Spirocyle Fragment of Calyculins

Vesa Rauhala

Dissertation for the degree of Doctor of Philosophy to be presented with due permission of the Department of Chemical Technology for public examination and debate in Auditorium KE2 (Komppa Auditorium) at Helsinki University of Technology (Espoo, Finland) on the 25th of August, 2007, at 12 o'clock noon.

**Keywords** Natural product, calyculin, spirocycle, Double Intramolecular Hetero-Michael Addition, DIHMA, triple bond

**ABSTRACT**

Calyculins are highly cytotoxic metabolites and protein phosphatase inhibitors isolated from the marine sponge *Discodermia calyx*. Despite several research groups’ efforts to synthesize naturally occurring Calyculin A or C, none has accomplished yet the fully synthetic route.

The literature part includes an overview of the synthesis of triple bonds. The very basis of these methods are elimination reactions. Historically name reactions are important. They have had bigger than normal influence on synthetic chemistry since they were invented. The most important part of this section for this thesis is chapter 1.4, which presents different methods for the conversion of aldehydes, ketones and lactones to alkynes. These are the backbone of the experimental section. Finally in the selected synthesis chapter I have chosen examples, which are closely related to the topics I worked during this thesis.

The experimental part presents my own results of synthetic efforts on the spiroketal part of calyculins. I succeeded to synthesize the spirocycle and proved that the cyclization rate is not critically dependent on the existence of a directing alkoxy group in the oxolane ring. I also carried out mechanistic studies for the spirocyclization mechanism. Results prove that the mechanism follows Baldwin’s rules for ring closure.

Asiakirjat

**TIIVISTELMÄ**

Kalikuliinit ovat erittäin voimakkaita solumyrkyjä ja proteiniin osuuseen, mutta niiden synteetisoimista on kolmen syynä. Niitä erittäin merkittävänä on Discodermia calyx. Useat tutkimusryhmät ovat pyrkineet synteetisoimaan luonnossa esiintyviä kaliumiinitiä ja C₃, mutta yrityksistä huolimatta täysin synteetistä tekotapaa ei ole onnistuttu kahdennään. Väitöskirjatyössä olen pyynnit synteetisoimaan kaliumiinitiä spiroketaaliorganen.


Kokeellinen osa esittää tulokseti kalikuliinitiä spiroketaaliorganen synteetisoimiseen. Omistuen spiroyskilisoimissa ja osostui että syklisointinopeus ei ole kriittisesti riippuvainen oskolatiiven renkaassa olevasta alkoksinyhdyystä. Tekemäni spiroyskilisoimin reaktiomekanismiin liittyvät kokeet osoittivat myös renkaiden muodostumisen noudattavan Baldwinin sääntöä.


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ACKNOWLEDGEMENTS

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Helsinki, December 2006

Vesa Rauhala
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Our knowledge about the environment is increasing all the time. Nature has had a lot more time to solve the problems that we have only recently started to address. Although humans despite this, have the advantage to be able to collect, save and analyze obtained information extremely effectively. The Figure 1 shows the amount of publications per year that we can find by using the term natural product as a research topic. In the last ten years we have succeeded to more than double the amount of publications.

![Natural product](image)

**Figure 1** Number of publications of natural products during the 1900-2006.

Chemistry like any other area of science will always have some hot topic, which lasts some time before something else comes along. This we can see for example in the case of calyculin (Figure 2). The most active time was during 1995-1999, when most of the total syntheses of calyculin were published. Despite this, calyculin belongs to a very interesting class of natural products, and so the publication activity remains quite high.
When we consider smaller details like dioaspiro we can see that the publication activity has gone in cycles (Figure 2). This indicates the need to improve the old and develop new methods. There are a lot of syntheses where the traditional ways to make the molecules is good enough, but there is also a growing need to be able to overcome the problems beyond the traditional ways. Methods for the preparation of the carbon-carbon triple bond have been known a long time. In the experimental part (Section 2.3.3) I will present the improvement to the original method of Ohira, which was envisioned to arise through a Seyferth-Gilbert-type homologation of the aldehyde/lactol corresponding to lactone. In the literature research part (Sections 1.1-1.5) I will first present some basics of the synthesis of the triple bond.
Carbon-Carbon triple bonds are long-known and well-studied functional groups. The amount of information accrued is enormous and we can find the books\textsuperscript{3,4} and review articles\textsuperscript{5} that are dedicated only to these triple bonds. To limit the area of information, it was decided to limit the text to methods, which take advantage of phosphonates and phosphoranes or those which are closely related or in some other way interesting (Figure 3).

**Figure 3.** Some methods for the synthesis of alkynes.
Carbon atoms in an acetylene are sp-hybridized and this means that the bond geometry is linear (Figure 4). It is much more reactive than the sp²- or sp³-hybridized carbons and it has more versatility, which gives the possibility to utilize it in a wide variety of reactions. This makes it a very interesting and useful functional group.

![Figure 4. π–Bonding in acetylene](image)

Some physical properties of carbon-carbon bonds are collected in Table 1. They give us much of basic information about the bonds character and reactivity. If we consider bond lengths, ethane has carbon-carbon (sp³-sp³) bond length of 1.54 Å, which decreases to 1.34 Å in ethene (sp²-sp²) and all the way to 1.20 Å in acetylene (sp-sp). On average, electrons in the s-orbitals are held closer to the nucleus than they are in p-orbitals. This fact is reflected in the bond lengths. sp¹-orbital has 25%, sp²-orbital 33% and sp-orbital 50% of s-character.

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<td>H₂C≡CH₂</td>
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In turn, this increases electrostatic attraction, which means that s-electrons have lower energy and greater stability. This we can see by comparing the pKₐ-values of protons of each group in Table 1. In general this means that the greater the amount of s-character in a
C-H bond orbital, the more acidic the proton and the less basic the corresponding conjugate base (Figure 5).

**Figure 5.** Acid and base strength

### 1.2 Elimination Reactions

Elimination reactions are basic methods for the preparation of triple bonds. The mechanisms are in principle similar to those for the preparation of double bonds. Even though it seems simple it is possible to find quite large variety of methods.

#### 1.2.1 1,1-Elimination

Delavarenne and Viehe published a preparation method for heterosubstituted acetylenes, which were prepared *via* HCl α-elimination and Onium-rearrangements (Scheme 1).\(^6\) The cleavage and rearrangement proceed with good yield as shown in Table 2.
β-elimination reaction has been well known a long time in the synthetic chemistry. Cambell and Whiting et al did published simple examples of dehydrohalogenation reactions to acetylenes (Scheme 2).[7] Organ, Ghasemi and Valente were studying small, polyfunctional olefin building blocks.[8] Their studies proved that elimination is not a
simple base mediated process (Table 3). They suggested that the base either plays a role in reducing the Pd(II)-species generated in the oxidative addition / elimination, or that it is activating the catalyst to oxidative addition, or both.

Scheme 2. β-elimination to acetylenes

Table 3. 1,2-Elimination

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<th>Entry</th>
<th>KOH</th>
<th>Pd(PPh₃)₄</th>
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_E-dibromostilbene_ was reacted under Suzuki conditions to study the possibility that the alkyne could be formed _via_ an intermediate allenyl species. Diphenyl acetylene was obtained in good yield (Scheme 3). This demonstrated that invoking allenyl intermediates to account for the dihalogen elimination is not necessary.

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<tr>
<td>1</td>
<td>210 mol-%</td>
<td>-</td>
<td>THF</td>
<td>60°C</td>
<td>18 h</td>
<td>100 : 0</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>105 mol-%</td>
<td>THF</td>
<td>60°C</td>
<td>360 min</td>
<td>8 : 92</td>
</tr>
<tr>
<td>3</td>
<td>210 mol-%</td>
<td>105 mol-%</td>
<td>THF</td>
<td>60°C</td>
<td>185 min</td>
<td>0 : 100</td>
</tr>
</tbody>
</table>

_E-dibromostilbene_ was reacted under Suzuki conditions to study the possibility that the alkyne could be formed _via_ an intermediate allenyl species. Diphenyl acetylene was obtained in good yield (Scheme 3). This demonstrated that invoking allenyl intermediates to account for the dihalogen elimination is not necessary.
Fürstner et al. reported in the total synthesis of Latrunculin B preparation of terminal triple bond. This relatively short method gave with good yields wanted functional group (Scheme 4).

Scheme 4. a) 4-dimethylaminopyridinium bromide perbromide, DMAP, CH₂Cl₂; b) LiHMDS, THF.

1.2.3 1,4-Elimination

During the total synthesis of 16-hydroxy-9Z,12Z,14E-octadecatrienoic acid, which is the self-defense substance found in the rice plant to protect against rice blast disease, Rama Rao et al. started with the 1,4-elimination. 1,4-dichloro-but-2-ylene 30 was treated with sodium amide in liquid ammonia and propanaldehyde in ether at -32°C. After work up hepta-5,6-diyn-3-ol 31 was obtained (Scheme 5).

Scheme 5. a) NaNH₂, liq. NH₃, CH₃CH₂CHO
Gao and Goroff reported the synthesis of 1,6-diiodohexa-1,3,5-triyne $35$ and 1,8-diiodoocta-1,3,5,7-tetrayne $39$ (Scheme 6). The disadvantage of this synthesis was the formation of silver alkynide intermediates, which are explosive substances.

Scheme 6. a) TsOH, KOH; b) 4 eq BuLi, THF/-78°C; c) TMSCl, THF/-30°C; d) NIS, AgNO$_3$, Acetone; e) MeLi-LiBr; f) Cu(TMEDA, Acetone/O$_2$; g) NIS, AgNO$_3$, Acetone.

To be able to synthesise these products on large scale Hlavatý, Kavan and Šticha developed a safer alternative. $35$ was synthesised by dehydrochlorination of 1,6-dichlorohexa-2,4-diyn $40$ and $39$ was synthesised from 1,8-bis(trimethylsilyl)-1,3,5,7-octatetrayne $38$ (Scheme 7). These are nice model examples of simple 1,6-eliminations.

Scheme 6. a) TsOH, KOH; b) 4 eq BuLi, THF/-78°C; c) TMSCl, THF/-30°C; d) NIS, AgNO$_3$, Acetone; e) MeLi-LiBr; f) Cu(TMEDA, Acetone/O$_2$; g) NIS, AgNO$_3$, Acetone.

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1.3 Name Reactions

1.3.1 Arens – van Dorp Synthesis; Isler Modification

The original Arens – van Dorp synthesis of vitamin A₂ aldehyde and vitamin A₂ was published in Nature. In this paper, Arens and van Dorp coupled Grignard reagent 42 to ketone 41 (Scheme 8). In the Isler modification β-chlorovinyl ether 46 was treated with lithium amide in liquid ammonia to yield lithium ethoxyacetylene 47 which without isolation was then condensed with ketone 48 or 50. This way the tedious preparation of ethoxyacetylene of the original paper was avoided and the synthesis of alkoxycetylnyl alcohols was improved.
1.3.2 Eschenmoser – Tanabe Fragmentation

The research groups of Eschenmoser and Tanabe discovered, that when α,β-epoxyketones 52 are treated with tosylhydrazine they react via sulfonylhydrazone intermediates 53 and 54 to yield acetylenes 55 and carbonyl compounds 56 (Scheme 9).\textsuperscript{15}
The reaction was originally proposed for ring expansions, but is also very useful for making keto-alkynes. With slight modifications it is also possible to produce acetylenic aldehydes (Scheme 10).

Scheme 9. Eschenmoser-Tanabe Fragmentation
Scheme 10. Preparation of 2,3-epoxy cyclohexanone 58 and its fragmentation to 5-hexynal 61.

1.3.3 Fritsch – Buttenberg – Wiechell Rearrangement

The original Fritsch-Buttenberg-Wiechell (FBW) rearrangement is a general method for the preparation of different type of tolans, in this case diphenylacetylene 26 (Scheme 11). This reaction was discovered already in the 1890’s but the actual mechanism was determined about 60 years later by Bothner-By (Scheme 12) and completed by Curtin and co-workers with the stereochemical information.18

Scheme 11. General formulation of FBW-rearrangement
Scheme 12. Mechanism studies with $^{14}C$ labelled compounds by Bothner-By

The mechanism studies of the Curtin et al. revealed more detailed information. Because they used BuLi instead of potassium $t$-butoxide it excluded the possibility of a carbene intermediate, at least in the major reaction pathway (Scheme 13).
1.4 Formation of Aldehyde, Ketone and Lactone to Alkyne

A few interesting methods to generate alkyne derivatives from ketones and aldehydes have been described in the literature. These offered a good starting point for studying the applications of such transformations in real cases.
Corey and Fuchs presented a simple and expeditious method for the transformation of aldehydes to acetylenes (Scheme 14). The dibromooxolins 74 were made by homologation of the corresponding aldehydes 73 either with or without Zn-dust. Treatment of dibromooxolins 74 with 200 mol-% of n-BuLi afforded the lithiated acetylates 75, which were transformed to the terminal acetylenes 76 by adding water or to the propargylic acids 77 by adding solid carbon dioxide.

Scheme 14. a) PPh₃ (400 mol-%), CBr₄ (200 mol-%), CH₂Cl₂, 0°C, 5 min; b) Zn-dust (200 mol-%), PPh₃ (200 mol-%), CBr₄ (200 mol-%), CH₂Cl₂, 23°C, 24-30 h; c) n-BuLi (200 mol-%), THF, -78°C, 1 h, 25°C, 1 h; d) H₂O; e) CO₂.

In the synthesis of Monensin Cai and Still use the Corey – Fuchs protocol to prepare the terminal acetylene 81 (Scheme 15). Acetylene 81 is structurally similar to the spirocyclization precursor we had for the spirotetral fragment of calyculin C, and the spirocyclization method used was also close to our one.
1.4.2 Preparation of Acetylenic Alcohols from Lactones

Lakhrissi and Chapleur developed a procedure to convert γ-lactones to the corresponding dichloromethylene compounds. Yadav et al. utilized this method for the conversion of lactones 85 to acetylenic alcohols 87 via reductive elimination of the halo-compound 86 through lithium insertion (Scheme 16).
The lithium insertion and following transformation to acetylenic alcohol 87 was achieved by refluxing the dichloromethylene compound 86 in THF with freshly prepared Li-sand. They tried this method for a few five or six membered lactones, which gave from 82% to 88% yield during the reaction time of 0.5 to 3 hours. Chapleur et al. continued to research the dibromoolefination of lactones using bromomethyltriphenylphosphonium phosphorane. Under slightly modified reaction conditions they tested a series of different type of lactones 88a - 88h (Scheme 17). Bromomethyltriphenyl-phosphonium bromide 90 was treated with tert- BuOK giving the corresponding phosphorane. This was then reacted with lactones 88a - 88h in refluxing THF to afford single products 89a - 89h (Table 4). Only lactones 88f and 88h produce clearly lower yields, mainly because of β-elimination of the benzylxoy group under the basic reaction conditions. From these products it is possible to synthesize the primary acetylenic group, as previously described.
Scheme 17. a) \( \text{BrCH}_2\text{P(Ph)}_3\text{Br} \) 90 (400 mol-%), \( \text{t-BuOK} \) (400 mol-%), THF, reflux.

### Table 4. Dibromomethylenations

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Product</th>
<th>Reaction time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>88a</td>
<td>89a</td>
<td>0.5</td>
<td>69</td>
</tr>
<tr>
<td>88b</td>
<td>89b</td>
<td>0.5</td>
<td>87</td>
</tr>
<tr>
<td>88c</td>
<td>89c</td>
<td>1</td>
<td>83</td>
</tr>
<tr>
<td>88d</td>
<td>89d</td>
<td>2</td>
<td>52</td>
</tr>
<tr>
<td>88e</td>
<td>89e</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>88f</td>
<td>89f</td>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td>88g</td>
<td>89g</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>88h</td>
<td>89h</td>
<td>2</td>
<td>32</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Starting material</th>
<th>Product</th>
<th>Reaction time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>88a</td>
<td>89a</td>
<td>0.5</td>
<td>69</td>
</tr>
<tr>
<td>88b</td>
<td>89b</td>
<td>0.5</td>
<td>87</td>
</tr>
<tr>
<td>88c</td>
<td>89c</td>
<td>1</td>
<td>83</td>
</tr>
<tr>
<td>88d</td>
<td>89d</td>
<td>2</td>
<td>52</td>
</tr>
<tr>
<td>88e</td>
<td>89e</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>88f</td>
<td>89f</td>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td>88g</td>
<td>89g</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>88h</td>
<td>89h</td>
<td>2</td>
<td>32</td>
</tr>
</tbody>
</table>
1.4.3 Synthesis of Terminal Alkynes via Diethyl Dichloromethylphosphonate

Savignac \textit{et al.} found a way to synthesize diethyl 1,1-dichloromethylphosphonate 4 by using simple, cheap and easily available materials (Scheme 18).\textsuperscript{24} The yield was over 90\% and they managed to purify the final product by distillation, which makes the method appealing in large scale reactions.

\[ (\text{EtO})_2P=CCl_3 \xrightarrow{a), b)} \xrightarrow{94\%} (\text{EtO})_2P=CCl_2H \]

\textbf{Scheme 18.} a) i-PrMgCl, THF, -78°C; b) EtOH, HCl (3M).

The phosphonate 4 was utilized in the synthesis of chlorocetylenes and acetylenes from aldehydes (Scheme 19, Table 5). The reaction mechanism between phosphonate carbanion and aldehyde is of the Horner-Emmons type, affording \textit{gem}-dichlororalkene 93a-f. LiHMDS-mediated \textit{trans}-elimination follows upon warming yielding chlorocycylene 94a-f. However, in the case of aliphatic aldehydes 92e and 92f, LiHMDS wasn’t a strong enough base to achieve \textit{trans}-elimination. Instead 100 mol-% of LDA was needed to accomplish the reaction from \textit{gem}-dichlororalkenes 93e and 93f. Another method was to use 220 mol-% of LDA with the dichloromethylphosphonate 4 and aldehydes 92b-f. In the synthesis of terminal acetylenes, 100 mol-% of LDA in THF at -78°C was added to the mixture of phosphonate and aldehyde followed by addition of 210 mol-% of BuLi at the same temperature to affect chlorine lithium exchange. Acidic hydrolysis afforded pure compounds 96b-f with good yield.

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Scheme 19. a) LiHMDS (220 mol-%) or LDA (100 mol-%), THF, -78°C, 0°C; b) HCl (2M); c) LDA (100 mol-%), THF, -78°C, 0°C; d) n-BuLi (200 mol-%), THF, -78°C, 0°C; e) HCl (3M).

Table 5. Synthesis of chloroacetenes and acetylenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>p-MePh</td>
<td>p-MeOPh</td>
<td>o-MeOPh</td>
<td>Ph</td>
<td>CH₃(CH(Ph)CH₂</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.4.4 Pyrylium-Based Route to Conjugate Dienynes

During the first synthesis of marine metabolite Cardusyne A Taylor et al. developed a stereorestricted route to conjugated dienynes (Scheme 20). The original Corey-Fuchs procedure was ineffective, instead rapid decomposition of the vinyl dibromide took place to prevent further elaboration. By using chloromethylene triphenylphosphorane they were able to synthesise vinyl chloride. This was easily converted to diene products 101, 102 and 103. The low yields of 101 and 102 were most likely due to volatility of these products.
1.4.5  Seyferth-Gilbert homologation

Another method to transform aldehydes into the alkenes is known as the Seyferth–Gilbert homologation. However, this type of reagent and synthesis had been used previously by Regitz et al. and Colvin et al. (Scheme 21). The disadvantage of the Colvin / Hamill approach was that attempts to extend the reaction to ketones and aldehydes containing enolizable protons or α,β-unsaturation were not satisfactory. Colvin and Hamill used n-BuLi or t-BuOK as a base to form the anion from the phosphonate 1 at -78°C. To this was added the carbonyl containing substrate and immediately after the addition the resulting mixture was allowed to warm up to ambient temperature (Table 6). Gilbert and Weerssorriya modified the method so that the slurred mixture was stirred 12 to 16 h at -78°C before it was allowed to warm up to ambient temperature.27
During his studies to find a convenient way to prepare phosphonate 2 Ohira noticed that the methoxide anion attacked the carbonyl group of the starting material 1 faster than the hydrogen of 2 (Scheme 22).\textsuperscript{28} The low concentration of methoxide anion also prevented 2 from decomposing. Phosphonate 2 was used for the synthesis of alkynes and enol ethers under Gilbert's conditions with similar results as with the original phosphonate 1.

Bestmann \textit{et al.} needed a smooth and efficient method for the direct conversion of \(\alpha\)-alkoxyaldehydes into the terminal alkynes and decided to conduct more complete studies of the method Ohira developed a few years earlier.\textsuperscript{29} The results of these studies can be seen in Table 6. These studies highlight that this method is a mild and easy way to form alkynes from aldehydes, without any need to use low temperatures or an inert atmospheres.
Table 6. Comparison of the yields between different reaction methods

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carbonyl compound</th>
<th>Product</th>
<th>Yield, Colvin</th>
<th>Yield, Gilbert</th>
<th>Yield, Bestmann</th>
<th>Yield, Bestmann in situ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OHC-CHO 73a</td>
<td>=C≡N 19</td>
<td>-</td>
<td>-</td>
<td>73 %</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>OHC-CHO 50</td>
<td>=C≡N 105</td>
<td>22 %</td>
<td>60 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>OHC-CHO 106</td>
<td>CH=CH 107</td>
<td>30 %</td>
<td>80 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>OHC-CHO 108</td>
<td>CH=CH 109</td>
<td>-</td>
<td>-</td>
<td>72 %</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>OHC-CNOMe 92b</td>
<td>=C≡N OMe 96b</td>
<td>-</td>
<td>80 %</td>
<td>78 %</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>OHC-CNCl 110</td>
<td>=C≡N Cl 111</td>
<td>-</td>
<td>-</td>
<td>97 %</td>
<td>83 %</td>
</tr>
<tr>
<td>7</td>
<td>OHC-CNCHO 112</td>
<td>CH=CH 113</td>
<td>-</td>
<td>-</td>
<td>74 %</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>OHC-CNCl 114</td>
<td>=C≡N Cl 115</td>
<td>-</td>
<td>50 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>OHC-CNCHO 116</td>
<td>CH=CH 117</td>
<td>-</td>
<td>-</td>
<td>80 %</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>OHC-CNCHO 118</td>
<td>=C≡N 119</td>
<td>-</td>
<td>50 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>n-C_{11}H_{22}CHO</td>
<td>n-C_{11}H_{22}CHO 121</td>
<td>-</td>
<td>-</td>
<td>96 %</td>
<td>89 %</td>
</tr>
<tr>
<td>12</td>
<td>MeO-CNCHO 122</td>
<td>MeO-CNCHO 123</td>
<td>-</td>
<td>-</td>
<td>96 %</td>
<td>72 %</td>
</tr>
<tr>
<td>13</td>
<td>MeO-CNCHO 124</td>
<td>MeO-CNCHO 125</td>
<td>-</td>
<td>-</td>
<td>82 %</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>OPMB-CNCHO 126</td>
<td>OPMB-CNCHO 127</td>
<td>-</td>
<td>-</td>
<td>80 %</td>
<td>73 %</td>
</tr>
<tr>
<td>15</td>
<td>MeO-CNCHO 128</td>
<td>MeO-CNCHO 129</td>
<td>-</td>
<td>-</td>
<td>83 %</td>
<td>-</td>
</tr>
</tbody>
</table>
Eight years later Bestmann et al. modified the method again (Scheme 23). The dimethyl-1-diazo-2-oxopropylphosphonate 1 is not a commercially available product, even though this can be prepared in one step. This is still sometimes a problem. However dimethyl-2-oxopropylphosphonate 8 is a commercial product, which makes it an interesting starting material. By combining the diazotisation step with the reaction step, following the procedure of Koskinen and Muñoz, Bestmann et al. succeed in creating a really easy method B to synthesise alkenes from aldehydes. Comparing the scope and limitations of the methods A and B, it could be said that if the yield is critical, it is better to use method A. In any other case it is better to use the simpler and almost as productive in situ method B.

![Scheme 23](image)

**Scheme 23.** a) K₂CO₃, MeOH, RT 4-16 h; b) p-TsN₂, K₂CO₃, CH₃CN, RT, 2 h; c) RCHO, MeOH, RT, 8 h.

Meffre et al. presented their version of in situ method to prepare an alkyne from the protected amino aldehydes 130 and 132 (Scheme 24). This method involves a similar type of formation of dimethyl-1-diazo-2-oxopropyl phosphate 8 to Bestmann et al., but uses 4-acetamidobenzene sulfonyl azide 9 as the aza source. They also changed the solvent from methanol to chloroform to decrease the possible side reactions of the formed sulphonamide with the aldehyde. The reaction was also performed at higher temperatures.

![Scheme 24](image)

**Scheme 24.** a) K₂CO₃, MeOH, RT 4-16 h; b) p-TsN₂, K₂CO₃, CH₃CN, RT, 2 h; c) RCHO, MeOH, RT, 8 h.
(40-50°C) without any effect on the yield, but with faster rates of reaction. Unfortunately, this led to some loss of enantiopurity.

Scheme 24. K₂CO₃, CHCl₃, MeOH, 0-10°C, 72 h.

1.5 Selected Syntheses

Mioskowski et al. presented in their synthesis of a precursor of arachidonic acid a simple method for the synthesis of acetylenic alcohol 135 from tetrahydrofurfuryl chloride 134. Previously Yadav et al. had presented a comparable synthesis for similar ring openings.

Tetrahydrofurfuryl chloride 134 was refluxed with BuLi in THF to afford acetylenic alcohol 135, which was protected as its tetrahydropyranoyl ether 136 (Scheme 25). Another way to prepare acetylenic lithium alkoxides is to treat tetrahydrofurfuryl chloride 134 with lithium amide in liquid ammonia. The ring opening of tetrahydrofurfuryl chloride 134 to a primary alcohol and an alkynyl group is a nice, simple way to increase functionality.

Scheme 25. a) n-BuLi, THF, reflux; b) DHP, Amberlyst-15, CH₂Cl₂, reflux.

(40-50°C) without any effect on the yield, but with faster rates of reaction. Unfortunately, this led to some loss of enantiopurity.

Scheme 24. K₂CO₃, CHCl₃, MeOH, 0-10°C, 72 h.

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On an industrial scale the use of phosphorous reagents in Wittig-type reactions causes problems in toxicity and volume of waste. Wang et al. have created an interesting method to overcome these problems (Scheme 26). To a stirred solution of trichloroacetic acid 138 and aldehyde 137a-i in DMF was added in portions sodium trichloroacetate with the internal temperature kept below 35°C. In the second step the solution was cooled to 5°C and acetic anhydride added, which caused strong CO₂ evolution. In the third step the mixture was warmed to RT, diluted with acetic acid and zinc powder added in one portion. After quenching and extraction most of the products were purified by distillation (Table 7). Finally, terminal alkynes 142a-h were prepared easily by elimination with methyllithium.

Scheme 26. a) CCl₃COONa (150 mol-%), DMF, 25-35°C; b) Ac₂O, 0-25°C; c) AcOH/Zn, 25-60°C; d) MeLi (300 mol-%), THF, -10°C; then H₂O°.

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Scheme 26. a) CCl₃COONa (150 mol-%), DMF, 25-35°C; b) Ac₂O, 0-25°C; c) AcOH/Zn, 25-60°C; d) MeLi (300 mol-%), THF, -10°C; then H₂O°.
Table 7. Yields of vinyl dichlorides 141a-i and acetylenes 142a-i (a = purified by chromatography, b = crude yield).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>141a-i % Yield</th>
<th>142a-i % Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>cyclopropyl</td>
<td>92</td>
<td>89</td>
</tr>
<tr>
<td>b</td>
<td>cyclohexyl</td>
<td>88</td>
<td>91</td>
</tr>
<tr>
<td>c</td>
<td>i-butyl</td>
<td>89</td>
<td>93</td>
</tr>
<tr>
<td>d</td>
<td>n-octyl</td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>e</td>
<td>t-butyl</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>f</td>
<td>i-propyl</td>
<td>89</td>
<td>82</td>
</tr>
<tr>
<td>g</td>
<td>phenyl</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>h</td>
<td>2-phenylethyl</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>i</td>
<td>styrene</td>
<td>85</td>
<td>decomposed</td>
</tr>
</tbody>
</table>

Elisapetin B is a potent \textit{in vitro} inhibitor of \textit{Mycobacterium tuberculosis} H37Rv. Rawal \textit{et al.} published a communication, where they described a stereocontrolled asymmetric synthesis of elisapetin B.\textsuperscript{37} During this synthesis a one carbon homologation starting from the lactone 143 was needed. First, lactone 143 was reduced with DIBAL in toluene to the corresponding lactol followed by Seyferth-Gilbert homologation (Scheme 27).

Scheme 27. a) DIBAL, toluene; b) (MeO)\textsubscript{2}P(O)CHN\textsubscript{2}, t-BuOK, THF.

One carbon Seyferth-Gilbert homologation of aldehydes next to quaternary centres are of great interest. To complete their formal total synthesis of \(\alpha\)- and \(\beta\)-cedrone, Kerr \textit{et al.}
needed to synthesize acetylene 146 from aldehyde 145, which is next to a quaternary carbon (Scheme 28). They chose Ohira’s reagent because they had previously good experience with this mild and simple procedure. Under standard conditions and five days reaction time 146 was obtained in 81% yield.

\[
\begin{align*}
\text{CHO} & \quad \text{a)} \quad 81\% \\
145 & \quad \rightarrow \\
146 & \quad \text{CHO}
\end{align*}
\]

**Scheme 28.** a) (MeO)₂P(O)(N₂)Ac 1, K₂CO₃, MeOH.

In the asymmetric synthesis of phytol, a precursor in the synthesis to vitamin E, Takano et al. twice used an almost identical procedure to prepare terminal alkynes (Scheme 29. and 30). In the first step they used a Katsuki-Sharpless asymmetric epoxidation in which diisopropyl (L)-tartrate worked as a chiral inducer affording epoxy alcohol 148. This was transformed to chloride 149 by refluxing 148 in carbon tetrachloride with triphenylphosphine in 91% yield. Chloride 149 was then treated with n-BuLi in THF at -30°C to provide the terminal alkyne 150.

\[
\begin{align*}
\text{CHO} & \quad \text{a)} \quad 81\% \\
145 & \quad \rightarrow \\
146 & \quad \text{CHO}
\end{align*}
\]

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Scheme 29. a) Diisopropyl L-tartrate, Ti(O-i-Pr)₃, t-BuOOH, 4Å MS, CH₂Cl₂, -20°C; b) Ph₃P, CCl₄, reflux, 91%; c) n-BuLi (300 mol-%), THF, -30°C.

On the second occasion they needed to synthesize a terminal alkyne they tried the same procedure. Unfortunately the yield (43%) was not satisfactory and they decided to use a method which was one step longer and appeared to be more productive (76% overall yield). Alcohol 160 was tosylated in the first step and the tosyl group substituted with chloride using lithium chloride in DMF at 50°C. Finally, treating 162 with n-BuLi (480 mol-%) produced the desired alkyne 163 (Scheme 30).

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Yamamoto et al. presented a stereospecific method to prepare (R)- or (S)-3-alkynols from aldehydes using the chiral allenyl boronic ester (Scheme 31). The requisite allenylboronic acid was synthesized from the propargylmagnesium borate and trimethylborate followed by acidic workup and recrystallization. The effect of different tartrate esters on the asymmetric condensation was also tested (Table 8).

Scheme 30. a) p-TsOH, DMAP (cat), TEA, CH₂Cl₂, RT; b) LiCl, DMF, 50°C; c) n-BuLi (480 mol-%), THF, -25°C.

Scheme 31. (R)- or (S)-3-alkynol
### Table 8. Efficiency and selectivity of different tartrate esters (a = The reaction was performed with 300 mol-% of the aldehyde).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Tartrate xx</th>
<th>Yield %</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Et</td>
<td>L-(+)</td>
<td>81</td>
<td>91</td>
</tr>
<tr>
<td>b</td>
<td>i-Pr</td>
<td>L-(+)</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>c</td>
<td>cyclopentyl</td>
<td>L-(+)</td>
<td>42</td>
<td>91</td>
</tr>
<tr>
<td>d</td>
<td>1-methyl</td>
<td>L-(+)</td>
<td>37</td>
<td>93</td>
</tr>
<tr>
<td>e</td>
<td>1-methyl</td>
<td>D(-)</td>
<td>69</td>
<td>92</td>
</tr>
<tr>
<td>f</td>
<td>cyclohexyl</td>
<td>L-(+)</td>
<td>85</td>
<td>98</td>
</tr>
<tr>
<td>g</td>
<td>2,4-dimethyl-3-pentyl</td>
<td>L-(+)</td>
<td>88</td>
<td>98</td>
</tr>
<tr>
<td>h</td>
<td>2,4-dimethyl-3-pentyl</td>
<td>L-(+)</td>
<td>89*</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

### 1.6 Summary

The preparation of the carbon-carbon triple bond is not restricted by a lack of knowledge or methods. Moreover, there are so many different ways to create alkynes, that to find the most appropriate method is a challenge. However, despite being well established small modifications to the existing methods might still act to improve yields or shorten synthetic routes. Different types of elimination reactions are the most basic methods in carbon-carbon triple bond synthesis. Through reaction of phosphoranes and phosphonates with aldehydes it is possible to perform one carbon chain extensions and synthesize the terminal acetylenes at the same time. Finally stereoselectivity is nowadays a crucial criterion of whether a method is useful or not. Control of the internal as well as the external source of chirality is also challenging in the triple bond synthesis.
2 Spirocycle-fragment of Calyculin A and C

2.1 Introduction

Synthetic studies towards the calyculins (Figure 6) have been undertaken for almost two decades. These natural products originally isolated from marine sponge Discodoraria calyx, have offered synthetic challenges for several research groups. Petri Pihko has recently presented a good review of these synthetic efforts. The spiroketal ring system as seen in the calyculins is a common motif in natural products. It is noteworthy that in most of these spiroketals, the configuration of the stereogenic carbon atom is dictated by the double anomeric effect, placing the oxygen in the oxolane ring axial with respect to the oxane ring. Due to the wide occurrence of such structures, a rapid and reliable entry into the spirocyclic structure is highly desirable. This was of special interest to us because of ongoing efforts towards the total synthesis of calyculin C, a potent protein phosphatase inhibitor.

![Calyculin C](image)

*Figure 6. Calyculin C*

The purpose of this work was to synthesize stereoselective model spirocycle of calyculins with a novel method. Equally important goal was to provide new information...
about the methods to synthesize spirocycles. Original plan was to utilize Intramolecular Silyl Modified Sakurai Reaction (ISMS), but appeared difficulties forced us to find out other way to do it. This was guiding us to do profound research about the methods to synthesize the spirocycle. After several attempts of the acid catalyzed cyclization we found Double Intramolecular Hetero-Michael Addition (DIHMA) process. However this was never utilized to the synthesis, where after the addition two quaternary carbon atoms were combined next to each other. This sterically extremely hindered structure was challenging us to find out the solution.

2.2 Methods used for spirocyclization

The spiroketal moiety of the calyculins is a synthetically challenging fragment. Previous efforts towards the spirocyclization have been more or less similar. The only exception is the synthesis of Trost and Flygare, in which they used an oxidative spirocyclization as opposed to the acid-catalyzed spirocyclization to existing carbonyl or equivalent carbon atoms used by others.

2.2.1 Spirocyclization methods used in approaches to the Calyculins

Scheme 32. shows the spirocyclization method used by Evans et al. They used a mixture of 48% aqueous HF/acetonitrile/water to transform the aldol adduct 167 to an equilibrium mixture (5:1) of spiroketal 168 and 169 in 85% yield.

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Scheme 32. shows the spirocyclization method used by Evans et al. They used a mixture of 48% aqueous HF/acetonitrile/water to transform the aldol adduct 167 to an equilibrium mixture (5:1) of spiroketal 168 and 169 in 85% yield.
Barrett et al. followed two similar types of reaction pathways for the C_{15}-C_{25} calyculin spiroketal residues 172 and 174 (Scheme 33). Their methodology produced a mixture of epimers in both syntheses and thus an additional oxidation-reduction procedure was needed to make the stereopure spiroketal fragments 175 and 176. However, they were able to isolate the epimeric alcohols 172 with 70% yield from the small scale reactions.
Scheme 33. Spirocyclization by Barrett et al.: a) LDA, THF, -78°C, add 171; TsOH, MeOH, 25°C; b) Swern oxidation; c) K-Selectride, THF, -78 to -10°C; NaOH, H2O2; d) LDA, THF, -78°C, add 173; TsOH, MeOH, 25°C.

Masamune et al. also used an acid-catalyzed spirocyclization (Scheme 34). Moreover, their approach delivered a more complex spirocycle than previously achieved with the entire C7-C25 portion being present. This helped to control the stereochemistry of the dipropionate fragment, but is not really a molecularly economic way to do so.
Scheme 34. a) n-Bu₄NF, THF, 0°C; b) HCO₂H-Et₂O (1:1), 25°C.

Trost and Flygare used an alternative method to synthesize the spiroketal fragments 180 and 181 (Scheme 35).⁴²k Oxidative spirocyclization, originally presented by Bartholomew and Kay,⁴⁷ in the presence of mercuric oxide and iodine in carbon tetrachloride afforded the two spiroketal epimers 180 and 181 in 67% yield.

Scheme 35. a) HgO, I₂, CCl₄, 70°C.

The group of Shioiri has conducted much work towards the synthesis of the calyculins and in 1996 they achieved a formal total synthesis of calycin A, C₉-C₃₇-fragment.⁴²a In keeping with most other groups they also used an acid-catalyzed spirocyclization (Scheme 36).
In 1991 Amos B. Smith, III published the synthesis pathway for the C_{14}-C_{25} spiroketal subunit of ent-calyculin A. They used the same acid-catalyzed method as Evans et al. but succeeded to obtain exclusively a single diastereomer (Scheme 37). This was interesting because both groups had closely related substrates.

The group of Armstrong and Ogawa are the only group who has published the total synthesis of calyculin C. They published the method for the spirocyclization earlier and it followed the usual acid-catalyzed cyclization approach (Scheme 38).
2.3 Synthesis of C_{16-25}–fragment

It was hoped that an alternative spirocyclization strategy could be implemented that would be both novel in the context of calyculins syntheses as well as more efficient than those previously reported! Of paramount importance was that any approach would afford the spirocycle stereoselectively and suitably functionalized for elaboration to the natural product (Figure 7).

Figure 7. Target spiroketal.
2.3.1 Intramolecular Silyl Modified Sakurai Reaction (ISMS)

The original plan for the synthesis of the spiroketal unit was to exploit the intramolecular silyl modified Sakurai (ISMS) reaction. This method was previously utilized for the more simple structure 190 by István E. Markó et al. (Scheme 39).²⁸

![Scheme 39. ISMS reaction: a) Et₂O·BF₄⁻, CH₂Cl₂, RT; b) 192, TMSOTf (cat), CCl₄, 25°C.](image)

In order to try the spirocyclization with the ISMS-method, it was necessary to prepare the allyl silane fragment 200 (Scheme 40) and lactone 203 (Scheme 41). Benzyl chloromethyl ether (BOM-Cl) 194 was prepared from 1,3,5-trioxane 270 and benzyl alcohol 271,⁴⁸ by bubbling anhydrous HCl gas from the gas bottle, carefully into the solution and keeping the internal temperature below 10°C to avoid the formation of dibenzylformal. The reaction was stopped when HCl addition no longer affected the temperature (2 h). The dianion of methyl acetoacetate 195 was used as a starting material in the preparation of β-keto ester 196,⁵⁰ but otherwise like in the original reference, starting materials were not precooled, which might be one reason for smaller yields. After purification the product was collected in only 33% of yield, when the literature reported 60% yield. Reduction of 5-benzylxoy-3-oxo-pentanoic acid methyl ester 196 with NaBH₄ produced racemic alcohol 197 in 77% yield.⁵⁰ TMS-protection of alcohol 198 proceeded well in 98% yield. TMS protected alcohol 198 was meant to be converted directly to allyl silane 200 through double addition of a silylmethyl nucleophile followed by Peterson-type elimination.⁵¹ Unfortunately, in initial attempts the base catalysed elimination reaction at 0°C did not

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occur but instead gave tertiary alcohol 199. The reaction was very sensitive and only careful work with the acid catalysed elimination at RT accomplished it.

Scheme 40. Synthesis of allyl silane 200: a) i. NaH, THF, 0°C; ii. BuLi, -22°C; iii. 194; b) NaBH₄, MeOH, 0°C; c) TMSOTf, 2,6-Lutidine, CH₂Cl₂, 0°C; d) i. TMSCH₂MgCl, CeCl₃, THF, -78°C; ii. sat. NH₄Cl, Et₂O, 0°C; e) i. TMSCH₂MgCl, CeCl₃, THF, -78°C; ii. Silica, HCl, CH₂Cl₂, RT.

3-Benzoyloxy-2,2-dimethylbutyrolactone 203 was synthesized as a model compound for the lactone counterpart (Scheme 41). Aldehyde 201 was condensed with ethyl isobutyrate to render aldol 202. Treatment of 202 with p-TsOH in toluene provided lactone 203 via in situ migration of the benzoyl group from the primary to the secondary alcohol and subsequent ring closure.
Scheme 41. Reagents: a) LDA, Me₂CHCO₂Et, THF, -78°C, then 201; b) p-TsOH, toluene, reflux.

Treatment of lactone 203 with Meerwein’s salt (RT, 3 h) to form the corresponding oxonium ion,⁵² followed by the addition of allyl silane 192 and a catalytic amount of TMSOTf at -78°C, did not provide the desired spiroketal 205 (Scheme 42). Instead, unreacted 203 was recovered along with fully desilylated 192.

Scheme 42. Attempts to synthesize spiroketals via ISMS. Reagents: a) Et₃O⁺BF₄⁻, CH₂Cl₂, RT; b) 192, TMSOTf; c) EtONa, EtOH, -78°C.
When γ-butyrolactone 190 was used instead of the sterically hindered lactone 203, the same result was obtained. Attempts to form ortholactone 206 by treatment of γ-butyrolactone with Meerwein’s salt at RT and with EtONa at −78°C also turned out to be troublesome. Indeed, a 2:1 mixture of methyl 4-hydroxybutyrate and the target was obtained. Spiroketel formation was observed neither when γ-butyrolactone was treated with BF₃·Et₂O at −78°C before addition of allyl silane 192 and TMSOTf, nor when 192 was treated at −78°C with SnCl₄ and then with γ-butyrolactone. Earlier in the professor Ari Koskinen’s group the graduate students Maija Moilanen and Yoshi Masuda did work with spirocycle. According the C¹³ spectra, Moilanen was able to synthesize wanted spirocycle 193 during the time she was visiting in the professor István Mrkó’s group. However neither Moilanen nor Masuda were able to repeat the synthesis afterwards. In view these results, we decided to change the synthetic strategy towards the spiroketel fragment of calyculin C.

2.3.2 Acid-Catalyzed Spirocyclization

Most of the research groups that have targeted the calyculins have utilized an acid-catalyzed spirocyclization approach. With the failure of the ISMS strategy our plan changed to use a similar type of method, focusing on ketone 209 as a precursor for model spiroketel 208 (Scheme 43). In the synthesis of methylketone 210 we were expanding our lactone synthesis presented in the Scheme 45. Weinreb amide 211 would be synthesized as described in the literature using the Evans oxazolidinone approach.⁵³

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Scheme 43. Retrosynthetic analysis for spiroketal 208.

2.3.2.1 Synthetic Attempt via Ketone 210

Model lactone fragment 203 was designed based on a crossed ester enolate aldol reaction of isobutyrate with a benzyl protected hydroxy aldehyde. The lactone 212 for the test spiroketal was prepared as shown in Scheme 44. Addition of the ester enolate of ethyl isobutyrate to 2-benzyloxyacetaldehyde 201 afforded the hydroxy ester 202 in 63% yield. Benzoyl migration with *in situ* benzyl protection of the hydroxy group (NaH, BnCl) afforded the lactone with 75% yield. If the initial ester aldol reaction was allowed to warm to higher temperatures, the intermediate alkoxy corresponding to 202 further reacted, by intramolecular benzoate transfer and ring closure, to give the hydroxy lactone directly. Quenching the reaction mixture with benzyl chloride gave 212 in a one-pot operation, however, yields were typically below 25%. It was therefore decided to rely on the more reproducible two-step operation.

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Scheme 44. Reagents: a) LDA, Me$_2$CHCO$_2$Et, THF, -78 °C, then 201; b) NaH, BnCl, DMF, THF, 0 °C.

Addition of MeLi (1.4M in Et$_2$O) to 212 rendered a mixture of methylketone 214 and its corresponding hemiacetal 213 (Scheme 45). Free alcohol 214 was protected using TMSCl, imidazole and DMF affording the desired methyl ketone 210, instead of TMS-lactol. Equilibrium favours strongly in this case the open chain from.

Scheme 45. a) MeLi, THF, -78°C; b) TMSCl, im, DMF.

The enantiopure Weinreb amide 217 was prepared using the diastereoselective Evans syn-alald reaction from the known propionyloxazolidinone 215 and 3-benzoyloxypropionaldehyde (Scheme 46). Thus, the reaction of the dibutylboron Z-enolate of 215 and the aldehyde gave the desired adduct 216 in 95% yield. Conversion of 216 to the Weinreb amide 217 (82%) followed by TMS protection gave the coupling partner 218 (64%). Alcohol 217 was also protected as its TES-ether 219 as there was no guarantee of the stability of TMS protecting group.

Scheme 44. Reagents: a) LDA, Me$_2$CHCO$_2$Et, THF, -78 °C, then 201; b) NaH, BnCl, DMF, THF, 0 °C.

Addition of MeLi (1.4M in Et$_2$O) to 212 rendered a mixture of methylketone 214 and its corresponding hemiacetal 213 (Scheme 45). Free alcohol 214 was protected using TMSCl, imidazole and DMF affording the desired methyl ketone 210, instead of TMS-lactol. Equilibrium favours strongly in this case the open chain from.

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Scheme 46. a) 215, Bu$_3$BOTf, Et$_3$N, CH$_2$Cl$_2$; then BnOCH$_2$CH$_2$CHO, -77 °C; b) MeOMeNH$_2$HCl, AlMe$_3$, THF, 0 °C; c) TMSOTf, 2,6-Lutidine, CH$_2$Cl$_2$; d) TESOTf, 2,6-Lutidine, CH$_2$Cl$_2$.

The first coupling attempts were made with coupling fragments 210 and 218 (Scheme 47). Starting material 210 dissolved in 1 mL of dry THF was added dropwise to freshly prepared LDA. This was allowed to stir 1 h 15 min at −78°C and starting material 218, dissolved in 1 mL of dry THF, was added dropwise. After 1 h 9 min the reaction was warmed to 0°C, stirred for 36 min and allowed to warm up to RT. No reaction was observed.

Scheme 47. a) i) DIPA, BuLi; ii) 218
Following the failure of the initial strategy it was proposed that the TMS groups in fragments 218 and 210 be changed to TBS-groups because of their greater stability. It was also proposed that methyl ketone 221 be converted to comparable N,N-dimethylhydrazine 222. Thus lactone 212 was converted to TBS ketone 221 as per the method of Schinzer and co-workers. TBS ketone 221 was converted to hydrazone 222 by refluxing with 1,1-dimethylhydrazine and p-TsOH in toluene under Dean–Stark conditions. After column chromatography hydrazone 222 was obtained in 83% yield. TBS protection of the Weinreb amide 217 under standard conditions gave the coupling partner 223 with 68% yield (Scheme 48).

\[ \text{BnO} \quad \xrightarrow{\text{a)} \text{MeLi, THF, } -78^\circ\text{C; TBSCI, im, DMF}} \quad \text{TBSO} \quad \xrightarrow{\text{b)} \text{NMe}_2} \quad \xrightarrow{\text{c)} \text{TBSO, im, DMF, } 0^\circ\text{C}} \quad \text{BnO} \]

Scheme 48. a) MeLi, THF, -78°C; TBSCI, im, DMF; b) 1,1-Dimethylhydrazine, p-TsOH, toluene, reflux; c) TBSCI, im, DMF, 0°C.

The second attempt to access the precursor to spioketal 224 was attempted with the coupling of the TBS-protected hydrazone 222 and Weinreb amide fragment 223 (Scheme 49). To the freshly made LDA was added dropwise the starting material 222, in freshly distilled THF. Reaction mixture was stirred 1h 20 min at 0°C and cooled to −78°C before starting material 223 in freshly distilled THF was added dropwise. Nothing seemed to happen and temperature was raised to −30 - −40°C. After 2 h nothing had happened and the
reaction was left to stir overnight. In the morning after 13 h the bath was still at +5°C, but no reaction was observed.

Scheme 49. a) i) DIPA, BuLi; ii) 223

The difficulty of the couplings was puzzling and therefore we tested the coupling of the simple fragments 225 and 226. Hydrazine 225 was enolized at −78°C with BuLi in THF and Weinreb amide 226 was added. After 3.5 h the reaction was quenched at −78°C with sat. NH₄Cl and a mixture of three isomers 227-229 was collected in 83% combined yield (Scheme 50).

Scheme 50. Test coupling.

As it was possible to make the coupling reaction with the simple model compounds, further investigations were required. To isolate the problem, the Weinreb amide coupling partner was changed to the simple model compound 226 (Scheme 51) and again the reaction was unsuccessful.

Scheme 51. a) i) DIPA, BuLi; ii) 223

The difficulty of the couplings was puzzling and therefore we tested the coupling of the simple fragments 225 and 226. Hydrazine 225 was enolized at −78°C with BuLi in THF and Weinreb amide 226 was added. After 3.5 h the reaction was quenched at −78°C with sat. NH₄Cl and a mixture of three isomers 227-229 was collected in 83% combined yield (Scheme 50).

Scheme 50. Test coupling.

As it was possible to make the coupling reaction with the simple model compounds, further investigations were required. To isolate the problem, the Weinreb amide coupling partner was changed to the simple model compound 226 (Scheme 51) and again the reaction was unsuccessful.
Scheme 51. a) i) DIPA, BuLi; ii) 226

This gave us reason to believe that some problem occurs during the enolation of the compounds 210 and 222. One reason for this could be the Li⁺-cation coordinating between the nitrogen and oxygen or two oxygen atoms (Figure 8). These intermediates 210a and 222a could be so stable that nucleophilic attack to the carbonyl carbon of the Weinreb amides does not occur.

Figure 8. Coordination of the Li⁺-cation.

2.3.2.3 Synthetic Attempt via Isoxazolidine234

Due to these results we decided to try alternative coupling partners which possessed better leaving group. The isoxazolidine moiety is a similar leaving group to the Weinreb amide but due to the high ring strain of five-membered rings it is more easily cleaved. Synthesis of isoxazolidine hydrochloride salt 232 (Scheme 52) was relatively easy but is handling
was a bit complicated due to its hygroscopic nature. According to the literature the corresponding hydrogen bromide salt is less hygroscopic.\(^5\)

\[
\begin{align*}
\text{Scheme 52. Synthesis of the Isoaxolidine hydrochloride salt } & \textbf{232}. \\
\end{align*}
\]

Synthesis of \((2S,3R)-5\)-benzylloxy-3-hydroxy-1-isoxazolidin-2-y1-2-methyl-pentan-1-one \textbf{233} was achieved following the same method as with the analogous Weinreb amide (Scheme 53). This type of compound is very reactive (even explosive) and must be handled with care. The reaction worked well and product \textbf{233} was isolated in 97\% yield. TBS protection of the alcohol was quick and afforded \textbf{234} as a yellow / orange solid in 94\% yield.

\[
\begin{align*}
\text{Scheme 53. a) } & \textbf{232}, \text{AlMe}_3, \text{THF/CH}_2\text{Cl}_2 (5:4), -10^\circ\text{C}; \text{b) TBSOTf, 2,6-Lutidine, CH}_2\text{Cl}_2. \\
\end{align*}
\]

The coupling of \textbf{222} and \textbf{234} was attempted as previously (Scheme 54). The LDA was cooled to \(-10^\circ\text{C}\) and added \textit{via} syringe to \textbf{222} in THF at \(-10^\circ\text{C}\). A strong yellow colour appeared and the reaction was allowed to stir for 50 min at 0 - 10\(^\circ\text{C}\) before it was cooled to \(-78^\circ\text{C}\). The anion solution was added to \textbf{234} in THF at \(-78^\circ\text{C}\) \textit{via} cannula and stirred for 1.5 h before warming to \(-18^\circ\text{C}\) and stirring overnight. After quenching the reaction only both starting materials were observed.
2.3.2.4 Synthetic Attempt via in situ Imidazole Amide 237

We decided to try one more coupling reaction with the hydrazine fragment 222. It was proposed to try to prepare an imidazole amide in situ with the imidazole portion acting as a very good leaving group.\(^{38}\) Firstly, acid 236 had to be made and to this end TBS protection of 216 proved easy and produced 235 as white crystals in very good 87% yield (Scheme 55). Cleavage of the Evans’ auxiliary then afforded the acid 236 in 88% yield.

\[ \text{Scheme 55. a) TBSOTf, 2,6-Lutidine, CH}_2\text{Cl}_2; b) 30\% \text{ H}_2\text{O}_2, 0.2M \text{ LiOH, 0°C.} \]

LDA was added via cannula to 222 (136 mg, 0.34 mmol) in benzene at 7°C, which caused reaction mixture colour to change to yellow. 1,1-Carbonyldimidazole (33 mg, 0.20 mmol) was added in to the acid 236 (59 mg, 0.17 mmol) in benzene (Scheme 56). This was allowed to stir at RT 30 min and added dropwise to enolate solution. This was stirred overnight and quenched with (1:1) EtOAc/brine. The crude product mixture was purified with the preparative TLC, because only a small amount of crude material was collected.
According to the mass spectrum a mass peak (M, 727) was found from the product mixture (24 mg) in the upper fraction, which could be from the product 224.

Scheme 56. a) 1,1-carbonyldiimidazole, benzene, RT; b) enolized 222.

To test whether the material was 224 we decided to test the spirocyclization (Scheme 57). Starting material 224 was treated with HF in aqueous solution and the reaction was allowed to stir at RT for 26 h. During this time starting material 224 disappeared and several spots appeared on the TLC-plate. $^{13}$C-NMR of the crude material was expected to show a signal around 108 ppm from the quaternary carbon of the spirocycle 208 if the reaction was successful. From the spectrum (Figure 9) two peaks were seen in that area, 108-110 ppm, as well as further signal around 210 ppm, which could be the carbonyl carbon of the six membered ring. As there was such a small amount of the material left and yields were very poor in the coupling as well as in the spirocyclization, it was decided not to proceed with this approach.

Scheme 57. a) HF / CH$_3$CN / H$_2$O.

According to the mass spectrum a mass peak (M, 727) was found from the product mixture (24 mg) in the upper fraction, which could be from the product 224.

Scheme 56. a) 1,1-carbonyldiimidazole, benzene, RT; b) enolized 222.

To test whether the material was 224 we decided to test the spirocyclization (Scheme 57). Starting material 224 was treated with HF in aqueous solution and the reaction was allowed to stir at RT for 26 h. During this time starting material 224 disappeared and several spots appeared on the TLC-plate. $^{13}$C-NMR of the crude material was expected to show a signal around 108 ppm from the quaternary carbon of the spirocycle 208 if the reaction was successful. From the spectrum (Figure 9) two peaks were seen in that area, 108-110 ppm, as well as further signal around 210 ppm, which could be the carbonyl carbon of the six membered ring. As there was such a small amount of the material left and yields were very poor in the coupling as well as in the spirocyclization, it was decided not to proceed with this approach.

Scheme 57. a) HF / CH$_3$CN / H$_2$O.
2.3.3 Double Intramolecular Hetero-Michael Addition, DIHMA process

With the failure of the acid-catalyzed spirocyclization approach the retro synthetic strategy of the model spirotetal 238 was changed (Scheme 58). A convergent strategy was maintained with the actual spirotetal formation based on the DIHMA (double intramolecular hetero-Michael addition) process of a suitably derived ynone. Thus, the penultimate goal became the synthesis of ynone 239, which would be available through a nuclophilic addition of the alkyne 240 to Weinreb amide 217, in turn available via the Evans aldol methodology from propionylxazolidinone 215 and benzozoxypropenal. The alkyne was envisioned to arise through a Seyferth-Gilbert-type homologation of the aldehyde (or lactol) corresponding to lactone 212.

With the failure of the acid-catalyzed spirocyclization approach the retro synthetic strategy of the model spirotetal 238 was changed (Scheme 58). A convergent strategy was maintained with the actual spirotetal formation based on the DIHMA (double intramolecular hetero-Michael addition) process of a suitably derived ynone. Thus, the penultimate goal became the synthesis of ynone 239, which would be available through a nuclophilic addition of the alkyne 240 to Weinreb amide 217, in turn available via the Evans aldol methodology from propionylxazolidinone 215 and benzozoxypropenal. The alkyne was envisioned to arise through a Seyferth-Gilbert-type homologation of the aldehyde (or lactol) corresponding to lactone 212.
Although seemingly well preceded, several questions about the DIHMA approach remained to be answered. Firstly, the electrophilic end of the ynone 239 is highly sterically crowded, which might affect the cyclization rate. Secondly, the formation of the highly substituted alkyne 240 is not trivial. Thirdly, the existence of the requisite alkoxy group in the oxalane ring might affect the cyclization rate and/or the stability of the ensuing spirocycle. To shed light on this latter issue, we decided to enter the spirocyclization with enantiopure 217 and racemic 240. Rate differences between the diastereomers would thus become evident experimentally.

Alkyne 242 was prepared in a straightforward fashion beginning with reduction of lactone 212 with DIBAL-H to give lactol 241 in near quantitative yield. The crude material was ready for the Seyferth-Gilbert homologation to the alkyne without further purification. Ohira’s reagent I is a mild alternative for the original Seyferth-Gilbert homologation,
widely used to transform an aldehyde to the corresponding alkyne.\textsuperscript{61} In this case, the lactol 241 was used as the aldehyde surrogate.\textsuperscript{62} The relative sluggishness of the lactol to ring-chain tautomeration was evident experimentally. Ohira’s reagent I had to be added slowly (in five ca 50 mol-% portions over five days), and the reaction temperature had to be kept low (between 36-44 °C) in order to achieve acceptable yields reproducibly (60-79%, based on recovered starting material). Higher reaction temperatures or faster addition of reagent I and the base led to decomposition products. This successful procedure represents the first successful example of using a hindered lactol in the Seyferth-Gilbert homologation. Finally, the secondary hydroxyl was protected (TBSOTf, 2,6-Lutidine, 88%) to give the alkyne 242 ready for coupling (Scheme 59).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=\textwidth]{scheme59.png}};
\end{tikzpicture}
\end{center}

**Scheme 59.** Reagents: a) Dibal-H, PhMe, -78 °C; b) I, K$_2$CO$_3$, MeOH, 36 °C; c) TBSOTf, 2,6-Lutidine, CH$_2$Cl$_2$, 0 °C.

Fragments 242 and 223 were coupled using the Weinreb-Nahm procedure to produce alkynone 239 (Scheme 60).\textsuperscript{63} Spirocyclization using the DIHMA procedure was then attempted in a stepwise protocol. In the first step, the TBS protecting groups were cleaved with CSA in MeOH. Some spirocyclization occurred already at this stage (TLC). The solvent was removed and replaced with benzene, and addition of p-TsOH took the spirocyclization to completion. As the starting alkyne 239 wasn’t optically pure, the two...
diastereoisomers 243 and 244 were observed in a 1:1 diastereomeric ratio (Scheme 60).
This supports the conclusion that the cyclization rate is not critically dependent on the
existence of a directing alkoxy group in the oxolane ring.

![Chemical structure image](image)

Scheme 60. Coupling of 242 and 223 and spirocyclization. Reagents: a) BuLi, 242, then
223, THF –78 °C; b) CSA, MeOH, then p-TsOH, PhH, RT.

Stereoselective synthesis of the spiroketal 257 was comparable to the non-selective
synthesis. The stereoselective synthesis of alkyne 250 is shown in Scheme 61. Sharpless
asymmetric dihydroxylation of enoate 245 using DHQ-PYR led to spontaneous
lactonization and gave the desired single enantiomer of lactone 246 with 82% yield and
75% ee, which was increased to >97% ee by recrystallization (Figure 10). Lactonization
was also tested with AD-mix α, but gave only 63-67% ee. The free alcohol was protected
as its the benzyl ether (benzyl 2,2,2-trichloroacetimidate, CF3SO2H, 91%). Reduction of
247 with DIBAL-H afforded lactol 248 in 90% yield after purification. Using the Ohira’s

![Chemical structure image](image)

Scheme 60. Coupling of 242 and 223 and spirocyclization. Reagents: a) BuLi, 242, then
223, THF –78 °C; b) CSA, MeOH, then p-TsOH, PhH, RT.

Stereoselective synthesis of the spiroketal 257 was comparable to the non-selective
synthesis. The stereoselective synthesis of alkyne 250 is shown in Scheme 61. Sharpless
asymmetric dihydroxylation of enoate 245 using DHQ-PYR led to spontaneous
lactonization and gave the desired single enantiomer of lactone 246 with 82% yield and
75% ee, which was increased to >97% ee by recrystallization (Figure 10). Lactonization
was also tested with AD-mix α, but gave only 63-67% ee. The free alcohol was protected
as its the benzyl ether (benzyl 2,2,2-trichloroacetimidate, CF3SO2H, 91%). Reduction of
247 with DIBAL-H afforded lactol 248 in 90% yield after purification. Using the Ohira’s
reagent, aldehyde surrogate 248 was transformed into alkyne 249 with 61% recycled yield. The primary hydroxyl group was protected as its TBS ether to give alkyne 250 (89%) ready for coupling.

Scheme 61. Reagents: a) DHQ-PYR, K$_2$Fe(CN)$_6$, K$_2$CO$_3$, H$_2$O / t-BuOH (1:1), OsO$_4$, 0°C; b) CH$_2$Cl$_2$ / Cyclohexane (1:3), benzyl 2,2,2-trichloroacetimidate, CF$_3$SO$_2$H, 35°C; c) DIBAL-H, PhMe, -78°C; d) I, K$_2$CO$_3$, MeOH, 36°C; e) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 0°C.
The enantiopure Weinreb amide fragment 254 was prepared as in the Scheme 62 starting with the aldol reaction of (4R)-4-benzyl-3-propionyl-2-oxazolidinone 251 and 3-benzyloxypropionaldehyde to give 252 in 80% yield. This delivered the requisite stereochemical conjugation of the spiroketal fragment of calyculin C. Synthesis of Weinreb amide 253 had been reported previously in the literature from a different propionyloxazolidinone.\textsuperscript{65} In our case conversion of 252 to 253 succeeded with 89% and subsequent TBS protection (TBSOTf, 2,6-lutidine, 89%) gave the desired coupling partner 254.

\textbf{Scheme 62.} Reagents: a) 251, Bu\textsubscript{3}BOTf, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, T < 2°C; then BnOCH\textsubscript{2}CH\textsubscript{2}CHO, -77°C; b) MeOMeNH\textsubscript{2}HCl, AlMe\textsubscript{3}, THF, 0°C; c) TBSOTf, 2,6-lutidine, CH\textsubscript{2}Cl\textsubscript{2}, 0°C.
Coupling of alkyne 250 and Weinreb amide 254 produced alkynone 255 with 62% yield (Scheme 63). A DPGFSE-NOE experiment between C(23)H and C(22)H / C(16)H2 confirmed the correct configuration (calyculin numbering, see also Figure 11). Stepwise DIHMA reaction performed as previously afforded spirocycle 256 as a single enantiomer (86%). Stereoselective reduction of spirotetral 256 with L-Selectride then afforded the desired axial diastereomer 257 in 68% yield.86

Scheme 63. Reagents: a) BuLi, 250, then 254, THF –78°C; b) CSA, MeOH, then p-TsOH, PhH, RT; c) L-Selectride, THF –78°C.

Figure 11. DPGFSE-NOE experiment of 256.
Finally it was time for the ultimate goal, the synthesis of the full spiroketal of calyculin C. Weinreb amide 254 and lactone 258 were proposed as coupling partners with the synthesis of 261 previously published by our group. With lactone 258 in hand it was first needed to synthesize alkyne 261 (Scheme 64). Applying the previously used methodology, lactone 258 was easily reduced to lactol 259 in 78% purified yield. Lactol 259 was transformed to alkyne 260 using the Ohira reagent in 58% recycled yield. This time the transformation was neither productive nor efficient, as even after 10 days the reaction was not complete. Finally the secondary hydroxyl group was protected as its TBS ether to give the alkyne 261 in 42% recycled yield ready for coupling. The poor yield of TBS protection was due to impure starting material 260, which we were not able to purify any other way than by protection of free OH-group.

**Scheme 64.** Reagents: a) DIBAL-H, PhMe, -78 °C; b) 1, K₂CO₃, MeOH, 33°C; c) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0°C.

Coupling of alkyne 261 and Weinreb amide 254 was performed as previously, following the Weinreb-Nahm procedure. This afforded the coupled alkyne 262 in 44% yield, based on recovered of starting material (Scheme 65). Unfortunately, carrying out the spirocyclization of 262 didn’t succeed. From NMR (¹H and COSY) and HRMS studies it
appears most likely that it affords either cleavage of the MEM group or both cleavage of the MEM group and elimination of TBSOH. Unfortunately we had only enough material to perform this reaction once and time constraints did not allow the repetition of the synthesis.

Scheme 65. a) BuLi, 261, then 254, THF –78°C; b) CSA, MeOH, then p-TsOH, PhH, RT.

2.4 Mechanistic studies of the spirocyclization via the DIHMA-process

The reaction mechanism of the formation of the sterically highly hindered 1,6-dioxaspiro[4.5]decane spiroketal was still unclear. The interest in the spirocyclization mechanism arose from the fact that it needed a stepwise protocol to complete the reaction in reasonable time, even though the formation of the spirocycle is dictated by double
anomeric effect. For this study we used model compound 256. To shed light on this question, we conducted the spirocyclization in an NMR tube in deuterated methanol and monitored the reaction at regular intervals by $^1$H-NMR. The TBS-protecting group from the primary alcohol group is cleaved first as evidenced by the disappearance of the signals at about 4.0 and 3.8 ppm immediately (Figure 12). After 0.5 h the first trace of the six-membered ring can be seen at the 4.2 ppm, which is caused by $CH$ signal. However $CH_2OH$ signals in the areas of 3.95 and 3.75 ppm start to appear also immediately, but it takes longer to see the traces of the signals of the $CH_2$ of the final spirocycle at ca. 3.75 and 3.80 ppm. In accordance with Baldwin’s rule for ring closure, the 6-endo-dig cyclization is clearly favourable, whereas 5-exo-dig is not so clear and it is said to be more disfavoured (Scheme 66).

![Figure 12. Reaction T(0) + 8 min – T(0) +16 h 14 min.](image1)

![Figure 12. Reaction T(0) + 8 min – T(0) +16 h 14 min.](image2)
The suggested reaction path is therefore path a. However, it is impossible to distinguish whether the spirocyclization occurs directly from A1 or through the intermediates A2 and C.

Scheme 66. Possible reaction pathways.
2.5 Conclusions and Future Prospects

A new strategy to prepare the spiroketal fragment of calyculins has been presented and right stereoisomer of model spirocycle was succeeded to synthesize. A novel Seyferth-Gilbert homologation of hindered lactols to the corresponding alkynes has been achieved for the first time. The spirocyclization was achieved efficiently via a DIHMA (double intramolecular hetero-Michael addition) process. The spirocyclization rate is not dependent on the stereochemistry of the alkoxy substituents in the oxolane ring. It was also discovered that the cyclization mechanism follows Baldwin’s rules and goes first via the six-membered ring (6-endo-dig) followed by five-membered ring cyclization (5-exo-trig). However, it is impossible ascertain the exact reaction pathway.

Our original plan to utilize ISMS was risky, but needed to be tested. Reaction was found too sensitive, even with the simple starting materials, and thus was not used in further steps. The next attempt to do acid-catalyzed spirocyclization appeared to be more difficult than we expected. Neither ketone nor hydrazine method worked despite of succeeded test coupling (Scheme 50). Later it was discovered that when Bn-protected oxygen is in β-position to carbonyl carbon, it has a tendency to strong Li⁺-cation coordination. Initially DIHMA-approach did not seem to be easy either. After the first test we thought that it wouldn’t work either, but a more detailed examination revealed a spot on TLC, that was at first very weak but got clearer during the synthesis. This was the first encouraging sign of successful DIHMA-process in synthesizing spiroketals. We decided to try this same procedure to fully substituted spiroketal of calyculins. We did succeed in synthesizing the necessary alkyne fragment but the cleavage of the MEM-group in the very last state (Scheme 65) was something we didn’t predict. We were facing lack of resources and were not able to continue the research work in the frame of this PhD thesis Despite the fact that the ultimate goal to prepare the fully substituted spiroketal wasn’t achieved we are very close to realising this aim.

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For the eventual total synthesis of calyculin C there is a need to reconsider the protection group strategy in the case of spirocyle. Replacing the TBS-protection groups from the 261 and 254 to TES is well worth trying since it is less stable than TBS and thus might prevent the MEM-group cleavage and help achieving spirocyclization. Modifying the protection group strategy would also be quick and easy route to test the coupling and spirocyclization. Even if 263 had been successfully synthesized the two Bn-protection groups one in each end, would most likely have caused problems in the later stage. To avoid difficulties changing Bn-group from the 254 to the TBDPS-group is recommended. Armstrong et al. utilized similar type of protection group strategy with the spiroketal in the total synthesis of calyculin C.42a

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3 Experimental

3.1 General

All reactions were conducted under a positive pressure of argon. THF was distilled prior to use from sodium-benzophenone ketyl, MeOH from Mg(OMe)_2 and toluene from sodium. Other solvents were pro analysis grade.

Melting points were determined on a Gallenkamp melting point apparatus MFB-595 and are uncorrected. TLC was conducted on Merck 0.25 mm silica gel 60 F plates and samples were visualized with UV light, anisaldehyde, PMA and ninhydrin staining. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh) as a stationary phase. HPLC was performed with a Waters 501 pump, Waters 486 tunable absorbance detector and a Waters 746 data module using the following columns: Shandon Hypersil Silica Column with Waters Guard-Pak™ precolumn fitted with Resolve™ silica inserts for normal phase chromatography and Daicel Chiracel OD 25 cm x 0.46 cm with Daicel Chiracel OD 5 cm x 0.46 cm precolumn for chiral chromatography. Optical rotations were measured at 20 °C on a Perkin Elmer polarimeter 343. IR spectra were measured with Perkin Elmer Spectrum One. Elemental analyses were performed with a Perkin Elmer Elemental Analyzer 2400 CHN. HRMS spectra were measured with a Jeol JMS-DX 303 and Micromass LCT. NMR spectra were measured with a Bruker AMX 400 (1H 400.13 MHz, 13C 100.61 MHz). The single-crystal X-ray diffraction for lactone 246 was performed with a Nonius KappaCCD diffractometer with graphite monochromatized MoKα(λ = 0.71073 Å) radiation. Collect-software was used in the measurement and DENZO-SMN in the processing of the data. The structure was solved and refined by fullmatrix least-squares on F^2 with WinGX-software package utilizing SHELXS97 and SHELXL97 modules. Hydrogen atoms were refined by a riding model. Absorption correction was not performed for the compound. CCDC-255366 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
1,3,5-Trioxane 270 (18 g, 0.20 mol, 33 mol-%) and benzyl alcohol 271 (62 mL, 0.60 mol, 100 mol-%) were placed in a 100 mL 3-neck flask and cooled to −10°C. HCl-gas was bubbled via a H₂SO₄ washing flask, keeping the internal temperature of the reaction below 10°C. After 2.5 h the reaction was allowed to warm to RT and bubbling was continued for a further 1.5 h when two clear layers separated. The upper layer was separated, dried with CaCl₂ and kept under water pump vacuum for 1 h to remove the residual HCl-gas. The crude product 194 was collected as a slightly yellow oil and used immediately to next reaction. \( R_f (50\% \text{EtOAc/Hexane, UV / acid-PMA}) = 0.61; \) \(^1\text{H} \) NMR (400 MHz, CDCl₃) \( \delta 4.69 \) (s, \(\text{CH}_2\text{Ph}, 2\text{H})), 5.46 (s, \(\text{CH}_2\text{Cl}, 2\text{H})), 7.32 \text{ (m, } \text{ArH}, 5\text{H}); \) \(^{13}\text{C} \) NMR (100 MHz, CDCl₃) \( \delta 71.2, 81.6, 128.2, 128.5, 128.6, 135.5.\)

3.1.2 5-Benzyloxy-3-oxo-pentanoic acid methyl ester (196)

Freshly distilled THF (160 mL) was added to NaH (6.4 g, 0.16 mol, 100 mol-%) and the mixture cooled to 0°C. Methyl acetoacetate 195 (17.3 mL, 0.16 mol, 100 mol-%) was added dropwise and the reaction mixture was stirred for 45 min at 0°C, then cooled to −40°C (CH₂CN/\(\text{N}_2\)) before BuLi (1.5 M, 107 mL, 0.16 mmol, 100 mol-%) was added dropwise over 1 h. The reaction was allowed to stir for 50 min at −40°C and BOM-Cl 194 (25.1 g, 0.16 mmol, 100 mol-%) was added over 70 min. The reaction was allowed to stir for a further 15 min and quenched with 1 M HCl (100 mL) and 6 M HCl (25 mL) adjusting the pH to 4.5. The aqueous phase was extracted with EtO (3*100 mL), the combined organic phases washed with brine (100 mL) and dried with Na₂SO₄. The crude product was purified by “dry” flash column chromatography (step (5%) gradient from 5%
to 40% EtOAc/Hexane) affording 196 (26.16 g, 69%). Rf (50% EtOAc/Hexane, UV / acid-PMA) = 0.39; Rf (HPLC, Shandon Hypersil, 5μ, 250mm, 4.6mm, 10% EtOAc/Hexane, 254nm, 1.5mL/min) = 14.2min; 1H NMR (400 MHz, CDCl3) δ 2.82 (t, CH2CHO3C(O), J 6.2 Hz, 2H), 3.50 (s, C(O)CH2C(O), 2H), 3.72 (s, CH3, 3H), 3.75 (t, CH2CH2C(O), J 6.2 Hz, 2H), 4.50 (s, CH3Ar, 2H), 7.30 (m, ArH, 5H); 13C NMR (100 MHz, CDCl3) δ 43.1, 49.5, 52.3, 64.9, 73.2, 127.6, 127.7, 128.4, 128.5, 137.8, 167.4, 201.2; HRMS (EI') calc. for C17H16O2Na 259.0946, found 259.0962.

3.1.3 5-Benzoyloxy-3-hydroxy-pentanoic acid methyl ester (197)

BnO       OMe
         /   
       OMe      OH
               /   
BnO       OMe
         /   
       OMe      OH

To a stirred solution of methyl ester 196 (10.0 g, 0.423 mmol, 100 mol%) in MeOH (200 mL) at -10°C was added NaBH4 (1.60 mg, 0.023 mmol, 100 mol%). After 50 min at -10°C 1M HCl (42 mL) was added and the reaction mixture diluted with EtO (150 mL) and brine (50 mL). The aqueous layer was extracted with EtO (3*100 mL) and the combined organic phases dried with MgSO4. The solvent was evaporated in vacuo and the product purified by column chromatography (25% EtOAc/Hexane). 1H NMR (400 MHz, CDCl3) δ 1.80 (m, CH2CH2CH(OH), 2H), 2.51 (d, C(O)CH2C(O), J 6.2 Hz, 2H), 3.37 (d, CHOH, J 3.3 Hz, 1H), 3.68 (m, CH2CH2CH(OH), 2H), 3.70 (s, CH3, 3H), 4.24 (m, CHOH, 1H), 4.52 (s, CH3Ar, 2H), 7.32 (m, ArH, 5H); 13C NMR (100 MHz, CDCl3) δ 40.0, 41.4, 51.7, 67.0, 68.0, 73.3, 127.6, 127.7, 128.4, 137.9, 172.8; HRMS (EI') calc. for C17H16O2Na 261.1103, found 261.1114.

3.1.3 5-Benzoyloxy-3-hydroxy-pentanoic acid methyl ester (197)

BnO       OMe
         /   
       OMe      OH
               /   
BnO       OMe
         /   
       OMe      OH

To a stirred solution of methyl ester 196 (10.0 g, 0.423 mmol, 100 mol%) in MeOH (200 mL) at -10°C was added NaBH4 (1.60 mg, 0.023 mmol, 100 mol%). After 50 min at -10°C 1M HCl (42 mL) was added and the reaction mixture diluted with EtO (150 mL) and brine (50 mL). The aqueous layer was extracted with EtO (3*100 mL) and the combined organic phases dried with MgSO4. The solvent was evaporated in vacuo and the product purified by column chromatography (25% EtOAc/Hexane). 1H NMR (400 MHz, CDCl3) δ 1.80 (m, CH2CH2CH(OH), 2H), 2.51 (d, C(O)CH2C(O), J 6.2 Hz, 2H), 3.37 (d, CHOH, J 3.3 Hz, 1H), 3.68 (m, CH2CH2CH(OH), 2H), 3.70 (s, CH3, 3H), 4.24 (m, CHOH, 1H), 4.52 (s, CH3Ar, 2H), 7.32 (m, ArH, 5H); 13C NMR (100 MHz, CDCl3) δ 40.0, 41.4, 51.7, 67.0, 68.0, 73.3, 127.6, 127.7, 128.4, 137.9, 172.8; HRMS (EI') calc. for C17H16O2Na 261.1103, found 261.1114.
Methyl ester 197 (200 mg, 0.843 mmol, 100 mol-%) in THF (10 mL) was treated with 1,1,1,3,3,3-hexamethyldisilazane (0.196 mL, 0.927 mmol, 110 mol-%) and TMSCl (0.118 mL, 0.927 mmol, 110 mol-%). After 2 h at reflux the solvent was evaporated in vacuo and the product purified by flash chromatography (15% MTBE/Hexane) to afford 198 (0.257 g, 98%). R<sub>f</sub> (50% EtOAc/Hexane, UV / acid-PMA) = 0.61; R<sub>f</sub> (HPLC, Shandon Hypersil, 5 μ, 250 mm, 4.6 mm, 10% EtOAc/Hexane, 254 nm, 1.5 mL/min) = 3.4 min; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.10 (s, (CH<sub>3</sub>)<sub>3</sub>Si, 9H), 1.80 (m, CH<sub>2</sub>CH<sub>2</sub>CH(O)TMS), 2H), 2.47 (d, C(TMS)CH<sub>2</sub>C(O), J 6.6 Hz, 2H), 3.53 (m, CH<sub>2</sub>CH<sub>2</sub>CH(O)TMS), 2H), 3.66 (s, CH<sub>2</sub>F, 2H), 4.32 (m, CHOTMS, 1H), 4.48 (d, CH<sub>2</sub>Ph, J<sub>ab</sub> 11.9 Hz, 2H), 7.32 (m, ArH, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 37.5, 43.0, 51.4, 66.5, 66.8, 72.9, 127.5, 127.6, 128.3, 138.3, 171.9; HRMS (EI) calc. for C<sub>14</sub>H<sub>20</sub>O<sub>4</sub>NaSi 333.1498, found 333.1478.

CeCl<sub>3</sub>·7H<sub>2</sub>O (360 mg, 0.966 mmol, 100 mol-%) was heated with heat gun under high vacuum for 3*15 min, cooling the flask back to RT in between the heatings. The flask was cooled to 0°C and freshly distilled THF (2.5 mL) was added slowly allowing the mixture to stir overnight at RT. The reaction mixture was cooled to −78°C and TMSCH<sub>2</sub>MeCl (1 M in Et<sub>2</sub>O, 0.966 mL, 0.966 mmol, 300 mol-%) added slowly. The reaction was allowed to stir for 25 min at −78°C before 5-benzyloxy-3-trimethylsilylanyloxy-pentanoic acid methyl ester 198 (100 mg, 0.322 mmol, 100 mol-%) in THF (1 mL) was added. The EtOAc/N<sub>2</sub>-bath was changed to an ice-bath and the
reaction was allowed to warm to RT. After 4 h the reaction was cooled to 0°C and 2 mL of Et₂O and 1 mL of sat. NH₄Cl was added. The reaction mixture was washed with 15 mL of brine, the aqueous layer extracted with 3×25 mL of Et₂O, the combined organic layers dried with MgSO₄ and the solvent evaporated in vacuo. The product was purified by flash chromatography (10% MTBE/Hexane) to afford 199 (73.7 mg, 50%). Rₚ (50% EtOAc/Hexane, UV / acid-PMAS) = 0.68; Rₘ (HPLC, Shandon Hypersil, 5 μ, 250 mm, 4.6 mm, 10% EtOAc/Hexane, 254 nm, 0.5 mL/min) = 7.9 min; ¹H NMR (400 MHz, CDCl₃) δ 0.04 (s, (CH₃)₂Si, (CH₃)₂Si, 18H), 0.16 (s, (CH₃)₂SiOCH₃, 9H), 0.95 (d, TMSCH₂CH₃, J 14.6 Hz, 1H), 0.98 (d, TMSCH₂CH₃, J 14.3 Hz, 1H), 1.06 (d, TMSCH₂CH₃, J 14.6 Hz, 1H), 1.21 (d, TMSCH₂CH₃, J 14.3 Hz, 1H), 1.57 (dd, CH(OTMS)CH₂CH₃, J 2.9 Hz, 14.3 Hz, 1H), 1.77 (m, BuOCH₂CH₂CH₃, 1H), 1.87 (d, CH(OTMS)CH₂CH₃, J 14.3 Hz, 1H), 1.89 (m, BuOCH₂CH₂CH₃, 1H), 3.50 (m, BuOCH₂, 2H), 3.85 (s, OH, 1H), 4.28 (m, CH(OTMS), 1H), 4.48 (s, CH₂Ph, 2H), 7.32 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 32.1, 34.4, 38.5, 48.9, 66.3, 69.4, 73.0, 75.7, 127.6, 127.6, 128.3, 138.3; IR (film) 3512, 3089, 3066, 3031, 2952, 2898, 2870 cm⁻¹; HRMS (M+OTMS) calc. for C₂₃H₃₄O₃Si⁺: 437.2727, found: 437.2740.

3.1.6 (5-Trimethylsilylalkyl-3-trimethylsilyloxy-hex-5-enoyl)methyl-benzene (200)

In a 250 mL 3-necked round-bottomed flask was placed CeCl₃·7H₂O (14.0 g, 37.6 mmol, 648 mol-%), and the solid stirred overnight at 150°C under high vacuum. The flask was filled with argon and allowed to cool to RT. Dry THF was added and the mixture stirred at RT during 1 h. The resulting slurry was cooled to ~78°C and TMSC₂H₂MgCl (1M in THF, 30 mL, 30 mmol, 517 mol-%) was added dropwise over 45 min. The cream-colored suspension was stirred for an additional hour at ~78°C before ester 198 (1.8 g, 5.8 mmol, 100 mol-%) was added dropwise over 5 min. The reaction mixture was then allowed to warm to RT, stirred for 30 min and quenched with 50 mL of sat. NH₄Cl. The reaction was allowed to warm to RT. After 4 h the reaction was cooled to 0°C and 2 mL of Et₂O and 1 mL of sat. NH₄Cl was added. The reaction mixture was washed with 15 mL of brine, the aqueous layer extracted with 3×25 mL of Et₂O, the combined organic layers dried with MgSO₄ and the solvent evaporated in vacuo. The product was purified by flash chromatography (10% MTBE/Hexane) to afford 199 (73.7 mg, 50%). Rₚ (50% EtOAc/Hexane, UV / acid-PMAS) = 0.68; Rₘ (HPLC, Shandon Hypersil, 5 μ, 250 mm, 4.6 mm, 10% EtOAc/Hexane, 254 nm, 0.5 mL/min) = 7.9 min; ¹H NMR (400 MHz, CDCl₃) δ 0.04 (s, (CH₃)₂Si, (CH₃)₂Si, 18H), 0.16 (s, (CH₃)₂SiOCH₃, 9H), 0.95 (d, TMSCH₂CH₃, J 14.6 Hz, 1H), 0.98 (d, TMSCH₂CH₃, J 14.3 Hz, 1H), 1.06 (d, TMSCH₂CH₃, J 14.6 Hz, 1H), 1.21 (d, TMSCH₂CH₃, J 14.3 Hz, 1H), 1.57 (dd, CH(OTMS)CH₂CH₃, J 2.9 Hz, 14.3 Hz, 1H), 1.77 (m, BuOCH₂CH₂CH₃, 1H), 1.87 (d, CH(OTMS)CH₂CH₃, J 14.3 Hz, 1H), 1.89 (m, BuOCH₂CH₂CH₃, 1H), 3.50 (m, BuOCH₂, 2H), 3.85 (s, OH, 1H), 4.28 (m, CH(OTMS), 1H), 4.48 (s, CH₂Ph, 2H), 7.32 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 32.1, 34.4, 38.5, 48.9, 66.3, 69.4, 73.0, 75.7, 127.6, 127.6, 128.3, 138.3; IR (film) 3512, 3089, 3066, 3031, 2952, 2898, 2870 cm⁻¹; HRMS (M+OTMS) calc. for C₂₃H₃₄O₃Si⁺: 437.2727, found: 437.2740.
layers were separated, the aqueous extracted 3*50 mL of Et₂O, the combined organic extracts dried with MgSO₄, filtered and the solvent removed in vacuo. The residue was dissolved in CH₂Cl₂ (19 mL), treated with 2.9 g of silica and 2-3 drops of 1% HCl. The suspension was stirred at RT for 5 h (until TLC showed consumption of starting material), filtered with the aid of CH₂Cl₂ and the solvent evaporated under reduced pressure to give a 1:1 mixture of product 200 and the corresponding free alcohol. The mixture was dissolved in dry CH₂Cl₂ (16 mL) and treated at 0°C with 2,6-Lutidine (0.6 mL, 6.1 mmol, 105mol-%) and TMSOTf (0.96 mL, 3.5 mmol, 61 mol-%). The reaction mixture was washed with 15 mL of brine, the aqueous layer extracted with 3*25 mL of Et₂O, the combined organic layers’ dried with MgSO₄ and the solvent evaporated in vacuo. The product was purified by flash chromatography (Hexane/EtOAc 20:1), the target was obtained as a clear liquid (1.3 g, 3.6 mmol, 62%). Rf (Hexane/EtOAc 20:1) = 0.30; ¹H NMR (400 MHz, CDCl₃) δ 0.01 (s, (CH₃)₂Si, 9H), 0.10 (s, (CH₃)₂SiO, 9H), 1.52 (ddd, CH₂TMS, J 14.1, 1.0 Hz, 2H), 1.63 (dd, BnOCH₂CH₂H₂O, J 14.0, 8.5, 5.5 Hz, 1H), 1.88 (ddd, BnOCH₂CH₂H₂O, J 14.0, 7.7, 6.9, 3.7 Hz, 1H), 2.06 (ddd, CH(OTMS)₂CH₂C₂H₅, J 13.6, 6.5, 0.8 Hz, 1H), 2.15 (ddd, CH(OTMS)₂CH₂C₂H₅, J 13.6, 6.5, 0.8 Hz, 1H), 3.49-3.58 (m, BnOCH₂CH₂, 2H), 3.98 (ddd, CH(OTMS), J 8.5, 3.7, 6.5 Hz, 1H), 4.49 (d, CH₂Ph, JAB 11.9 Hz, 1H), 4.59 (td, CH₂C₂, J 18.8, 1.0 Hz, 2H), 7.33-7.25 (m, ArH, 5H; ¹³C NMR (100 MHz, CDCl₃) δ -1.4, 0.4, 27.2, 37.1, 47.0, 67.2, 68.5, 72.9, 110.1, 127.5, 127.6, 128.3, 138.6, 144.0.

3.1.7 3-(Ethoxycarbonyl)-2-hydroxy-3,3-dimethylbutyl benzoate (202).

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{i) LDA} \\
\text{BzO} & \quad \text{202} \\
\text{HO} & \quad \text{201} \\
\text{EtO} & \quad \text{CO}_2\text{Et} \\
\end{align*}
\]

Diisopropylamine (2.82 mL, 20.1 mmol, 110 mol-%) was dissolved in freshly distilled THF (20 mL) at 0°C. BuLi (2.3 M, 8.7 mL, 20.1 mmol, 110 mol-%) was added over 10 min and the light yellow solution was cooled to −78°C. Ethyl isobutyrate 266 (2.69 mL, 20.1 mmol, 110 mol-%) was added dropwise over 5 min, the light yellow reaction

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3.1.7 3-(Ethoxycarbonyl)-2-hydroxy-3,3-dimethylbutyl benzoate (202).

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{i) LDA} \\
\text{BzO} & \quad \text{202} \\
\text{HO} & \quad \text{201} \\
\text{EtO} & \quad \text{CO}_2\text{Et} \\
\end{align*}
\]

Diisopropylamine (2.82 mL, 20.1 mmol, 110 mol-%) was dissolved in freshly distilled THF (20 mL) at 0°C. BuLi (2.3 M, 8.7 mL, 20.1 mmol, 110 mol-%) was added over 10 min and the light yellow solution was cooled to −78°C. Ethyl isobutyrate 266 (2.69 mL, 20.1 mmol, 110 mol-%) was added dropwise over 5 min, the light yellow reaction
mixture stirred 1.5 h at −78 °C and a solution of aldehyde 201 (3.0 g, 18.3 mmol, 100 mol-%) in THF (20 mL) was added dropwise over 20 min. After 2 h stirring at −78 °C, the reaction was quenched with sat. NH₄Cl (20 mL) and allowed to warm up RT. The aqueous phase was washed three times with Et₂O (30 mL), the combined organic phases washed with brine (20 mL) and dried (Na₂SO₄). The product was purified by flash column chromatography (30% EtOAc/Hexane) affording 202 3.25 g (63%). Rf (50% EtOAc/Hexane, UV/PMA) = 0.49; IR (vₜₚ, mm) 1141, 1366, 1386, 1581, 1598, 1737, 3565 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.25 (t, CH₃C₂H, 7.1 Hz, 3H), 1.29 (s, CH₃C₂H, 3H), 1.32 (s, CH₃C₂H, 3H), 3.15 (d, CHOH, J 6.6 Hz, 1H), 4.05 (ddd, CHOH, J 7.2, 6.3, 2.9 Hz, 1H), 4.14 (dd, CH₂CH₂, J 7.1, 4.9 Hz, 2H), 4.37 (dd, BzOCH₂H₂O, J 11.7 7.3 Hz, 1H), 4.48 (dd, BzOCH₂H₂O, J 11.7 2.9 Hz, 1H), 7.44 (m, ArH, 2F), 7.57 (m, ArH, 1H), 8.06 (m, ArH, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 14.0, 20.9, 22.6, 45.4, 51.0, 66.2, 75.1, 128.4, 128.9, 129.7, 133.1, 166.7, 176.8; HRMS (TOF MS El⁺) calc. for C₁₃H₁₀O₃Na 303.1208, found 303.1221.

3.1.8 4-(Benzoyloxy)-dihydro-3,3-dimethylfururan-2(3H)-one (203)

In a 50 mL 2-necked round-bottomed flask under argon was placed ester 202 (155 mg, 0.55 mmol, 100 mol-%) in dry toluene (23 mL). p-TsOH (22 mg, 0.067 mmol, 12 mol-%) was added and the resulting solution stirred at 100°C for 1 h. The flask was then attached to a distillation system equipped with Vigreux column and the azeotrope Toluene/EtOH was distilled off (T = 77°C). Distillation was continued until the temperature reached 110°C, the reaction mixture allowed to cool to RT and the remaining toluene evaporated in vacuo. The residue was dissolved in Et₂O (20 mL) and washed with 10% NaHCO₃ (3*10 mL). The organic phase was dried with MgSO₄, filtered and the solvent removed in vacuo. The residue was purified by flash chromatography (Hex/EtOAc 5:1). The target 203 was obtained as colorless oil (105 mg, 0.45 mmol, 82%). Rf (Hexane/EtOAc 10:1) =

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3.1.8 4-(Benzoyloxy)-dihydro-3,3-dimethylfururan-2(3H)-one (203)

In a 50 mL 2-necked round-bottomed flask under argon was placed ester 202 (155 mg, 0.55 mmol, 100 mol-%) in dry toluene (23 mL). p-TsOH (22 mg, 0.067 mmol, 12 mol-%) was added and the resulting solution stirred at 100°C for 1 h. The flask was then attached to a distillation system equipped with Vigreux column and the azeotrope Toluene/EtOH was distilled off (T = 77°C). Distillation was continued until the temperature reached 110°C, the reaction mixture allowed to cool to RT and the remaining toluene evaporated in vacuo. The residue was dissolved in Et₂O (20 mL) and washed with 10% NaHCO₃ (3*10 mL). The organic phase was dried with MgSO₄, filtered and the solvent removed in vacuo. The residue was purified by flash chromatography (Hex/EtOAc 5:1). The target 203 was obtained as colorless oil (105 mg, 0.45 mmol, 82%). Rf (Hexane/EtOAc 10:1) =
To a stirred suspension of NaH (60% oil dispersion, 476 mg, 11.9 mmol, 110 mol%-%) in dry DMF at 0 °C was added dropwise a solution of ester 202 (3.03 g, 10.8 mmol, 100 mol-%) in THF (6 mL). The reaction mixture was stirred for 5 min at 0 °C then 15 min at RT. BnCl (1.37 mL, 11.9 mmol, 110 mol%-%) was added dropwise and the reaction was stirred for 4 h at RT. After quenching at 0 °C with sat. NH₄Cl, the aqueous phase was extracted three times with 25 mL of Et₂O, the combined organic phases were washed with brine (50 mL) and dried with MgSO₄. After flash column chromatography (15% EtOAc/Hexane) lactone 212 was isolated (1.77 g, 75%). Rₐ (30% EtOAc/Hexane, UV/PMA) = 0.27; IR (νmax, film) 1773 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.26 (s, CH₃, 3H), 1.28 (s, CH₃, 3H), 3.91 (dd, CH₂, 4.0, 5.1 Hz, 1H), 4.15 (dd, CH₂, 4.0, 10.1Hz, 1H), 4.31 (dd, CH₂, 5.1, 10.1 Hz, 1H), 4.59 (d, CH₂Ph, J₆₇ 11.1 Hz, 2H), 7.30-7.39 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 17.9, 23.3, 42.9, 68.9, 72.1, 81.8, 127.5, 128.0, 128.5, 137.4, 180.6; HRMS (EI⁺) calc. for C₁₅H₁₈O₂ 220.1099, found 220.1092.

To a stirred suspension of NaH (60% oil dispersion, 476 mg, 11.9 mmol, 110 mol%-%) in dry DMF at 0 °C was added dropwise a solution of ester 202 (3.03 g, 10.8 mmol, 100 mol-%) in THF (6 mL). The reaction mixture was stirred for 5 min at 0 °C then 15 min at RT. BnCl (1.37 mL, 11.9 mmol, 110 mol%-%) was added dropwise and the reaction was stirred for 4 h at RT. After quenching at 0 °C with sat. NH₄Cl, the aqueous phase was extracted three times with 25 mL of Et₂O, the combined organic phases were washed with brine (50 mL) and dried with MgSO₄. After flash column chromatography (15% EtOAc/Hexane) lactone 212 was isolated (1.77 g, 75%). Rₐ (30% EtOAc/Hexane, UV/PMA) = 0.27; IR (νmax, film) 1773 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.26 (s, CH₃, 3H), 1.28 (s, CH₃, 3H), 3.91 (dd, CH₂, 4.0, 5.1 Hz, 1H), 4.15 (dd, CH₂, 4.0, 10.1Hz, 1H), 4.31 (dd, CH₂, 5.1, 10.1 Hz, 1H), 4.59 (d, CH₂Ph, J₆₇ 11.1 Hz, 2H), 7.30-7.39 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 17.9, 23.3, 42.9, 68.9, 72.1, 81.8, 127.5, 128.0, 128.5, 137.4, 180.6; HRMS (EI⁺) calc. for C₁₅H₁₈O₂ 220.1099, found 220.1092.
A solution of Lactone 212 (0.5 g, 2.27 mmol, 100 mol-%) in THF (10 mL) at -78°C was treated dropwise over 5 min with MeLi (1.4 M in Et₂O, 1.79 mL, 2.50 mmol, 110 mol-%). The reaction was stirred for 1 h 15 min and quenched (-78°C) with 0.16 mL of glacial AcOH followed by 30 mL of sat. NaHCO₃ and allowed to warm to RT. The aqueous phase was extracted with 3*20 mL of Et₂O, the combined organics washed with 30 mL of brine and dried with MgSO₄. The solvent was evaporated to afford 0.567 g of a mixture of compounds 213 and 214. The crude product was dissolved in dry DMF (5 mL) and imidazole (0.77 g, 11.4 mmol, 500 mol-%) followed by TMSCl (0.576 mL, 4.54 mmol, 200 mol-%) added. The reaction was stirred for 15 h at RT, further TMSCl (0.576 mL, 4.54 mmol, 200 mol-%) added and stirring continued for another 4 h 30 min. The reaction mixture was partitioned between 20 mL of EtOAc and 20 mL of brine and stirred for 30 min. The organics were separated and dried with MgSO₄. The crude product was purified by flash chromatography (50% EtOAc/Hexane, UV / acid-PMA) to give 210 (0.38 g, 54%). Rf (50% EtOAc/Hexane, UV / acid-PMA) = 0.66; ¹H NMR (400 MHz, CDCl₃) δ 0.09 (s, CH₂Si, 9H), 1.13 (s, CH₃, 3H), 1.15 (s, CH₂, 3H), 2.12 (s, CH₂, 3H), 3.63-3.65 (m, TMSOCH₂CH₂, CHOBN, 2H), 3.76 (t, TMSOCH₂CH₂, CHOBN, 2H), 7.29 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ -0.73, 20.1, 21.7, 26.4, 51.1, 62.5, 74.0, 84.3, 127.5, 127.6, 128.2, 138.7, 212.1; HRMS (EI⁺) calc. for C₁₇H₁₇O₃S⁺ 309.1880, found 309.1845. A solution of Lactone 212 (0.5 g, 2.27 mmol, 100 mol-%) in THF (10 mL) at -78°C was treated dropwise over 5 min with MeLi (1.4 M in Et₂O, 1.79 mL, 2.50 mmol, 110 mol-%). The reaction was stirred for 1 h 15 min and quenched (-78°C) with 0.16 mL of glacial AcOH followed by 30 mL of sat. NaHCO₃ and allowed to warm to RT. The aqueous phase was extracted with 3*20 mL of Et₂O, the combined organics washed with 30 mL of brine and dried with MgSO₄. The solvent was evaporated to afford 0.567 g of a mixture of compounds 213 and 214. The crude product was dissolved in dry DMF (5 mL) and imidazole (0.77 g, 11.4 mmol, 500 mol-%) followed by TMSCl (0.576 mL, 4.54 mmol, 200 mol-%) added. The reaction was stirred for 15 h at RT, further TMSCl (0.576 mL, 4.54 mmol, 200 mol-%) added and stirring continued for another 4 h 30 min. The reaction mixture was partitioned between 20 mL of EtOAc and 20 mL of brine and stirred for 30 min. The organics were separated and dried with MgSO₄. The crude product was purified by flash chromatography (50% EtOAc/Hexane, UV / acid-PMA) to give 210 (0.38 g, 54%). Rf (50% EtOAc/Hexane, UV / acid-PMA) = 0.66; ¹H NMR (400 MHz, CDCl₃) δ 0.09 (s, CH₂Si, 9H), 1.13 (s, CH₃, 3H), 1.15 (s, CH₂, 3H), 2.12 (s, CH₂, 3H), 3.63-3.65 (m, TMSOCH₂CH₂, CHOBN, 2H), 3.76 (t, TMSOCH₂CH₂, CHOBN, 2H), 7.29 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ -0.73, 20.1, 21.7, 26.4, 51.1, 62.5, 74.0, 84.3, 127.5, 127.6, 128.2, 138.7, 212.1; HRMS (EI⁺) calc. for C₁₇H₁₇O₃S⁺ 309.1880, found 309.1845.
A solution of Lactone 212 (0.824 g, 3.74 mmol, 100 mol-%) in 25 mL of dry THF at −78°C was treated dropwise over 9 min with MeLi (1.4 M in Et₂O, 2.94 mL, 4.12 mmol, 110 mol-%) The reaction was allowed to stir for 50 min and quenched (−78°C) with 0.24 mL of glacial AcOH followed by 30 mL of sat. NaHCO₃ and allowed to warm to RT. The aqueous phase was extracted 3×30 mL of Et₂O, the combined organics washed with 10 mL of brine and dried with MgSO₄. The solvent was evaporated to afford a mixture of equilibrium compounds 213 and 214 (0.858 g). The crude product was dissolved in dry DMF (5 mL) and imidazole (1.12 g, 16.5 mmol, 500 mol-%) followed by a solution of TBSCI (0.995 g, 6.6 mmol, 200 mol-%) in 5 mL of DMF added. The reaction was stirred for 30 min at RT, partitioned between 20 mL of EtOAc and 20 mL of brine and the mixture stirred for 30 min. The phases were separated and the aqueous phase extracted with 4×25 mL of Et₂O. The combined organic phases were dried with MgSO₄ and the solvent evaporated in vacuo. The crude 221 was purified by flash column chromatography (10% EtOAc/Hexane) to afford 221 (1.03 g, 87%) as a slightly yellow oil. Rₜ (30% EtOAc/Hexane, UV / acid-PMA) = 0.58; ¹H NMR (400 MHz, CDCl₃) δ 0.05 (s, (CH₃)₂Si, 6H), 0.89 (s, (CH₃)₃C, 9H), 1.13 (s, CH₃, 3H), 1.15 (s, CH₃, 3H), 2.13 (s, COCH₃, 3H), 3.68-3.69 (m, TBSOCH₂CH₃, CHOBN, 2H), 3.75 (dd, TBSOCH₂CH₃, J 4.8, 3.8 Hz, 1H), 4.69 (d, Jₕₖ 11.7 Hz, 2H), 7.27 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ -5.6, -5.5, 18.2, 20.5, 21.4, 25.9, 26.5, 51.1, 63.6, 74.0, 84.6, 127.4, 127.5, 128.2, 138.8, 212.2; HRMS (EI⁺) calc. for C₂₀H₂₃O₃Si 350.2277, found 350.2337.
3.1.12 \(N^\prime\)-[3-Benzylxy-4-(tert-butyl-dimethyl-silylxyloxy)-1,2,2-trimethyl-butylidene]-N,N-dimethyl-hydrazine (222)

A solution of ketone 221 (2.5 g, 7.13 mmol, 100 mol-%) in freshly distilled toluene (10 mL) was treated with 1,1-dimethylhydrazine (2.2 mL, 28.5 mmol, 400 mol-%) and p-TsOH (68 mg, 0.36 mmol, 5 mol-%). The reaction was refluxed under Dean – Stark conditions (trap volume 2 mL) for 20 h then further 1,1-dimethylhydrazine (2.2 mL, 28.5 mmol, 400 mol-%) added. The reaction was allowed to reflux for further 27 h, cooled to RT and the organic phase was washed once with 30 mL of H₂O and once with 10 mL of brine. The combined aqueous phases were extracted with 3x20 mL of Et₂O and the combined organic phases were dried (MgSO₄). The crude product was purified by column chromatography (5% MTBE/Hexane) to give 222 (1.56 g, 83%) recycled yield: Rₚ (15%) EtOAc/Hexane, UV, ninyhydrin) = 0.36; \(^1\)H NMR (400 MHz, CDCl₃) δ 0.05 (s, (CH₃)₂Si, 6H), 0.90 (s, (CH₂)₃C, 9H), 1.09 (s, C(CH₃)₂H, 3H), 1.15 (s, C(CH₃)₂H, 3H), 1.93 (s, C(N(CH₃)₂)CH₂H, 3H), 2.40 (s, N(CH₂)₂, 6H), 3.65 (m, TBSOCH₂CH₃, CHOBn, 2H), 3.79 (dd, TBSOCH₂CH₃, J 0.9, 9.5 Hz, 1H), 4.77 (d, CH₂Ph, Jₖₗ 11.3 Hz, 1H), 7.24-7.36 (m, ArH, 5H); \(^13\)C NMR (100 MHz, CDCl₃) δ -5.4, -5.3, 13.8, 18.2, 21.6, 23.9, 25.9, 25.9, 45.2, 46.9, 65.3, 74.6, 86.1, 127.1, 127.4, 127.5, 128.1, 128.2, 139.5, 170.6; HRMS (EI⁺) calc. for (M-C₄H₇) C₃H₇N₂O₂Si 377.2624, found 377.2643.

3.1.13 \(N,N\)-Dimethyl-\(N^\prime\)-(1,2,2-trimethyl-propylidene)-hydrazine (225)

A mixture of pinacolone 267 (10 mL, 0.08 mol, 100 mol-%), 1,1-dimethylhydrazine (12.1 mL, 0.16 mol, 200 mol-%) and p-toluenesulfonic acid (1.5 g, 8.0 mmol, 10 mol-%) in
benzene (100 mL) was refluxed under Dean-Stark conditions for 3 h 40 min to remove water. The reaction mixture was washed with 50 mL of water and 50 mL of brine. The combined aqueous phases were extracted with 2×50 mL of Et₂O and the combined organic phases were dried (Na₂SO₄). Solvent was separated by distillation (Tbath) 35-51 °C, bp 23-25 °C and the product was purified (T(bath) 62-80 °C, bp 39-43 °C) by distillation under water pump vacuum. A clear oily product 225 was obtained 5.9 g, 52%: Rₚ (50 % EtOAc/Hexane, UV, ninhydrin) = 0.51; GC, Rₜ (240, 28, 60-220, 8, 270) = 4.19 min (3%), 4.88 min (97%); ¹H NMR (400 MHz, CDCl₃) δ 1.09 (s, (CH₃)₂C, 9H), 1.91 (s, CH₃, 3H), 2.40 (s, N(CH₃)₂, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 12.4, 28.0, 38.1, 46.9, 172.3.

3.1.14  N-Methoxy-N-methyl-isobutyramide (226)

\[
\begin{align*}
268 & \rightarrow \quad \text{Cl} & \quad \text{O} & \quad \text{N} & \quad \text{OMe} \\
\text{Cl} & \quad \text{O} & \quad \text{N} & \quad \text{OMe} \\
226 & \quad \text{Cl} & \quad \text{O} & \quad \text{N} & \quad \text{OMe}
\end{align*}
\]

N,O-Dimethyl hydroxylamine hydrochloride (4.95 g, 51 mmol, 110 mol%) and isobutyric acid chloride 268 (5.0 mL, 46 mmol, 100 mol%) were dissolved in 70 mL of chloroform. The mixture was stirred for 45 min at RT, cooled to 0°C and pyridine (8.2 mL, 0.1 mol, 220 mol%) added dropwise over 5 min. After addition the reaction mixture was allowed to warm to RT and washed with 2×50 mL of 0.5 M H₂PO₄ and 2×50 mL of sat. NaHCO₃. The organic phase was dried with Na₂SO₄ and the solvent removed by distillation (61-62°C at normal pressure). The product 226 was purified by distillation (60 °C, water pump vacuum) affording 4.9 g, 81% as a clear oil: Rₜ (50 % EtOAc/Hexane, UV) = 0.35; GC, Rₜ (240, 28, 60-220, 8, 270) = 7.93 min; ¹H NMR (400 MHz, CDCl₃) δ 1.13 (d, (CH₃)₂CH, J 6.8 Hz, 6H), 2.97 (br, (CH₃)₂CH, 1H), 3.19 (s, CH₃N, 3H), 3.70 (s, CH₃O, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 19.0, 29.7, 32.2, 61.3, 178.4.

3.1.14  N-Methoxy-N-methyl-isobutyramide (226)

\[
\begin{align*}
\text{Cl} & \quad \text{O} & \quad \text{N} & \quad \text{OMe} \\
268 & \rightarrow \quad \text{Cl} & \quad \text{O} & \quad \text{N} & \quad \text{OMe} \\
226 & \quad \text{Cl} & \quad \text{O} & \quad \text{N} & \quad \text{OMe}
\end{align*}
\]

N,O-Dimethyl hydroxylamine hydrochloride (4.95 g, 51 mmol, 110 mol%) and isobutyric acid chloride 268 (5.0 mL, 46 mmol, 100 mol%) were dissolved in 70 mL of chloroform. The mixture was stirred for 45 min at RT, cooled to 0°C and pyridine (8.2 mL, 0.1 mol, 220 mol%) added dropwise over 5 min. After addition the reaction mixture was allowed to warm to RT and washed with 2×50 mL of 0.5 M H₂PO₄ and 2×50 mL of sat. NaHCO₃. The organic phase was dried with Na₂SO₄ and the solvent removed by distillation (61-62°C at normal pressure). The product 226 was purified by distillation (60 °C, water pump vacuum) affording 4.9 g, 81% as a clear oil: Rₜ (50 % EtOAc/Hexane, UV) = 0.35; GC, Rₜ (240, 28, 60-220, 8, 270) = 7.93 min; ¹H NMR (400 MHz, CDCl₃) δ 1.13 (d, (CH₃)₂CH, J 6.8 Hz, 6H), 2.97 (br, (CH₃)₂CH, 1H), 3.19 (s, CH₃N, 3H), 3.70 (s, CH₃O, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 19.0, 29.7, 32.2, 61.3, 178.4.
3.1.15 5-(N,N-Dimethyl-hydrazino)-6,6-dimethyl-2-methyl-hept-4-en-3-one

(228)

To a solution of N,N-Dimethyl-N’-(1,2,2-trimethyl-propylidene)-hydrazine 225 (0.5 g, 3.52 mmol, 100 mol-%) in freshly distilled THF 10 mL at −78 °C was added n-BuLi (2.5 M in Hexanes, 1.55 mL, 3.87 mmol, 110 mol-%) dropwise. The reaction mixture was stirred for 45 min at −78 °C then warmed to 0°C. This mixture was added dropwise via cannula to a solution of N-Methoxy-N-methyl-isobutyramide 226 (0.69 g, 5.27, 150 mol-%) in 10 mL of freshly distilled THF at −78 °C. The reaction stirred for 3.5 h at −78 °C and quenched with 20 mL of sat. NH₄Cl. The phases were separated, the aqueous phase washed with 3×20 mL of CH₂Cl₂ and the combined organic phases washed with brine. The organic was dried with MgSO₄ and the solvent evaporated in vacuo. The crude product 228 (0.85 g, 83%, based on GC): Rf (50% EtOAc/Hexane, UV, ninhydrin) = 0.44; Rf (GC, Inj. 240 °C, vel. 28, 60-220 °C 8 °C/min, Det. 270°C) = 12.78 min; ¹H NMR (400 MHz, CDCl₃) δ 1.09 (d, CH(CH₃)₃, J 7.0 Hz, 6H), 1.13 (s, C(CH₃)₃, 9H), 2.26 (s, N(CH₃)₂, 6H), 2.48 (q, CH₂CH₃, J 6.9 Hz, 1H), 3.16 (s, C(NH(NMe)₂)CH₂C(O), 2H); ¹³C NMR (100 MHz, CDCl₃) δ 18.6, 27.4, 37.7, 39.8, 45.1, 87.5, 176.1, 204.7.

3.1.16 (S)-4-Benzyl-3-((2S,3R)-5-benzyloxy-3-hydroxy-2-methylpentanoyl)-2-oxazolidinone (216)

i) Bu₂BOTf, Et₂N
ii) 269

3.1.16 (S)-4-Benzyl-3-((2S,3R)-5-benzyloxy-3-hydroxy-2-methylpentanoyl)-2-oxazolidinone (216)

To a solution of N,N-Dimethyl-N’-(1,2,2-trimethyl-propylidene)-hydrazine 225 (0.5 g, 3.52 mmol, 100 mol-%) in freshly distilled THF 10 mL at −78 °C was added n-BuLi (2.5 M in Hexanes, 1.55 mL, 3.87 mmol, 110 mol-%) dropwise. The reaction mixture was stirred for 45 min at −78 °C then warmed to 0°C. This mixture was added dropwise via cannula to a solution of N-Methoxy-N-methyl-isobutyramide 226 (0.69 g, 5.27, 150 mol-%) in 10 mL of freshly distilled THF at −78 °C. The reaction stirred for 3.5 h at −78 °C and quenched with 20 mL of sat. NH₄Cl. The phases were separated, the aqueous phase washed with 3×20 mL of CH₂Cl₂ and the combined organic phases washed with brine. The organic was dried with MgSO₄ and the solvent evaporated in vacuo. The crude product 228 (0.85 g, 83%, based on GC): Rf (50% EtOAc/Hexane, UV, ninhydrin) = 0.44; Rf (GC, Inj. 240 °C, vel. 28, 60-220 °C 8 °C/min, Det. 270°C) = 12.78 min; ¹H NMR (400 MHz, CDCl₃) δ 1.09 (d, CH(CH₃)₃, J 7.0 Hz, 6H), 1.13 (s, C(CH₃)₃, 9H), 2.26 (s, N(CH₃)₂, 6H), 2.48 (q, CH₂CH₃, J 6.9 Hz, 1H), 3.16 (s, C(NH(NMe)₂)CH₂C(O), 2H); ¹³C NMR (100 MHz, CDCl₃) δ 18.6, 27.4, 37.7, 39.8, 45.1, 87.5, 176.1, 204.7.
(S)-4-Benzyl-3-propionyl-2-oxazolidinone 215 (6.1 g, 25.7 mmol, 100 mol-%) was dissolved in 100 mL of dry CH₂Cl₂ and cooled to 0 °C before dibutylboron triflate (1 M in CH₂Cl₂, 41.2 mL, 41.2 mmol, 160 mol-%) was added dropwise keeping the internal temperature below 2 °C. The color changed from colorless to dark red-brown but when Et₂N (6.23 mL, 44.7 mmol, 174 mol-%) was added (T ≤ 2 °C) the reaction turned yellow. After 40 min, the reaction mixture was cooled to −77 °C and 3-phenylalcohol (269) (6.2 g, 37.8 mmol, 147 mol-%) in 10 mL CH₂Cl₂ was added slowly (45 min) keeping the internal temperature stable. Stirring was continued for a further 3 h at −77 °C and then for 30 min at 0 °C. Phosphate buffer (80 mL, pH 7.0) and methanol (60 mL) were added and the mixture cooled to −10 °C before slow (15 min) addition of 120 mL of (1:1) H₂O₂ (30%) and MeOH. The mixture was then stirred for 30 min at 0 °C, the organic solvents evaporated in vacuo, Et₂O added and the reaction cooled to 0 °C. Sat. Na₂S₂O₇ (120 mL) was added (slowly) (30 min) and the phases separated. The aqueous phase was extracted 3×80 mL of Et₂O and the combined organic phases washed with 80 mL of sat. NaHCO₃, 50 mL of brine and dried with Na₂SO₄. The crude product was purified by flash column chromatography (25% EtOAc/Hexane) to afford pure 216 (9.7 g, 71%). R₉ (50% EtOAc/Hexane, UV/PMA) = 0.31; [α]D⁰ = +44.7 (c 1.0; CHCl₃); IR (KBr, film) 1111, 1694, 1780, 3480 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.28 (d, CH₃CH, J 7.0 Hz, 3H), 1.74 (m, CH₃(CH₂)₂O, 1H), 1.89 (m, CH₃(CH₂)₂O, 1H), 2.78 (dd, CH₃(CH₂)₂Ph, J 13.2, 9.5 Hz, 1H), 3.26 (dd, CH₃(CH₂)₂Ph, J 13.5, 3.3 Hz, 1H), 3.29 (d, OCH, J 2.6 Hz, 1H), 3.69 (m, CH₃O, 2H), 3.82 (dq, CH₃CH, J 7.0, 3.7 Hz, 1H), 4.18 (m, CHOH, 1H), 4.19 (m, OCH₂CH(Bn)N, 2H), 4.52 (s, OCH₂Ph, 2H), 4.68 (m, OCH₂CH(Bn)N, 1H), 7.34-7.19 (m, ArH, ArH, 10H); ¹³C NMR (100 MHz, CDCl₃) δ 11.1, 33.7, 37.8, 42.6, 55.2, 66.1, 68.4, 70.4, 73.3, 127.4, 127.7, 128.4, 129.0, 129.4, 135.1, 138.0, 153.1, 176.7; HRMS (EI⁺) calc. for C₂₃H₂₃NO₃ 397.1889, found 397.1880.

(S)-4-Benzyl-3-propionyl-2-oxazolidinone 215 (6.1 g, 25.7 mmol, 100 mol-%) was dissolved in 100 mL of dry CH₂Cl₂ and cooled to 0 °C before dibutylboron triflate (1 M in CH₂Cl₂, 41.2 mL, 41.2 mmol, 160 mol-%) was added dropwise keeping the internal temperature below 2 °C. The color changed from colorless to dark red-brown but when Et₂N (6.23 mL, 44.7 mmol, 174 mol-%) was added (T ≤ 2 °C) the reaction turned yellow. After 40 min, the reaction mixture was cooled to −77 °C and 3-phenylalcohol (269) (6.2 g, 37.8 mmol, 147 mol-%) in 10 mL CH₂Cl₂ was added slowly (45 min) keeping the internal temperature stable. Stirring was continued for a further 3 h at −77 °C and then for 30 min at 0 °C. Phosphate buffer (80 mL, pH 7.0) and methanol (60 mL) were added and the mixture cooled to −10 °C before slow (15 min) addition of 120 mL of (1:1) H₂O₂ (30%) and MeOH. The mixture was then stirred for 30 min at 0 °C, the organic solvents evaporated in vacuo, Et₂O added and the reaction cooled to 0 °C. Sat. Na₂S₂O₇ (120 mL) was added (slowly) (30 min) and the phases separated. The aqueous phase was extracted 3×80 mL of Et₂O and the combined organic phases washed with 80 mL of sat. NaHCO₃, 50 mL of brine and dried with Na₂SO₄. The crude product was purified by flash column chromatography (25% EtOAc/Hexane) to afford pure 216 (9.7 g, 71%). R₉ (50% EtOAc/Hexane, UV/PMA) = 0.31; [α]D⁰ = +44.7 (c 1.0; CHCl₃); IR (KBr, film) 1111, 1694, 1780, 3480 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.28 (d, CH₃CH, J 7.0 Hz, 3H), 1.74 (m, CH₃(CH₂)₂O, 1H), 1.89 (m, CH₃(CH₂)₂O, 1H), 2.78 (dd, CH₃(CH₂)₂Ph, J 13.2, 9.5 Hz, 1H), 3.26 (dd, CH₃(CH₂)₂Ph, J 13.5, 3.3 Hz, 1H), 3.29 (d, OCH, J 2.6 Hz, 1H), 3.69 (m, CH₃O, 2H), 3.82 (dq, CH₃CH, J 7.0, 3.7 Hz, 1H), 4.18 (m, CHOH, 1H), 4.19 (m, OCH₂CH(Bn)N, 2H), 4.52 (s, OCH₂Ph, 2H), 4.68 (m, OCH₂CH(Bn)N, 1H), 7.34-7.19 (m, ArH, ArH, 10H); ¹³C NMR (100 MHz, CDCl₃) δ 11.1, 33.7, 37.8, 42.6, 55.2, 66.1, 68.4, 70.4, 73.3, 127.4, 127.7, 128.4, 129.0, 129.4, 135.1, 138.0, 153.1, 176.7; HRMS (EI⁺) calc. for C₂₃H₂₃NO₃ 397.1889, found 397.1880.
(S)-4-Benzyl-3-((2S,3R)-5-benzyloxy-3-(tert-butylidimethylsilyloxy)-2-methyl-pentanoyl)-2-oxazolidinone (235)

\[ \text{Bn} \xrightarrow{\text{O}} \text{OBn} \]

**216** (0.5 g, 1.26 mmol, 100 mol-%) in 10 mL of freshly distilled CH$_2$Cl$_2$ at 0 °C was treated with Lutidine (0.58 mL, 2.8 mmol, 220 mol-%), stirred for 5 min and TBSOTf (0.32 mL, 2.5 mmol, 200 mol-%) added dropwise. After 13 min the reaction was quenched with 10 mL of sat. K$_2$CO$_3$ and the aqueous phase extracted with 4×10 mL of Et$_2$O. The combined organic phases were washed with 3×10 mL of 0.5 M H$_3$PO$_4$ and dried with Na$_2$SO$_4$. The crude was purified by column chromatography (10% EtOAc/Hexane, UV, acid-PMA) = 0.64; mp 87.5-89.5 °C; [α]$_D^{20}$ = -5.9 (c 0.1; CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 0.05 (s, CH$_3$Si, 3H), 0.06 (s, CH$_3$Si, 3H), 0.88 (s, CH$_3$C, 3H), 0.89 (s, CH$_3$C, 3H), 0.90 (s, CH$_3$C, 3H), 1.26 (d, CH$_3$CH, J 7.0 Hz, 3H), 1.93 (m, CH$_2$CH$_2$OBn, 2H), 2.75 (dd, CH$_3$H$_2$Ph, J 13.4, 9.7 Hz, 1H), 3.24 (dd, CH$_3$H$_2$Ph, J 13.4, 3.1 Hz, 1H), 3.53 (dd, CH$_3$H$_2$OBn, J 9.2, 6.4, 5.9 Hz, 1H), 3.64 (dd, CH$_3$H$_2$OBn, J 9.3, 6.5, 6.1 Hz, 1H), 3.80 (dd, OCH$_3$CH$_2$CH(Bn)N, J 9.0, 7.7 Hz, 1H), 3.91 (q, CH$_2$CH$_3$, J 6.9 Hz, 1H), 4.05 (dd, OCH$_3$CH$_2$CH(Bn)N, J 9.0, 2.2 Hz, 1H), 4.14 (dd, CH$_3$TBS, J 6.5, 5.1 Hz, 1H), 4.47 (d, CH$_3$Ph, J$_{ab}$ 11.8 Hz, 2H), 4.53 (ddddd, OCH$_3$CH$_2$CH(Bn)N, J 9.6, 7.6, 3.2, 2.2 Hz, 1H), 7.34-7.19 (m, ArH, ArH, 10H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 48.4, 44.4, 13.6, 18.0, 25.8, 35.1, 37.7, 43.1, 55.4, 65.8, 66.3, 71.0, 72.9, 127.3, 127.4, 127.6, 128.3, 128.9, 129.4, 135.4, 138.6, 152.9, 175.5; HRMS (EI) calc. for C$_2$H$_{14}$NO$_2$NaSi 534.2652, found 534.2665.
3.1.18 (2S,3R)-5-(Benzyloxy)-3-(tert-butyldimethylsilyloxy)-2-methylpentanoic acid (236)

![Chemical Structure](image)

(S)-4-Benzyl-3-(2S,3R)-5-benzyloxy-3-(tert-butyldimethylsilyloxy)-2-methylpentanoyl)-2-oxazolidinone 235 (0.1 g, 0.20 mmol, 100 mol-%) in 5.3 mL of p.a. THF at 0 °C was treated with 30% H₂O₂ (54 µl, 0.53 mmol, 270 mol-%) and 0.2 M LiOH (2.0 mL, 0.40 mmol 200 mol-%). After 3 h the reaction warmed to RT, stirred over the weekend (70 h) and quenched with 3.3 mL of 1.5 M Na₂SO₃. The aqueous phase was washed with 2*10 mL of Et₂O, the pH adjusted to 2 with 13 mL of 0.5 M H₂PO₄ and the aqueous further extracted with 4*10 mL of Et₂O. The combined organic phases were dried over MgSO₄ and concentrated in vacuo. The crude was purified by step gradient column chromatography (30%, 40%, 50% in 100 mL portions, EtOAc/Hexane) to afford 236 60 mg, 88%: Rₐ (50% EtOAc/Hexane, UV, acid-PMA) = 0.51; [α]D²⁰ = +2.6 (c 1.0; CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.06 (s, CH₃Si, 3H), 0.07 (s, CH₂Si, 3H), 0.87 (s, CH₃, 3H), 0.87 (s, CH₂C, 3H), 0.88 (s, CH₂C, 3H), 1.14 (d, CH₃CH, J 7.1 Hz, 3H), 1.83 (m, CH₂CH₂OBN, 2H), 2.62 (qd, CHCH₃, J 4.8, 6.8 Hz, 1H), 3.54 (t, CH₂OBn, J 6.3 Hz, 2H), 4.20 (td, CHOTBS, J 4.9, 6.7 Hz, 1H), 4.49 (dd, CH₂Ph, J 11.9, 20.3 Hz, 2H), 7.25-7.34 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ -4.8, -4.7, 11.2, 18.0, 25.7, 34.2, 44.9, 66.3, 70.8, 73.0, 127.6, 127.6, 128.4, 138.2, 179.2; HRMS (EI) calc. for C₁₀H₁₂O₂NaSi 375.1968, found 375.1977.

3.1.19 Isoxazolidine hydrochloride salt (232)

![Chemical Structure](image)

3.1.19 Isoxazolidine hydrochloride salt (232)

![Chemical Structure](image)
A solution of hydroxylamine hydrochloride (11.4 g, 0.16 mol, 100 mol-%) and 1,3-dibromopropane 231 (33.1 g, 0.16 mol, 100 mol-%) in 95% EtOH (150 mL) at 65°C was treated dropwise over 45 min with a solution of KOH (30.4 g, 0.54 mol, 340 mol-%) in EtOH (150 mL). The reaction mixture was stirred for 90 min, cooled to 36°C, filtered and the solvent evaporated under reduced pressure. The oily crude product was distilled under water pump vacuum (bp 25-45°C). The product cooled with an ice bath and sat. HCl in EtO added slowly. The solvent was evaporated to leave a white solid. Recrystallization from EtOH-THF gave isoxazolidine hydrochloride 232 as slightly off-white crystals 4.54 g (26 %): mp 121°C (lit. 57 124-125°C); 1H NMR (400 MHz, CDCl3) δ 2.17 (q, CH3CH2CH3, J 7.3 Hz, 2H), 3.14 (s, CH2CH2CH2N, 2H), 3.84 (s, OCH2CH2CH3, 2H); 13C NMR (100 MHz, CDCl3) δ 29.6, 48.3, 69.3.

3.1.20 (2S,3R)-5-(Benzyl)-3-hydroxy-1-isoxazolidin-2-yl-methyl-pentan-1-one (233)

![Chemical Structure](image)

To a solution of isoxazolidine hydrochloride salt 232 (0.31 g, 2.8 mmol, 220 mol-%) in 4 mL THF at –15°C was added dropwise trimethylaluminium (1.3 mL, 2.6 mmol, 210 mol-%, 2 M in Hex). The reaction was stirred 10 min at –10°C and 30 min at RT before it was cooled back to –10°C and solution of oxazolidinone 216 (0.50 g, 1.26 mmol, 100 mol-%) in 9 mL of THF/CH2Cl2 (5:4) was added dropwise over 9 min. The reaction was stirred for 2 h 15 min in which time cooling bath was allowec to warm slowly to RT. The reaction mixture was cooled again to 0°C poured into an ice-cooled beaker containing 10 mL CH2Cl2 and 10 mL aqueous 0.5 M HCl and stirred for 1 h 15 min at 0°C. The phases were separated and the aqueous phase washed with 3×20 mL of CH2Cl2. The combined organic phases were washed with 20 mL of brine and dried with MgSO4. The solvent was evaporated and the crude purified by column chromatography (50% EtOAc/Hexane to separate Evan’s ligand and finally EtOAc) to give 233 359 mg (97 %): Rf (50 %)
EtOAc/Hexane, UV, acid-PMA = 0.06; [α]D20 = +0.2 (c 1.0; CHCl3); 1H NMR (400 MHz, CDCl3) δ 1.19 (d, CH3CH, J 7.3 Hz, 3H), 1.68-1.89 (m, CH3(CH2)OBn, 2H), 2.33 (td, OCH3-CH2CH2N, J 6.9, 14.9 Hz, 2H), 2.92 (br s, CH2CH2, 1H), 3.66 (t, OCH3-CH2CH2N, J 5.9 Hz, 2H), 3.68-3.73 (m, CH2OBn, 2H), 3.85 (br s, OH, 1H), 3.98 (t, OCH3-CH2CH2N, J 6.8 Hz, 2H), 3.96-4.11 (m, CHOH, 1H), 4.52 (s, CH3Ph, 2H), 7.26-7.33 (m, ArH, 5H); 13C NMR (100 MHz, CDCl3) δ 10.7, 27.3, 33.9, 40.5, 42.7, 68.2, 69.4, 69.8, 73.2, 127.6, 127.6, 128.4, 138.3, 171.7; HRMS (EI) calc. for C15H23NO3Na 316.1525, found 316.1545.

3.1.21 (2S,3R)-5-(Benzylxoy)-3-(tert-butyldimethylsilanyloxy)-1-oxazolidin-2-yl-2-methyl-pentan-1-one (234)

![Diagram]

To a solution of alcohol 233 (0.30 g, 1.02 mmol, 100 mol-%) in 10 mL of freshly distilled CH2Cl2 at 0°C was added 2,6-lutidine (0.26 mL, 2.25 mmol, 200 mol-%). After 5 min TBSOTf (0.47 mL, 2.05 mmol, 200 mol-%) was added dropwise and the reaction stirred for 12 min at 0°C prior to quenching with 10 mL of sat. K2CO3. The phases were separated and the aqueous extracted with 4 x 10 mL of Et2O. The combined organic phases were washed with 3 x 10 mL 0.5 M H3PO4 and dried with Na2SO4 and the solvent was removed in vacuo. The crude was purified by column chromatography (30% EtOAc/Hexane) to afford 234 394 mg, 94 % as a yellow / orange solid: Rf (50 % EtOAc/Hexane, UV, acid-PMA) = 0.27; [α]D20 = -0.3 (c 1.0; CHCl3); 1H NMR (400 MHz, CDCl3) δ 0.04 (s, CH3Si, 3H), 0.05 (s, CH3Si, 3H), 0.86 (s, CH2C, 3H), 0.87 (s, CH2C, 3H), 0.88 (s, CH2C, 3H), 1.12 (d, CH2CH, J 7.0 Hz, 3H), 1.88 (td, CH3(CH2)OBn, J 7.0, 5.1 Hz, 2H), 2.24 (m, OCH3(CH2)CH2N, 2H), 3.01 (br s, CH2CH2, 1H), 3.57 (t, CH2OBn, J 7.0 Hz, 2H), 3.61 (td, OCH3-CH2CH2H, J 10.8, 7.6 Hz, 1H), 3.76 (td, OCH3-CH2CH2H, J 10.6, 7.5 Hz, 1H), 3.86 (m, OCH3-CH2CH2N, 2H), 4.09 (td, CHOTBS, J 7.1, 5.0 Hz, 1H), 4.48 (d, CH3Ph, J 11.9 Hz, 2H), 7.25-7.33 (m, ArH, 5H);
A 25 mL 2-neck flask was charged with \(N,O\)-Dimethyl hydroxylamine hydrochloride (1.08 g, 11.1 mmol, 220 mol-%) and 4 mL THF. The suspension was cooled to \(-10^\circ\)C (NaCl/ice) and \(\text{AlMe}_3\) (5.3 mL, 10.6 mmol, 210 mol-%) was added over 5 min. After 12 min, the cooling bath was removed and the reaction mixture was allowed to stir for 1 h at RT before it was cooled again to \(-10^\circ\)C. A solution of oxazolidinone \(216\) (2.0 g, 5.0 mmol, 100 mol-%) in a mixture (4:5) of \(\text{CH}_2\text{Cl}_2\) (2.9 mL) and THF (3.5 mL) was slowly added, the mixture stirred for 1 h at 0°C and then poured into a mixture (32 mL) of (1:1) HCl [0.5 M] and \(\text{CH}_2\text{Cl}_2\) at 0°C. The mixture was stirred for 1 h 15 min at 0°C and the phases separated. The aqueous phase was extracted with 3\(^\times\)60 mL of \(\text{CH}_2\text{Cl}_2\) and the combined organic phases were washed with 50 mL of brine and dried with MgSO\(_4\). The crude product was purified by step gradient column chromatography (1:3, 2:5:1:1 and 1:5 EtoAc / Hexane in 900 mL fractions) to afford 217 as a light yellow oil (1.16 g, 82%). \(R_t\) (50% EtoAc/Hexane, UV/PMA) = 0.12; \([\alpha]_D^{20} = +11.4\) (c 1.0; CHCl\(_3\)); IR (\(\nu_{\text{max}}\) m, film) 1102, 1637, 3468 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.20 (d, \(\text{CH}_2\text{CH}, J 7.3\) Hz, 3H), 1.89-1.66 (m, \(\text{CH}_2\text{CH}_2\text{OBn}, 2\)H), 2.93 (br s, \(\text{CHCH}_2\text{H}, 1\)H), 3.18 (s, N\(\text{CH}_3\), 3H), 3.63-3.73 (m, \(\text{CH}_2\text{OBn}, 2\)H), 3.66 (s, \(\text{CH}_3\text{O}, 3\)H), 3.92 (s, \(\text{OH}, 1\)H), 4.05 (m, \(\text{CHOH}, 1\)H), 4.52 (s, \(\text{CH}_3\text{Ph}, 2\)H), 7.26-7.34 (m, ArH, 5H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 11.1, 31.9, 34.0, 39.5, 61.5, 68.3, 70.3, 73.2, 127.6, 127.6, 128.4, 138.2, 177.8; HRMS (TOF MS El\(^+\)) calc. for C\(_{25}\)H\(_{32}\)NO\(_4\)Na 304.1525, found 304.1550.
3.1.23 (2S,3R)-5-(Benzoyloxy)-3-(trimethylsilyl oxy)-N-methoxy-N,2-dimethylpentanamide (218)

A solution of the Weinreb amide 217 (513 mg, 1.82 mmol, 100 mol-%) in 15 mL of dry CH₂Cl₂ at 0°C was treated dropwise over 10 min with 2,6-lutidine (0.43 mL, 3.65 mmol, 200 mol-%), the mixture stirred for 10 min then TMSOTf (0.50 mL, 2.74 mmol, 150 mol-%) added dropwise over 17 min. The reaction was quenched after 7 min by addition of 10 mL of sat K₂CO₃, 20 mL of [0.5 M] phosphate buffer (pH = 7.0) added, the mixture stirred for 40 min and the phases separated. The aqueous phase was extracted with 3 x 20 mL of CH₂Cl₂, the combined organics washed with 20 mL of brine and the organics dried with MgSO₄. Residual lutidine was removed under high vacuum to afford product 218 409 mg, 64%. Rₑ (50% EtOAc/Hexane, UV / acid-PMA) = 0.39; [α]₀²⁰ = +0.1 (c 1.0; CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.11 (s, (CH₃)₅Si, 9H), 1.15 (d, CH₂CH, J 7.0 Hz, 3H), 1.66-1.90 (m, CH₂CH₂OBn, 2H), 2.97 (br s, CHCH₂, 1H), 3.15 (s, NCH₂, 3H), 3.49-3.59 (m, CH₂O, 2H), 3.61 (s, CH₃O, 3H), 4.02 (td, CHOTMS, J 3.6, 7.7 Hz, 1H), 4.48 (d, CH₂Ph, J 1.8 Hz, 2H), 7.26-7.36 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 0.4, 14.6, 32.0, 35.6, 41.8, 61.3, 66.9, 71.7, 72.8, 127.3, 127.4, 127.7, 128.3, 128.9, 138.5, 176.2; HRMS (EI⁺) calc. for C₁₈H₃₅NO₂NaSi 376.1920, found 376.1916.

3.1.24 (2S,3R)-5-(Benzoyloxy)-3-(triethylsilyl oxy)-N-methoxy-N,2-dimethylpentanamide (219)

85

3.1.24 (2S,3R)-5-(Benzoyloxy)-3-(triethylsilyl oxy)-N-methoxy-N,2-dimethylpentanamide (219)

85
A solution of the Weinreb amide 217 (112 mg, 0.40 mmol, 100 mol-%) and 2,6-lutidine (0.61 g, 8.89 mmol, 500 mol-%) in dry CH₂Cl₂ (5 mL) at 0°C was treated dropwise with TESOTf (114 μL, 0.60 mmol, 150 mol-%). After 10 min the reaction was allowed to warm to RT, stirred for 40 min, then re-cooled to 0°C and quenched with 5 mL of sat. K₂CO₃. The phases were separated, the aqueous phase extracted with 3 * 8 mL of Et₂O and the combined organic phases washed with 10 mL of [1M] HCl, 10 mL of brine and dried with MgSO₄. Solvent was evaporated in vacuo and the crude product 219 was obtained 0.14 g, (88%) used without further purification. Rf (50% EtOAc/Hexane, UV / acid-PMA) = 0.48; [α]D²⁰ = +0.5 (c 1.0; CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.61 (q, Si(CH₂CH₃), J 8.2 Hz, 6H), 0.61 (t, Si(CH₂CH₃), J 8.1 Hz, 9H), 1.15 (d, CH₂CH₃, J 7.0 Hz, 3H), 1.78-1.88 (m, CH₂CH₂OCH₂, 2H), 2.97 (br s, CH₂CH₃, 1H), 3.13 (s, CH₃N, 3H), 3.52-3.57 (m, CH₂OBn, 2H), 3.58 (s, CH₂O, 3H), 4.05 (td, CHOTES, J 5.1, 8.1 Hz, 1H), 4.48 (d, CH₂Ph, J 1.5 Hz, 2H), 7.24-7.33 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 50.6, 6.3, 6.7, 6.9, 14.4, 32.0, 35.7, 41.5, 61.2, 66.6, 71.6, 72.8, 127.4, 127.6, 128.2, 138.5, 176.2; HRMS (EI) calc. for C₂₃H₂₁NO₅Na₂Si 418.2390, found 418.2381.

3.1.25 (2S,3R)-5-(Benzyloxy)-3-(tert-butyldimethylsilyloxy)-N-methoxy-N₂,N₂-dimethylpentanamide (223)

A solution of alcohol 217 (0.50 g, 1.78 mmol, 100 mol-%) and imidazole (0.61 g, 8.89 mmol, 500 mol-%) were dissolved in 5 mL of dry DMF at 0°C were treated dropwise over 10 min with TBSCI (0.54 g, 3.55 mmol, 200 mol-%) in 5 mL DMF. The reaction was allowed warm to RT, stirred for 43 h, quenched with 20 mL of Et₂O and 20 mL of brine and stirred for 30 min. The phases were separated and the aqueous phase washed with 3 *20 mL of Et₂O. The combined organic phases were dried over MgSO₄. The crude product was purified by column chromatography (5% MTBE/Hex) affording the product 223 (0.48 g, 68%). Rf (50% EtOAc/Hexane, UV/PMA) = 0.46; [α]D²⁰ = -2.4 (c 1.0;
A solution of lactol 241 (0.214 g, 0.963 mmol, 100 mol-%) in 10 mL of dry MeOH was treated with dimethyl 1-diazo-2-oxopropyl phosphonate I (0.370 g, 1.925 mmol, 200 mol-%) and K$_2$CO$_3$ (0.266 g, 1.925 mmol, 200 mol-%). The reaction mixture was warmed to 36 °C and allowed to stir for five days, during which further phosphonate I (0.092 g, 0.481 mmol, 50 mol-%) and K$_2$CO$_3$ (0.067 g, 0.481 mmol, 50 mol-%) in 0.5 mL of dry MeOH were added once per day. The blue-green reaction mixture was evaporated to dryness and partitioned between 30 mL of 1:1 mixture of Et$_2$O and H$_2$O. The phases were separated and the aqueous extracted four times with 10 mL of Et$_2$O and the organics dried with MgSO$_4$. Solvent was evaporated in vacuo and the crude 240 was purified by column chromatography (15% EtOAc/Hexane) to afford 240 0.122 g (58%) of a slightly yellow oil. R$_f$ (50% EtOAc/Hexane, UV/anisaldehyde) = 0.50; IR (v$_{max}$, film) 1096, 1382, 2254, 3306, 3690 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.27 (s, CH$_3$, 3H), 1.30 (s, CH$_3$, 3H), 1.86 (dd, J$_{HH}$, 7.3, 5.3 Hz, 1H), 2.19 (s, CH$_3$COCH$_3$, 1H), 3.40 (dd, CH$_2$OBn, J 6.6, 3.8 Hz, 1H), 3.77 (ddd, CH$_2$H$_2$OH, J 11.9, 6.6, 5.3 Hz, 1H), 3.92 (ddd, CH$_2$H$_2$OH, J 11.7, 7.5 Hz, 3.9 Hz, 1H), 4.72 (d, CH$_2$H$_2$Ph, J$_{AB}$ 11.5 Hz, 1H), 4.78 (d, CH$_2$H$_2$Ph, J$_{AB}$ 11.5 Hz, 1H), 7.29-7.38 (m, ArH, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 24.7, 26.7, 34.7, 62.6, 69.8, 74.7, 85.6, 89.7, 127.8, 127.9, 128.5, 138.3; HRMS (TOF MS El$^+$) calc. for C$_{13}$H$_{24}$O$_2$NaSi 241.1204, found 241.1216.

A solution of lactol 241 (0.214 g, 0.963 mmol, 100 mol-%) in 10 mL of dry MeOH was treated with dimethyl 1-diazo-2-oxopropyl phosphonate I (0.370 g, 1.925 mmol, 200 mol-%) and K$_2$CO$_3$ (0.266 g, 1.925 mmol, 200 mol-%). The reaction mixture was warmed to 36 °C and allowed to stir for five days, during which further phosphonate I (0.092 g, 0.481 mmol, 50 mol-%) and K$_2$CO$_3$ (0.067 g, 0.481 mmol, 50 mol-%) in 0.5 mL of dry MeOH were added once per day. The blue-green reaction mixture was evaporated to dryness and partitioned between 30 mL of 1:1 mixture of Et$_2$O and H$_2$O. The phases were separated and the aqueous extracted four times with 10 mL of Et$_2$O and the organics dried with MgSO$_4$. Solvent was evaporated in vacuo and the crude 240 was purified by column chromatography (15% EtOAc/Hexane) to afford 240 0.122 g (58%) of a slightly yellow oil. R$_f$ (50% EtOAc/Hexane, UV/anisaldehyde) = 0.50; IR (v$_{max}$, film) 1096, 1382, 2254, 3306, 3690 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ .27 (s, CH$_3$, 3H), 1.30 (s, CH$_3$, 3H), 1.86 (dd, J$_{HH}$, 7.3, 5.3 Hz, 1H), 2.19 (s, CH$_3$COCH$_3$, 1H), 3.40 (dd, CH$_2$OBn, J 6.6, 3.8 Hz, 1H), 3.77 (ddd, CH$_2$H$_2$OH, J 11.9, 6.6, 5.3 Hz, 1H), 3.92 (ddd, CH$_2$H$_2$OH, J 11.7, 7.5 Hz, 3.9 Hz, 1H), 4.72 (d, CH$_2$H$_2$Ph, J$_{AB}$ 11.5 Hz, 1H), 4.78 (d, CH$_2$H$_2$Ph, J$_{AB}$ 11.5 Hz, 1H), 7.29-7.38 (m, ArH, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 24.7, 26.7, 34.7, 62.6, 69.8, 74.7, 85.6, 89.7, 127.8, 127.9, 128.5, 138.3; HRMS (TOF MS El$^+$) calc. for C$_{13}$H$_{24}$O$_2$NaSi 241.1204, found 241.1216.
A solution of alcohol 240 (0.120 g, 0.550 mmol, 100 mol-%) in dry CH₂Cl₂ (6 mL) at 0 °C was treated with 2,6-Lutidine (0.256 mL, 2.2 mmol, 400 mol-%), the reaction mixture allowed to stir for 36 min and TBSOTf (0.253 mL, 1.1 mmol, 200 mol-%) added. After 12 min the reaction was quenched with 3 mL of sat. K₂CO₃. The mixture was partitioned between water and Et₂O (20 mL, 1:1) and the phases separated. The aqueous phase was extracted three times with 10 mL of Et₂O and the combined organic phases dried with Na₂SO₄. Solvent was evaporated in vacuo and the crude 242 was purified by column chromatography (15% EtOAc/Hexane) to afford pure 242 (0.161 g, 88%) as a slightly yellow oil. Rₖ (50% EtOAc/Hexane, UV/PMA) = 0.67; IR (νmax, film) 839, 1096, 1257, 1383, 2254, 3306, 3690 cm⁻¹; ¹H NMR (400 MHz, CDCl₃)  δ 0.07 (s, CH₃, 3H), 0.08 (s, CH₃, 3H), 0.92 (s, C(CH₃)₃, 9H), 1.20 (s, CH₂, 3H), 1.27 (s, CH₂, 3H), 2.13 (s, C(CH₃)₂CCH, 1H), 3.36 (dd, CH, J 7.3, 2.7 Hz, 1H), 3.80 (dd, OCH₃, J 1.0, 7.3 Hz, 1H), 4.10 (dd, OCH₃, J 10.8, 2.7 Hz, 1H), 4.64 (d, CH₂OCH₂, JAB 11.5 Hz, 1H), 4.92 (d, CH₂OCH₂, JAB 11.5 Hz, 1H), 7.24-7.38 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ -5.4, -5.3, 18.2, 24.4, 25.9, 27.1, 34.7, 65.4, 69.1, 74.5, 86.1, 90.0, 127.3, 127.8, 128.2, 139.0; HRMS (TOF MS EI) calc. for C₂₃H₂₂O₂NaSi 355.2069, found 355.2110. 

A solution of alcohol 240 (0.120 g, 0.550 mmol, 100 mol-%) in dry CH₂Cl₂ (6 mL) at 0 °C was treated with 2,6-Lutidine (0.256 mL, 2.2 mmol, 400 mol-%), the reaction mixture allowed to stir for 36 min and TBSOTf (0.253 mL, 1.1 mmol, 200 mol-%) added. After 12 min the reaction was quenched with 3 mL of sat. K₂CO₃. The mixture was partitioned between water and Et₂O (20 mL, 1:1) and the phases separated. The aqueous phase was extracted three times with 10 mL of Et₂O and the combined organic phases dried with Na₂SO₄. Solvent was evaporated in vacuo and the crude 242 was purified by column chromatography (15% EtOAc/Hexane) to afford pure 242 (0.161 g, 88%) as a slightly yellow oil. Rₖ (50% EtOAc/Hexane, UV/PMA) = 0.67; IR (νmax, film) 839, 1096, 1257, 1383, 2254, 3306, 3690 cm⁻¹; ¹H NMR (400 MHz, CDCl₃)  δ 0.07 (s, CH₃, 3H), 0.08 (s, CH₃, 3H), 0.92 (s, C(CH₃)₃, 9H), 1.20 (s, CH₂, 3H), 1.27 (s, CH₂, 3H), 2.13 (s, C(CH₃)₂CCH, 1H), 3.36 (dd, CH, J 7.3, 2.7 Hz, 1H), 3.80 (dd, OCH₃, J 1.0, 7.3 Hz, 1H), 4.10 (dd, OCH₃, J 10.8, 2.7 Hz, 1H), 4.64 (d, CH₂OCH₂, JAB 11.5 Hz, 1H), 4.92 (d, CH₂OCH₂, JAB 11.5 Hz, 1H), 7.24-7.38 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ -5.4, -5.3, 18.2, 24.4, 25.9, 27.1, 34.7, 65.4, 69.1, 74.5, 86.1, 90.0, 127.3, 127.8, 128.2, 139.0; HRMS (TOF MS EI) calc. for C₂₃H₂₂O₂NaSi 355.2069, found 355.2110. 

3.1.29 (3R,4S,9R,S)-1,9-Bis(benzyloxy)-3,10-di(tert-butylsilyloxy)-4,8,8-trimethyldec-6-yn-5-one (239) 

A solution of alkyn 242 (0.057 g, 0.172 mmol, 200 mol-%) in 1.7 mL of dry THF at −78 °C was treated with BuLi (2.27 M in hexanes, 83 µL, 0.189 mmol, 220 mol-%) and the reaction allowed to stir for 1 h before a solution of Weinreb amide 223 (0.034 g, 0.086 mmol, 100 mol-%) in 0.9 mL of dry THF was added. After 50 min, the reaction mixture was allowed to warm to RT, stirred for another 2 h 15 min then quenched with 5 mL of H₂O. Et₂O (10 mL), H₂O (5 mL) and brine (5 mL) were added and the phases were

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separated. The aqueous phase was extracted three times with 10 mL of Et₂O and the combined organic phases were dried with MgSO₄. The crude product was purified by step gradient chromatography (150 mL 5% EtOAc/Hexane, 150 mL 10% EtOAc/Hexane) to afford 239 (0.045 g, 79%). Rₜ (50% EtOAc/Hexane, UV/PMA) = 0.66; IR (νmax, film) 838, 1095, 1257, 1669, 2208, 2247 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.01 (s, CH(Si)₃, 3H), 0.04 (s, CH₂Si, 3H), 0.06 (s, CH₂Si, 3H), 0.07 (s, CH₂Si, 3H), 0.84 (s, CH(CH₃)₂, 9H), 0.91 (s, CH(CH₃)₂, 9H), 1.13 (d, CH₂CH, 6.9 Hz, 3H), 1.23 (s, CH₂C, 3H), 1.28 (s, CH₂C, 3H), 1.76-1.92 (m, CH(OTBS)CH₂, J 14.0, 6.4 Hz, 2H), 2.53-2.60 (m, CHMe, 1H), 3.38 (dd, CHOBn, J 7.1, 3.0 Hz, 1H), 3.49 (t, CH₂OBn, J 6.5 Hz, 2H), 3.78 (dd, CHCH₂H₂OTBS, J 10.8, 7.1 Hz, 1H), 4.00 (dd, CHCH₂H₂OTBS, J 10.8, 3.3 Hz, 1H), 4.43-4.51 (m, CHOTBS, OCH₂Ph, 3H), 4.61 (dd, CH(OCH₂)₂Ph, J 11.4, 3.6 Hz, 1H), 4.89 (dd, CH(OCH₂)₂Ph, J 11.5 Hz, 1H), 7.25-7.35 (m, ArH, 10H); ¹³C NMR (100 MHz, CDCl₃) δ -5.4, -5.4, -4.5, -4.4, 9.5, 9.6, 18.1, 18.2, 23.9, 24.0, 25.8, 25.9, 26.1, 35.4, 35.7, 53.5, 65.1, 65.1, 66.7, 70.0, 73.0, 74.5, 81.3, 85.5, 85.5, 96.3, 127.4, 127.4, 127.5, 127.7, 127.7, 128.2, 138.3, 138.4, 138.7, 138.8, 190.2; HRMS (TOF MS EI⁺) calc. for C₂₉H₄₄O₂NaSi₂: 689.0434, found: 689.0425.

3.1.30 (7R,8S)-3-Benzoyloxy-7-(2-benzoyloxy-ethyl)-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decan-9-one (243) and (244)

The mixture of yonones 239 (13 mg, 19.5 μmol, 100 mol%-%) was dissolved in 0.5 mL of dry MeOH, and camphor sulphonic acid (0.7 mg, 3.0 μmol, 15 mol%-%) was added. The reaction was allowed to stir at RT for 2 h 20 min before the solvent was evaporated in vacuo. The residue was dissolved in 1 mL benzene and the reaction was stirred for 3 h 30 min, after which time p-TsOH (1.4 mg, 7.4 μmol, 38 mol%-%) was added. Stirring was continued for further 15 h and the reaction quenched by adding TEA (0.02 mL) followed

3.1.30 (7R,8S)-3-Benzoyloxy-7-(2-benzoyloxy-ethyl)-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decan-9-one (243) and (244)

The mixture of yonones 239 (13 mg, 19.5 μmol, 100 mol%-%) was dissolved in 0.5 mL of dry MeOH, and camphor sulphonic acid (0.7 mg, 3.0 μmol, 15 mol%-%) was added. The reaction was allowed to stir at RT for 2 h 20 min before the solvent was evaporated in vacuo. The residue was dissolved in 1 mL benzene and the reaction was stirred for 3 h 30 min, after which time p-TsOH (1.4 mg, 7.4 μmol, 38 mol%-%) was added. Stirring was continued for further 15 h and the reaction quenched by adding TEA (0.02 mL) followed
by 1 mL of sat. NaHCO₃. The phases were separated and the aqueous extracted with 3+3 mL of toluene. The combined organic phases were washed with 5 mL of brine and dried with MgSO₄. The crude product was first purified by step gradient column chromatography (5%, 10%, 15% and 20% EtOAc/Hexane in 50 mL portions) affording the two diastereomers 243 and 244 (8.2 mg, 96%). The diastereomers were separated with HPLC chromatography, which afforded (4.1 mg each).

(Fraction 1) Rₜ (50% EtOAc/Hexane, UV/PMA) = 0.59; Rₜ (Shandon Hypersil 5 μ column, EtOAc/Hexane, 1:20, flow rate 1.0 mL/min, λ = 254 nm) = 30.52 min; [α]D₂₀ = +105 (c 0.1; CHCl₃); IR (νmax, film) 1718 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 0.94 (s, CH₃, 3H), 1.07 (d, CHCH₃, J 7.0 Hz, 3H), 1.16 (s, CH₂, 3H), 1.64-1.72 (m, CH₂CH₂CH₂O, 1H), 1.81-1.90 (m, CH₂CH₂CH₂O, 1H), 2.32 (dd, CH₃CH₂CH₂O, Jₖₜ 14.6 Hz, 1H), 2.33 (qd, CH₃C, J 7.0, 2.6 Hz, 1H), 2.58 (dd, CH₂CH₂CH₂O, Jₖₜ 15.0 Hz, 1H), 3.46-3.54 (m, CH₂CH₂O, 2H), 3.59 (dd, CH₃CH₂CH₂O, J 8.8, 6.7 Hz, 1H), 3.38 (dd, CH₂CH₂CH₂O, J 8.7, 7.8 Hz, 1H), 4.12 (dd, CH₂CH₂O, J 7.7, 6.7 Hz, 1H), 4.24 (td, CH₂CH₂CH₂O, J 9.8, 3.0 Hz, 1H), 4.46 (dd, CH₂CH₂CH₂O, J 9.8, 11.8 Hz, 1H), 4.47 (dd, CH₂CH₂O, J 9.8, 11.9 Hz, 2H), 4.56 (dd, CH₂CH₂CH₂O, J 11.8 Hz, 1H), 7.28-7.35 (m, ArH, ArH, 10H); 13C NMR (100 MHz, CDCl₃) δ 10.5, 17.2, 20.3, 29.7, 40.8, 47.6, 66.9, 67.2, 69.3, 72.9, 73.1, 84.5, 110.0, 127.4, 127.7, 127.8, 128.4, 138.2, 138.4, 209.9; HRMS (TOF MS El) calcd. for C₃₂H₅₃O₃Na 461.2304, found 461.2318.

(Fraction 2) Rₜ (50% EtOAc/Hexane, UV/PMA) = 0.59; Rₜ (Shandon Hypersil 5 μ column, EtOAc/Hexane, 1:20, flow rate 1.0 mL/min, λ = 254 nm) = 35.69 min; [α]D₂₀ = +90 (c 0.1; CHCl₃); IR (νmax, film) 1718 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 0.91 (s, CH₃, 3H), 1.11 (d, CHCH₃, J 7.1 Hz, 3H), 1.25 (s, CH₂, 3H), 1.59-1.67 (m, CH₂CH₂CH₂O, 1H), 1.85-1.94 (m, CH₂CH₂CH₂O, 1H), 2.24 (dd, CH₂CH₂CH₂O, J 14.5, 1.1 Hz, 1H), 2.34 (qd, CH₃C, J 7.2, 2.0 Hz, 1H), 2.60 (d, CH₂CH₂O, J 14.5 Hz, 1H), 3.54-3.67 (m, CH₂O, 2H), 3.61 (dd, CH₂O, J 6.4, 3.1 Hz, 1H), 3.67 (dd, CH₂O, J 9.7, 3.2 Hz, 1H), 4.16 (dd, CH₂O, J 9.7, 6.4 Hz, 1H), 4.28 (td, CH₂CH₂O, J 10.6, 2.5 Hz, 1H), 4.30 (dd, CH₂O, J 12.1 Hz, 2H), 4.49 (dd, CH₂CH₂O, J 11.7, 12.1 Hz, 2H), 7.23-7.36 (m, ArH, ArH, 10H); 13C NMR (100 MHz, CDCl₃) δ 10.7, 16.6, 24.5, 29.7, 41.1, 49.0, 66.6, 67.0, 71.3, 72.5, 72.8, 85.4, by 1 mL of sat. NaHCO₃. The phases were separated and the aqueous extracted with 3+3 mL of toluene. The combined organic phases were washed with 5 mL of brine and dried with MgSO₄. The crude product was first purified by step gradient column chromatography (5%, 10%, 15% and 20% EtOAc/Hexane in 50 mL portions) affording the two diastereomers 243 and 244 (8.2 mg, 96%). The diastereomers were separated with HPLC chromatography, which afforded (4.1 mg each).

(Fraction 1) Rₜ (50% EtOAc/Hexane, UV/PMA) = 0.59; Rₜ (Shandon Hypersil 5 μ column, EtOAc/Hexane, 1:20, flow rate 1.0 mL/min, λ = 254 nm) = 30.52 min; [α]D₂₀ = +105 (c 0.1; CHCl₃); IR (νmax, film) 1718 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 0.94 (s, CH₃, 3H), 1.07 (d, CHCH₃, J 7.0 Hz, 3H), 1.16 (s, CH₂, 3H), 1.64-1.72 (m, CH₂CH₂CH₂O, 1H), 1.81-1.90 (m, CH₂CH₂CH₂O, 1H), 2.32 (dd, CH₂CH₂CH₂O, J 14.6 Hz, 1H), 2.33 (qd, CH₃C, J 7.0, 2.6 Hz, 1H), 2.58 (dd, CH₂CH₂CH₂O, J 15.0 Hz, 1H), 3.46-3.54 (m, CH₂CH₂O, 2H), 3.59 (dd, CH₃CH₂CH₂O, J 8.8, 6.7 Hz, 1H), 3.38 (dd, CH₂CH₂CH₂O, J 8.7, 7.8 Hz, 1H), 4.12 (dd, CH₂CH₂O, J 7.7, 6.7 Hz, 1H), 4.24 (td, CH₂CH₂CH₂O, J 9.8, 3.0 Hz, 1H), 4.46 (dd, CH₂CH₂CH₂O, J 9.8, 11.8 Hz, 1H), 4.47 (dd, CH₂CH₂O, J 9.8, 11.9 Hz, 2H), 4.56 (dd, CH₂CH₂CH₂O, J 11.8 Hz, 1H), 7.28-7.35 (m, ArH, ArH, 10H); 13C NMR (100 MHz, CDCl₃) δ 10.5, 17.2, 20.3, 29.7, 40.8, 47.6, 66.9, 67.2, 69.3, 72.9, 73.1, 84.5, 110.0, 127.4, 127.7, 127.8, 128.4, 138.2, 138.4, 209.9; HRMS (TOF MS El) calcd. for C₃₂H₅₃O₃Na 461.2304, found 461.2318.
3.1.31 (R)-dihydro-4-hydroxy-3,3-dimethylfuran-2(3H)-one (246)

DHQ-PYR (0.264 g, 0.30 mmol, 1.0 mol%), K$_3$Fe(CN)$_6$ (29.6 g, 90 mmol, 300 mol%) and K$_2$CO$_3$ (12.4 g, 90 mmol, 300 mol%) were dissolved in a mixture of H$_2$O (140 mL) and t-BuOH (140 mL) and OsO$_4$ (1.5 mL of 2.5 wt% in 2-methylpropan-2-ol) added. The reaction mixture was cooled to 0°C and a solution of 245 (3.85 g, 30 mmol, 100 mol%) in a mixture of H$_2$O (10 mL) and t-BuOH (10 mL) added. The mixture was stirred overnight at 0°C and after 18.5 h quenched by adding 37.9 g of Na$_2$SO$_3$ and 50 mL of H$_2$O. The phases were separated, the aqueous phase extracted five times with 50 mL of EtOAc, the combined organic phases washed with 50 mL of brine and dried with MgSO$_4$. The crude product was filtered through a pad of silica gel using 50% EtOAc/Hexane and pure EtOAc as eluent. The crude was purified by re-crystallizing twice from a mixture of pentane (10 mL) and EtOAc (2.8 mL) affording 246 (3.2 g, 82%, 97.5% ee) as white needle-like crystals; mp = 59-60°C; R$_f$ (50% EtOAc/Hexane, UV/permanaganate) = 0.20; R$_f$ (GC, cyclodextrin beta, Inj. 270°C, vel. 28, 100-220°C 4°C/min, 220°C 30min, Det. 270°C) = 20.61 min; [α]$_D^{20}$ = -5.1 (c 1.0; CHCl$_3$); IR (ν$_{max}$ film) 1760, 3459 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.24 (s, CH$_3$, 6H), 2.51 (d, OH, J 4.4 Hz, 1H), 4.13 (dd, CH$_2$H$_2$O, J 3.2, 10.0 Hz, 1H), 4.20 (ddd, CH$_3$J 3.2, 4.4, 4.4 Hz, 1H), 4.45 (dd, CH$_2$H$_2$O, J 4.4, 10.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 17.2, 22.7, 43.6, 71.9, 75.5, 181.2; Anal. calc. for C$_8$H$_{16}$O$_5$C, 55.37; H, 7.74. Found C, 55.13; H, 7.83.

3.1.31 (R)-dihydro-4-hydroxy-3,3-dimethylfuran-2(3H)-one (246)

DHQ-PYR (0.264 g, 0.30 mmol, 1.0 mol%), K$_3$Fe(CN)$_6$ (29.6 g, 90 mmol, 300 mol%) and K$_2$CO$_3$ (12.4 g, 90 mmol, 300 mol%) were dissolved in a mixture of H$_2$O (140 mL) and t-BuOH (140 mL) and OsO$_4$ (1.5 mL of 2.5 wt% in 2-methylpropan-2-ol) added. The reaction mixture was cooled to 0°C and a solution of 245 (3.85 g, 30 mmol, 100 mol%) in a mixture of H$_2$O (10 mL) and t-BuOH (10 mL) added. The mixture was stirred overnight at 0°C and after 18.5 h quenched by adding 37.9 g of Na$_2$SO$_3$ and 50 mL of H$_2$O. The phases were separated, the aqueous phase extracted five times with 50 mL of EtOAc, the combined organic phases washed with 50 mL of brine and dried with MgSO$_4$. The crude product was filtered through a pad of silica gel using 50% EtOAc/Hexane and pure EtOAc as eluent. The crude was purified by re-crystallizing twice from a mixture of pentane (10 mL) and EtOAc (2.8 mL) affording 246 (3.2 g, 82%, 97.5% ee) as white needle-like crystals; mp = 59-60°C; R$_f$ (50% EtOAc/Hexane, UV/permanaganate) = 0.20; R$_f$ (GC, cyclodextrin beta, Inj. 270°C, vel. 28, 100-220°C 4°C/min, 220°C 30min, Det. 270°C) = 20.61 min; [α]$_D^{20}$ = -5.1 (c 1.0; CHCl$_3$); IR (ν$_{max}$ film) 1760, 3459 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.24 (s, CH$_3$, 6H), 2.51 (d, OH, J 4.4 Hz, 1H), 4.13 (dd, CH$_2$H$_2$O, J 3.2, 10.0 Hz, 1H), 4.20 (ddd, CH$_3$J 3.2, 4.4, 4.4 Hz, 1H), 4.45 (dd, CH$_2$H$_2$O, J 4.4, 10.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 17.2, 22.7, 43.6, 71.9, 75.5, 181.2; Anal. calc. for C$_8$H$_{16}$O$_5$C, 55.37; H, 7.74. Found C, 55.13; H, 7.83.
3.1.32  (R)-4-(benzoxyl)-dihydro-3,3-dimethylfuran-2(3H)-one (247)

A solution of lactone 246 (0.105 g, 0.807 mmol, 100 mol-%) was in CH₂Cl₂ (2 mL) and cyclohexane (6 mL) was treated with benzyl 2,2,2-trichloroacetimidate (0.369 mL, 1.94 mmol, 240 mol-%) and CF₃SO₂H (17 μL, 0.192 mmol, 24 mol-%) and reaction mixture heated to 35°C. After three hours the trichloroacetimidate precipitate was filtered off and washed twice with 5 mL of cyclohexane. The combined organic phases were washed with 2·10 mL of sat. NaHCO₃, 10 mL of brine and dried with MgSO₄. The crude was purified by step gradient column chromatography (10%, 15% and 25% MTBE/hexane in 100 mL portions) to afford 247 as a light yellow oil 0.163 g (91%). Rf (50% EtOAc/Hexane, UV/PMA) = 0.46; [α]D²⁰ = -5.3 (c 1.0, CHCl₃); IR (νmax, film) 1773 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.25 (s, CH₃, 3H), 1.28 (s, CH₃, 3H), 3.90 (dd, CH, J 4.0, 5.2 Hz, 1H), 4.15 (dd, CH₂H, J 4.0, 10.0 Hz, 1H), 4.31 (dd, CH₂H, J 5.2, 10.0 Hz, 1H), 4.58 (dd, CH₂Ph, JAB 12.1 Hz, 2H), 7.29-7.38 (m, ArHt, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 17.9, 23.4, 42.9, 68.9, 72.1, 81.9, 127.5, 128.0, 128.5, 137.4, 180.6; HRMS (TOF MS El⁺) calc. for C₁₃H₁₆O₃Na 243.0997, found 243.0979.

3.1.32  (R)-4-(benzoxyl)-dihydro-3,3-dimethylfuran-2(3H)-one (247)

A solution of lactone 246 (0.105 g, 0.807 mmol, 100 mol-%) was in CH₂Cl₂ (2 mL) and cyclohexane (6 mL) was treated with benzyl 2,2,2-trichloroacetimidate (0.369 mL, 1.94 mmol, 240 mol-%) and CF₃SO₂H (17 μL, 0.192 mmol, 24 mol-%) and reaction mixture heated to 35°C. After three hours the trichloroacetimidate precipitate was filtered off and washed twice with 5 mL of cyclohexane. The combined organic phases were washed with 2·10 mL of sat. NaHCO₃, 10 mL of brine and dried with MgSO₄. The crude was purified by step gradient column chromatography (10%, 15% and 25% MTBE/hexane in 100 mL portions) to afford 247 as a light yellow oil 0.163 g (91%). Rf (50% EtOAc/Hexane, UV/PMA) = 0.46; [α]D²⁰ = -5.3 (c 1.0, CHCl₃); IR (νmax, film) 1773 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.25 (s, CH₃, 3H), 1.28 (s, CH₃, 3H), 3.90 (dd, CH, J 4.0, 5.2 Hz, 1H), 4.15 (dd, CH₂H, J 4.0, 10.0 Hz, 1H), 4.31 (dd, CH₂H, J 5.2, 10.0 Hz, 1H), 4.58 (dd, CH₂Ph, JAB 12.1 Hz, 2H), 7.29-7.38 (m, ArHt, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 17.9, 23.4, 42.9, 68.9, 72.1, 81.9, 127.5, 128.0, 128.5, 137.4, 180.6; HRMS (TOF MS El⁺) calc. for C₁₃H₁₆O₃Na 243.0997, found 243.0979.

3.1.33  (4R)-4-(benzoxyl)-tetrahydro-3,3-dimethylfuran-2-ol (248)

A solution of lactone 247 (0.342 g, 1.55 mmol, 100 mol-%) in toluene (15 mL) at -78 °C was treated slowly over 10 min with DIBAL-H (1 M in toluene, 2.64 mL, 2.64 mmol, 170 mol-%). After 11 min, the reaction was quenched by addition of MeOH (1.0 mL) and allowed to warm to RT. The solution was partitioned between 25 mL of 1 M HCl and 25 mL of EtOAc and stirred for 1 h. The phases were separated and the aqueous phase
extracted three times with 15 mL of EtOAc. The combined organic phases were washed with 10 mL of sat. NaHCO₃ and 10 mL of brine and dried with MgSO₄. The crude was purified by step gradient column chromatography (15%, 20%, 25% and 30% EtOAc/Hexane in 200 mL portions) to afford pure 248 (0.310 g, 90%) as a slightly yellow oil. Rₜ (50% EtOAc/Hexane, UV/PMA) = 0.41; IR (νmax, film) 1725, 3435 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.00 (s, CH₃, 3H), 1.23 (s, CH₃, 3H), 3.56 (d, CHOH, J 12.0 Hz, 1H), 3.61 (d, CHOBr, J 3.8 Hz, 1H), 4.05 (dd, CH₂Br₂, J 10.2, 3.8 Hz, 1H), 4.22 (d, CH₂Br₂, J 10.2 Hz, 1H), 4.43 (d, CH₂H₃Ph, JLab 11.9 Hz, 1H), 4.61 (d, CH₂H₃Ph, JLab 11.9 Hz, 1H), 4.80 (d, CHOBr, J 11.0 Hz, 1H), 7.29-7.38 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 17.2, 24.0, 46.5, 70.9, 72.1, 85.3, 105.2, 127.6, 127.9, 128.5, 137.4; HRMS (TOF MS El⁺) calc. for C₁₃H₁₉O₃Na 245.1154, found 245.1171.

To a solution of lactol 248 (0.148 g, 0.666 mmol, 100 mol-%) in 7 mL of dry MeOH was added dimethyl 1-diazo-2-exopropyl phosphonate 1 (0.264 g, 1.332 mmol, 200 mol-%) and K₂CO₃ (0.184 g, 1.332 mmol, 200 mol-%). The reaction was warmed to 33 °C and allowed to stir for five days, during which more phosphonate 1 (0.066 g, 0.33 mmol, 50 mol-%) and K₂CO₃ (0.046 g, 0.33 mmol, 50 mol-%) were added once a day. The blue-green reaction mixture was evaporated to dryness and dissolved in 20 mL of 1:1 mixture of EtOAc and H₂O. The phases were separated, the aqueous extracted four times with 10 mL of EtOAc and the combined orgs washed with 10 mL of brine and dried with MgSO₄. The crude was purified by step gradient column chromatography (10%, 15%, 20% and 25% EtOAc/Hexane in 250 mL portions) to afford 249 0.088 g (61%) as a slightly yellow oil. Rₜ (50% EtOAc/Hexane, UV/anisaldehyde) = 0.48; Rₜ (GC, cyclodextrin beta, Inj. 270°C, vell. 28, 100-220°C 4°C/min, 220°C 30min, Det. 270°C) = 27.63 min; [α]D 20 = 0.58 (c 1.0; CHCl₃); IR (νmax, film) 1029, 1102, 3295, 3436 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 17.2, 24.0, 46.5, 70.9, 72.1, 85.3, 105.2, 127.6, 127.9, 128.5, 137.4; HRMS (TOF MS El⁺) calc. for C₁₃H₁₉O₃Na 245.1154, found 245.1171.

### 3.1.34 (R)-2-(benzylxoy)-3,3-dimethylpent-4-yn-1-ol (249)

To a solution of lactol 248 (0.148 g, 0.666 mmol, 100 mol-%) in 7 mL of dry MeOH was added dimethyl 1-diazo-2-exopropyl phosphonate 1 (0.264 g, 1.332 mmol, 200 mol-%) and K₂CO₃ (0.184 g, 1.332 mmol, 200 mol-%). The reaction was warmed to 33 °C and allowed to stir for five days, during which more phosphonate 1 (0.066 g, 0.33 mmol, 50 mol-%) and K₂CO₃ (0.046 g, 0.33 mmol, 50 mol-%) were added once a day. The blue-green reaction mixture was evaporated to dryness and dissolved in 20 mL of 1:1 mixture of EtOAc and H₂O. The phases were separated, the aqueous extracted four times with 10 mL of EtOAc and the combined orgs washed with 10 mL of brine and dried with MgSO₄. The crude was purified by step gradient column chromatography (10%, 15%, 20% and 25% EtOAc/Hexane in 250 mL portions) to afford 249 0.088 g (61%) as a slightly yellow oil. Rₜ (50% EtOAc/Hexane, UV/anisaldehyde) = 0.48; Rₜ (GC, cyclodextrin beta, Inj. 270°C, vell. 28, 100-220°C 4°C/min, 220°C 30min, Det. 270°C) = 27.63 min; [α]D 20 = 0.58 (c 1.0; CHCl₃); IR (νmax, film) 1029, 1102, 3295, 3436 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 17.2, 24.0, 46.5, 70.9, 72.1, 85.3, 105.2, 127.6, 127.9, 128.5, 137.4; HRMS (TOF MS El⁺) calc. for C₁₃H₁₉O₃Na 245.1154, found 245.1171.
δ 1.26 (s, CH₃, 3H), 1.30 (s, CH₃, 3H), 1.88 (dd, OH, J 7.4, 5.3 Hz, 1H), 2.19 (s, C(CH₃)₂CH₂H, 1H), 3.40 (dd, CHO⁻Bn, J 6.6, 3.8 Hz, 1H), 3.77 (dd, CH₂OH, J 11.8, 6.6, 5.3 Hz, 1H), 3.92 (dd, CH₃OH, J 11.8, 7.4, 3.8 Hz, 1H), 4.72 (d, CH₂Ph, Jₖₜ 11.5 Hz, 1H), 4.78 (d, CH₂Ph, Jₖₜ 11.5 Hz, 1H), 7.30-7.39 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 24.7, 26.3, 34.7, 62.6, 69.8, 74.7, 85.6, 89.7, 127.8, 127.8, 128.5, 138.3; HRMS (TOF MS El⁺) calc. for C₁₄H₁₈O₃NaSi 241.1204, found 241.1206.

To a solution of alcohol 249 (0.073 g, 0.334 mmol, 100 mol-%) in dry CH₂Cl₂ (4 mL) at 0 °C was added 2,6-lutidine (0.156 mL, 1.34 mmol, 400 mol-%), the reaction mixture was stirred for 1 h 13 min and TBSOTf (0.154 mL, 0.67 mmol, 200 mol-%) was added. After 20 min the reaction was quenched with 2 mL of sat. K₂CO₃. The mixture was partitioned between water and Et₂O (20 mL, 1:1) and the phases separated. The aqueous phase was extracted four times with 10 mL of Et₂O and the combined organic phase dried with MgSO₄. The crude was purified by column chromatography (10% EtOAc/hexane) to afford pure product 250 (0.099 g, 89%) as a slightly yellow oil. Rₗ (50% EtOAc/hexane, UV/PMA) = 0.72; [α]ₚ₂₀ = -1.1 (c 1.0; CHCl₃); IR (νₜₜₚ, film) 837, 1069, 1256, 3309 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.07 (s, CH₃, 3H), 0.08 (s, CH₃, 3H), 0.92 (s, C(CH₃)₂, 9H), 1.20 (s, CH₃, 3H), 1.27 (s, CH₃, 3H), 2.14 (s, C(CH₃)₂CH₂H, 1H), 3.36 (dd, CH₃, J 7.3, 2.7 Hz, 1H), 3.80 (dd, OCH₂H, J 10.8, 7.3 Hz, 1H), 4.10 (dd, OCH₂H, J 10.8, 2.7 Hz, 1H), 4.65 (dd, CH₂Ph, Jₖₜ 11.5 Hz, 1H), 4.92 (dd, CH₂Ph, Jₖₜ 11.5 Hz, 1H), 7.24-7.38 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ -5.4, -5.3, 18.2, 24.4, 25.9, 27.0, 34.7, 65.4, 69.1, 74.5, 86.1, 90.0, 127.3, 127.8, 128.1, 139.0; HRMS (TOF MS El⁺) calc. for C₂₀H₂₆O₃NaSi 355.2069, found 355.2079.
To a stirred solution of oxazolidinone 251 (1.00 g, 4.29 mmol, 100 mol-%) in 20 mL of dry CH₂Cl₂ at 0°C was added dropwise dibutylboron triflate (1M in CH₂Cl₂, 6.75 mL, 6.8 mmol, 157 mol-%) keeping the internal temperature under 2°C. The colour from colourless to brown but when Et₃N (1.02 mL, 7.3 mmol, 171 mol-%) was added (T ≤ 2°C) it turned from transparent to yellow and shortly afterwards to burgundy. After 40 minutes the reaction mixture was cooled to -77 °C and 3-benzoxylpropionaldehyde 269 (1.02 g, 6.2 mmol, 144 mol-%) dissolved in 2 mL of dry CH₂Cl₂ was added slowly (35 min) keeping the internal temperature stable. Stirring was continued for a further 3 h at -77 °C and then for 30 min at 0 °C. Phosphate buffer (10 mL, pH 7.0) and methanol (8 mL) were added and the mixture was cooled to -10 °C before slow (15 min) addition of 20 mL of (1:1) H₂O₂ (30% in H₂O) and MeOH. The mixture was stirred for 30 min at 0 °C before the organic solvents were evaporated in vacuo. Et₂O was added and reaction was cooled to -10 °C. Sat. Na₂S₂O₃ (17 mL) was added slowly (20 min) and the phases were separated. The aqueous phase was extracted three times with 10 mL of Et₂O, the combined organic phases washed with 12 mL of sat. NaClO₃ and 8 mL of brine and dried with MgSO₄. The crude was purified by gradient flash column chromatography (15%, 20%, 40%, 25% EtOAc/Hexane in 200 mL portions) to afford pure 252 (1.36 g, 80%, 99% ee). Rₜ (50% EtOAc/Hexane, UV / acid-PMA) = 0.31; [α]D < Subscript>20 </Subscript> = -44.7 (c 1.0; CHCl₃); Rₜ (HPLC, Daicel, Chiracel® OD, 250 mm, 4.6 mm, 20% IPA/Hex, 254 nm, 1.0 mL/min) = 17.52 min; IR (νmax, film) 1111, 1694, 1780, 3480 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.28 (d, CH₃, J 7.0 Hz, 3H), 1.71-1.80 (m, CH(OH)CH₂H₃, 1H), 1.83-1.92 (m, CH(OH)CH₂H₃, 1H), 2.77 (dd, PhCH₂H₂, J 13.4, 9.5 Hz, 1H), 3.25 (dd, PhCH₂H₂, J 13.4, 3.3 Hz, 1H), 3.34 (d, OH, J 2.4 Hz, 1H), 3.63-3.73 (m, CH₂OBn 2H), 3.82 (dq, CHMe J 1
7.0, 3.8 Hz, 1H), 4.13-4.20 (m, CH₂OH, OCH₂CH(Bn)CH₂N, 3H), 4.51 (s, OCH₃Ph, 2H), 4.67 (m, OCH₂CH(Bn)N, 1H), 7.19-7.34 (m, ArH, 10H); ¹³C NMR (100 MHz, CDCl₃) δ 11.1, 33.7, 37.7, 42.5, 55.2, 66.1, 68.3, 70.4, 73.2, 127.3, 127.6, 128.4, 128.4, 128.9, 129.4, 135.1, 138.0, 153.0, 176.6; HRMS (EI) calcd for C₂₃H₂₇N₂O₄Na 420.1787, found 420.1815.

3.1.37 (2R,3S)-5-(Benzyloxy)-3-hydroxy-N-methoxy-N,2-dimethylpentanamide

![Chemical structure](image)

A 25 mL 2-neck flask was charged with N,O-dimethyl hydroxylamine hydrochloride (0.54 g, 5.5 mmol, 220 mol-%) and 4 mL THF. The suspension was cooled to −10 °C (NaCl/ice) and AlMe₃ (2 M in hexane, 2.64 mL, 5.3 mmol, 210 mol-%) was added over 5 min. After 12 min, the cooling bath was removed and the reaction mixture was allowed to stir for 1 h at RT before it was cooled again to −10 °C. A solution of Oxazolidinone 252 (1.0 g, 2.5 mmol, 100 mol-%) in a mixture (4:5) of CH₂Cl₂ (2.9 mL) and THF (4 mL) was slowly added, the mixture stirred for 3 h 15 min at 0 °C and at RT for another 1 h 30 min before it was poured into a mixture (32 mL) of (1:1) HCl [0.5 M] and CH₂Cl₂ at 0°C. The mixture was stirred for 2 h at 0 °C and the phases separated. The aqueous phase was extracted with 3×30 mL of CH₂Cl₂ and the combined organic phases were washed with 40 mL of H₂O and dried with MgSO₄. The crude product was purified by step gradient column chromatography (30%, 40%, 50% EtOAc / Hexane and pure EtOAc in 700 mL fractions) to afford 253 as a yellow oil (0.617 g, 89%). Rf (50% EtOAc/Hexane, UV/PMA) = 0.16; [α]₂⁰° = −1.8 (c 0.5; CHCl₃); IR (νmax, liq. CHCl₃) 1637, 3440 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.20 (d, CH₃, J 7.3 Hz, 3H), 1.67-1.74 (m, CH(OH)CH₂H₃, 1H), 1.80-1.89 (m, CH(OH)CH₂H₃, 1H), 2.93 (br s, CHMe, 1H), 3.18 (s, CH₂N, 3H), 3.63-3.71 (m, CH₂OBn, 2H), 3.66 (s, NOCH₃, 3H), 3.87 (s, OH, 1H), 4.05 (ddt, CH₂OH, J 9.0, 3.7, 1.6 Hz, 1H), 4.52 (s, OCH₃Ph, 2H), 7.26-7.34 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 11.1, 33.7, 37.7, 42.5, 55.2, 66.1, 68.3, 70.4, 73.2, 127.3, 127.6, 128.4, 128.4, 128.9, 129.4, 135.1, 138.0, 153.0, 176.6; HRMS (EI) calcd for C₂₃H₂₇N₂O₄Na 420.1787, found 420.1815.

3.1.37 (2R,3S)-5-(Benzyloxy)-3-hydroxy-N-methoxy-N,2-dimethylpentanamide

![Chemical structure](image)

A 25 mL 2-neck flask was charged with N,O-dimethyl hydroxylamine hydrochloride (0.54 g, 5.5 mmol, 220 mol-%) and 4 mL THF. The suspension was cooled to −10 °C (NaCl/ice) and AlMe₃ (2 M in hexane, 2.64 mL, 5.3 mmol, 210 mol-%) was added over 5 min. After 12 min, the cooling bath was removed and the reaction mixture was allowed to stir for 1 h at RT before it was cooled again to −10 °C. A solution of Oxazolidinone 252 (1.0 g, 2.5 mmol, 100 mol-%) in a mixture (4:5) of CH₂Cl₂ (2.9 mL) and THF (4 mL) was slowly added, the mixture stirred for 3 h 15 min at 0 °C and at RT for another 1 h 30 min before it was poured into a mixture (32 mL) of (1:1) HCl [0.5 M] and CH₂Cl₂ at 0°C. The mixture was stirred for 2 h at 0 °C and the phases separated. The aqueous phase was extracted with 3×30 mL of CH₂Cl₂ and the combined organic phases were washed with 40 mL of H₂O and dried with MgSO₄. The crude product was purified by step gradient column chromatography (30%, 40%, 50% EtOAc / Hexane and pure EtOAc in 700 mL fractions) to afford 253 as a yellow oil (0.617 g, 89%). Rf (50% EtOAc/Hexane, UV/PMA) = 0.16; [α]₂⁰° = −1.8 (c 0.5; CHCl₃); IR (νmax, liq. CHCl₃) 1637, 3440 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.20 (d, CH₃, J 7.3 Hz, 3H), 1.67-1.74 (m, CH(OH)CH₂H₃, 1H), 1.80-1.89 (m, CH(OH)CH₂H₃, 1H), 2.93 (br s, CHMe, 1H), 3.18 (s, CH₂N, 3H), 3.63-3.71 (m, CH₂OBn, 2H), 3.66 (s, NOCH₃, 3H), 3.87 (s, OH, 1H), 4.05 (ddt, CH₂OH, J 9.0, 3.7, 1.6 Hz, 1H), 4.52 (s, OCH₃Ph, 2H), 7.26-7.34 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 11.1, 33.7, 37.7, 42.5, 55.2, 66.1, 68.3, 70.4, 73.2, 127.3, 127.6, 128.4, 128.4, 128.9, 129.4, 135.1, 138.0, 153.0, 176.6; HRMS (EI) calcd for C₂₃H₂₇N₂O₄Na 420.1787, found 420.1815.
3.1.38 (2R,3S)-(Benzyloxy)-3-(tert-butyldimethylsilyloxy)-N-methoxy,N2-
dimethylpentanamide (254)

To a solution of alcohol 253 (0.697 g, 2.5 mmol, 100 mol%) in dry CH2Cl2 (20 mL) at 0 °C was added 2,6-lutidine (1.16 mL, 10 mmol, 400 mol%). The reaction mixture stirred for 22 min before TBSOTf (1.72 mL, 7.5 mmol, 200 mol%) was added dropwise. The reaction was quenched after 15 min with sat. K2CO3 (20 mL). The phases were separated and organic phase was extracted with 5x20 mL of 0.5 Maq. H3PO4 and 20 mL of H2O. The combined organic phases were dried with MgSO4. The crude was purified by step gradient column chromatography (10%, 15%, 20% and 25% EtOAc / Hexane in 500 mL portions) to afford pure 254 (0.512 g, 89%) as a yellow oil. Rf (50% EtOAc/Hexane, UV/PMA) = 0.45; [α]D20 = +2.3 (c 1.0; CHCl3); IR (νmax; film) 836, 1103, 1663 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 0.04 (s, CH3, 3H), 0.06 (s, CH3, 3H), 0.88 (s, C(CH3)3, 9H), 1.13 (d, CH2CH, J 7.0 Hz, 3H), 1.82-1.88 (m, CH(OTBS)CH2, 2H), 2.98 (br s, CHMe, 1H), 3.13 (s, CH2N, 3H), 3.49-3.62 (m, CH2OBn, 2H), 3.59 (s, NOCH3, 3H), 4.04 (td, CHOTBS, J 7.8, 5.0 Hz, 1H), 4.45 (d, OCH2H2Ph, Jτ= 12.1 Hz, 1H), 4.49 (d, OCH2H2Ph, Jτ= 12.1 Hz, 1H), 7.23-7.34 (m, ArH, 5H); 13C NMR (100 MHz, CDCl3) δ -4.5, -4.4, 14.4, 18.1, 25.9, 32.1, 35.4, 41.3, 61.2, 66.5, 71.4, 72.9, 127.4, 127.7, 128.3, 138.6, 176.3; HRMS (EI) calc. for C25H38NO2NaSi 418.2390, found 418.2397.

3.1.38 (2R,3S)-(Benzyloxy)-3-(tert-butyldimethylsilyloxy)-N-methoxy,N2-
dimethylpentanamide (254)

To a solution of alcohol 253 (0.697 g, 2.5 mmol, 100 mol%) in dry CH2Cl2 (20 mL) at 0 °C was added 2,6-lutidine (1.16 mL, 10 mmol, 400 mol%). The reaction mixture stirred for 22 min before TBSOTf (1.72 mL, 7.5 mmol, 200 mol%) was added dropwise. The reaction was quenched after 15 min with sat. K2CO3 (20 mL). The phases were separated and organic phase was extracted with 5x20 mL of 0.5 Maq. H3PO4 and 20 mL of H2O. The combined organic phases were dried with MgSO4. The crude was purified by step gradient column chromatography (10%, 15%, 20% and 25% EtOAc / Hexane in 500 mL portions) to afford pure 254 (0.512 g, 89%) as a yellow oil. Rf (50% EtOAc/Hexane, UV/PMA) = 0.45; [α]D20 = +2.3 (c 1.0; CHCl3); IR (νmax; film) 836, 1103, 1663 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 0.04 (s, CH3, 3H), 0.06 (s, CH3, 3H), 0.88 (s, C(CH3)3, 9H), 1.13 (d, CH2CH, J 7.0 Hz, 3H), 1.82-1.88 (m, CH(OTBS)CH2, 2H), 2.98 (br s, CHMe, 1H), 3.13 (s, CH2N, 3H), 3.49-3.62 (m, CH2OBn, 2H), 3.59 (s, NOCH3, 3H), 4.04 (td, CHOTBS, J 7.8, 5.0 Hz, 1H), 4.45 (d, OCH2H2Ph, Jτ= 12.1 Hz, 1H), 4.49 (d, OCH2H2Ph, Jτ= 12.1 Hz, 1H), 7.23-7.34 (m, ArH, 5H); 13C NMR (100 MHz, CDCl3) δ -4.5, -4.4, 14.4, 18.1, 25.9, 32.1, 35.4, 41.3, 61.2, 66.5, 71.4, 72.9, 127.4, 127.7, 128.3, 138.6, 176.3; HRMS (EI) calc. for C25H38NO2NaSi 418.2390, found 418.2397.
A solution of alkyne 250 (0.057 g, 0.172 mmol, 200 mol-%) in 1.7 mL of dry THF at −78 ºC was treated with BuLi (2.25 M, 84 µl, 0.189 mmol, 220 mol-%) and the reaction allowed to stir for 1 h before a solution of Weinreb amide 254 (0.034 g, 0.086 mmol, 100 mol-%) in 0.9 mL of dry THF was added. After 55 min, the reaction mixture was allowed to warm to RT, stirred for another 3 h 21 min then quenched with 5 mL of H2O. Et2O (10 mL) and brine (5 mL) were added and the phases were separated. The aqueous phase was extracted three times with 10 mL of Et2O and the combined organic phases were dried with MgSO4. The crude product was purified by step gradient chromatography (5%, 10%, and 15% EtOAc/Hexane in 15 mL portions) to afford 255 (0.035 g, 62%) as yellow oil. Rf (50% EtOAc/Hexane, UV/PMA) = 0.73; [α]D20 = -1.1 (c 1.0; CHCl3); IR (νmax: Hm) 836, 1095, 1256, 1677, 2209 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 0.01 (s, CH3Si, 3H), 0.03 (s, CH2Si, 3H), 0.06 (s, CH3Si, 3H), 0.07 (s, CH2Si, 3H), 0.84 (s, C(CH3)3, 9H), 0.91 (s, C(CH3)2, 9H), 1.13 (d, CH2CH, 6.9 Hz, 3H), 1.24 (s, CH2C, 3H), 1.28 (s, CH2C, 3H), 1.77-1.92 (m, CH2OTBS)CH2, J 14.0, 6.4 Hz, 2H), 2.57 (qd, CHMe, J 6.9, 3.8 Hz, 1H), 3.38 (dd, CH2OBn, J 7.1, 3.0 Hz, 1H), 3.49 (t, CH2OBn, J 6.4 Hz, 2H), 3.78 (dd, CH2CH2OTBS, J 10.8, 7.1 Hz, 1H), 4.00 (dd, CH2CH2OTBS, J 10.8, 3.3 Hz, 1H), 4.46-4.50 (m, CHOTBS, 1H), 4.52 (d, OCH3Hph, JAB 12.0 Hz, 1H), 4.48 (d, OCH3Hph, JAB 12.0 Hz, 1H), 4.60 (d, CHOCCH3Hph, JAB 11.5 Hz, 1H), 4.88 (d, CHOCCH3Hph, JAB 11.5 Hz, 1H), 7.25-7.33 (m, ArH, 10H); 13C NMR (100 MHz, CDCl3) δ 54.4, 54.2, 45.5, 44.9, 46.4, 81.3, 85.5, 99.3, 127.4, 127.5, 127.5, 127.7, 128.2, 128.3, 138.4, 138.5, 190.2; HRMS (TOF MS Ei) calc. for C33H33O2NaSi2 689.4035, found 689.4040.

A solution of alkyne 250 (0.057 g, 0.172 mmol, 200 mol-%) in 1.7 mL of dry THF at −78 ºC was treated with BuLi (2.25 M, 84 µl, 0.189 mmol, 220 mol-%) and the reaction allowed to stir for 1 h before a solution of Weinreb amide 254 (0.034 g, 0.086 mmol, 100 mol-%) in 0.9 mL of dry THF was added. After 55 min, the reaction mixture was allowed to warm to RT, stirred for another 3 h 21 min then quenched with 5 mL of H2O. Et2O (10 mL) and brine (5 mL) were added and the phases were separated. The aqueous phase was extracted three times with 10 mL of Et2O and the combined organic phases were dried with MgSO4. The crude product was purified by step gradient chromatography (5%, 10%, and 15% EtOAc/Hexane in 15 mL portions) to afford 255 (0.035 g, 62%) as yellow oil. Rf (50% EtOAc/Hexane, UV/PMA) = 0.73; [α]D20 = -1.1 (c 1.0; CHCl3); IR (νmax: Hm) 836, 1095, 1256, 1677, 2209 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 0.01 (s, CH3Si, 3H), 0.03 (s, CH2Si, 3H), 0.06 (s, CH3Si, 3H), 0.07 (s, CH2Si, 3H), 0.84 (s, C(CH3)3, 9H), 0.91 (s, C(CH3)2, 9H), 1.13 (d, CH2CH, 6.9 Hz, 3H), 1.24 (s, CH2C, 3H), 1.28 (s, CH2C, 3H), 1.77-1.92 (m, CH2OTBS)CH2, J 14.0, 6.4 Hz, 2H), 2.57 (qd, CHMe, J 6.9, 3.8 Hz, 1H), 3.38 (dd, CH2OBn, J 7.1, 3.0 Hz, 1H), 3.49 (t, CH2OBn, J 6.4 Hz, 2H), 3.78 (dd, CH2CH2OTBS, J 10.8, 7.1 Hz, 1H), 4.00 (dd, CH2CH2OTBS, J 10.8, 3.3 Hz, 1H), 4.46-4.50 (m, CHOTBS, 1H), 4.52 (d, OCH3Hph, JAB 12.0 Hz, 1H), 4.48 (d, OCH3Hph, JAB 12.0 Hz, 1H), 4.60 (d, CHOCCH3Hph, JAB 11.5 Hz, 1H), 4.88 (d, CHOCCH3Hph, JAB 11.5 Hz, 1H), 7.25-7.33 (m, ArH, 10H); 13C NMR (100 MHz, CDCl3) δ 54.4, 54.2, 45.5, 44.9, 46.4, 81.3, 85.5, 99.3, 127.4, 127.5, 127.5, 127.7, 128.2, 128.3, 138.4, 138.5, 190.2; HRMS (TOF MS Ei) calc. for C33H33O2NaSi2 689.4035, found 689.4040.
The ynone 255 (21.7 mg, 32.5 \( \mu \)mol, 100 mol-%) was dissolved in 0.5 mL of dry MeOH, and camphor sulphonic acid (1.4 mg, 6.0 \( \mu \)mol, 18 mol-%) was added. The reaction was allowed to stir at RT for 2 h 30 min before the solvent was evaporated. The residue was dissolved in 1 mL of dry benzene and the reaction was stirred for 15 min, after which time p-TsOH (2.7 mg, 14 \( \mu \)mol, 44 mol-%) was added. Stirring was continued for another 18 h. The reaction was quenched by adding TEA (0.02 mL) followed by 1 mL of sat. NaHCO\(_3\). 1 mL of H\(_2\)O and 3 mL of toluene was added, the phases were separated and the aqueous one was extracted three times with 3 mL of tluene. The combined organic phases were extracted once with 5 mL of brine and dried with MgSO\(_4\). The crude product was purified by step gradient column chromatography (5%, 10%, 15% and 20% EtOAc/Hexane in 50 mL portions) affording the light yellow oil 256 (12.3 mg, 86%). \( R_f \) (50% EtOAc/Hexane, UV/PMA) = 0.61; [\( \alpha \)]\(_D\)\(^{20} = -5.7 \) (c 0.5; CHCl\(_3\)) ; IR (\( \nu_{max} \), film) 1102, 1719 cm\(^{-1} \); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.94 (s, \( CH_3 \), 3H), 1.07 (d, \( CH_3 \), \( J = 7.1 \) Hz, 3H), 1.26 (s, \( CH_3 \), 3H), 1.64-1.72 (m, \( CH_3CH_2OCH_2CH_3 \), 1H), 2.28-2.34 (m, \( CHMe \), 1H), 2.30 (d, \( CH_2OCH_2CH_2OCH_2CH_3 \), 1H), 2.56 (d, \( CH_2OCH_2CH_2OCH_2CH_3 \), 1H), 3.46-3.55 (m, \( CH_2OCH_2CH_2OCH_2CH_3 \), 1H), 3.59 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 3.82 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 4.10 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 4.22 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 4.43 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 4.44 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 4.47 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 4.54 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 7.28-7.37 (m, \( ArH, 10H \)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 10.5, 17.2, 20.3, 31.7, 40.9, 47.6, 48.4, 67.0, 67.2, 69.3, 73.0, 73.1, 84.6, 110.1, 127.4, 127.7, 128.4, 128.8, 138.2, 138.4, 209.9; HRMS (TOF MS E\(^{+}\)) calc. for C\(_{27}\)H\(_{38}\)O\(_3\)Na 461.2304, found 461.2306.

The ynone 255 (21.7 mg, 32.5 \( \mu \)mol, 100 mol-%) was dissolved in 0.5 mL of dry MeOH, and camphor sulphonic acid (1.4 mg, 6.0 \( \mu \)mol, 18 mol-%) was added. The reaction was allowed to stir at RT for 2 h 30 min before the solvent was evaporated. The residue was dissolved in 1 mL of dry benzene and the reaction was stirred for 15 min, after which time p-TsOH (2.7 mg, 14 \( \mu \)mol, 44 mol-%) was added. Stirring was continued for another 18 h. The reaction was quenched by adding TEA (0.02 mL) followed by 1 mL of sat. NaHCO\(_3\). 1 mL of H\(_2\)O and 3 mL of toluene was added, the phases were separated and the aqueous one was extracted three times with 3 mL of tluene. The combined organic phases were extracted once with 5 mL of brine and dried with MgSO\(_4\). The crude product was purified by step gradient column chromatography (5%, 10%, 15% and 20% EtOAc/Hexane in 50 mL portions) affording the light yellow oil 256 (12.3 mg, 86%). \( R_f \) (50% EtOAc/Hexane, UV/PMA) = 0.61; [\( \alpha \)]\(_D\)\(^{20} = -5.7 \) (c 0.5; CHCl\(_3\)) ; IR (\( \nu_{max} \), film) 1102, 1719 cm\(^{-1} \); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.94 (s, \( CH_3 \), 3H), 1.07 (d, \( CH_3 \), \( J = 7.1 \) Hz, 3H), 1.26 (s, \( CH_3 \), 3H), 1.64-1.72 (m, \( CH_3CH_2OCH_2CH_3 \), 1H), 2.28-2.34 (m, \( CHMe \), 1H), 2.30 (d, \( CH_2OCH_2CH_2OCH_2CH_3 \), 1H), 2.56 (d, \( CH_2OCH_2CH_2OCH_2CH_3 \), 1H), 3.46-3.55 (m, \( CH_2OCH_2CH_2OCH_2CH_3 \), 1H), 3.59 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 3.82 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 4.10 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 4.22 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 4.43 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 4.44 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 4.47 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 4.54 (dd, \( CH(\text{O})\text{OBn})CH_2_2OCH_2H, 1H), 7.28-7.37 (m, \( ArH, 10H \)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 10.5, 17.2, 20.3, 31.7, 40.9, 47.6, 48.4, 67.0, 67.2, 69.3, 73.0, 73.1, 84.6, 110.1, 127.4, 127.7, 128.4, 128.8, 138.2, 138.4, 209.9; HRMS (TOF MS E\(^{+}\)) calc. for C\(_{27}\)H\(_{38}\)O\(_3\)Na 461.2304, found 461.2306.
The spirocycle 256 (6 mg, 13.7 μmol, 100 mol%-%) was dissolved in 0.1 mL of dry THF and cooled to −78 °C. L-Selectride (41 μL, 41 μmol, 300 mol%-%) was added dropwise and the reaction was allowed to stir for 1 h 23 min before adding 0.2 mL of MeOH. 0.1 mL of 2.0 M NaOH, 0.1 mL of 30% H₂O₂ and 2 mL of THF quenched it. The reaction mixture was allowed to stir at 37 min at 0 °C and 38 min at RT after which 1 mL H₂O and 3 mL of Et₂O was added. The phases were separated and the aqueous one was extracted five times with 3 mL of Et₂O. The combined organic phases were extracted once with 5 mL of brine and dried with MgSO₄. The crude product was purified by step gradient column chromatography (10%, 20%, 30%, 40% and 50% EtOAc/Hexane in 20 mL portions) affording the colourless oil 257 (4.1 mg, 68%). Rf (50% EtOAc/Hexane, UV/PMA) = 0.51; [α]D²⁰ = −9.8 (c 0.31; CHCl₃). IR (νmax, liq) 1248, 3608 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 0.82 (d, CHCH₃, J 7.2 Hz, 3H), 0.93 (s, CH₃, 3H), 1.06 (s, CH₃, 3H). 1.61-1.67 (m, CHMe, CH₂CH₂CH₂OBN, CH₂CH₂CH(OH)CH, 3H), 1.72-1.79 (m, CH₂CH₂CH₂OBN, CH₂CH₂CH(OH)CH), 2H), 3.45-3.54 (m, CH₂CH₂OBN, 2H), 3.60 (dd, CH(OBn)CH₂H₂O, J 8.6, 6.5 Hz, 1H), 3.65 (d, OH, J 9.7 Hz, 1H), 3.79 (qd, CHOH, J 9.7, 3.1 Hz, 1H), 3.86 (dd, CH(OBn)CH₂H₂O, J 8.6, 7.8 Hz, 1H), 4.05 (dd, CHOBn, J 7.7, 6.5 Hz, 1H), 4.22 (dd, CHCH₂CH₂OBN, J 9.9, 2.9 Hz, 1H), 4.43 (d, OCH₂CH₂Ph, JAB 11.8 Hz, 1H), 4.46 (d, OCH₂CH₂Ph, JAB 12.0 Hz, 1H), 4.50 (d, OCH₂CH₂Ph, JAB 12.0 Hz, 1H), 4.54 (d, OCH₂CH₂Ph, JAB 11.8 Hz, 1H), 7.28-7.38 (m, ArH, 10H). ¹³C NMR (100 MHz, CDCl₃) δ 10.6, 17.3, 20.4, 28.3, 29.7, 32.6, 37.9, 47.8, 63.4, 67.5, 69.5, 71.0, 73.0, 84.7, 109.5, 127.4, 127.6, 127.7, 128.4, 138.5, 138.5; HRMS (TOF MS El⁺) calc. for C₂₇H₅₉O₂Na 463.2460, found 463.2469.

The spirocycle 256 (6 mg, 13.7 μmol, 100 mol%-%) was dissolved in 0.1 mL of dry THF and cooled to −78 °C. L-Selectride (41 μL, 41 μmol, 300 mol%-%) was added dropwise and the reaction was allowed to stir for 1 h 23 min before adding 0.2 mL of MeOH. 0.1 mL of 2.0 M NaOH, 0.1 mL of 30% H₂O₂ and 2 mL of THF quenched it. The reaction mixture was allowed to stir at 37 min at 0 °C and 38 min at RT after which 1 mL H₂O and 3 mL of Et₂O was added. The phases were separated and the aqueous one was extracted five times with 3 mL of Et₂O. The combined organic phases were extracted once with 5 mL of brine and dried with MgSO₄. The crude product was purified by step gradient column chromatography (10%, 20%, 30%, 40% and 50% EtOAc/Hexane in 20 mL portions) affording the colourless oil 257 (4.1 mg, 68%). Rf (50% EtOAc/Hexane, UV/PMA) = 0.51; [α]D²⁰ = −9.8 (c 0.31; CHCl₃). IR (νmax, liq) 1248, 3608 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 0.82 (d, CHCH₃, J 7.2 Hz, 3H), 0.93 (s, CH₃, 3H), 1.06 (s, CH₃, 3H). 1.61-1.67 (m, CHMe, CH₂CH₂CH₂OBN, CH₂CH₂CH(OH)CH, 3H), 1.72-1.79 (m, CH₂CH₂CH₂OBN, CH₂CH₂CH(OH)CH), 2H), 3.45-3.54 (m, CH₂CH₂OBN, 2H), 3.60 (dd, CH(OBn)CH₂H₂O, J 8.6, 6.5 Hz, 1H), 3.65 (d, OH, J 9.7 Hz, 1H), 3.79 (qd, CHOH, J 9.7, 3.1 Hz, 1H), 3.86 (dd, CH(OBn)CH₂H₂O, J 8.6, 7.8 Hz, 1H), 4.05 (dd, CHOBn, J 7.7, 6.5 Hz, 1H), 4.22 (dd, CHCH₂CH₂OBN, J 9.9, 2.9 Hz, 1H), 4.43 (d, OCH₂CH₂Ph, JAB 11.8 Hz, 1H), 4.46 (d, OCH₂CH₂Ph, JAB 12.0 Hz, 1H), 4.50 (d, OCH₂CH₂Ph, JAB 12.0 Hz, 1H), 4.54 (d, OCH₂CH₂Ph, JAB 11.8 Hz, 1H), 7.28-7.38 (m, ArH, 10H). ¹³C NMR (100 MHz, CDCl₃) δ 10.6, 17.3, 20.4, 28.3, 29.7, 32.6, 37.9, 47.8, 63.4, 67.5, 69.5, 71.0, 73.0, 84.7, 109.5, 127.4, 127.6, 127.7, 128.4, 138.5, 138.5; HRMS (TOF MS El⁺) calc. for C₂₇H₅₉O₂Na 463.2460, found 463.2469.
A solution of lactone 258 (44.0 mg, 0.111 mmol, 100 mol-%) in toluene (1.5 mL) at −78 °C was treated dropwise over 1 min with DIBAL-H (1 M in toluene, 0.189 mL, 0.189 mmol, 170 mol-%). After 8 min, the reaction was quenched by addition of MeOH (50 μL) and allowed to warm to RT. The solution was poured over 1:1 mixture of 1 M HCl and EtOAc (20 mL) and stirred for 30 min. The phases were separated and the aqueous phase extracted with 3×8 mL of EtOAc. The combined organic phases were washed 10 mL of brine and dried with MgSO₄. The crude was purified by step gradient column chromatography (30%, 50% and 60% EtOAc/Hexane in 500 mL portions) to afford pure 259 (32 mg, 78%) as a slightly yellow oil. Rᵣ (50% EtOAc/Hexane, UV/PMA) = 0.09; IR (νmax, film) 1098, 3401 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.01 (s, 1/2 CH₃, 1.5H), 1.03 (s, 1/2 CH₃, 1.5H), 1.08 (s, 1/2 CH₃, 1.5H), 1.12 (s, 1/2 CH₃, 1.5H), 1.66-1.76 (m, CH₂CH₂CH₂OBn, 1H), 1.88-1.98 (m, CH₂CH₂CH₂OBn, 1H), 2.78 (d, 1/2 OH, J 5.3 Hz, 0.5H), 3.35 (s, CH₂OCH₂CH₂, 3H), 3.40-3.49 (m, CH₂OBn, 2H), 3.46 (s, 1/2 CH₂OCH, 1.5H), 3.51 (s, 1/2 CH₂OCH, 1.5H), 3.60-3.68 (m, CH₂CH₂CH₂OCH₂, CH₂CH₂OCH₂, CHOCH₂, 4H), 3.75-3.82 (m, CH₂CH₂CH₂OCH₂, 1H), 3.76 (d, 1/2 CHOMEM, J 4.7 Hz, 0.5H), 3.84 (d, 1/2 CHOMEM, J 4.7 Hz, 0.5H), 4.17 (dd, 1/2 BOCH₂CH₂CH(OCH3)CHO, J 7.0, 4.7 Hz, 0.5H), 4.24 (dd, 1/2 BOCH₂CH₂CH(OCH3)CHO, J 7.6, 4.7 Hz, 0.5H), 4.49 (s, CH₂Ph, 2H), 4.73-4.79 (m, CHOH, OCH₂O, 3H), 5.12 (d, 1/2 OH, J 5.1 Hz, 0.5H), 7.27-7.34 (m, ArH, 5H; ¹³C NMR (100 MHz, CDCl₃) δ 18.3, 20.2, 20.3, 24.7, 29.3, 29.7, 31.4, 31.5, 46.5, 47.1, 59.0, 59.2, 66.3, 66.3, 68.1, 68.4, 71.7, 73.0, 73.1, 81.9, 84.2, 85.4, 86.3, 96.9, 97.0, 103.8, 105.2, 127.5, 127.5, 127.6, 127.7, 128.3, 128.3, 138.4, 138.5; HRMS (TOF MS E) calc. for C₃₁H₄₀O₁₃Na 421.2212, found 421.2219. A solution of lactone 258 (44.0 mg, 0.111 mmol, 100 mol-%) in toluene (1.5 mL) at −78 °C was treated dropwise over 1 min with DIBAL-H (1 M in toluene, 0.189 mL, 0.189 mmol, 170 mol-%). After 8 min, the reaction was quenched by addition of MeOH (50 μL) and allowed to warm to RT. The solution was poured over 1:1 mixture of 1 M HCl and EtOAc (20 mL) and stirred for 30 min. The phases were separated and the aqueous phase extracted with 3×8 mL of EtOAc. The combined organic phases were washed 10 mL of brine and dried with MgSO₄. The crude was purified by step gradient column chromatography (30%, 50% and 60% EtOAc/Hexane in 500 mL portions) to afford pure 259 (32 mg, 78%) as a slightly yellow oil. Rᵣ (50% EtOAc/Hexane, UV/PMA) = 0.09; IR (νmax, film) 1098, 3401 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.01 (s, 1/2 CH₃, 1.5H), 1.03 (s, 1/2 CH₃, 1.5H), 1.08 (s, 1/2 CH₃, 1.5H), 1.12 (s, 1/2 CH₃, 1.5H), 1.66-1.76 (m, CH₂CH₂CH₂OBn, 1H), 1.88-1.98 (m, CH₂CH₂CH₂OBn, 1H), 2.78 (d, 1/2 OH, J 5.3 Hz, 0.5H), 3.35 (s, CH₂OCH₂CH₂, 3H), 3.40-3.49 (m, CH₂OBn, 2H), 3.46 (s, 1/2 CH₂OCH, 1.5H), 3.51 (s, 1/2 CH₂OCH, 1.5H), 3.60-3.68 (m, CH₂CH₂CH₂OCH₂, CH₂CH₂OCH₂, CHOCH₂, 4H), 3.75-3.82 (m, CH₂CH₂CH₂OCH₂, 1H), 3.76 (d, 1/2 CHOMEM, J 4.7 Hz, 0.5H), 3.84 (d, 1/2 CHOMEM, J 4.7 Hz, 0.5H), 4.17 (dd, 1/2 BOCH₂CH₂CH(OCH3)CHO, J 7.0, 4.7 Hz, 0.5H), 4.24 (dd, 1/2 BOCH₂CH₂CH(OCH3)CHO, J 7.6, 4.7 Hz, 0.5H), 4.49 (s, CH₂Ph, 2H), 4.73-4.79 (m, CHOH, OCH₂O, 3H), 5.12 (d, 1/2 OH, J 5.1 Hz, 0.5H), 7.27-7.34 (m, ArH, 5H; ¹³C NMR (100 MHz, CDCl₃) δ 18.3, 20.2, 20.3, 24.7, 29.3, 29.7, 31.4, 31.5, 46.5, 47.1, 59.0, 59.2, 66.3, 66.3, 68.1, 68.4, 71.7, 73.0, 73.1, 81.9, 84.2, 85.4, 86.3, 96.9, 97.0, 103.8, 105.2, 127.5, 127.5, 127.6, 127.7, 128.3, 128.3, 138.4, 138.5; HRMS (TOF MS E) calc. for C₃₁H₄₀O₁₃Na 421.2212, found 421.2219.
A solution of lactol 259 (30.0 mg, 75.3 μmol, 100 mol-%) in 1.5 mL of dry MeOH was treated with dimethyl 1-diazo-2-oxopropyl phosphate 1 (28.9 mg, 0.151 mmol, 200 mol-%) and K₂CO₃ (20.8 mg, 0.151 mmol, 200 mol-%). The reaction mixture was warmed to 33 °C and allowed to stir for 10 days, during which further phosphate 1 (7.2 mg, 37.6 μmol, 50 mol-%) and K₂CO₃ (5.2 g, 37.6 μmol, 50 mol-%) were added once per day. The green reaction mixture was evaporated to dryness and partitioned between in 20 mL of 1:1 mixture of EtOAc and H₂O. The phases were separated and the aqueous extracted with 3×10 mL of EtOAc, combined organic phase once with 10 mL of brine and the organics dried with MgSO₄. The crude was purified by step gradient column chromatography (30%, 40%, 50%, 60% and 70% EtOAc/Hexane in 100 mL portions) to afford 260 8.0 mg (58% based on recycling) of slightly yellow oil, which contains some impurity. Rₚ (50% EtOAc/Hexane, UV/anisaldehyde) = 0.27; IR (νmax, film) 1024, 1101, 3291, 3522 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.24 (s, CCH₃, 3H), 1.29 (s, CCH₃, 3H), 1.89 (dt, BrOCH₂CH₂CH₂O, J 13.1, 6.8 Hz, 1H), 2.03 (dt, BrOCH₂CH₂CH₂O, J 13.1, 6.8 Hz, 1H), 2.07 (s, CCH, 1H), 2.86 (d, OH, J 6.4 Hz, 1H), 3.37 (s, CH₂OCH₂, 3H), 3.39 (m, 3H, BrOCH₂CH₂CH₂O, JAB 4.5 Hz, 1H), 3.42 (s, CHOCH₂, 3H), 3.46 (d, CHOMEM, J 2.4 Hz, 1H), 3.54 (t, CH₂OCH₂CH₂O, J 4.5 Hz, 2H), 3.62 (t, BrOCH₂, J 6.8 Hz, 2H), 3.78 (d, CH₂OCH₂CH₂O, JAB 4.5 Hz, 1H), 3.80 (d, CH₂OCH₂CH₂O, JAB 4.5 Hz, 1H), 3.92 (tq, CH₂OH, J 6.5, 2.4 Hz, 1H), 4.51 (s, PhCH₂O, 2H), 4.88 (d, CH₂OCH₂CH₂OCH₂O, JAB 6.6 Hz, 1H), 4.95 (d, CH₂OCH₂CH₂OCH₂O, JAB 6.6 Hz, 1H), 7.26-7.32 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 23.7, 26.8, 29.9, 36.2, 58.2, 59.0, 66.9, 68.4, 69.9, 71.3, 71.7, 73.0, 80.8, 82.8, 89.8, 97.8, 127.5, 127.7, 128.3, 138.4; HRMS (TOF MS El⁺) calc. for C₃₂H₃₄O₇Na 417.2253, found 417.2265.
A solution of the impure alcohol 260 (0.032 g, 81.1 µmol, 100 mol-%) in dry CH₂Cl₂ (1 mL) at 0 °C was treated with 2,6-lutidine (47 µL, 0.406 mmol, 500 mol-%), the reaction mixture allowed to stir for 1 h and TBSOTf (47 µL, 0.233 mmol, 250 mol-%) added. After 16 min the reaction was quenched with 0.5 mL of sat. K₂CO₃. The mixture was partitioned between water and Et₂O (10 mL, 1:1) and the phases separated. The aqueous phase was extracted three times with 5 mL of EtOAc and the combined organic phases dried with MgSO₄. The crude was purified by step gradient column chromatography (5%, 10% and 15% EtOAc/Hexane in 50 mL portions) to afford pure 261 (17.3 mg, 42%) as a slightly yellow oil. Rₖ (50% EtOAc/Hexane, UV/PMA) = 0.67; [α]D₂⁰ = -3.9 (c 0.29; CHCl₃); IR (νmax, film) 775, 835, 1027, 1096, 1154, 1361, 1307 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.07 (s, CH₃Si, 3H), 0.11 (s, CH₂Si, 3H), 0.89 (s, C(CH₃)₃, 9H), 1.28 (s, CH₃, 3H), 1.31 (s, CH₂, 3H), 1.85 (ddt, BrOCH₂CH₂CH₂Br, J=14.2, 5.8, 4.2 Hz, 1H), 2.04 (s, CH₂, 1H), 2.05 (ddt, BrOCH₂CH₂CH₂Br, J=14.2, 7.0, 4.2 Hz, 1H), 3.38 (s, OC₃H₃, 3H), 3.39 (s, OC₃H₃, 3H), 3.51 (m, BrOCH₂CH₂CH₂, J=4.2 Hz, 1H), 3.55 (d, CH₃OCH₂CH₂O, J=5.4 Hz, 2H), 3.56 (d, CH₂OCH₂O, J=7.0, 5.8 Hz, 2H), 3.67 (dd, CH₂OCH₂CH₂O, J=5.4, 4.4 Hz, 1H), 3.81 (dd, CH₂OCH₂CH₂O, J=5.4, 4.4 Hz, 1H), 3.95 (m, CHOTBS, J=4.8, 4.2 Hz, 1H), 4.49 (d, PhCH₂H₂, J=11.9 Hz, 1H), 4.54 (d, PhCH₂H₂, J=11.9 Hz, 1H), 4.72 (d, CH₃OCH₂CH₂O, J=7.0 Hz, 1H), 4.94 (d, CH₂OCH₂CH₂O, J=7.0 Hz, 1H), 7.26-7.34 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ -46.3, -39.1, 18.3, 26.0, 26.1, 27.8, 29.7, 31.2, 35.5, 59.0, 59.3, 67.3, 67.7, 70.0, 71.8, 72.8, 73.8, 80.4, 81.0, 90.3, 96.3, 127.4, 127.6, 128.3, 138.7; HRMS (TOF MS El⁺) calcd. for C₂₉H₄₆O₇NaSi 531.3118, found 531.3124.

A solution of the impure alcohol 260 (0.032 g, 81.1 µmol, 100 mol-%) in dry CH₂Cl₂ (1 mL) at 0 °C was treated with 2,6-lutidine (47 µL, 0.406 mmol, 500 mol-%), the reaction mixture allowed to stir for 1 h and TBSOTf (47 µL, 0.233 mmol, 250 mol-%) added. After 16 min the reaction was quenched with 0.5 mL of sat. K₂CO₃. The mixture was partitioned between water and Et₂O (10 mL, 1:1) and the phases separated. The aqueous phase was extracted three times with 5 mL of EtOAc and the combined organic phases dried with MgSO₄. The crude was purified by step gradient column chromatography (5%, 10% and 15% EtOAc/Hexane in 50 mL portions) to afford pure 261 (17.3 mg, 42%) as a slightly yellow oil. Rₖ (50% EtOAc/Hexane, UV/PMA) = 0.67; [α]D₂⁰ = -3.9 (c 0.29; CHCl₃); IR (νmax, film) 775, 835, 1027, 1096, 1154, 1361, 1307 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.07 (s, CH₃Si, 3H), 0.11 (s, CH₂Si, 3H), 0.89 (s, C(CH₃)₃, 9H), 1.28 (s, CH₃, 3H), 1.31 (s, CH₂, 3H), 1.85 (ddt, BrOCH₂CH₂CH₂Br, J=14.2, 5.8, 4.2 Hz, 1H), 2.04 (s, CH₂, 1H), 2.05 (ddt, BrOCH₂CH₂CH₂Br, J=14.2, 7.0, 4.2 Hz, 1H), 3.38 (s, OC₃H₃, 3H), 3.39 (s, OC₃H₃, 3H), 3.51 (m, BrOCH₂CH₂CH₂, J=4.2 Hz, 1H), 3.55 (d, CH₃OCH₂CH₂O, J=5.4 Hz, 2H), 3.56 (d, CH₂OCH₂O, J=7.0, 5.8 Hz, 2H), 3.67 (dd, CH₂OCH₂CH₂O, J=5.4, 4.4 Hz, 1H), 3.81 (dd, CH₂OCH₂CH₂O, J=5.4, 4.4 Hz, 1H), 3.95 (dd, CHOTBS, J=4.8, 4.2 Hz, 1H), 4.49 (d, PhCH₂H₂, J=11.9 Hz, 1H), 4.54 (d, PhCH₂H₂, J=11.9 Hz, 1H), 4.72 (d, CH₃OCH₂CH₂O, J=7.0 Hz, 1H), 4.94 (d, CH₂OCH₂CH₂O, J=7.0 Hz, 1H), 7.26-7.34 (m, ArH, 5H); ¹³C NMR (100 MHz, CDCl₃) δ -46.3, -39.1, 18.3, 26.0, 26.1, 27.8, 29.7, 31.2, 35.5, 59.0, 59.3, 67.3, 67.7, 70.0, 71.8, 72.8, 73.8, 80.4, 81.0, 90.3, 96.3, 127.4, 127.6, 128.3, 138.7; HRMS (TOF MS El⁺) calcd. for C₂₉H₄₆O₇NaSi 531.3118, found 531.3124.
A solution of alkyne 261 (18 mg, 35.4 μmol, 200 mol-%) in 0.4 mL of dry THF at –78 °C was treated with BuLi (2.2 M, 18 μl, 38.9 μmol, 220 mol-%) and the reaction allowed to stir for 1 h before a solution of Weinreb amide 254 (7 mg, 17.7 μmol, 100 mol-%) in 0.2 mL of dry THF was added dropwise. After 46 min, the reaction mixture was allowed to warm to RT, stirred for another 3 h 44 min then quenched with 1 mL of H₂O. Et₂O (5 mL) and H₂O (4 mL) were added and the phases were separated. The aqueous phase was extracted four times with 5 mL of Et₂O, combined organic phases once with 5 mL of brine and dried with MgSO₄. The crude product was purified by step gradient chromatography (5%, 10, 15% and 20% EtOAc/Hexane in 50 mL portions) to afford 262 (6.6 mg, 44% based on recycling) as slightly yellow oil. Rₜ (50% EtOAc/Hexane, UV/PMA) = 0.67; [α]D20 = -0.8 (c 0.33; CHCl₃); IR (νmax, film) 836, 1096, 1253, 1674, 2208 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.02 (s, CH₂Si, 3H), 0.05 (s, CH₂Si, 3H), 0.07 (s, CH₂Si, 3H), 0.10 (s, CH₂Si, 3H), 0.84 (s, CH₂Si, 3H), 0.89 (s, CH₂Si, 3H), 1.12 (d, CH₂CH, 1H, 3J. 6.9 Hz, 3H), 1.33 (t, CH₂CH, 3H), 1.54 (s, CH₂Si, 3H), 1.73-1.91 (m, CH₂OTBS)CH₂CH₂OBn, CH₂CH₂CH₂OBn, CH₂CH₂OBn, 3H), 1.97-2.05 (m, CH₂CH₂CH₂OBn, CH₂CH₂OBn, 3H), 2.56 (dd, CH₂CH₂, 1J. 13.9, 6.9, 3.8 Hz, 1H), 3.35 (s, CH₂CH₂, 3H), 3.36 (s, CH₂CH₂, 3H), 3.40 (dt, CH₂CH₂, 3H, OTBS), 3J. 8.4, 4.2 Hz, 1H), 3.50 (t, CH₂OTBS)CH₂CH₂OBn, CH₂CH₂OBn, 3H), 4.64 (tt, CH₂OTBS)CH₂CH₂OBn, CH₂CH₂OBn, 3H), 5.55 (s, CH₂CH₂, 3H), 5.55 (s, CH₂CH₂, 3H), 6.98 (s, CH₂CH₂, 3H), 6.98 (s, CH₂CH₂, 3H), 7.25-7.33 (m, ArH, ArH, 10H); ¹³C NMR (100 MHz, CDCl₃) δ -4.4, -4.4, -4.4, -4.4, 9.7, 18.1, 18.3, 25.5, 25.9, 26.1, 26.8, 30.9, 35.8, 36.5, 53.6, 59.0, 59.1, 66.7.
67.3, 67.8, 69.9, 71.8, 72.9, 73.0, 73.5, 80.2, 80.5, 81.8, 96.5, 99.7, 127.4, 127.5, 127.6, 128.3, 128.3, 138.4, 138.7, 189.8; HRMS (TOF MS EI') calc. for C₄₇H₇₉O₃NaSi₂ 865.5082, found 865.5085.

67.3, 67.8, 69.9, 71.8, 72.9, 73.0, 73.5, 80.2, 80.5, 81.8, 96.5, 99.7, 127.4, 127.5, 127.6, 128.3, 128.3, 138.4, 138.7, 189.8; HRMS (TOF MS EI') calc. for C₄₇H₇₉O₃NaSi₂ 865.5082, found 865.5085.
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