2868, 1746, 1613, 1513, 1441, 1275, 1248, 1097.

To a stirred solution of copper (1) iodide (6.80 g, 35.7 mmole), lithium iodide (4.78 g, 35.7 mmole) and THF (220 mL) was added a [1.4 M] solution of methylithium (51 mL, 71.4 mmole) at -78°C SLOWLY. The mixture was stirred for 45 minutes at -78°C before a solution of crude carbonate and THF (37 mL) was added via cannula. Once complete the reaction was stirred for 15 minutes, then immediately warmed to 0°C and stirred overnight. The black mixture was quenched by the slow addition of 9:1 saturated aqueous NH₄Cl: concentrated NH₄OH (water could be added later for clarification). Extraction with ethyl ether (x3), washing with water and brine, then drying over MgSO₄, filtration and concentration gave the crude alkene. Flash chromatography elueting with 15:1 Hexanes: Ethyl Acetate procured 8.08 g, of alkene 280 as a clear colourless oil.

**Yield:** 99 % ¹H NMR (CDCl₃, 300MHz): δ 7.25 (d, J= 8.8 Hz, 2H), 6.86 (d, J= 8.6 Hz, 2H), 4.82 (d, J= 9.5 Hz, 1H), 4.38 (ABQ, J= 14.5 Hz, 2H), 3.80 (s, 3H), 3.45-3.30 (m, 2H), 2.65-2.48 (m, 1H), 2.25 (dd, J= 12.2, 3.4 Hz, 1H), 1.91 (octet, J= 6.8 Hz, 1H), 1.81-1.25 (m, 6H), 1.17-1.08 (m, 1H), 0.93 (d, J= 6.7 Hz, 3H), 0.89 (d, J= 6.4 Hz, 3H), 0.86 (d, J= 6.6 Hz, 3H), 0.81 (d, J= 6.6 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 159.0 (s), 138.5 (s), 130.7 (s), 129.2 (d), 128.2 (d), 113.6 (d), 72.6 (t), 68.6 (t), 55.1 (q), 51.4 (d), 37.7 (t), 34.7 (t), 31.7 (t), 31.1 (t), 28.3 (d), 26.2 (d, t), 22.0 (q), 21.9 (q), 20.2 (q), 19.8 (q). IR (film, cm⁻¹): 2956, 2867, 1615, 1587. LRMS (m/z (relative intensity)): 343 (M⁺ - H, 40), 237 (100), 121 (70). HRMS calculated for C₂₃H₃₅O₂ (M⁺ - H): 343.2637 found: 343.2629. [α]D: -3.80 (c 2.83, CHCl₃)
Alcohol 281:

To a cooled 0°C biphasic mixture of PMB ether 280 (1.65 g, 4.80 mmole), dichloromethane (40 mL), and water (2.2 mL) was added DDQ (1.42 g, 6.24 mmole). The initially deep green suspension slowly turns (about 2.25 hours) yellow, at which time tlc indicates reaction completion. The mixture was poured into a separatory funnel containing saturated aqueous NaHCO₃. The layers were separated and the aqueous extracted with dichloromethane (x4). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. Flash chromatography eluenting with 100% toluene followed by a 9:1 mixture of hexanes: ethyl acetate yielded 1.02 g of alcohol 281 as a clear colourless oil.

Yield: 95% ¹H NMR (CDCl₃, 300MHz): δ 4.87 (d, J= 9.6 Hz, 1H), 3.67-3.53 (m, 2H), 2.62-2.52 (m, 1H), 2.33-2.27 (m, 1H), 1.92 (sextet, J= 6.8Hz, 1H), 1.82-1.66 (m, 4H), 1.65-1.54 (m, 2H), 1.49-1.42 (m, 1H), 1.40 (bs, 1H), 1.35-1.26 (m, 1H), 1.17-1.08 (m, 1H), 0.96 (d, J=6.6 Hz, 3H), 0.91 (d, J= 6.4 Hz, 3H), 0.87 (d, J= 6.6 Hz, 3H), 0.84 (d, J= 6.6 Hz, 3H).

¹³C NMR (CDCl₃, 75 MHz): δ 139.0 (s), 128.1 (d), 61.8 (t), 51.4 (d), 40.7 (t), 34.9 (t), 32.0 (d), 31.3 (t), 28.5 (d), 26.4 (t), 26.3 (d), 22.0 (q), 20.3 (q), 19.8 (q).

IR (film, cm⁻¹): 3332, 2953, 2868, 1454, 1379, 1051.

LRMS (m/z (relative intensity)): 224 (M⁺, 30), 95 (100), 163 (98), 81 (87).

HRMS calculated for C₁₅H₂₈O: 224.2140 found: 224.2137

Silyl ether 282:

To a stirred solution of alcohol 281 (504 mg, 2.25 mmole), imidazole (383 mg, 5.62 mmole), and dichloromethane (4 mL) was added TBDPSCI (645 µl, 2.47 mmole) at room temperature. The resulting suspension was stirred for overnight
before water was added. The layers were separated and the aqueous extracted once with dichloromethane. After a brine wash, the organics were dried over MgSO$_4$, filtered and concentrated. Purification by flash chromatography (25:1 hexanes:ethyl acetate) yielded 960 mg of silyl ether 282 as a white solid.

**Yield:** 92%  
$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.67-7.64 (m, 4H), 7.43-7.33 (m, 6H), 4.78 (d, J= 9.4Hz, 1H), 3.66-3.54 (m, 2H), 2.63-2.59 (m, 1H), 2.23 (dd, J= 12.8, 4.0 Hz, 1H), 1.87 (sextet, J= 6.8Hz, 1H), 1.76-1.36 (m, 6H), 1.27-1.18 (m, 1H), 1.14-0.94 (m, 2H), 0.91 (d, J= 6.7 Hz, 3H), 0.85 (d, J= 6.5 Hz, 3H), 0.82 (d, J= 6.6 Hz, 3H), 0.77 (d, J= 6.6 Hz, 3H).  

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 138.4 (s), 135.5 (d), 134.2 (s), 129.4 (d), 128.3 (d), 127.5 (d), 62.5 (t), 51.3 (d), 40.7 (t), 35.0 (t), 31.9 (d), 31.4 (t), 27.9 (d), 26.9 (q), 26.4 (t), 26.3 (d), 22.0 (q), 21.7 (q), 20.4 (q), 19.8 (q), 19.2 (s).

IR (film, cm$^{-1}$): 3070, 2953, 2929, 2863, 1461, 1427, 1382, 1109, 702.

LRMS (m/z (relative intensity)): 405 (M$^+$ - C$_4$H$_9$, 82), 183 (100), 199 (88), 327 (84).

HRMS calculated for C$_{27}$H$_{37}$OSi (M$^+$ - C$_4$H$_9$): 405.2614 found: 405.2612.

Melting Point: 65.4°C

**Alcohol 283:**

![Alcohol 283](image)

Ozone was bubbled through a cooled -78°C solution of alkene 280 (8.08 g, 23.4 mmole), dichloromethane (120 mL), and methanol (120 mL) for a total of approximately 20 minutes (monitored by tlc). Argon was then bubbled through the reaction mixture to remove any excess ozone. Sodium borohydride (4.42 g, 117 mmole) was added portionwise at -78°C, once complete the mixture was allowed to warm to room temperature and be stirred overnight. The mixture was brought to a pH of 7 by the addition of 1N HCl. The product was extracted with ethyl ether (x3), and dichloromethane (x2), and the combined organics were then washed with brine, dried over MgSO$_4$, filtered, and concentrated. Purification by flash chromatography (6:1 to 1:1 hexanes:ethyl acetate) yielded 4.55 g, of alcohol 283 as a clear colourless oil.

**Yield:** 93%  
$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.25 (d, J= 8.6 Hz, 2H), 6.87 (d, J= 8.6 Hz, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.60-3.37 (m, 4H), 2.63 (dd, J= 7.0, 5.4 Hz, 1H), 1.83-1.77 (m, 1H), 1.67-1.54 (m, 2H), 0.91 (d, J= 6.8 Hz, 3H).  

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 159.0 (s), 129.9 (s), 129.2 (d), 113.6 (d), 72.5 (t), 68.2 (t), 67.7 (t), 55.0 (q), 33.8 (d), 33.8 (t), 17.0 (q). IR (film, cm$^{-1}$): 3413, 2953, 2929, 2863, 1461, 1427, 1382, 1109, 702.  

LRMS (m/z (relative intensity)): 224 (M$^+$, 10), 121 (80), 137 (100).  

HRMS calculated for C$_{13}$H$_{20}$O$_3$: 224.1412 found: 224.1416.  

$[\alpha]_D$: +8.11 (c 1.503, CHCl$_3$).
Silyl ether 284:

![Chemical Structure](image)

To a solution of alcohol 283 (6.65 g, 29.6 mmole), imidazole (5.04 g, 74.0 mmole) and dichloromethane (55 mL) was added TBSCI (4.68g, 31.1 mmole) resulting in a cloudy white suspension that was stirred overnight. Addition of water (50mL) and dichloromethane (50 mL) gave a biphasic mixture that was separated. Extraction with dichloromethane, and washing the organics with brine, drying over MgSO₄, filtration and evaporation gave a crude residue that could be used without further purification. Flash chromatography (15:1 Hexanes:ethyl acetate) through a short plug of silica gel gave a clear colourless oil in quantitative yield (10.0 g)

Yield: 100% ¹H NMR (CDCl₃, 300MHz): δ 7.25 (d, J= 8.6 Hz, 2H), 6.87 (d, J= 8.6 Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.48 (t, J= 6.7 Hz, 2H), 3.44 (dd, J= 9.8, 4.4 Hz, 1H), 3.37 (dd, J= 9.8, 5.9 Hz, 1H), 1.77-1.70 (m, 2H), 1.38-1.36 (m, 1H), 0.88 (d, J= 6.4 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 6H). ¹³C NMR (CDCl₃, 75 MHz): δ 159.0 (s), 130.6 (s), 129.1 (d), 113.6 (d), 72.3 (t), 68.2 (t), 68.1 (t), 55.1 (q), 33.1 (t), 32.9 (d), 25.8 (q), 18.2 (s), 16.7 (q), -5.4 (q). IR (film, cm⁻¹): 2955, 2856, 1613, 1514, 1249, 1094, 1039, 836. LRMS (m/z (relative intensity)) NH₄: 339 (MH⁺, 10), 121 (100), 219 (48). HRMS calculated for C₁₉H₃₅O₃Si (MH⁺): 339.2355 found: 339.2365.

General procedure for Mosher esters 285 and 286

To a stirred solution of alcohol 283 (1.0 eq.), DMAP (0.2 eq.), (+) or (-)-MTPA (1.2 eq.) and distilled dichloromethane (0.3M) was added DCC (1.2 eq.). The reaction was stirred overnight, quenched with saturated aqueous NaHCO₃, and the aqueous layer extracted with dichloromethane (x3). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (15:1 hexanes:ethyl acetate) yielded Mosher esters 285 and 286.

Mosher ester 285:
See ‘General procedure for Mosher esters’. Alcohol 283 (66.0 mg, 0.298 mmole), (+)-MTPA (84 mg, 0.358 mmole), DMAP (7 mg, 0.06 mmole), dichloromethane (1 mL), DCC (74 mg, 0.358 mmole). Yields 113 mg of 285.

Yield: 85% $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.51-7.49 (m, 2H), 7.41-7.36 (m, 3H), 7.23 (d, J= 8.6 Hz, 2H), 6.86 (d, J= 8.6 Hz, 2H), 4.39 (s, 2H), 4.26 (dd, J= 10.8, 6.4 Hz, 1H), 4.10 (dd, J= 10.8, 6.4 Hz, 1H), 3.80 (s, 3H), 3.53 (s, 3H), 3.49-3.43 (m, 2H), 2.05 (sextet, J= 6.6 Hz, 1H), 1.67 (septet, J= 6.6 Hz, 1H), 1.46 (sextet, J= 6.1 Hz, 1H), 0.92 (d, J= 6.8 Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 166.5 (s), 159.1 (s), 132.2 (s), 130.4 (s), 129.5 (d), 129.1 (d), 128.3 (d), 127.3 (d), 125.2 (s), 121.4 (s), 113.7 (d), 72.5 (t), 71.0 (t), 67.3 (t), 55.3 (q), 55.1 (q), 32.9 (t), 29.7 (d), 16.6 (q).

IR (film, cm$^{-1}$): 3064, 2953, 2852, 1747, 1513, 1464, 1248, 1171, 1121, 1025. LRMS (m/z (relative intensity)): 440 (M$^+$, 10), 189 (100), 137 (95), 121 (92), 77 (78). HRMS calculated for C$_{23}$H$_{27}$F$_3$O$_5$: 440.1810 found: 440.1815

Mosher ester 286 (from racemic Mosher acid):

$$\text{Ph} \quad \text{CF}_3 \quad \text{MeO}$$

See ‘General procedure for Mosher esters’. Alcohol 283 (56.6 mg, 0.252 mmole), (+)-MTPA (71 mg, 0.303 mmole), DMAP (6 mg, 0.05 mmole), dichloromethane (1 mL), DCC (62.5 mg, 0.303 mmole). Yielding 89.4 mg of 286.

Yield: 80% $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.52-7.49 (m, 2H), 7.43-7.38 (m, 3H), 7.23 (d, J= 8.6 Hz, 2H), 6.87 (d, J= 8.6 Hz, 2H), 4.39 (s, 3H), one diastereomer 4.26 (dd, J= 10.7, 5.3 Hz, 1H), 4.11 (dd, J= 10.7, 6.5 Hz, 1H), other diastereomer 4.18 (d, J= 5.8 Hz, 2H), 3.80 (s, 3H), 3.54 (s, 3H), 3.50-3.43 (m, 2H), 2.06 (sextet, J= 6.6 Hz, 1H), 1.67 (septet, J= 6.7 Hz, 1H), 1.51-1.42 (m, 1H), 0.93 (d, J= 6.8 Hz, 3H), 0.92 (d, J= 6.8 Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 166.5 (s), 159.1 (s), 132.2 (s), 130.4 (s), 129.5 (d), 129.1 (d), 128.3 (d), 127.3 (d), 125.2 (s), 121.4 (s), 113.7 (d), 72.5 (t), 71.0 (t), 67.3 (t), 55.3 (q), 55.1 (q), 32.9 (t), 29.7 (d), 16.7 (q).

IR (film, cm$^{-1}$): 3064, 2953, 2852, 1747, 1513, 1464, 1248, 1171, 1121, 1025. LRMS (m/z (relative intensity)): 440 (M$^+$, 10), 189 (100), 137 (95), 121 (92), 77 (78). HRMS calculated for C$_{23}$H$_{27}$F$_3$O$_5$: 440.1810 found: 440.1815

trans-Vinyllic halides 287 and 288:

$$\text{Br} \quad \text{OPMB} \quad \text{I} \quad \text{OPMB}$$

To a cooled 0°C solution of Cp$_2$ZrCl$_2$ (1.5eq) and THF [0.14M] was added dropwise a 1.0M solution of Super-Hydride (1.5eq), producing a white suspension. The suspension was guarded from light and the ice bath removed. After 70 minutes a solution of alkyne 272 (1.0 eq) and THF [0.60M] was added via cannula resulting in a clear yellow solution. After 30 minutes iodine or NBS
(1.7eq) was added. This mixture was stirred for 1 hour further before being poured into a solution of saturated aqueous NaHCO$_3$. The product was extracted with ethyl ether (x3), washed with aqueous Na$_2$S$_2$O$_3$, dried over MgSO$_4$, filtered and concentrated. Flash chromatography (9:1 hexanes:ethyl acetate) provided pure vinylhalides as clear yellow liquids. **Yield:** 87% **$^1$H NMR** (CDCl$_3$, 300MHz): $\delta$ 7.25 (d, J= 8.6 Hz, 2H), 6.88 (d, J= 8.6 Hz, 2H), 6.54 (dt, J= 14.5, 7.2 Hz, 1H), 6.09 (d, J= 14.5 Hz, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.47 (t, J= 6.6 Hz, 2H), 2.34 (dt, J= 7.6, 6.6 Hz, 2H). **$^{13}$C NMR** (CDCl$_3$, 75 MHz): $\delta$ 159.1 (s), 142.9 (d), 130.1 (s), 129.1 (d), 76.4 (d), 72.5 (t) 68.0 (t), 55.1 (q), 36.2 (t). **IR** (film, cm$^{-1}$): 2855, 1611, 1513, 1301, 1247, 1098, 1035, 944, 820. **LRMS** (m/z (relative intensity)): 318 (M$^+$, 8), 191 (100), 121 (92), 135 (72). **HRMS** calculated for C$_{12}$H$_{15}$O$_2$I: 318.0117 found: 318.0113

**Alcohol 302:**

Sodium borohydride (790 mg, 20.8 mmole) was added to a cooled 0°C solution of lactone 301 (5.00 g, 20.8 mmole), and ethyl alcohol (42 mL). The reaction mixture was stirred at 0°C for 1 hour before being quenched by the addition of water (20mL) and neutralized with 1N HCl. The ice bath was then removed and phosphate buffer (40mL) was added, followed by sodium periodate (5.78 g, 27.0 mmole). The reaction mixture was stirred less than one hour and the resulting suspension filtered through celite. The alcohol was extracted with dichloromethane (x4), washed with brine, dried over MgSO$_4$, filtered and concentrated. Purification by flash chromatography (3:1 to 1:1 hexanes:ethyl acetate to 100% ethyl acetate) yielded 3.46 g of alcohol 302 as a white solid. **Yield:** 78% **$^1$H NMR** (CDCl$_3$, 300MHz): $\delta$ 4.59-4.54 (m, 1H), 4.24-4.20 (m, 2H), 2.80 (dd, J= 7.6, 3.6 Hz, 1H), 2.71-2.63 (m, 2H), 2.47-2.39 (m, 1H), 2.23 (bs, 1H), 1.90-1.86 (m, 2H), 1.78-1.61 (m, 6H). **$^{13}$C NMR** (CDCl$_3$, 75 MHz): $\delta$ 208.9 (s), 118.7 (s), 74.4 (d), 72.1 (d), 67.7 (d), 41.5 (t), 40.2 (t), 39.8 (t), 35.4 (t), 23.9 (t), 22.8 (t). **IR** (film, cm$^{-1}$): 3427, 2961, 2917, 1713, 1339, 1105, 1075. **LRMS** (m/z (relative intensity)): 212 (M$^+$, 35), 183 (100). **HRMS** calculated for C$_{11}$H$_{16}$O$_4$: 212.1048 found: 212.1056. $[\alpha]_D$: +121.8 (c 0.92, CHCl$_3$). **Melting Point:** 60.5°C
Enone 303

To a cooled 0°C solution of alcohol 302 (1.62 g, 7.63 mmole), triethylamine (3.2 mL, 22.9 mmole), and dichloromethane (22 mL) was added a solution of methanesulfonyl chloride (710 µL, 9.16 mmole) and dichloromethane (2.5 mL). After 2 hours at 0°C, the reaction was quenched with water. After extraction with dichloromethane (x3), the organics were washed with saturated aqueous NaHCO₃, and brine, then dried over MgSO₄. Filtration, concentration and purification by flash chromatography (1:1 hexanes:ethyl aceate) yielded 1.27 g of ketone 303 as a colourless oil.

**Yield:** 86% **¹H NMR (CDCl₃, 300MHz):** δ 6.64 (dt, J= 10.4, 2.3 Hz, 1H), 6.03 (d, J= 10.4 Hz, 1H), 4.70-4.68 (m, 1H), 4.59-4.55 (m, 1H), 2.93 (dd, J= 17.5, 2.9 Hz, 1H), 2.68 (dd, 17.5, 3.9 Hz, 1H), 1.81-1.62 (m, 8H). **¹³C NMR (CDCl₃, 75 MHz):** δ 195.2 (s), 145.4 (d), 129.1 (d), 119.5 (s), 73.4 (d), 70.5 (d), 38.7 (t), 37.4 (t), 23.3 (t), 23.1 (t). **IR (film, cm⁻¹):** 2961, 2876, 1687, 1333, 1107, 1037. **LRMS (m/z (relative intensity)):** 194 (M⁺, 25), 165 (100). **HRMS** calculated for C₁₁H₁₄O₃: 194.0943 found: 194.0947. [α]D: +175.0 (c 0.56, CHCl₃)

Bromide 304
To a cooled 0°C solution of ketone 303 (1.24 g, 6.36 mmole) in dichloroethane (58 mL) was added a solution of Br₂ (310 µL, 6.04 mmole) in dichloroethane (13 mL) over a 1.5 hour period using an addition funnel. After 60 minutes further at 0°C a solution of triethylamine (1.6 mL, 11.4 mmole) in dichloroethane (12 mL) was added over 30 minutes to the reaction mixture. The reaction was stirred for 30 minutes further at 0°C before being filtered through a pad of celite. The filtrate was washed with 1N HCl and saturated aqueous NaHCO₃ and the aqueous layers extracted with dichloromethane (x2). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated to dryness. The crude product was purified by flash chromatography eluting with a 3:1 mixture of hexanes:ethyl acetate to give 1.13 g of 304 as a white solid.

Yield: 65% ¹H NMR (CDCl₃, 300MHz): δ 7.06-7.04 (m, 1H), 4.71 (dd, J= 4.9, 3.2 Hz, 1H), 4.57-4.53 (m, 1H), 3.12 (dd, J= 17.3, 2.8 Hz, 1H), 2.77 (dd, J= 17.3, 3.7 Hz, 1H), 1.80-1.56 (m, 8H). ¹³C NMR (CDCl₃, 75 MHz): δ 187.3 (s), 145.8 (d), 124.3 (s), 120.0 (s), 73.5 (d), 72.5 (d), 38.7 (t), 37.4 (t), 23.3 (t), 23.1 (t). IR (film, cm⁻¹): 2963, 2874, 1701, 1611, 1334, 1109. LRMS (m/z (relative intensity)): 272 (M⁺, 18), 274 (M⁺, 17), 243 (100), 245 (90). HRMS calculated for C₁₁H₁₃O₃Br: 272.0048 found: 272.0052. Melting Point: 57.9°C

Allylic alcohol 305

To a cooled 0°C solution of tetravinyltin (615 µL, 3.38 mmole) in THF (68 mL) was added a [1.47 M]solution of n-BuLi (6.2 mL, 9.2 mmole). After 10 minutes the reaction mixture was warmed to room temperature and stirred for 50 minutes before being added via cannula to a cooled -78°C suspension of CeCl₃ (4.60 g, 12.3 mmole), ketone 304 (1.68 g, 6.15 mmole) in THF (62 mL). The reaction was stirred at -78°C for a total of 1 hour before being quenched with aqueous NH₄Cl. The mixture was extracted with ethyl ether (x3) and the organics washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude alcohol was purified by flash chromatography using hexanes:ethyl acetate (3:1) as the eluent to give 1.37 g of a white solid.
Yield: 74 % ¹H NMR (CDCl₃, 300MHz): δ 6.11 (d, J= 3.2 Hz, 1H), 5.70 (dd, J= 17.1, 10.6, 1H), 5.42 (dd, J= 17.1, 1.0 Hz, 1H), 5.22 (dd, J= 10.6, 1.0 Hz, 1H), 4.47 (dd, J= 5.3, 3.2 Hz, 1H), 4.39-4.34 (m, 1H), 3.71 (bs, 1H), 2.37 (dd, J= 14.8, 5.0 Hz, 1H), 2.12 (dd, J= 14.8, 2.6 Hz, 1H), 1.94-1.59 (m, 8H). ¹³C NMR (CDCl₃, 75 MHz): δ 140.7 (d), 132.2 (s), 128.5 (d), 119.8 (s), 115.0 (t), 73.2 (d), 72.6 (s), 72.4 (d), 37.7 (t), 37.6 (t), 37.2 (t), 23.1 (t). IR (film, cm⁻¹): 3507, 2961, 2874, 1634, 1418, 1330, 1103. LRMS (m/z (relative intensity)): 300 (M⁺, 30), 302 (M⁺, 32), 120 (100), 271 (65), 273 (63). HRMS calculated for C₁₃H₁₇O₃Br: 300.0361 found: 300.0366. [α]D: -6.92 (c 4.987, CHCl₃). Melting Point: 63.1°C

Allylic acetate 306

To a stirred solution of alcohol 305 (1.68 g, 5.58 mmole) and dichloromethane (7mL) was added acetic anhydride (1.05 mL, 11.1 mmole), triethylamine (2.33 mL, 16.7 mmole) and DMAP (135 mg, 1.11 mmole) at room temperature. The mixture was stirred at room temperature for 7 days gradually becoming deep red-dark brown. The mixture was washed with 1 N HCl, and saturated aqueous NaHCO₃. The aqueous layer were then extracted with ethyl ether (x3), the combined organsics dried over MgSO₄, filtered and concentrated. Purification by flash chromatography using a 9:1 hexanes:ethyl acetate mixture yielded 1.85 g of acetate 306 as a pale yellow oil.

Yield: 97 % ¹H NMR (CDCl₃, 300MHz): δ 6.43 (d, J= 4.2 Hz, 1H), 5.85 (dd, J= 17.2, 10.8, 1H), 5.31 (d, J=10.7 Hz, 1H), 5.29 (d, J= 17.3, 1H), 4.31-4.22 (m, 2H), 2.85-2.78 (m, 1H), 2.33-2.27 (m, 1H), 2.09 (s, 3H), 2.04-1.85 (m, 2H), 1.76-1.64 (m, 6H). ¹³C NMR (CDCl₃, 75 MHz): δ 168.8 (s), 135.5 (d), 130.6 (s), 128.0 (d), 120.1 (s), 116.8 (t), 81.6 (s), 72.0 (d), 70.8 (d), 37.3 (t), 37.1 (t), 34.5 (t), 23.1 (t), 21.8 (q). IR (film, cm⁻¹): 2959, 2873, 1747, 1634, 1327, 1229, 1101, 1044, 874 LRMS (m/z (relative intensity)): 342 (M⁺, 1), 344 (M⁺, 1), 84 (100), 120 (95), 91 (90), 203 (90), 221 (80). HRMS calculated for C₁₅H₁₉O₄Br: 342.0467 found: 342.0472. [α]D: +84.6 (c 0.363, CHCl₃)
Peroxyde 313:

\[
\begin{align*}
\text{Acetate } &306\text{ was placed in the refrigerator for a few days. Purification by flash chromatography (9:1 to 3:1 hexanes:ethyl acetate) yielded significant quantities of peroxide 313.}
\end{align*}
\]

\[\text{H NMR (acetone d-6, 300MHz): } \delta \text{ 10.98 (s, 1H), 6.59 (s, 1H), 5.85 (dd, 17.3, 10.7 Hz, 1H), 5.37 (d, J= 17.3 Hz, 1H), 5.32 (d, J= 10.7 Hz, 1H), 4.30 (dd, J= 11.0, 6.1 Hz, 1H), 2.94 (t, J= 11.6 Hz, 1H), 2.82 (s, 1H), 2.32 (dd, J= 12.3, 6.1 Hz, 1H), 2.03-1.76 (m, 4H), 1.68-1.60 (m, 4H).}
\]

\[\text{C NMR (acetone d-6, 75 MHz): } \delta \text{ 169.9 (s), 136.6 (d), 131.7 (s), 129.0 (d), 124.0 (s), 117.9 (t), 108.4 (s), 82.8 (s), 76.6 (d), 39.7 (t), 37.6 (t), 24.4 (t), 24.3 (t), 22.3 (q).}
\]

\[\text{IR (film, cm}^{-1}\text{): 3356, 2959, 1747, 1369, 1230, 1025, 999, 940.}
\]

\[\text{LRMS (m/z (relative intensity)): 341 (M}^+\text{ - HO}_2, 20), 343 (M}^+\text{ - HO}_2, 20), 135 (100), 101 (88), 83 (68).}
\]

\[\text{HRMS calculated for C}_{15}\text{H}_{18}\text{O}_4\text{Br (M}^+\text{ - HO}_2): 341.0388 found: 341.0390}
\]

Peroxyde 314:

\[
\begin{align*}
\text{To a stirred solution of peroxide 313 (51.4 mg, 0.137 mmole), imidazole (23 mg, 0.342 mmole) and dichloromethane (1mL) was added TBSCI (25 mg, 0.164 mmole). The mixture was stirred overnight and quenched with water. Extraction with CH}_2\text{Cl}_2 (x3), drying over MgSO}_4, filtration and concentration yielded a crude}
\end{align*}
\]
product that could be purified by flash chromatography (3:1 hexanes:ethyl acetate) to give 46 mg of peroxide 314.

**Yield**: 69% ¹H NMR (acetone d-6, 300MHz): δ 6.46 (s, 1H), 5.87 (dd, J= 17.3, 10.7 Hz, 1H), 5.40 (d, J= 17.3 Hz, 1H), 5.33 (d, J= 10.7 Hz, 1H), 4.43 (dd, J= 11.1, 6.0 Hz, 1H), 2.93 (t, J= 11.7 Hz, 1H), 2.31 (dd, J= 12.3, 6.0 Hz, 1H), 2.03 (s, 3H), 1.98-1.77 (m, 4H), 1.66-1.59 (m, 4H), 0.94 (s, 9H), 0.16 (d, J= 2.1 Hz, 6H)

**¹³C NMR** (acetone d-6, 75 MHz): δ 170.0 (s), 136.7 (d), 132.2 (s), 129.4 (d), 124.4 (s), 118.1 (t), 108.8 (s), 82.9 (s), 76.5 (d), 40.1 (t), 39.9 (t), 37.7 (t), 27.1 (q), 24.5 (t), 22.4 (q), 19.4 (s), -4.8 (q)

**IR** (film, cm⁻¹): 2956, 2858, 1750, 1642, 1365, 1229, 1119, 999, 830

**LRMS** (m/z (relative intensity)): IC: NH₃: 506 (MNH₄⁺, 5), 508 (MNH₄⁺, 5), 343 (100), 341 (98)

**HRMS** calculated for C_{21}H_{37}NO_{6}BrSi (MNH₄⁺): 506.1573 found: 506.1578.

**Lactone 322:**

![Lactone 322](image)

To a stirred solution of diol 321 (8.05 g, 30.4 mmole), imidazole (10.3 g, 152.0 mmole), DMAP (750 mg, 6.08 mmole) and dichloromethane (300 mL) was added TBDPSCl (7.9 mL, 30.4 mmole) at room temperature. The reaction was stirred for 7 days before being partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (x5), washed with brine, dried over MgSO₄, filtered and concentrated. Purification by flash chromatography eluting with 9:1 to 6:1 to 1:1 hexanes:ethyl acetate yielded 12.0 g (78%) of silyl ether 322 and 1.82 g (22%) of starting diol 321, resulting in a corrected overall yield of 100%.

**Yield**: 100% ¹H NMR (CDCl₃, 300MHz): δ 7.73-7.59 (m, 4H), 7.44-7.23 (m, 9H), 7.07-7.04 (m, 2H), 4.40 (t, J= 5.4 Hz, 1H), 4.27-4.21 (m, 3H), 3.48-3.41 (m, 1H), 2.84 (d, J=11.3 Hz, 1H), 2.66 (s, 1H), 2.31-2.13 (m, 3H), 1.08 (s, 9H). **¹³C NMR** (CDCl₃, 75 MHz): δ 177.8 (s), 137.5 (s), 136.0 (d), 135.6 (d), 133.2 (s), 132.4 (s), 129.9 (d), 129.6 (d), 128.0 (d), 127.6 (d), 127.3 (d), 76.1 (d), 73.3 (d), 72.3 (s), 70.7 (t), 65.8 (d), 36.8 (t), 36.5 (t), 26.8 (q), 19.2 (s). **IR** (film, cm⁻¹): 3439, 3069, 2931, 2857, 1794, 1427, 1105, 1051, 701. **LRMS** (m/z (relative intensity)): 445
β-Hydroxy ketone 323:

Sodium borohydride (499 mg, 13.2 mmole) was added to a cooled 0°C solution of lactone 322 (6.66 g, 13.2 mmole), and ethyl alcohol (45 mL). The reaction mixture was stirred at 0°C for a total of 2 hours before being quenched by the slow addition of aqueous NH₄Cl. The ice bath was then removed and phosphate buffer and water were added, followed by sodium periodate (3.67 g, 17.1 mmole). The reaction mixture was stirred overnight and the resulting suspension filtered through celite. The alcohol was extracted with dichloromethane (x4), washed with brine, dried over MgSO₄, filtered and concentrated. Purification by flash chromatography (3:1 hexanes:ethyl acetate) yielded 4.67g of alcohol 323 as an oil.

**Yield:** 75 %

**¹H NMR (CDCl₃, 300MHz):** δ 7.76-7.67 (m, 4H), 7.45-7.18 (m, 11H), 4.42 (d, J= 11.7 Hz, 1H), 4.32 (d, J= 11.7 Hz, 1H), 4.17-4.15 (m, 1H), 4.08 (dd, J= 6.4, 2.3 Hz, 1H), 3.84-3.79 (m, 1H), 2.91-2.81 (m, 2H), 2.48 (dd, J= 14.2, 3.9 Hz, 1H), 2.31-2.24 (m, 1H), 1.77 (d, J= 3.1 Hz, 1H), 1.10 (s, 9H).

**¹³C NMR (CDCl₃, 75 MHz):** δ 207.5 (s), 138.0 (s), 136.1 (d), 135.8 (d), 133.6 (s), 132.9 (s), 130.0 (d), 129.8 (d), 128.2 (d), 127.8 (d), 127.5 (d), 127.3 (d), 75.5 (d), 73.5 (d), 70.9 (t), 69.5 (d), 44.8 (t), 43.4 (t), 27.0 (q), 19.3 (s).

**IR (film, cm⁻¹):** 3433, 3061, 2930, 2854, 1714, 1471, 1427, 1136, 1112. **LRMS (m/z (relative intensity)):** 417 (M – C₄H₉, 8), 249 (95), 91 (100). **HRMS calculated for C₂₅H₂₅O₄Si(M – C₄H₉):** 417.1522 found: 417.1533. **[α]₀D:** -22.6 (c 3.163, CHCl₃)
\(\alpha,\beta\)-Unsaturated ketone 324:

![Diagram of \(\alpha,\beta\)-Unsaturated ketone 324]

To a cooled 0°C solution of alcohol 323 (4.51g, 9.49 mmole), methanesulfonyl chloride (880 µL, 11.4 mmole), and dichloromethane (32 mL) was added triethylamine (4 mL, 28.5 mmole). After 15 minutes at 0°C, the reaction was quenched with water. After extraction with dichloromethane (x3), the organics were washed with saturated aqueous NaHCO₃ and brine, then dried over MgSO₄. Filtration, concentration and purification by flash chromatography (3:1 hexanes:ethyl acetate) yielded 4.03g of ketone 324 as an oil.

Yield: 93 %

\(^1\)H NMR (CDCl₃, 300MHz): \(\delta\) 7.73-7.65 (m, 4H), 7.47-7.24 (m, 11H), 6.60 (dd, \(J=10.3, 3.2\) Hz, 1H), 5.93 (d, \(J=10.5\) Hz, 1H), 4.62 (d, \(J=12.2\) Hz, 1H), 4.60-4.57 (m, 1H), 4.54 (d, \(J=12.2\) Hz, 1H), 3.84-3.80 (m, 1H), 2.89 (dd, \(J=16.5, 7.1\) Hz, 1H), 2.43 (dd, \(J=16.5, 3.2\) Hz, 1H), 1.10 (s, 9H).

\(^13\)C NMR (CDCl₃, 75 MHz): \(\delta\) 197.1 (s), 148.5 (d), 138.0 (s), 135.8 (d), 133.3 (s), 132.9 (s), 129.9 (d), 129.6 (d), 128.2 (d), 127.7 (d), 127.4 (d), 76.6 (d), 71.3 (t), 68.4 (d), 40.9 (t), 26.8 (q), 19.2 (s).

IR (film, cm⁻¹): 3069, 2930, 1682, 1427, 1112, 821, 740, 702.

LRMS (m/z (relative intensity)): 399 (M – C₄H₉, 8), 231 (38), 91 (100).

HRMS calculated for C₂₅H₂₃O₃Si (M – C₄H₉): 399.1416 found: 399.1422. \([\alpha]_D^\circ: +78.1\) (c 3.606, CHCl₃)

Bromoketone 325:

![Diagram of Bromoketone 325]

To a cooled 0°C solution of ketone 324 (8.45 g, 18.5 mmole) in carbontetrachloride (170 mL) was added a solution of Br₂ (950 µL, 18.5 mmole) in carbontetrachloride (60 mL) over a 1.5 hour period using an addition funnel. After 15 minutes further at 0°C a solution of triethylamine (4.64 mL, 33.3 mmole)
in carbontetrachloride (60 mL) was added over 30 minutes to the reaction mixture. The reaction was stirred for 1.5 hours further at 0°C before being filtered through a pad of celite. The filtrate was washed with 1N HCl and saturated aqueous NaHCO₃ and the aqueous layers extracted with dichlormethane (x3). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated to dryness. The crude product was purified by flash chromatography eluting with a 6:1 mixture of hexanes:ethyl acetate to give 9.27 g of 325 as an oil.

**Yield:** 94 %

1H NMR (CDCl₃, 300MHz): δ 7.73-7.63 (m, 4H), 7.48-7.22 (m, 11H), 6.99 (d, J= 4.2 Hz, 1H), 4.58 (d, J= 12.3 Hz, 1H), 4.56-4.52 (m, 1H), 4.50 (d, J= 12.2 Hz, 1H), 3.80 (dt, J= 7.1, 3.2 Hz, 1H), 3.10 (dd, J= 16.4, 7.7 Hz, 1H), 2.60 (dd, J= 16.4, 3.2 Hz, 1H), 1.10 (s, 9H).

13C NMR (CDCl₃, 75 MHz): δ 189.1 (s), 148.7 (d), 137.6 (s), 135.8 (d), 132.9 (s), 132.6 (s), 130.1 (d), 128.3 (d), 127.9 (d), 127.5 (d), 125.1 (s), 75.9 (d), 71.3 (t), 69.7 (d), 40.3 (t), 26.8 (q), 19.3 (s).

IR (film, cm⁻¹): 3069, 2957, 1700, 1427, 1113, 1066, 741, 702.

LRMS (m/z (relative intensity)): 477 (M⁺ - C₄H₉, 5), 479 (M⁺ - C₄H₉, 5), 311 (30), 309 (30), 91 (100).

HRMS calculated for C₂₅H₂₂O₃SiBr (M⁺ - C₄H₉): 477.0521 found: 477.0511. [α]D: +81.9 (c 1.81, CHCl₃)

**Allylic acetate 326:**

To a cooled 0°C solution of tetravinyltin (1.75 mL, 9.63 mmole) in THF (190 mL) was added a [2.0M] solution of n-BuLi (13.1 mL, 26.3 mmole). After 20 minutes the reaction mixture was warmed to room temperature and stirred for 45 minutes before being added (over 25 minutes) via cannula to a cooled -78°C suspension of CeCl₃ (8.66g, 35.1mmole), ketone 325 (9.41 g, 17.5 mmole) in THF (175 mL). The resulting mixture became deep red. The reaction was stirred at -78°C for a total of 2.5 hours before being quenched with acetic anhydride (8.2 mL, 87.5 mmole). This mixture was gradually warmed to -10°C over 1.5 hours, then quenched with saturated aqueous NH₄Cl. The mixture was extracted with ethyl ether (x3) and the organics washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude acetate was purified by flash chromatography using hexanes:ethyl acetate (9:1) as the eluent to give 8.77 g of a clear pale yellow oil.

232
Yield: 83 % ¹H NMR (CDCl₃, 300MHz): δ 7.78-7.74 (m, 4H), 7.44-7.28 (m, 9H), 7.18-7.15 (m, 2H), 5.98 (d, J= 6.0 Hz, 1H), 5.84 (dd, J= 17.3, 10.7 Hz, 1H), 5.20 (d, J= 10.7 Hz, 1H), 5.16 (d, J= 17.3 Hz, 1H), 4.39 (d, J= 12.0 Hz, 1H), 4.30 (d, J= 12.0 Hz, 1H), 4.14-4.12 (m, 1H), 3.38 (dt, J= 12.2, 3.0 Hz, 1H), 3.24 (dd, J= 12.0, 11.7 Hz, 1H), 2.33-2.29 (m, 1H), 2.12 (s, 3H), 1.09 (s, 9H).

¹³C NMR (CDCl₃, 75 MHz): δ 168.4 (s), 138.0 (s), 136.1 (d), 134.1 (s), 133.3 (s), 132.5 (d), 129.6 (d), 129.0 (s), 128.1 (d), 127.4 (d), 116.6 (t), 82.4 (s), 73.1 (d), 69.8 (t), 66.2 (d), 32.7 (t), 26.7 (q), 21.8 (q), 19.3 (s). IR (film, cm⁻¹): 3068, 2931, 1749, 1472, 1427, 1366, 1228, 1112, 1022, 739, 702. LRMS (m/z (relative intensity)): 547 (M⁺ - C₄H₉, 1), 91 (85), 199 (89), 181 (94), 241 (96), 397 (98), 399 (100). HRMS calculated for C₂₉H₂₈BrO₄Si: 547.0940 found: 547.0947

[α]₀D: + 126.5 (c 4.443, CHCl₃)

Vinylbromide 327:

![Vinylbromide 327](image)

To a cooled -78°C solution of alkyl iodide 109 (2.74g, 8.34 mmole) in Et₂O (78 mL) was added a [1.7M] solution of tert-butyllithium (9.8 mL, 16.7 mmole) fairly rapidly. After 5 minutes this solution was warmed to 0°C and stirred for 25 minutes before being cooled to -78°C (upon warming the solution becomes yellow only to fade to near colourless after 25 minutes). This cooled solution was then added via cannula to a stirred suspension of CuCN (746 mg, 8.34 mmole) in THF (64 mL) at -70°C. This suspension was stirred for 20 minutes further before a solution of acetate 326 (3.20 g, 5.27 mmole) in THF (43 mL) was added via cannula at -65°C. After 25 minutes the reaction mixture was warmed to 0°C and stirred 6.5 hours further before being quenched with a 9:1 solution of saturated aqueous NH₄Cl: concentrated NH₄OH. The mixture was extracted with ethyl ether (x3), washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography using 25:1 hexanes: ethyl acetate to give 3.79 g of 327 as a clear colourless oil.

Yield: 96 % ¹H NMR (CDCl₃, 300MHz): δ 7.76-7.64 (m, 5H), 7.44-7.22 (m, 10H), 6.02 (t, J= 7.3 Hz, 1H), 5.90 (d, J= 5.5 Hz, 1H), 4.51 (d, J= 12.1 Hz, 1H), 4.37 (d, J= 12.1 Hz, 1H), 4.33-4.30 (m, 1H), 3.49-3.34 (m, 3H), 2.84-2.81 (m,
1H), 2.62-2.56 (m, 1H), 2.18-2.11 (m, 2H), 1.60-1.37 (m, 5H), 1.08 (s, 9H), 0.89 (s, 9H), 0.87 (d, J = 6.6 Hz, 3H), 0.03 (s, 6H).  

13C NMR (CDCl3, 75 MHz): δ 138.4 (s), 136.0 (d), 134.9 (d), 134.1 (s), 133.6 (s), 130.5 (s), 130.1 (d), 129.7 (d), 128.2 (d), 127.8 (s), 127.6 (d), 75.4 (d), 70.4 (t), 68.2 (t), 67.8 (d), 35.7 (d), 33.0 (t), 28.5 (t), 27.9 (t), 26.9 (q), 26.6 (t), 25.9 (q), 19.4 (s), 18.3 (s), 16.7 (q), -5.3 (q).  

IR (film, cm⁻¹): 2929, 2856, 1471, 1427, 1361, 1250, 1111, 836, 700.  

LRMS (m/z (relative intensity)): 691 (M⁺ - C₄H₉, 18), 689 (M⁺ - C₄H₉, 16), 91 (100), 74 (65), 199 (58), 135 (52).  

HRMS calculated for C₃₈H₅₀BrO₃Si₂ (M⁺ - C₄H₉): 689.2482 found: 689.2489.  

[α]D: +94.6 (c 1.80, CHCl₃)

Aldehyde 328:

To a solution of vinylbromide 327 (3.79 g, 5.06 mmole) in THF (100 mL) was added a [1.98M] solution of n-butyllithium (2.81 mL, 5.57 mmole) at -78°C, producing a yellow solution. After 15 minutes at -78°C, DMF (1.17 mL, 15.2 mmole) was added giving a clear colourless solution. The mixture was stirred another 20 minutes further before being quenched with saturated aqueous NH₄Cl. The layers were separated and the aqueous extracted with ethyl ether (x3), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using 25:1 hexane:ethyl acetate as the eluent, providing 2.81 g of aldehyde 328 as a clear colourless oil.

Yield: 80 %  

1H NMR (CDCl₃, 300MHz): δ 9.38 (s, 1H), 7.74-7.65 (m, 4H), 6.78 (t, J = 7.4 Hz, 1H), 6.15 (d, J = 3.5 Hz, 1H), 4.61-4.58 (m, 1H), 4.56 (ABQ, J = 19.4 Hz, 2H), 3.59-3.54 (m, 1H), 3.42 (dd, J = 9.7, 5.8 Hz, 1H), 3.32 (dd, J = 9.7, 5.8 Hz, 1H), 2.79 (dd, J = 15.6, 7.2 Hz, 1H), 2.24-2.19 (m, 1H), 2.07 (q, J = 7.2 Hz, 2H), 1.57-1.26 (m, 5H), 1.11 (s, 9H), 0.87 (s, 9H), 0.85 (d, J = 6.6 Hz, 3H), 0.02 (s, 6H).  

13C NMR (CDCl₃, 75 MHz): δ 193.4 (d), 148.6 (d), 138.5 (s), 137.5 (s), 135.9 (d), 133.7 (d), 133.3 (s), 129.9 (d), 128.2 (d), 127.7 (d), 127.4 (d), 125.8 (s), 75.2 (d), 71.1 (t), 69.3 (d), 68.2 (t), 35.6 (d), 33.0 (t), 28.6 (t), 28.1 (t), 26.9 (q), 26.6 (t), 25.9 (q), 19.3 (s), 18.3 (s), 16.6 (q), -5.4 (q).  

IR (film, cm⁻¹): 3070, 2954, 2856, 1700, 1471, 1427, 1255, 1112, 836, 702.  

LRMS (m/z (relative intensity)): 696 (M⁺, 20), 639 (M⁺ - C₄H₉, 68), 91 (100), 74
Acetal 329:

A solution of aldehyde 328 (2.45 g, 3.51 mmole), PPTS (265 mg, 1.05 mmole), and ethylene glycol (20 mL) and benzene (20 mL) was heated to reflux for 14 hours. The solvent was removed in vacuo and the residue taken up in Et$_2$O. The etheric layer was washed with saturated aqueous NaHCO$_3$, and brine. The combined aqueous layers were extracted once with ethyl ether. The organics were then dried over MgSO$_4$, filtered and concentrated. Purification by flash chromatography eluting with a 15:1 to 6:1 hexanes: ethyl acetate mixtures provides 2.46 g of acetal 329 as a colourless oil.

**Yield:** 95%  

$^1$H NMR (CDCl$_3$, 300MHz): $\delta$ 7.77-7.66 (m, 4H), 7.43-7.22 (m, 11H), 5.82 (d, $J$ = 5.1 Hz, 1H), 5.75 (t, $J$ = 7.1 Hz, 1H), 5.54 (s, 1H), 4.52 (d, $J$ = 12.2 Hz, 1H), 4.41-4.37 (m, 2H), 3.91-3.81 (m, 4H), 3.47-3.41 (m, 2H), 3.34 (dd, $J$ = 9.7, 6.6 Hz, 1H), 2.80-2.72 (m, 1H), 2.54-2.47 (m, 1H), 2.17-2.12 (m, 2H), 1.59-1.33 (m, 5H), 1.07 (s, 9H), 0.89 (s, 9H), 0.86 (d, $J$ = 6.7 Hz, 3H), 0.03 (s, 6H)  

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 138.8 (s), 136.1 (d), 135.7 (s), 134.5 (s), 134.0 (s), 130.7 (s), 129.5 (d), 128.6 (d), 128.1 (d), 127.4 (d), 127.2 (d), 125.3 (d), 101.2 (d), 76.0 (d), 70.2 (t), 68.3 (t), 66.2 (d), 64.7 (t), 35.7 (d), 33.0 (t), 28.5 (t), 27.2 (t), 27.0 (q), 26.9 (q), 25.9 (d), 19.3 (s), 18.3 (s), 16.7 (q), -5.3 (q).  

IR (film, cm$^{-1}$): 3070, 2954, 2856, 1471, 1426, 1360, 1252, 1098.  

LRMS (m/z (relative intensity)): 683 (M$^+$ - C$_4$H$_9$, 30), 91 (100).  

HRMS calculated for C$_{41}$H$_{55}$O$_5$Si$_2$ (M$^+$ - C$_4$H$_9$): 683.3588 found: 683.3593.  

$[\alpha]_D$: +105.3 (c 0.74, CHCl$_3$)
Alcohol 330:

To a cooled 0°C solution of silyl ether 329 (4.27 g, 5.75 mmole) and THF (115 mL) was added a [1.0M] solution of TBAF (5.75 mL, 5.75 mmole). The reaction was gradually warmed to room temperature overnight. The solvent was removed in vacuo and the residue purified by flash chromatography (6:1 to 3:1 to 1:1 hexanes:ethyl acetate, followed by 100% ethyl acetate) to give 2.10 g of alcohol 330 as a clear colourless oil and 908mg of diol 331 as a colourless oil

**Yield:** 58 %

**¹H NMR** (CDCl₃, 300MHz): δ 7.81-7.70 (m, 4H), 7.46-7.27 (m, 11H), 5.88 (d, J= 6.0 Hz, 1H), 5.80 (t, J= 7.2 Hz, 1H), 5.59 (s, 1H), 4.57 (d, J= 12.3 Hz, 1H), 4.44 (d, J= 12.3 Hz, 1H), 4.46-4.42 (m, 1H), 3.93-3.83 (m, 4H), 3.52-3.47 (m, 2H), 3.41 (dd, J= 10.5, 6.4 Hz, 1H), 2.86-2.78 (m, 1H), 2.58-2.52 (m, 1H), 2.22-2.15 (m, 2H), 1.73 (s, 1H), 1.65-1.61 (m, 1H), 1.56-1.40 (m, 3H), 1.22-1.15 (m, 1H), 1.12 (s, 9H), 0.94 (d, J= 6.7Hz, 3H).

**¹³C NMR** (CDCl₃, 75 MHz): δ 138.7 (s), 136.0 (d), 135.6 (s), 134.4 (s), 133.9 (s), 130.6 (s), 129.4 (d), 128.4 (d), 128.0 (d), 127.4 (d), 127.1 (d), 125.4 (d), 101.1 (d), 75.9 (d), 70.2 (t), 68.0 (t), 66.2 (d), 64.7 (t), 35.5 (d), 32.8 (t), 28.2 (t), 27.3 (t), 26.9 (q), 26.7 (d), 19.3 (s), 16.5 (q).

**IR** (film, cm⁻¹): 3439, 3069, 2929, 2857, 1471, 1427, 1361, 1111, 1072.

**LRMS** (m/z (relative intensity)): 626 (M⁺, 1), 569 (M⁺ - C₄H₉, 20), 91 (100), 83 (80), 199 (65).

**HRMS** calculated for C₃₉H₅₀O₅Si: 626.3427 found: 626.3417.

**HRMS** calculated for C₃₅H₄₁O₅Si (M⁺ - C₄H₉): 569.2723 found: 569.2712.

[α]D: +70.6 (c 1.33, CHCl₃)
To a stirred solution of alcohol 330 (1.88 g, 3.0 mmole) in dichloromethane (25 mL) at room temperature was added Dess-Martin periodinane (1.91 g, 4.5 mmole). After 1.5 hours ethyl ether was added to the reaction mixture, producing a white suspension, followed by a solution of Na₂S₂O₅ (25 g) in saturated aqueous NaHCO₃. The mixture was stirred for 45 minutes until all the solids had entered solution. The layers were separated and the aqueous extracted with ethyl ether (x2). The etheric layer was washed with saturated aqueous NaHCO₃, water, then dried over MgSO₄, filtered and concentrated, yielding the aldehyde as a clear colourless oil that was used in the next step without further purification.

**¹H NMR** (CDCl₃, 300MHz): δ 9.60 (d, J= 1.9 Hz, 1H), 7.76-7.65 (m, 4H), 7.44-7.22 (m, 11H), 5.84 (d, J= 5.1 Hz, 1H), 5.73 (t, J= 7.2 Hz, 1H), 5.52 (s, 1H), 4.52 (d, J= 12.3 Hz, 1H), 4.41-4.37 (m, 2H), 3.91-3.81 (m, 4H), 3.49-3.42 (m, 1H), 2.80-2.72 (m, 1H), 2.51-2.45 (m, 1H), 2.20-2.10 (m, 2H), 1.74-1.69 (m, 1H), 1.51-1.37 (m, 3H), 1.23-1.18 (m, 1H), 1.08 (d, J= 6.9 Hz, 3H), 1.06 (s, 9H). **IR** (film, cm⁻¹): 3069, 2930, 2856, 1724, 1427, 1116. **LRMS** (m/z (relative intensity)): 624 (M⁺, 1), 567 (M⁺ - C₄H₉, 25), 199 (100), 91 (92), 135 (60). **HRMS** calculated for C₃₉H₄₈O₅Si: 624.3271 found: 624.3261. **HRMS** calculated for C₃₅H₃₉O₅Si (M⁺ - C₄H₉): 567.2567 found: 567.2556

To a cooled 0°C suspension of 60% w/w NaH (156 mg, 3.9 mmole) in THF (16.3 mL) was added MDEPA (716 µL, 3.9 mmole). After 1 hour at 0°C this clear colourless solution was added via cannula to a solution of crude aldehyde (3.0 mmole) in THF (15 mL) at 0°C. After 1.5 hours at 0°C the reaction was quenched with saturated aqueous NH₄Cl and the layers separated. The mixture was extracted with ethyl ether (x3) and the combined organics dried over MgSO₄, filtered and concentrated. The crude residue was purified by flash chromatography eluenting with a 6:1 mixture of hexanes:ethyl acetate yielding 1.34 g of 332 as clear colourless oil.

**Yield:** 66 % **¹H NMR** (CDCl₃, 300MHz): δ 7.78-7.67 (m, 4H), 7.44-7.23 (m, 11H), 6.87 (dd, J= 15.7, 8.0 Hz, 1H), 5.85 (d, J= 5.1 Hz, 1H), 5.79 (d, J= 15.9 Hz, 1H), 5.74 (t, J= 7.1 Hz, 1H), 5.54 (s, 1H), 4.53 (d, J= 12.3 Hz, 1H), 4.42-4.40 (m,
1H), 4.40 (d, J= 12.3 Hz, 1H), 3.92-3.82 (m , 4H), 3.72 (s, 3H), 3.45 (dt, J= 10.0, 3.5 Hz, 1H), 2.81-2.73 (m, 1H), 2.53-2.47 (m, 1H), 2.34-2.29 (m, 1H), 2.15-2.13 (m, 2H), 1.42-1.39 (m, 4H), 1.08 (s , 9H), 1.05 (d, J= 6.7 Hz, 3H).  

13C NMR (CDCl3, 75 MHz): δ 167.2 (s), 154.7 (d), 138.8 (s), 136.1 (d), 135.7 (s), 134.5 (s), 134.0 (s), 131.0 (s), 129.5 (d), 128.1 (d), 127.4 (d), 127.3 (d), 125.6 (d), 119.3 (d), 101.2 (d), 76.0 (d), 70.3 (t), 66.2 (d), 64.8 (t), 51.4 (q), 36.5 (d), 35.8 (t), 28.1 (t), 27.3 (t), 27.0 (q), 19.4 (q). IR (film, cm⁻¹): 3046, 2929, 2856, 1722, 1427, 1272, 1111, 983. LRMS (m/z (relative intensity)): 680 (M⁺, 2), 623 (M⁺ - C₄H₉, 35), 91 (100). HRMS calculated for C₄₂H₅₂O₆Si: 680.3533 found: 680.3526. HRMS calculated for C₃₈H₄₃O₆Si (M – C₄H₉): 623.2829 found: 623.2822. [α]D: +19.5 (c 1.32, CHCl₃)

Aldehyde 335:

A solution of acetal 332 (546 mg, 0.801 mmole), PPTS (60mg, .240 mmole), and wet acetone (16 mL) was refluxed overnight. The solvent was removed in vacuo and the residue taken up in ethyl acetate, then washed with aqueous NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated. After purification by flash chromatography (6:1 hexanes: ethyl acetate) 467 mg of aldehyde 335 was procured as a clear colourless oil.

Yield: 92 % 1H NMR (CDCl₃, 300MHz): δ 9.39 (s, 1H), 7.76-7.68 (m, 4H), 7.48-7.24 (m, 11H), 6.86 (dd, J= 15.7, 8.0 Hz, 1H), 6.80 (t, J= 7.4 Hz, 1H), 6.20 (d, J= 3.5 Hz, 1H), 5.78 (d, J= 15.6 Hz, 1H), 4.64-4.62 (m, 1H), 4.59 (ABQ, J= 21.0 Hz, 2H), 3.71 (s, 3H), 3.62-3.58 (m, 1H), 2.81 (dd, J= 15.6, 7.0 Hz, 1H), 2.32-2.20 (m, 2H), 2.14-2.05 (m, 2H), 1.46-1.34 (m, 4H), 1.13 (s, 9H), 1.04 (d, J= 6.8 Hz, 3H). 13C NMR (CDCl₃, 75 MHz): δ 193.3 (d), 167.1 (s), 154.5 (d), 149.0 (d), 138.4 (s), 137.3 (s), 135.8 (s), 133.5 (s), 133.2 (s), 133.0 (d), 129.8 (d), 127.6 (d), 127.4 (d), 127.3 (d), 125.9 (s), 119.2 (d), 75.1 (d), 71.1 (t), 69.2 (d), 51.2 (q), 36.4 (d), 35.6 (t), 28.1 (t), 26.8 (q), 19.3 (q). IR (film, cm⁻¹): 3069, 2930, 2857, 1722, 1698, 1428, 1272, 1112. LRMS (m/z (relative intensity)): 636 (M⁺, 10), 579 (M⁺ - C₄H₉, 25), 471 (100), 91 (48). HRMS calculated for C₄₀H₄₆O₅Si: 636.3271 found: 636.3277. [α]D: +16.4 (c 0.63, CHCl₃)
A solution of freshly distilled ethyl vinyl ether (7.5 mL), aldehyde 335 (457 mg, 0.716 mmole) and Yb(fod)$_3$ (114 mg, 0.107 mmole) were stirred under argon for 4 days. Water was then added and the mixture vigorous stirred for 30 minutes. The layers were separated and the aqueous washed with ethyl ether (x3). The organics were then dried over MgSO$_4$, filtered and concentrated. Flash chromatography yielded 414 mg of a mixture of two tetracycles of which only one could be isolated pure.

Yield: **82 %**

Stereochemistry of isolated tetracycle shown

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.73-7.61 (m, 4H), 7.41-7.22 (m, 9H), 7.10-7.07 (m, 2H), 4.76 (t, J= 7.1 Hz, 1H), 4.36-4.33 (m, 1H), 4.28 (s, 2H), 4.14-4.13 (m, 1H) 3.67 (dq, J= 9.8, 7.1 Hz, 1H), 3.56-3.52 (m, 2H), 3.35 (dq, J= 9.8, 7.1 Hz, 1H), 2.91 (dd, J= 9.2, 6.7 Hz, 1H), 2.50-2.35 (m, 2H), 2.21-2.17 (m, 1H), 2.05-2.02 (m, 1H), 1.80-1.77 (m, 2H), 1.71-1.57 (m, 2H), 1.47-1.18 (m, 6H), 1.14 (t, J= 7.1 Hz, 3H), 1.04 (s, 9H), 0.89 (d, J= 6.4 Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 175.8 (s), 138.7 (s), 136.5 (d), 136.3 (d), 134.7 (s), 134.6 (s), 134.1 (s), 129.2 (d), 128.8 (s), 128.1 (d), 127.4 (d), 127.1 (d), 98.0 (d), 78.7 (d), 70.2 (d), 70.1 (t), 65.3 (d), 62.5 (t), 51.3 (q), 49.7 (d), 47.8 (d), 39.6 (d), 39.1 (d), 36.4 (q), 35.8 (t), 31.0 (t), 29.1 (t), 27.9 (t), 27.3 (q), 25.8 (t), 20.1 (q), 19.9 (s), 15.2 (q).

IR (film, cm$^{-1}$): 2928, 2855, 1736, 1427, 1150, 1111, 1062, 702.

LRMS (m/z (relative intensity)): 651 ($M^+$ - C$_4$H$_9$, 8), 199 (100), 135 (88), 183 (89), 91 (88), 437 (70), 299 (68), 605 (67).

HRMS calculated for C$_{40}$H$_{57}$O$_6$Si ($M^+$ - C$_4$H$_9$): 651.3142 found: 651.3148
To a solution of tetracycles 336 (440 mg, 0.62 mmole) and THF (1 mL) was added a [1.0M] solution of TBAF (2.5 mL, 2.5 mmole). The mixture was refluxed for 4 hours before being cooled and concentrated to dryness. The crude residue was purified by flash chromatography (3:1 to 1:1 hexanes: ethyl acetate) to give 205 mg of tetracycle 338 and 69 mg of tetracycle 337 as amorphous solids.

**Tetracycle 338 Yield: 70 %**

**1H NMR** (C\textsubscript{6}D\textsubscript{6}, 300MHz): \(\delta 7.30-7.09 \text{ (m, 5H)}, 5.06 \text{ (t, J= 7.2 Hz, 1H)}, 4.41-4.37 \text{ (m, 1H)}, 4.28 \text{ (s, 2H)}, 3.92 \text{ (dq, J= 9.6, 7.0 Hz, 1H)}, 3.83 \text{ (m, 1H)}, 3.52-3.47 \text{ (m, 1H)}, 3.46 \text{ (s, 3H)}, 3.42 \text{ (dq, J= 9.7, 7.0 Hz, 1H)}, 2.94 \text{ (dd, J= 8.9, 6.0 Hz, 1H)}, 2.44-2.26 \text{ (m, 3H)}, 2.18 \text{ (dt, J= 13.8, 7.1 Hz, 1H)}, 2.09-2.00 \text{ (m, 1H)}, 1.98-1.95 \text{ (bs, 1H)}, 1.73-1.70 \text{ (m, 1H)}, 1.58-1.53 \text{ (m, 1H)}, 1.48-1.40 \text{ (m,1H)}, 1.37-1.24 \text{ (m, 2H)}, 1.19 \text{ (t, J= 7.0 Hz, 3H)}, 1.07-1.00 \text{ (m, 3H)}, 0.93 \text{ (s, 3H)}, 0.90-0.78 \text{ (m,1H)}. **13C NMR** (C\textsubscript{6}D\textsubscript{6}, 75 MHz): \(\delta 175.3 \text{ (s), 139.3 \text{ (s), 135.2 \text{ (s), 129.3 \text{ (s), 128.6 \text{ (d), 128.3 \text{ (d), 127.7 \text{ (d), 98.7 \text{ (d), 78.4 \text{ (d), 70.3 \text{ (t), 67.3 \text{ (d), 66.2 \text{ (d), 63.1 \text{ (t), 51.1 \text{ (q), 49.9 \text{ (d), 48.3 \text{ (d), 39.5 \text{ (d), 39.0 \text{ (d), 36.1 \text{ (t), 34.8 \text{ (d), 31.1 \text{ (t), 29.2 \text{ (t), 27.2 \text{ (t), 26.0 \text{ (t), 20.4 \text{ (q), 15.5 \text{ (q). IR (film, cm\textsuperscript{-1})}: 3482, 2925, 1736, 1456, 1374, 1154, 1061. LRMS (m/z (relative intensity)): 424 (M\textsuperscript{+}-C\textsubscript{2}H\textsubscript{6}O, 35), 91 (100), 315 (72). HRMS calculated for C\textsubscript{26}H\textsubscript{32}O\textsubscript{5} (M\textsuperscript{+}-C\textsubscript{2}H\textsubscript{6}O): 424.2250 found: 424.2248.**

**Tetracycle 337 Yield: 24 %**

**1H NMR** (C\textsubscript{6}D\textsubscript{6}, 300MHz): \(\delta 7.25-7.07 \text{ (m, 5H)}, 4.43 \text{ (dd, J= 9.4, 1.9 Hz, 1H)}, 4.38 \text{ (s, 2H)}, 3.91 \text{ (dq, J= 9.5, 7.1 Hz, 1H)}, 3.80-3.78 \text{ (m, 1H)}, 3.55-3.52 \text{ (m,1H)}, 3.48 \text{ (s, 3H)}, 3.39 \text{ (dq, J= 9.5, 7.1 Hz,1H)}, 3.26 \text{ (dd, J= 8.0, 2.3 Hz, 1H)}, 2.59 \text{ (dd, J= 12.0, 7.7 Hz, 1H)}, 2.44-2.37 \text{ (m, 3H)}, 2.05-1.99 \text{ (m, 1H)}, 1.91-1.51 \text{ (m, 5H)}, 1.49-1.19 \text{ (m, 5H)}, 1.14 \text{ (t, J= 7.1 Hz, 3H)}, 0.99 \text{ (s, 3H)}, 0.87-0.76 \text{ (m 1H)}. **13C NMR** (C\textsubscript{6}D\textsubscript{6}, 75 MHz): \(\delta 172.7 \text{ (s), 139.5 \text{ (s), 130.6 \text{ (s), 128.6 \text{ (d), 128.3 \text{ (d), 127.7 \text{ (d), 126.2 \text{ (s), 101.9 \text{ (d), 76.7 \text{ (d), 74.1 \text{ (d), 71.6 \text{ (t), 69.4 \text{ (d), 63.7 \text{ (t), 50.6 \text{ (q), 49.3 \text{ (d), 43.7 \text{ (d), 42.8 \text{ (d), 40.5 \text{ (d), 39.2 \text{ (d), 37.6 \text{ (t), 36.9 \text{ (t), 30.8 \text{ (t), 29.8 \text{ (t), 26.9 \text{ (t), 21.1 \text{ (q), 15.5 \text{ (q)}}.
To a solution of tetracycle 203 (39.0 mg, 0.107 mmole) and THF (500 µL) was added NaH (29 mg, 0.72 mmole) at room temperature. The reaction was stirred 2 hours before 350 (50 mg, 0.27 mmole) was added and the mixture stirred for 7 hours further at which time iodomethane (68 µL, 1.07 mmole) was added. The reaction was stirred overnight at room temperature and the solvent removed in vacuo. NaH (21 mg, 0.535 mmole) was added to a solution of PhSeSePh (93 mg, 0.297 mmole) and THF (3 mL). This mixture was stirred at reflux for 1 hour before being added via cannula to the dried reaction mixture. The resulting suspension was heated at reflux for 1.25 hours before being quenched with H₂O. The aqueous layer was extracted with ethyl ether (x3), dried over MgSO₄, filtered and concentrated. Flash chromatography (hexane to 15:1 to 9:1 to 6:1 to 3:1 hexanes:ethyl acetate) yielded 10.9 mg of tetracycle 371 and 10.3 mg of starting tetracycle 203 (24%).

**Yield: 19%** ¹H NMR (CDCl₃, 300MHz): δ 7.59-7.56 (m, 2H), 7.27-7.23 (m, 3H), 5.33 (ABQ, J= 20.4 Hz, 2H), 4.46 (dd, J= 9.8, 1.8 Hz, 1H), 3.86-3.71 (m, 2H), 3.67 (s, 3H), 3.48-3.33 (m, 2H), 3.47 (dd, J= 12.1, 7.0 Hz, 1H), 2.63-2.18 (m, 2H), 2.08-1.97 (m, 4H), 1.83-1.55 (m, 4H), 1.41-1.22 (m, 5H), 1.18 (t, J= 7.1 Hz, 3H), 1.07-0.93 (m, 1H), 0.85 (d, J= 6.1 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 173.4 (s), 133.0 (s), 132.8 (d), 129.1 (d), 127.0 (d), 124.9 (s), 101.6 (d), 79.8 (d), 70.5 (t), 69.5 (d), 63.8 (t), 50.9 (d), 49.0 (q), 44.4 (d), 41.9 (d), 41.0 (d), 40.0 (d), 37.7 (t), 36.6 (t), 29.3 (t), 26.7 (t), 26.3 (t), 20.7 (q), 15.1 (q).

**Silyl ethers 375 and 376:**
To a solution of tetracycle 337 or 338 (1.0 eq), imidazole (2.5 eq) and CH₂Cl₂ [0.54M] was added (bromomethyl)chlorodimethylsilane (1.5 eq) at room temperature. The reaction was stirred overnight then quenched with water. The layers were separated and the aqueous extracted with dichloromethane (x3). The combined organics were washed (brine), dried over MgSO₄, filtered and concentrated. Purification by flash chromatography (6:1 to 1:1 Hexanes: ethyl acetate) yielded silyl ethers 375 and 376 as amorphous solids.

**Tetracycle 376 Yield:** 87% **¹H NMR** (CDCl₃, 300MHz): δ 7.38-7.28 (m, 5H), 4.97 (t, J= 7.3 Hz, 1H), 4.55 (ABQ, J= 15.2, 2H), 4.31-4.27 (m, 1H), 4.07-4.06 (m, 1H), 3.78 (dq, J= 9.9, 7.1 Hz, 1H), 3.62 (s, 3H), 3.60-3.55 (m, 1H), 3.48 (dq, J= 9.9, 7.1 Hz, 1H), 2.89 (dd, J= 9.1, 6.5 Hz, 1H), 2.49 (ABQ, J= 21.0 Hz, 2H), 2.42-2.32 (m, 2H), 2.20-2.15 (m, 1H), 1.99-1.87 (m, 2H), 1.79-1.62 (m, 4H), 1.56 (dt, J= 13.8, 7.5 Hz, 1H), 1.35-1.12 (m, 3H), 1.21 (t, J= 7.1 Hz, 3H), 1.04-0.96 (m, 1H), 0.89 (d, J= 6.4 Hz, 3H), 0.24 (s, 6H). **IR** (film, cm⁻¹): 2934, 2854, 1737, 1369, 1152, 1056. **LRMS** (m/z (relative intensity)): 576 (M⁺-C₂H₆O, 22), 574 (M⁺-C₂H₆O, 21), 91 (100), 315 (43). **HRMS** (Cl: NH₃) calculated for C₃₁H₄₄BrO₆Si (M⁺-H): 619.2090 found: 619.2078. **Tetracycle 375 Yield:** 78% **¹H NMR** (CDCl₃, 300MHz): δ 7.35-7.28 (m, 5H), 4.66 (ABQ, J= 14.4 Hz, 2H), 4.55 (dd, J= 9.6, 2.0 Hz, 1H), 3.92-3.90 (m, 1H), 3.82 (dq, J= 9.6, 7.1 Hz, 1H), 3.75-3.72 (m, 1H), 3.67 (s, 3H), 3.55 (dd, J= 8.6, 1.8 Hz, 1H), 3.47 (dq, J= 9.6, 7.1 Hz, 1H), 2.74 (dd, J= 12.2, 7.6 Hz, 1H), 2.60-2.56 (m, 1H), 2.37 (s, 2H), 2.20-2.15 (m, 3H), 2.04-1.98 (m, 1H), 1.80-1.75 (m, 1H), 1.67-1.57 (m, 3H), 1.53-1.46 (m, 1H), 1.38-1.25 (m, 3H), 1.20 (t, J= 7.1 Hz, 3H), 1.01-0.96 (m, 1H), 0.84 (d, J= 6.0 Hz, 3H), 0.24 (s, 6H).

**Tetracycles 380 and 381**
To a refluxing solution of tetracycle 375 (61.9 mg, 0.10 mmole) and benzene (5 mL) was added a solution of AIBN (4 mg, 0.025 mmole), Ph₃SnH (43.7 mg, 0.124 mmole) and benzene (2 mL) via syringe pump over 24 hours. The solvent was removed in vacuo and TBAF (1.0 mL, 1.0 mmole) was added. After 2 hours the solvent was removed and the residue purified by flash chromatography (9:1 to 3:1 to 1:1 hexanes:ethyl acetate to 1:1 methanol:ethyl acetate). Yielding 4.5 mg of tetracycle 380, 4.0 mg of tetracycle 381, 5.3 mg of an unknown tetracycle (11%), and 20 mg of tetracycle 375 (43%)

Yield: 10% tetracycle 380

**¹H NMR (CDCl₃, 300MHz):** δ 7.39-7.27 (m, 5H), 4.75 (dd, J= 9.0, 3.7 Hz, 1H), 4.65 (s, 2H), 4.37-4.36 (m, 1H), 4.07-4.06 (m, 1H), 3.97-3.85 (m, 1H), 3.72-3.50 (m, 2H), 3.65 (s, 3H), 3.03 (dd, J= 7.0, 3.0 Hz, 1H), 2.61 (s, 1H), 2.54-2.47 (m, 1H), 2.35-2.22 (m, 2H), 2.16-2.05 (m, 2H), 1.98-1.71 (m, 6H), 1.47-1.15 (m, 3H), 1.22 (t, J= 8.0 Hz, 3H), 0.95 (d, J= 6.3 Hz, 3H)

**¹³C NMR (CDCl₃, 75 MHz):** δ 175.6 (s), 138.1 (s), 135.6 (s), 128.5 (d), 127.9 (d), 127.7 (d), 125.4 (s), 100.1 (d), 77.8 (d), 71.4 (d), 70.6 (t), 66.3 (d), 64.2 (t), 51.8 (q), 51.1 (d), 45.7 (d), 41.1 (d), 39.3 (d), 37.6 (d), 36.1 (t), 32.0 (t), 30.0 (t), 26.5 (t), 25.7 (t), 19.9 (q), 15.3 (q).

Yield: 9% tetracycle 381

**¹H NMR (CDCl₃, 300MHz):** δ 7.39-7.28 (m, 5H), 4.92 (dd, J= 5.5, 2.6 Hz, 1H), 4.60 (ABQ, J= 15.6Hz, 2H), 4.11-4.06 (m, 2H), 3.85-3.66 (m, 2H), 3.62 (s, 3H), 3.59-3.45 (m, 1H), 2.94 (dd, J= 8.5, 6.0 Hz, 1H), 2.69-2.61 (m, 1H), 2.55-2.47 (m, 1H), 2.35-2.25 (m, 1H), 2.19-1.94 (m, 3H), 1.87-1.65 (m, 5H), 1.35-1.15 (m, 4H), 1.19 (t, J= 7.2 Hz, 3H), 0.90 (d, J= 6.3 Hz, 3H).

**LRMS (m/z (relative intensity)):** 424 (M⁺-C₂H₆O, 22), 91 (100)
References


33. O. Tsuge, S. Kanemasa, E. Wada, H. Sakoh, Yuki Gosei Kagaky Kyohashi. 44, 756 (1986)

36. M. Gomberg, Chem. Ber., 33, 3150 (1900)
51. Refer to reference 35 for an excellent review.
62. Cerium trichloride was dried overnight at 200°C under high vacuum prior to use.
65. These attempts included (1) Raney Nickel, (2) Pd-C transfer hydrogenation, (3) NBS in the presence of hv, (4) DDQ, and (5) BBr$_3$


96. See reference 23
98. See reference 23
99. See reference 23
102. Unpublished results Eric Fillion
103. See reference 49
106. Unpublished results Eric Fillion (b) see reference 49
110. Unpublished results Sophie Gagnon
114. See reference 22
117. Prepared from 1-bromoethane and DHP.
118. Prepared with bromobutyryl chloride
119. Prepared from (+)-Norephedrine, which gives the opposite enantiomer from those depicted in the schemes. (-)-Norephedrine was required however for simplicity, all the products made from (+)-Norephedrine were drawn this way. In reality the opposite enantiomer was formed during the sequence.
123. See reference 121
132. See reference 115
136. See reference 115
142. See reference 49