Studies towards the Total Synthesis of Solanoeclepin A

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Studies towards the Total Synthesis of Solanoeclipin A

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ten overstaan van een door het college voor promoties ingestelde commissie
in het openbaar te verdedigen in de Aula der Universiteit
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LIST OF ABBREVIATIONS

Ac  acetyl
Bn  benzyl
br  broad (spectral)
Boc  tert-butoxycarbonyl
Bz  benzoyl
t-Bu  tert-butyl
CSA  10-camphorsulfonic acid
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DABCO  1,4-diazabicyclo[2.2.2]octane
DIBAL-H  diisobutylaluminum hydride
DCM  dichloromethane
DIPA  N,N-diisopropylamine
DIPEA  N,N-diisopropylethylamine
DMAP  4-(dimethylamino)pyridine
DME  1,2-dimethoxyethane
DMF  N,N-dimethylformamide
DMSO  dimethylsulfoxide
EE  1-ethoxyeth-1-yl
EI  electron impact
       (in mass spectrometry)
Et  ethyl
FAB  fast atom bombardment
       (in mass spectrometry)
HMPA  hexamethyolphosphoric triamide
IR  infrared
J  coupling constant (in NMR)
KHMDS  potassium bis(trimethylsilyl)amide
LDA  lithium diisopropylamide
LHMDS  lithium bis(trimethylsilyl)amide
Me  methyl
MOM  methoxymethyl
Mp  melting point (range)
Ms  methanesulfonyl
NMO  4-methylmorpholine N-oxide
NMR  nuclear magnetic resonance
NOE  nuclear Overhauser effect
Ph  phenyl
PPTS  pyridinium para-toluenesulfonate
i-Pr  isopropyl
pTsOH  para-toluenesulfonic acid monohydrate
PE  petroleum ether (60-80)
PG  protective group
Rf  retention factor (in chromatography)
rt  room temperature
TBS  tert-butyldimethylsilyl
TEA  triethylamine
Tf  trifluoromethanesulfonate
THF  tetrahydrofuran
TIPS  triisopropylsilyl
TLC  thin layer chromatography
TMS  trimethylsilyl
Ts  para-toluenesulfonyl
UV  ultraviolet
Chapter 1

Introduction

1.1 The Potato Eelworm Hatching Agents

Potato eelworms (Figure 1.1), also known as potato cyst nematodes (PCN), parasitize on potato plants and are a serious menace to agriculture in several parts of the world. There are two species of PCN known as the golden cyst nematode (*Globodera rostochiensis*) and the pale cyst nematode (*Globodera pallida*).

![Figure 1.1 Potato cyst nematode](image1.png)

![Figure 1.2 Cysts on a potato root](image2.png)

The life cycle of PCN is well-known. The larvae hatched from cysts in the soil enter the growing roots of the potato plant where the worms are true parasites feeding solely on roots and causing the disease known as potato sickness. When attaining maturity, the body of the fertilized female swells to a cyst (Figure 1.2) containing hundreds of fully formed larvae, which drop off into the soil as a mature cyst. The cysts lie dormant in the soil until being stimulated to hatch by the growing of a new potato crop. They can remain dormant but viable for up to thirty years withstanding drought and frost. The disastrous effect of continued growing of potatoes on the same soil is thus readily understood. The reason for the hatching of larvae from cysts is that the growing potato roots secrete into the soil substances, known as potato eelworm hatching agents, which stimulate the hatching of the encysted worms.¹

Much work has been devoted to the control of the pest and the main difficulty lies in the dormancy of the cysts which are largely protected from attack by many chemical agents until the larvae emerge. An obvious alternative would be to apply a hatching agent to infected soil in the absence of potato plants. This would lead to the hatch of the larvae and they would die from starvation within a period of eight weeks. The use of hatching agents as a method to control PCN is highly attractive from an environment point of view due to their high specificity and biodegradability. However, the hatching agents are secreted from the plants in only minute quantities so that the isolation and identification of these interesting compounds are extremely difficult.²
1.2 Solanoeclepin A

In order to investigate the feasibility of the use of the hatching agent as a novel method to control the PCN, a research project was started in the Netherlands in 1985. This project was funded by the government, in particular the Ministry of Economic Affairs. LUXAN served as the company leading the investigation in close corporation with several expert research laboratories, viz. the Netherlands Institute for Carbohydrate Research-TNO (Groningen) for the production and isolation of the crude concentrate of the hatching agent, TNO-Biotechnology and Chemical Institute (Zeist) for the final purification of the hatching agent and the HLB Agricultural Research Centre (Assen) for testing the samples for hatching activity at several stages of purification.

After extensive and complicated research, 0.245 mg of the most active natural hatching agent could eventually be isolated pure from the extracts of approximately one thousand potato plants. The structural elucidation using $^1$H NMR appeared to be extremely difficult until the natural product suddenly and unexpectedly crystallized in the NMR tube. The structure of the natural product was then disclosed based on the X-ray crystal structure determination carried out in the group of Schenk (University of Amsterdam) in 1992. The structure was named solanoeclepin A (1) (figure 1.3) to indicate the structural relationship with the previously reported hatching factor of the soybean cyst nematode glycinoeclepin A (2).

![Figure 1.3](image)

The fascinating structure of 1 (C$_{27}$H$_{30}$O$_{9}$) contains all ring sizes ranging from three to seven and includes nine asymmetric carbon atoms, with the systematic name as trans-2-(2,13-dihydroxy-9-methoxy-7,7,16-trimethyl-5,10,20-triexo-19-oxahexacyclo[9.7.0.1$^{3,6}$,1$^{12}$,16]eicosa-1(11),8-dien-15-yl)-cyclopropanecarboxylic acid. The most distinctive structural feature of solanoeclepin A is the tricyclic core containing the bicyclo[2.1.1]cyclohexanone skeleton which is an unprecedented structural feature in natural products. Solanoeclepin A shows hatching activity in concentration as low as $10^{-9}$ g/L. The limited information available indicates that the molecule is unstable at pH below 2 and above 7 and at the temperature above about 35 °C. It is not clear what parts of the molecule are responsible for its remarkable base and thermal instability.

The similarities between solanoeclepin A and glycinoeclepin A are quite interesting although the latter shows no stimulus for the potato cyst nematode. The total synthesis of glycinoeclepin A has been reported by three research groups. Some studies on the structure-activity relationship of glycinoeclepin A have also published, which indicate the relevance of the carboxylic acid moiety.
The unavailability of the natural product in useful amounts from natural sources and its unique structural characteristic render solanoeclepin A a challenging synthetic target. Moreover, the synthetic work will provide information on structure-activity relationship which could lead to simpler analogs of solanoeclepin A possessing sufficient hatching activity for PCN.

1.3 Retrosynthesis of Solanoeclepin A

The retrosynthetic analysis of solanoeclepin A (1) reveals two synthetic fragments 5 and 6 of comparable size and complexity (Scheme 1.1). The highly oxygenated seven-membered ring was envisioned to be a good connection point for these two synthetic substructures. The first key disconnection is therefore the bond between the α-diketone moiety. An intramolecular Grubbs coupling of divinyl 4 should furnish the seven-membered ring. Dihydroxylation of the formed alkene followed by further oxidation and methylation then give the methylated α-diketone 3. Divinyl 4 can be constructed based on a chromium-mediated coupling reaction between aldehyde 6 and β-keto ester derived vinyl triflate 5.

![Scheme 1.1](image)

The synthesis of aldehyde 6 in enantiopure form and the proof of principle for the formation of the seven-membered ring have been published recently (Scheme 1.2). Starting from furfural 7, (R)-phenylglycine (9) and 3,3-dimethylacryloyl chloride (8), the left-hand fragment 6 was synthesized through a sixteen-step sequence. This fragment was then coupled with the simple vinyl triflate 10 followed by a six-step transformation to provide divinyl 12. The ring closing metathesis took place smoothly on 12 to furnish the cycloheptadiene 13 which underwent dihydroxylation followed by further oxidation and methylation to complete the tetracycle (14) in enantiopure form. These results indicate that the synthesis of solanoeclepin A is possible once the "real" vinyl triflate 5 has become available.
The retrosynthesis of fragment 3 is delineated in Scheme 1.3. The tricyclic core containing the bicyclo[2.1.1]cyclohexanone skeleton of 5 can be constructed based on the key intramolecular [2+2] photocycloaddition of either dioxenone 17 or allene 16. Further functionalization of 15 should afford 5 and hence, solanoeclepin A. Parts of these studies have been published recently.13,14

1.4 Purpose and Outline of the Investigation

This thesis is devoted to the development of a synthetic strategy for the synthesis of the right-hand substructure 5 of solanoeclepin A. The major breakthrough involves the construction of the most intricate tricyclic core of 5 with the correct substitution patterns which allows further functionalization to complete the synthesis of solanoeclepin A. Chapter 2 presents the first generation approach towards the right-hand subunit 5 of the natural product based on an intramolecular [2+2] photocycloaddition of a 6-methylidioxenone. A
subsequent functional group transformation study on the photocycloadduct successfully introduces the cyclopropane moiety in a chemoselective fashion.

Further study on the photocycloaddition reaction leads to the second generation approach towards the right-hand fragment of solanoeclepin A. By using an allene butenolide as the photosubstrate, the tricyclic core of containing the bicyclo[2.1.1]hexane skeleton is efficiently constructed. Furthermore, several models of cyclic enones bearing an allene-containing substituent are prepared and irradiated in order to acquire knowledge on the regioselectivity of the intramolecular photocycloaddition of allenes. These results are presented in chapter 3.

Chapter 4 describes further chemistry developed for the model photocycloadduct towards the right-hand substructure. These functional group transformations successfully put in place the required structural features of solanoeclepin A, including the angular methyl, the secondary hydroxyl group and the cyclobutanone moiety, in the correct stereochemical arrangement.

The photochemistry behavior of several models of substituted allene butenolides is presented in chapter 5. This study is followed by the successful preparation and the completely regioselective photocycloaddition of the fully functionalized allene butenolide. This breakthrough led to the formation of the key photocycloadduct bearing the required substituents for the complete synthesis of fragment of solanoeclepin A.

Chapter 6 describes further chemistry on the key photocycloadduct towards the right-hand substructure of the natural product. These functional group transformations successfully install the bridgehead methyl group and especially, the crucial vinyl triflate, the connection handle for connecting the right- and the left-hand parts of solanoeclepin A. Initial results on the chromium-mediated coupling reaction between this vinyl triflate and the left-hand fragment is also described in this chapter. Parts of this thesis have been published or will be published in the near future.

1.5 References

15) Another approach towards the oxabicyclo[2.2.1]heptane segment of solanoeclepin A has been published very recently: Isobe, M; Tojo, S. Synthesis 2005, 1237.
Chapter 2

First Approach towards the Right-Hand Substructure of Solanoeclepin A: Intramolecular [2+2] Photocycloadditions of Dioxenones

2.1 Introduction

The distinctive tricyclic core containing the bicyclo[2.1.1]hexanone moiety contributes to the unique structural features of solanoeclepin A (1) (eq 2.1). Its compact nature and interesting structural characteristics render the right-hand substructure 3, and hence solanoeclepin A, an especially challenging target for total synthesis.

The most direct approach to the bicyclo[2.1.1]hexanone skeleton of 3 would be an intramolecular ketene olefin cycloaddition, but this process was expected to be unproductive based on a literature precedent. In the hope of achieving a fast construction of the cyclobutane containing tricyclic core of solanoeclepin A, we planned to make use of the intramolecular [2+2] photocycloadditon. In previous studies in our laboratory it was discovered that acetone sensitized irradiation of dioxenone 5 produced the bicyclo[2.1.1]cyclohexane skeleton of 6 in very high yield (Scheme 2.1). Exhaustive reduction of the cycloadduct 6 to tetraol 7 followed by chemoselective protection gave triacetate 8 which deemed to contain appropriate functionalities in the correct stereochemical arrangement for further elaboration toward the right-hand subunit 3.

Scheme 2.1
However, the C-6 methyl group seems to preclude the formation of the cyclobutanone although its presence has greatly facilitated the preparation of the dioxenone photosubstrate.

Alternatively, in order to avoid the disadvantage of the C-6 methyl group, the tricyclic core of fragment 3 could be constructed through photocycloaddition of 6-unsubstituted dioxenones. Initial investigations\(^3\) in this direction revealed that the intramolecular [2+2] photocycloaddition of unsubstituted dioxenone model 11 proceeds satisfactorily (eq 2.2). Further studies with the model cycloadduct 12 afforded the intermediate 13 containing the required substitution pattern for the synthesis of the right-hand fragment 3.

![Chemical structures and textual information](image)

Having achieved success with the model, we turned our attention to explore the potential of utilizing a dioxenone bearing an appropriate functional handle for connecting the right- and the left-hand fragments of solanoeclipin A. To meet that requirement, dioxenone 16 bearing a ketone protected as a dioxolane would be the photosubstrate of choice (Scheme 2.2). The critical installation of a β-keto ester derived vinyl triflate on the six-membered ring at a later phase of the synthesis would then complete the synthesis of the right-hand subunit 3.

**Scheme 2.2**

![Chemical structures and textual information](image)

For the preparation of the required cyclization precursor 16, it was our intention to make use of the silver trifluoroacetate mediated coupling reaction between silyloxyfuran 18 and allylic iodide 17 according to the procedure reported by Jefford et al.\(^4\) Thus, the first goal was the preparation of these two coupling components.
2.2 Preparation and Photoreaction of the 6-Unsubstituted Dioxenone

2.2.1 Preparation of the 6-Unsubstituted Dioxenone

Our efforts began with the preparation of iodide 17 as delineated in Scheme 2.3. Meldrum’s acid 10 was formylated using trimethyl orthoformate followed by hydrolysis to afford 19. The formylated Meldrum’s acid 19 was then converted into diacetate 24 based on a three-step procedure reported by Kaneko et al. In the course of this sequence, formylketene 20 formed in situ upon heating 19 in toluene with the loss of acetone and carbon dioxide, reacts with tert-BuOH and N,N-dimethylformamide dimethylacetal to give tert-butyl ester 21 in good yield. Compound 21 was then converted into the corresponding diformyl acetate 22 which subsequently underwent cyclocondensation with cyclohexanone in the presence of acetic anhydride and p-toluenesulfonic acid to provide 24 in 63%. The in situ formed ketene intermediate 23 from 22 is supposed to be involved in this reaction. Finally, treatment of diacetate 24 with triethylsilane in the presence of BF$_3$.OEt$_2$ effectively generated the monoacetate 25 which was converted into the corresponding iodide 17 in excellent yield through reaction with trimethylsilyl iodide. This two step procedure successfully produced the iodide 17 in good yield as a stable yellow crystalline solid (mp 59–60 °C).

With the iodide 17 in hand, we turned to the preparation of its eventual coupling partner, silyloxyfuran 18. Starting from the commercially available monoethylene acetal of 1,4-cyclohexanedione (26), butenolide 29 was synthesized through a four-step sequence as depicted in eq 2.3. Monomethoxycarbonylation was achieved in 90% yield with dimethyl carbonate by using sodium hydride in conjunction with potassium hydride. The enol 27 was subsequently converted into its triflate upon treatment with DIPEA and triflic anhydride followed by reduction of the ester moiety with DIBAL-H to give the allylic alcohol 28. Palladium-catalyzed carbonylation of the vinyl triflate finally furnished butenolide 29 in 85% overall yield as a stable crystalline solid (mp 100–104 °C).
In the preparation of triisopropylsilyl dienolate 18, our first effort relied on the use of excess triisopropylsilyl trifluoromethanesulfonate (TIPS-OTf) and LDA as a base in the presence of HMPA at -78 °C. However, these reaction conditions appeared to be too harsh as the product slowly decomposed upon work-up even at low temperature. Another drawback of this method was the irreproducible purification via vacuum distillation. These unsatisfactory results prompted us to look for a milder method. We were very pleased to find that exposure of butenolide 29 to TIPS-OTf and DIPEA\(^9\) in CH\(_2\)Cl\(_2\) at 0 °C to room temperature for 20 h furnished the desired silyloxyfuran 18 as remarkably clean oil which was used for the next step without any further purification (eq 2.4). The silver-mediated coupling reaction of 18 and iodide 17 (1.2 equiv) in CH\(_2\)Cl\(_2\) at -78 °C followed by addition of silver trifluoroacetate (1.2 equiv) led to the formation of the photochemistry precursor 16 in 60% yield.

A possible mechanism for the reaction is that the "soft" iodide is complexed by the silver cation, a "soft" Lewis acid, thereby enhancing the electrophilicity of the iodide toward nucleophilic attack by the silyloxyfuran in an S_N2 fashion to give the oxycarbenium ion II (Scheme 2.4). Subsequent desilylation of II by trifluoroacetate then provides dioxenone butenolide 16.

**Scheme 2.4**
First Approach towards the Right-Hand Substructure of Solanoelepin A: Intramolecular [2+2] Photocycloadditions of Dioxenones

The highly regioselective alkylation at the C-5 position of the eventual butenolide 16 under these mild conditions is noteworthy as the C-3 mono and dialkylated products are formed exclusively in the alkylation of the lithium furanolate 31 (eq 2.5).

\[
\begin{align*}
\text{furan-2(5H)-one} & \xrightarrow{\text{LDA, HMPA}} \text{LiO} & \text{RBr} \\
\end{align*}
\]

\[
\text{30} \quad \text{31} \quad \text{32} \quad \text{33} \quad \text{R} = \text{CH}_2\text{CH} = \text{CMe}_2
\]

2.2.2 Photocycloaddition of the 6-Unsubstituted Dioxenone

With the required C-6 unsubstituted dioxenone 16 in hand, our next goal was to examine its potential for photocycloaddition. It was our hope that the dioxenone 16 would give the same result as the analogue 11, lacking the dioxolane moiety (eq 2.2). Unfortunately, irradiation of precursor 16 at 300 nm, using a 9:1 mixture of acetonitrile and acetone as the solvent, did not give any cyclized adduct but led to the decomposition of the substrate (eq 2.6). This result is probably due to the instability of lactone dioxenone 16 under these cycloaddition conditions.

\[
\text{300 nm} \quad \text{CH}_3\text{CN / acetone (9:1, v / v)} \quad \text{X} \quad \text{16} \quad \text{15}
\]

In view of this disappointing result and the conception of an idea for a new synthetic strategy, we decided to abandon the approach of using unsubstituted dioxenones as photosubstrate and reinvestigate the application of C-6 methylated dioxenones.

2.3 Further Chemistry with the 6-Methyldioxenone Cycloadduct

As mentioned earlier in this chapter, by employing the 6-methyldioxenone 5 as a photosubstrate, the bicyclo[2.1.1]hexane skeleton of 6 could be constructed in very high yield (Scheme 2.1). Further chemistry with the cycloadduct led to the advanced intermediate 8 containing suitable functional groups to attain the right-hand fragment 3. However, the extra C-6 methyl group renders the formation of the cyclobutanone less obvious. Taking this into consideration, we envisioned that if the tertiary hydroxyl function could be converted into the xanthate 37 (Scheme 2.5), the latter could undergo, upon heating, elimination to the corresponding alkene 38. The conversion of this exocyclic methylene into the carbonyl in a later phase of the synthesis should be possible \textit{via} ozonolysis\textsuperscript{10} or an alternative oxidative cleavage procedure.\textsuperscript{11} In other words, the double bond would then function as a protective group for the ketone moiety although this presented an additional unsaturated site where
cyclopropanation could potentially take place. However, it is well known that alkenes of allylic alcohols are considerably more reactive towards cyclopropanation so that chemoselective cyclopropanation of an allylic alcohol in the presence of an alkene lacking an allylic hydroxyl group should be possible.\textsuperscript{12} We believed, therefore, that the introduction of the double bond \textit{via} pyrolysis of the xanthate would be advantageous.

\textbf{Scheme 2.5}

\begin{center}
\begin{tikzpicture}[scale=0.8]
\node at (0,0) {34};
\node at (2,2) {35};
\node at (4,0) {36};
\node at (6,2) {37};
\node at (8,0) {38};
\node at (10,2) {39};
\node at (1,1) {hv};
\node at (3,1) {1) LiAlH$_4$};
\node at (5,1) {2) protection};
\node at (7,1) {pyrolysis};
\node at (9,1) {PGO$^\circ$};
\end{tikzpicture}
\end{center}

\textbf{2.3.1 Preparation of the Xanthate and Pyrolysis}

The thermal decomposition of a xanthate into an olefin is well known as the Chugaev reaction.\textsuperscript{13} By far, the most commonly used xanthate is the S-methyl derivative. Like the ester analogue, pyrolysis of a xanthate is believed to proceed through an intramolecular pericyclic process (eq 2.7). The hydrogen is removed by the thiocarbonyl sulfur followed by a rapid decomposition of 42 into carbon oxy sulfide and methylmercaptan. In view of the higher temperature required for ester pyrolysis which might cause thermal rearrangement of the products of elimination, the Chugaev reaction has been found much wider application.

\begin{center}
\begin{equation}
\begin{array}{c}
\begin{tikzpicture}[scale=0.8]
\node at (0,0) {40};
\node at (2,2) {41};
\node at (4,0) {42};
\node at (6,3) {COS} ;
\node at (8,3) {CH$_3$SH};
\end{tikzpicture}
\end{array}
\end{equation}
\end{center}

While many xanthates of primary and secondary alcohols are reported in the literature, xanthates of tertiary alcohols have been rarely characterized.\textsuperscript{14} This is due to the frequent instability of tertiary xanthates towards elimination to give olefins or rearrangement to give S-alkyl dithiocarbonates. These reactions are believed to proceed \textit{via} tertiary carbocations. Keeping this in mind, we commenced our studies with the synthesis of xanthate 47 as a model system, starting from alcohol 46\textsuperscript{2} (Scheme 2.6).
First Approach towards the Right-Hand Substructure of Solanoelepin A: Intramolecular \([2+2]\) Photocycloadditions of Dioxenones

There is a large body of literature on the synthesis of O-alkyl S-methyl dithiocarbonates by the reaction of alcohols with \(\text{CS}_2\) and \(\text{MeI}\) in the presence of base.\(^{14}\) The success of the dithiocarbonylation of alcohol 46 appeared to depend strongly on the base and the reaction temperature. An alkoxide induced ring opening of the tricyclic core could occur easily leading to decomposition of the substrate. In early work,\(^2\) KHMDS appeared to be the best base for the deprotonation of alcohol 46. Thus alcohol 46 was treated with KHMDS at –78 °C for 1 h followed by addition of carbon disulfide and methyl iodide, successively. In this way, the desired xanthate 47 was successfully isolated in 60% yield (eq 2.8). Xanthate 47 turned out to be reasonably stable and could be purified by column chromatography. This stability has undoubtedly to do with the cyclobutane nature preventing formation of a tertiary carbocation. Interestingly, elimination can only occur in an exocyclic fashion as the two adjacent cyclobutane carbons are quaternary.

Thus, upon heating at reflux in xylene for 1 h, pyrolysis of 47 took place smoothly furnishing alkene 48 in 60% yield. The formation of the exocyclic methylene moiety of 48 is clearly apparent by the presence of two singlets at 4.72 and 4.34 ppm in its \(^1\)H NMR spectrum. The tricyclic core of olefin 48 was surprisingly stable under the reaction conditions despite the fact that solanoelepin A is stable only at a temperature below 35 °C. Other parts of the molecule are, therefore, responsible for this thermal instability.

The success of this olefin transformation offered a possibility for the preparation of the cyclobutanone moiety by turning the presence of the C-6 methyl group into an advantage. At this stage of our synthetic work, it was our interest to investigate whether the cyclobutanone moiety could be indeed obtained from the exocyclic methylene function. An ideal approach for this functional group transformation would be the ozonolysis of the double bond. This procedure was successfully
applied for methylenecyclobutane (49) (eq 2.9) to form the corresponding cyclobutanone (50) in good yield. It was our hope, therefore, that this methodology would be applicable for olefin 48 to generate the desired cyclobutanone function.

\[
\begin{align*}
\text{49} & \quad 1) \text{O}_3/\text{CH}_2\text{Cl}_2 \quad \text{CH}_3\text{OH}, -78 \, ^\circ\text{C} \\
& \quad 2) (\text{NH}_2)_2\text{CS} / \text{NaHCO}_3 \\
\text{50} & \quad 71\%
\end{align*}
\]

Unfortunately, treatment of methylene cyclobutane 48 in dichloromethane at -78 °C with ozone followed by reductive workup with dimethyl sulfide led only to decomposition of the starting material (eq 2.10). This is likely due to the instability of the tricyclic core of 48 under these oxidative cleavage conditions. A more efficient procedure is, therefore, required for the success of this transformation.

\[
\begin{align*}
\text{48} & \quad 1) \text{O}_3 / \text{CH}_2\text{Cl}_2 \quad \text{MeOH}, -78 \, ^\circ\text{C} \\
& \quad 2) \text{Me}_2\text{S} / \text{NaHCO}_3 \\
\text{51} & \quad \text{OTBS}
\end{align*}
\]

### 2.3.2 Chemoselective Cyclopropanation

With the desired olefin in hand, our next goal was to further investigate the chemistry required for the completion of the right hand substructure 3. Especially, the issue of chemoselective cyclopropanation was our first concern. From previous work and also from literature precedent, we planned to construct the cyclopropane ring based on a Simmons-Smith cyclopropanation of an allylic alcohol. For the preparation of the required Simmons-Smith precursor, the chemoselection of the three hydroxyl groups, especially the two rather similar primary alcohols, was obviously not an easy task. In line with the previous results the use of a catalytic amount of camphorsulfonic acid (CSA) might lead to selective hydrolysis of the primary TBS-ethers and would leave the secondary one intact. Thus, treatment of olefin 48 with 10 mol% of CSA in a mixture of CH2Cl2 and MeOH at 0 °C led to the formation of diol 52 in a yield of 67% (eq 2.11). Upon oxidation of the two primary alcohols using the mild Dess-Martin periodinane, dialdehyde 53 was efficiently isolated which was used for the next step without purification. Interestingly, treatment of 53 with TBAF affected liberation of the secondary hydroxyl group which subsequently cyclized with the nearby aldehyde moiety to form lactol 54 in reasonable yield as a single diastereomer. The relative stereochemistry at the lactol stereocenter is unknown.
The aldehyde function of the lactol 54 was available for further transformation toward the required allylic alcohol. This aldehyde moiety was expected to be a good precursor for the next Horner-Emmons reaction step.\textsuperscript{17} We envisioned that by carefully controlling the amount of the reagents used, homologation of the aldehyde moiety could be accomplished without protection of the lactol. Thus, lactol 54 was treated with the \textit{in situ} formed anion of ethyl 2-(diethoxyphosphoryl)acetate (55) in THF at 0 °C for 1 h leading to the desired (E)-\(\alpha,\beta\)-unsaturated ester 56 in good yield (eq 2.12).

\[
\begin{array}{ccc}
\text{HO} & \text{O} & \text{O} \\
\text{H} & \text{H} & \text{O} \\
54 & \text{EtO} & \text{OEt} \\
\text{KHMDS, THF} & \rightarrow & \text{HO} & \text{CO}_2\text{Et} \\
 & & \text{56} & \text{83\%} \\
\end{array}
\]

The (E)-olefin 56 was expected to give the \textit{trans}-substituted cyclopropane moiety \textit{via} the Simmons-Smith cyclopropanation. In early studies, it was found that the application of Charette’s reagent\textsuperscript{18} on the model allylic alcohol 57 led to the desired \textit{trans}-cyclopropane in good yield although with a slight preference for the undesired diastereoisomer (eq 2.13).\textsuperscript{15}

\[
\begin{array}{ccc}
\text{OTES} & \text{Zn(\text{CH}_2\text{I})_2.DME} & \text{CH}_2\text{Cl}_2 \\
\text{57} & \rightarrow & \text{OTES} & \text{OH} \\
 & & \text{H} & \text{OH} \\
 & & \text{58} & \text{88 \% (60:40)} \\
\end{array}
\]

It was hoped that the same conditions as applied for model 57 could bring about the chemoselective cyclopropanation of allylic alcohol 60 which was prepared in modest yield by DIBAL reduction of the ester moiety of 56 (eq 2.14).

\[
\begin{array}{ccc}
\text{HO} & \text{O} & \text{CO}_2\text{Et} \\
\text{60} & \text{46\%} & \text{DIBAL-H} & \text{CH}_2\text{Cl}_2, -78 \degree \text{C} \\
\end{array}
\]

Unfortunately, treatment of 60 with Charette’s reagent led only to decomposition of the starting material. A plausible explanation for this result is that the zinc carbenoid deprotonates the free hydroxyl group of the lactol moiety leading to ring opening of the tetracyclic system.

To prevent this side reaction, the lactol moiety of 56 was protected as an acetal using trimethyl orthoformate under acidic conditions\textsuperscript{19} to afford \(\alpha,\beta\)-unsaturated ester 62 in good yield as a 3:1 mixture of two diastereoisomers (eq 2.15). Subsequent reduction of the ester moiety using DIBAL at -78 °C produced the desired allylic alcohol 63 in good yield.
With the trans-allylic alcohol 63 (3:1 mixture of two diastereoisomers) containing the protected lactol moiety in hand, we could subsequently examine its suitability for a Simmons-Smith chemoselective cyclopropanation reaction. Subjection of 63 to Charette’s reagent in CH$_2$Cl$_2$ at -78 °C led, interestingly, to the formation of the desired cyclopropane 64 in 50% yield as an inseparable mixture of four diastereoisomers (eq 2.16).

The ratio of the two major isomers was close to 50:50. Cyclopropanation only took place at the allylic double bond in view of the characteristic presence of four singlets of two exocyclic methylene groups (from the two major isomers) from 5.00 ppm to 4.50 ppm in $^1$H NMR. The stereoselectivity of the cyclopropanation, however, was not yet fully determined due to lack of material although it has been observed very often that trans-cyclopropanes are normally formed under Simmons-Smith cyclopropanation of trans-allylic alcohols.

The success of this sequence of reactions proves the feasibility of our synthetic strategy towards the right-hand subunit 3. By installing the exocyclic methylene moiety, the cyclobutanone function can be put in place via oxidative cleavage methodology. Introduction of the cyclopropane carboxylic acid moiety can be accomplished by chemoselective cyclopropanation of an allylic alcohol without interference of the other double bond.

### 2.3.3 Generation of the Bridgehead Methyl Group

With the cyclopropane ring installed chemoselectively, our next goal was to investigate possibilities for generating the angular methyl group from the lactol moiety. Towards that end, compound 64, in principle, would be a good precursor for further transformation. However, lack of this material led us to commence our study with a simpler system and lactol 54 was our first choice (eq 2.17). The highly strained tetracyclic core of 54 was expected not to be stable under chemical transformations which involved radical or cation intermediates. Radical or cation formation would lead to rearrangement, and hence, decomposition of the substrate. A process involving a carbanion intermediate would be feasible for the generation of the bridgehead methyl group. Our first attempt relied on the deoxygenation of the lactol to form the methyl group via base treatment of a hydrazone
intermediate. This reaction is often referred to as the Wolff-Kishner reduction. Alkali metal hydroxide or alkoxide is normally used as the base catalyst. High temperatures (180-190 °C) are normally required and use of excess of hydrazine is necessary for the success of the reaction.

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

In principle, the Wolff-Kishner reduction can be performed on substrates containing free hydroxyl groups. We hoped that the desired hydrazone intermediate could be formed directly from the lactol moiety. Thus, the aldehyde function of lactol 54 was selectively reduced by NaBH₄ in MeOH at ~78 °C to give lactol 66 in good yield (eq 2.18). Unfortunately, when heating lactol 66 at reflux in a mixture of ethylene glycol and n-BuOH in the presence of excess hydrazine and potassium hydroxide, only decomposition of the substrate was observed. This result suggests the instability of lactol 66 or product 68 under harsh alkaline conditions. A competitive radical decomposition of the diazene intermediate might also account for the failure of this sequence.

\[
\text{54} \quad \begin{array}{c}
\text{H} \\
\text{O}
\end{array} \quad \text{Me}
\]

A modified procedure which utilizes hydride reduction of p-toluenesulfonylhydrazone (tosylhydrazone) has been recently recommended to offer much milder conditions compared to those of the Wolff-Kishner reduction. However, this methodology failed to give compound 68. These unsatisfactory results indicate that more efficient methods need to be developed for installing the bridgehead methyl group.

2.4 Conclusions

In this chapter a straightforward synthetic pathway towards the right-hand substructure 3 of solanoeclepin A is described. By employing the methyl substituted dioxenone 43 as a photosubstrate, the [2+2] photocycloaddition occurred smoothly to give the cycloadduct 44 in good yield. Exhaustive reduction of the cycloadduct followed by protection gave alcohol 46 which was efficiently transformed into the corresponding xanthate 47 in good yield. Pyrolytic elimination successfully converted the xanthate into olefin 48 in reasonable yield. The success of this transformation offered a possibility for the introduction of the cyclobutanone moiety at the later stage of the synthesis. Successful chemoselective cyclopropanation was accomplished by a Simmons-Smith protocol.
although a mixture of diastereoisomers was obtained. The generation of the angular methyl group, however, failed under the usual Wolff-Kishner conditions or the modified deoxygenation of the tosylhydrazone. Therefore, other efficient procedures need to be developed for the completion of the right-hand subunit 3 of solanoecepin A.

2.5 Acknowledgments

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2.6 Experimental Section

General information. All reactions involving oxygen or moisture sensitive compounds were carried out under a dry nitrogen atmosphere. THF and Et₂O were distilled from sodium/benzophenone and CH₂Cl₂ was distilled from CaH₂. DMF and toluene were distilled from CaH₂ and stored over 4 Å molecular sieves. Triethylamine was stored over KOH pellets. DMSO was dried and stored over 4 Å molecular sieves. Column chromatography was performed using Acros silica gel (0.030-0.075 mm). Petroleum ether (PE, 60/80) used for chromatography was distilled prior to use. TLC analyses were performed on Merck F-254 silica gel plates. IR spectra were measured using a Bruker IFS 28 FT-spectrophotometer and wavelengths ($\nu$) are reported in cm⁻¹. ¹H NMR spectra were recorded on a Bruker AC 200 (200 MHz), a Bruker ARX 400 (400 MHz) and Varian Inova (500 MHz). The latter machines were also used for ¹³C NMR spectra (50, 100 and 125 MHz, respectively). Unless otherwise indicated, CDCl₃ was used as the solvent. Chemical shifts are given in ppm ($\delta$) relative to an internal standard of chloroform (7.26 ppm for ¹H NMR and 77.0 for ¹³C NMR). Mass spectra and accurate mass determinations were performed on a JEOL JMS SX/SX102A, coupled to a JEOL MS-MP7000 data system. Elemental analyses were performed by Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany.

Synthesis of monoacetate 25

To a stirred solution of 24a (5.96 g, 20 mmol) in CH₂Cl₂ (100 mL) at -25 °C was added Et₃SiH (31.9 mL, 10 equiv) and BF₃OEt₂ (7.61 mL, 3 equiv). The resulting mixture was stirred at -20 °C for 2 h and cooled to -25 °C. Another portion of BF₃OEt₂ (5.1 mL, 2 equiv) was added and the reaction mixture was stirred at -20 °C for additional 3.5 h and then poured into aqueous saturated solution of NaHCO₃ (100 mL). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3x50 mL). The combined organic layers were washed with brine (300 mL), dried over MgSO₄, and concentrated in vacuo to
afford 25 which was used for the next step without further purification. \(^1\)H NMR: 7.32 (s, 1 H), 4.71 (s, 2 H), 2.06 (s, 3 H), 2.05 – 1.92 (m, 4 H), 1.76 – 1.55 (m, 6 H).

**Synthesis of iodide 17**

To a stirred solution of 25 (4.00 g, 16.67 mmol) in CH₂Cl₂ (50 mL) at 0 °C was added TMSI (2.97 mL, 1.2 equiv). The resulting mixture was stirred at rt for 1.5 h and solvent was evaporated. The residue was dissolved in CH₂Cl₂ (50 mL). The organic layer was washed with ice-cold 10% aqueous Na₂S₂O₃ (50 mL), saturated solution of NaHCO₃ (50 mL), brine (50 mL), dried over MgSO₄, and concentrated *in vacuo* to afford 17 (5.82 g, 94%) as a yellow solid (mp 59–60 °C) after purification by column chromatography (PE:EtOAc= 2:1). \(^1\)H NMR: 7.35 (s, 1 H), 4.05 (s, 2 H), 2.03 – 1.93 (m, 4 H), 1.72 – 1.43 (m, 6 H). \(^1\)C NMR: 159.3, 154.8, 109.2, 108.4, 34.1, 24.2, 21.9, -4.67. Elemental analysis: calcd for C₁₀H₁₃O₃I C: 38.98%, H: 4.25%; found C: 39.06%, H: 4.33%. IR (neat): 2939, 1732, 1628, 1210.

**Synthesis of butenolide 29**

To a stirred solution of β-ketoester 27\(^8\) (8.56 g, 40 mmol) in CH₂Cl₂ (100 mL) at –78 °C was added dropwise DIPEA (35 mL, 5 equiv) and triflic anhydride (8.1 mL, 1.2 equiv). The reaction mixture was warmed to rt for 4 h, and then stirred for 18 h. The reaction mixture was washed with ice-water (100 mL), 10% aqueous solution of citric acid (2x100 mL), dried over MgSO₄ and concentrated *in vacuo*. The residue was dissolved in EtOAc and filtered over silica and solvent was evaporated to afford the crude vinyl triflate (14.45 g) as a yellow oil which was used for the next step without purification. \(^1\)H NMR: 4.05 - 3.96 (m, 4 H), 3.80 (s, 3 H), 2.67 - 2.62 (m, 4 H), 1.90 (t, J = 6.4 Hz, 2 H). To a stirred solution of the crude triflate (3.46 g) in THF (75 mL) at –78 °C was added DIBAL-H (1.5 M in toluene, 15.3 mL, 2.3 equiv) over 40 min. The resulting mixture was stirred at –78 °C for 2 h and allowed to warm to rt. Saturated aqueous Na₂SO₄ was then added at 0 °C. After stirring for 1 h at rt, solid Na₂SO₄ was added. The mixture was stirred for 2 days at rt and filtered through Celite® and concentrated *in vacuo* to afford the crude alcohol 28 (3.06 g, 96%) which was used for the next step without further purification. \(^1\)HNMR: 4.19 (s, 2 H), 4.02 - 3.97 (m, 4 H), 2.60 - 2.50 (m, 4 H), 1.90 (t, J = 6.4 Hz, 2 H). CO was bubbled through a solution of the crude 28 (3.06 g), Pd(PPh₃)₄ (25.55 mg, 5 mol%) and LiCl (20 mg, 5 mol%) in MeCN (30 mL) for 20 min. To this solution was added Et₃N (2.7 mL) and the resulting mixture was refluxed for 7 h under an atmosphere of CO (1 bar, balloon). After cooling to rt, the reaction mixture was filtered over Celite® and concentrated in vacuo. The residue was purified by flash chromatography (PE:EtOAc=1:1) affording the desired butenolide 29 (1.59 g, 86% from 27 as white crystals (Rf = 0.17). Mp: 100-104 °C. IR: 2935, 1755, 1682. \(^1\)H NMR: 4.67 (t, J = 2.6 Hz, 2 H), 4.02 (s, 4 H), 2.56 (s, 2 H), 2.48 - 2.42 (m, 2 H), 1.87 (t, J = 6.4 Hz, 2 H). \(^1\)C NMR: 173.0, 158.5, 126.0, 107.6, 71.1, 64.7, 34.5, 30.7, 18.9. HRMS (El+) calcd for C₁₀H₁₂O₄ 196.07, found 196.0733.
Chapter 2

Synthesis of silyloxyfurane 18
To a stirred solution of lactone 29 (70 mg, 0.35 mmol) in CH₂Cl₂ (5 mL) at 0 °C was added dropwise trisopropylsilyl triflate (0.15 mL, 1.3 equiv) and diisopropylethylamine (0.1 mL, 2 equiv). The reaction mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with ice-cold saturated aqueous NH₄Cl (5 mL). The layers were separated and the aqueous phase was extracted with ether (3x10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄, and concentrated in vacuo to afford 18 as a colorless oil, which was used for the next step without further purification. ¹H NMR: 6.58 (s, 1 H), 4.02 – 3.99 (m, 4 H), 2.69 (s, 2 H), 2.54 (t, J = 6.6 Hz, 2 H), 1.83 (t, J = 6.6 Hz, 2 H), 1.31 – 1.17 (m, 3 H), 1.08 (s, 6 H), 1.06 (s, 6 H), 1.04 (s, 6 H).

Synthesis of unsubstituted lactone dioxenone 16
To a suspension of silver trifluoroacetate (41 mg, 1.05 equiv) in CH₂Cl₂ (5 mL) at –78 °C was added solution of iodide 17 (55 mg, 1.05 equiv) in CH₂Cl₂ (1 mL) followed by solution of crude silyloxy furane 18 (60 mg) in CH₂Cl₂ (1 mL). The reaction mixture was stirred at –78 °C for 20 min, then at –20 °C for 3 h and at rt overnight. The mixture was filtered through Celite® and solvent was concentrated in vacuo. Purification by chromatography (PE:EtOAc=2:1) afforded the desired product as a lightly yellow oil (39 mg, 60%). (Rf = 0.11). ¹H NMR: 7.05 (s, 1 H), 5.00 – 4.90 (m, 1 H), 4.25 (s, 2 H), 4.00 – 3.90 (m, 4 H), 2.80 – 2.20 (m, 5 H), 2.00 – 1.40 (m, 11 H). ¹³C NMR: 172.1, 161.1, 156.4, 127.5, 107.7, 107.5, 102.2, 79.9, 64.8, 64.6, 60.3, 34.5, 33.8, 32.3, 30.9, 27.8, 24.5, 22.1, 22.0, 19.1. HRMS (FAB) calcd for C₂₀H₂₅O₇ (MH⁺) 377.16, found 377.1604. IR: 2940, 1755, 1724.

Synthesis of the xanthate 47
To a solution of alcohol 46 (900 mg, 1.54 mmol) in freshly distilled THF (15 mL) at –78 °C was added dropwise KHMDs in THF (0.5 M in toluene, 6 mL, 2 equiv). The resulting mixture was stirred at –78 °C for 1 h and then carbon disulfide was added (0.5 mL, 5 equiv). The reaction mixture was then warmed up to –10 °C and stirred for an additional 2 h. Methyl iodide (0.5 mL, 5 equiv) was added and the reaction mixture was warmed to rt and stirred for 1.5 h. The reaction was quenched by saturated aqueous NH₄Cl (15 mL). The layers were separated and the aqueous phase was extracted with ether (3×15 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (3% Et₃N in PE) afforded the xanthate 47 (623 mg, 60%) as a colorless oil. Rr = 0.4. ¹H NMR: 4.48 (dd, J = 2 Hz, J = 11 Hz, 1 H), 3.95 (d, J = 11 Hz, 1 H), 3.89 (dd, J = 3 Hz, J = 7 Hz, 1 H), 3.82 (d, J = 11 Hz, 1 H), 3.28 (d, J = 11 Hz, 1 H), 2.54 (s, 3 H), 2.4 (dd, J = 7 Hz, J = 13 Hz, 1 H), 2.17-2.11 (m, 1 H), 1.97 - 1.75 (m, 1 H), 1.76 - 1.72 (m, 4 H), 1.69 - 1.20 (m, 6 H), 0.89 - 0.87 (m, 27 H), 0.18 - 0.00 (m, 18 H). ¹³C NMR: 212.3, 99.1, 71.6, 62.4, 61.4, 59.5, 58.5, 50.2, 36.8, 29.5, 25.73, 25.71, 25.5, 25.2, 21.57, 21.50, 20.2, 19.5, 17.98, 17.91, 17.8, 17.7. IR: 2928, 2855, 1471, 1234, 1064.
Synthesis of olefin 48
A solution of the xanthate 47 (224 mg, 0.33 mmol) in xylene (5 mL) was added drop wise to boiling xylene (5 mL) and the resulting mixture was refluxed for 1.5 h and concentrated in vacuo. Purification by chromatography (5% Et3N in PE) afforded olefin 48 (147 mg, 78%) as a colorless oil. Rf = 0.43. 1H NMR: 4.72 (s, 1 H), 4.35 (d, J = 12 Hz, 1 H), 4.34 (s, 1 H), 3.85 (dd, J = 2 Hz, J = 7 Hz, 1 H), 3.79 - 3.73 (m, 2 H), 3.38 (d, J = 11 Hz, 1 H), 1.50 - 1.10 (m, 7 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.04 (s, 6 H), 0.01 (s, 6 H), 0.00 (s, 6 H). 13C NMR: 157.4, 93.3, 73.2, 61.2, 61.0, 60.6, 59.5, 47.1, 38.4, 25.77, 25.71, 25.6, 25.5, 25.3, 21.8, 21.2, 20.4, 18.0, 17.9, 17.7, -4.9, -5.2, -5.5, -5.7, -5.81, -5.88. IR: 2930, 2857, 1471, 1255, 1066.

Synthesis of diol 52
To a solution of olefin 48 (260 mg, 0.459 mmol) in CH2Cl2 /MeOH (8 mL, 9:1, v/v) at 0 °C was added CSA (13.5 mg, 0.11 equiv). The reaction mixture was allowed to warm to rt and stirred for 4 h. The reaction was quenched by addition of saturated aqueous NaHCO3 (10 mL). The layers were separated and the aqueous phase was extracted with ether (3×10 mL). The combined organic layers were washed with brine (40 mL), dried over MgSO4 and concentrated in vacuo to afford crude dialdehyde 53 that was used for the next step without purification. 1H NMR: 9.9 (s, 1 H), 9.8 (s, 1 H), 4.9 (s, 1 H), 4.6 (s, 1 H), 4 (d, J = 4 Hz, 1 H), 2.3 - 1.2 (m, 8 H), 0.9 (s, 9 H), 0.1 (s, 6 H).

Synthesis of lactol 54
To a stirred solution of Dess-Martin periodinane (Aldrich) (0.4 g, 3 equiv) in CH2Cl2 (2 mL) at rt was added solution of diol 52 (100 mg, 0.295 mmol) in CH2Cl2 (2 mL). The reaction mixture was stirred at rt for 1 h and ether (5 mL) was added. The suspended mixture was poured into 1.3 M aqueous NaOH (7 mL) and the aqueous layer was extracted with ether (3×10 mL). The combined organic layers were washed with brine (40 mL), dried over MgSO4 and concentrated in vacuo to afford crude dialdehyde 53 that was used for the next step without purification. 1H NMR: 9.9 (s, 1 H), 9.8 (s, 1 H), 4.9 (s, 1 H), 4.6 (s, 1 H), 4 (d, J = 4 Hz, 1 H), 2.3 - 1.2 (m, 8 H), 0.9 (s, 9 H), 0.1 (s, 6 H).

To a solution of crude dialdehyde 53 in THF (3 mL) at 0 °C was added TBAF (1M in THF) (0.5 mL, 2 equiv). The resulting mixture was allowed to warm to rt and stirred for 1 h. The reaction was quenched by addition of saturated aqueous NaHCO3 (5 mL). The layers were separated and the aqueous phase was extracted with ether (3×5 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO4 and concentrated in vacuo. Purification by chromatography (PE/EtOAc = 1:1) afforded lactol 54 (38 mg, 60% over two steps) as a colorless oil and as a single diastereoisomer (Rf = 0.3). 1H NMR: 9.85 (s, 1 H), 5.53 (d, J = 4 Hz, 1 H), 4.97 (s, 1 H), 4.64 (s, 1 H), 4.31 (d, J = 4 Hz, 1 H), 3.49 (d, J = 4 Hz, 1 H), 2.51 (d, J = 11 Hz, 1 H), 2.08 (dd, J = 4 Hz, J = 11 Hz, 1 H), 2.06
- 1.05 (m, 8 H). $^{13}$C NMR: 200, 149, 99, 96, 81, 65, 63, 60, 37, 20.8, 20.7, 20.6, 19. IR: 3401, 2931, 2861, 1710, 800.

**Synthesis of $\alpha,\beta$-unsaturated ester 56**

To a solution of triethylphosphonoacetate (43.4 $\mu$L, 1.2 equiv) in THF (3 mL) was added KHMDS (0.5 M in toluene) (1.3 mL, 1.2 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and the solution of lactol 54 (40 mg, 0.18 mmol) in THF (3 mL) was added drop wise. The resulting mixture was stirred for 30 min and warmed to rt. Saturated aqueous NH₄Cl (10 mL) was added and the mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with ether (3x10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄ and concentrated in vacuo.

Purification by chromatography (PE:EtOAc=1.5:1) afforded ester 56 (43.3 mg, 83%) (Rf = 0.32). $^1$H NMR: 7.04 (d, J = 16 Hz, 1 H), 6.02 (d, J = 16 Hz, 1 H), 5.52 (s, 1 H), 4.68 (s, 1 H), 4.51 (s, 1 H), 4.27 (d, J = 4.5 Hz, 1 H), 4.18 (q, J = 7 Hz, 2 H), 3.50 - 3.30 (br, 1 H), 2.34 (d, J = 11 Hz, 1 H), 1.96 (dd, J = 5 Hz, J = 11 Hz, 1 H), 1.87 - 1.77 (m, 2 H), 1.62 - 1.25 (m, 5 H), 1.28 (t, J = 7 Hz, 3 H), 1.25 - 1.06 (m, 1 H). $^{13}$C NMR: 166.4, 153.3, 143.0, 122.8, 100.0, 94.3, 81.9, 64.1, 60.1, 58.7, 58.5, 39.8, 20.8, 20.6, 20.5, 19.2, 14.0. IR: 3394, 2938, 1706, 1650.

**Synthesis of allylic alcohol 60**

To a stirred solution of ester 56 (53 mg, 0.18 mmol) in toluene (5 mL) at -78 °C was added drop wise DIBAL-H (1.5 M in toluene, 0.6 mL, 5 equiv). The resulting mixture was warmed to -60 °C and stirred for 3 h. The reaction was carefully quenched with EtOAc and saturated aqueous Na₂SO₄ (10 drops) were added. The mixture was stirred for 1 h. After addition of solid Na₂SO₄ the mixture was filtered through Celite® and concentrated in vacuo.

Purification by chromatography (EtOAc) afforded allylic alcohol 60 (20 mg, 46%) as a colorless oil and as a 9:1 unseparable two diastereoisomers (Rf = 0.33). $^1$H NMR (Benzene, major diastereoisomer): 5.87 (s, 2 H), 5.25 (s, 1 H), 4.65 (s, 1 H), 4.37 (s, 1 H), 4.13 (d, 1 H), 3.61 (s, 2 H), 2.50 (d, 1 H), 1.82 (dd, 1 H), 1.75-0.75 (m, 8 H).

**Synthesis of protected lactol 62**

To a solution of the lactol 56 (175 mg, 0.6 mmol) in CH₂Cl₂ (10 mL) was added at rt trimethylorthoformate (0.8 mL, 12 equiv) and PPTS (45 mg, 0.3 equiv). The reaction mixture was stirred at rt overnight. The reaction was quenched by saturated aqueous NaHCO₃ (10 mL). The layers were separated and the aqueous phase was extracted with ether (3x10 mL). The combined organic layers were washed with brine (40 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (PE:EtOAc=4:1) afforded the product 62 (157 mg, 87%, 3:1 mixture of two diastereoisomers) as a colorless oil (Rf = 0.43). IR: 2923, 1710, 1650. $^1$H NMR (major): 6.99 (d, J = 16 Hz, 1 H), 5.97 (d, J = 16 Hz, 1 H), 5.00 (s, 1 H), 4.68 (s, 1 H), 4.51 (s, 1 H), 4.25 (d, J = 4.6 Hz, 1 H), 4.19 (q, J = 7 Hz, 2 H), 3.41 (s, 3 H), 2.24 (d, J = 11 Hz, 1 H), 1.92 - 1.84 (m, 2 H), 1.75 (d, J = 11 Hz, 2 H), 1.61 - 1.32 (m 4 H), 1.29 (t, J = 7 Hz, 3 H), 1.11 - 0.89 (m, 1 H).
Synthesis of allylic alcohol 63
To a solution of ester 62 (66 mg, 0.217 mmol) in CH₂Cl₂ (3 mL) at -78 °C was added dropwise DIBAL-H (1.5 M in toluene, 0.4 mL, 3 equiv). The resulting mixture was stirred at -78 °C for 1 h and allowed to warm to rt. The reaction was carefully quenched with EtOAc and saturated aqueous Na₂SO₄ (10 drops) were added. The mixture was stirred for 1 h. After addition of solid Na₂SO₄ the mixture was filtered through Celite® and concentrated in vacuo. Purification by chromatography (PE:EtOAc=1:1) afforded allylic alcohol 63 (45 mg, 81%) as a colorless oil and as an unseparable 4:1 mixture of two diastereoisomers (Rₜ = 0.3). ¹H NMR (major): 5.88 - 5.75 (m, 2 H), 4.99 (s, 1 H), 4.63 (s, 1 H), 4.45 (s, 1 H), 4.23 (d, J = 4.6 Hz, 1 H), 4.15 - 4.14 (m, 2 H), 3.39 (s, 3 H), 2.19 (d, J = 11 Hz, 1 H), 1.86 - 1.78 (m, 2 H), 1.72 - 1.67 (m, 2 H), 1.59 - 1.34 (m, 4 H), 1.11 - 1.06 (m, 1 H). ¹³C NMR (mixture): 155.9, 154.8, 132.0, 131.5, 126.9, 125.3, 107.3, 104.7, 93.4, 82.1, 79.8, 63.6, 63.5, 63.3, 58.7, 58.5, 57.1, 56.6, 39.3, 38.5, 22.0, 21.0, 20.8, 20.79, 20.73, 20.2, 19.6, 19.3.

Synthesis of cyclopropyl methyl alcohol 64
To a solution of allylic alcohol 63 (13 mg, 0.049 mmol) in CH₂Cl₂ (0.5 mL) at -78 °C was added dropwise ZnEt₂ (1 M in hexane, 50 µL, 1 equiv). The reaction mixture was stirred at -78 °C for 1 h and the previously prepared Zn(CH₂I)₂.DME reagent¹⁵ (340 µL, 2 equiv) was added. The resulting mixture was allowed to warm to rt and stirred for 6 h. Saturated aqueous NH₄Cl (2 mL) was added at 0 °C and the mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with ether (3×5 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (PE:EtOAc=1.5:1) afforded the desired product 64 (7.5 mg, 56%) as a mixture of 4 diastereoisomers. (Rₜ = 0.3). ¹H NMR (two major isomers): 4.98 (s, 1 H), 4.96 (s, 1 H), 4.66 (s, 1 H), 4.64 (s, 1 H), 4.42 (s, 1 H), 4.41 (s, 1 H), 4.15 (d, J = 4.7 Hz, 1 H), 4.13 (d, J = 4.7 Hz, 1 H), 3.71 (br, 1 H), 3.46 (d, J = 6.9 Hz, 1 H), 3.41 (s, 3 H), 3.39 (s, 3 H), 3.06 (t, J = 10, 1 H), 1.85 - 1.06 (m, 20 H), 0.98 – 0.76 (m, 2 H), 0.75 – 0.50 (m, 2 H), 0.49 – 0.34 (m, 2 H), 0.33 – 0.30 (m, 2 H).

Synthesis of alcohol 66
To a solution of aldehyde 54 (10 mg, 0.047 mmol) in MeOH (1 mL) at -78 °C was added NaBH₄ (5.5 mg, 3 equiv). The resulting reaction mixture was stirred at -78 °C for 30 min and then saturated aqueous NaHCO₃ (2 mL) was added and the mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (PE:EtOAc=1:2) afforded the desired product 66 (9.5 mg, 92%) as a single diastereoisomer. (Rₜ = 0.3). ¹H NMR: 5.41 (s, 1 H), 4.50 (s, 1 H), 4.41 (s, 1 H), 4.25 (d, J = 2.5 Hz, 1 H), 4.75 (d, J = 8 Hz, 1 H), 4.61 (d, J = 8 Hz, 1 H), 2.37 (d, J = 14 Hz, 1 H), 1.98 – 1.75 (m, 3 H), 1.70 – 1.00 (m, 7 H).
2.7 References


Chapter 3

Second Approach towards the Right-Hand Substructure of Solanoeclepin A:
Intramolecular [2 + 2] Photocycloadditions of Allenes*

3.1 Introduction

As described in chapter 2, the tricyclic core containing the bicyclo[2.1.1]hexanone skeleton of
the right-hand substructure 3 was successfully constructed based on a [2+2] photocycloaddition
reaction of dioxenone 1 (Scheme 3.1). Exhaustive reduction of the cycloadduct 2 followed by selective
protection gave alcohol 4 which was subsequently converted into the corresponding xanthate. The
Chugaev elimination reaction of this xanthate took place smoothly to provide olefin 5 in good yield.
Further transformations on olefin 5 eventually led to intermediate 6 with the cyclopropane moiety
being introduced chemoselectively.

\[
\text{Scheme 3.1}
\]

The photocycloaddition of the dioxenone 1 proceeded satisfactorily with the lactone
connection being essential to obtain the desired crossed regioselectivity. The C-6-methyl(dioxenone
moiety, however, caused not only instability of the cycloadduct 2 but also regiochemical complications
in the later phase of the synthesis, involving the differentiation between this moiety and the five-
membered lactone. These drawbacks limit the application of this methodology for the synthesis of the
right hand fragment, and hence, solanoeclepin A. Therefore, a more suitable strategy was required.

Compound 5 contains the tricyclic core of fragment 3 with the exocyclic methylene group as a
possible protective group for the ketone moiety. This double bond was introduced through a four step
sequence from the photocycloadduct 2. Taking this into consideration we envisioned that the
structural motif of olefin 5 could also be assembled in a single step using an intramolecular [2+2]
photocycloaddition of butenolide 8 (Scheme 3.2). This photochemistry precursor would preserve the advantage of the lactone function. The allene moiety is anticipated to remedy the problems associated with the dioxenone functionality. Reductive opening of the lactone moiety of the photocycloadduct 7 should eventually lead to the angular methyl and the hydroxyl functions in the correct stereochemical arrangement. The introduction of the cyclopropenecarboxylic acid moiety and the vinyl triflate would conclude the synthesis of the right-hand substructure 3. We believed, therefore, that the use of allene butenolide 8 as a photosubstrate would allow a more efficient synthetic approach towards the right-hand fragment 3, and hence, solanoeclepin A.

In order to establish the feasibility of this new synthetic strategy, we planned to initially investigate the intramolecular [2+2] photocycloaddition of a model system of 8 (R=H, PG=H₂). In addition, several cyclic α,β-unsaturated carbonyl compounds bearing allene substituents were prepared and irradiated in order to acquire knowledge on the regioselectivity of the intramolecular photocycloaddition of allenes.

3.2 Intramolecular [2+2] Photocycloaddition of the Model Allene Butenolide

When we began our study on allenes only one example of an intramolecular [2+2] photocycloaddition of a fused α,β-unsaturated γ–lactone with an allene in the side chain at the γ–position had been reported. Coates et al. studied the photochemistry of the homologous system 10 and found only low regioselectivity (eq 3.1). The cycloadduct 11 was formed predominantly along with a nearly 2:1 mixture of adducts 12 and 13, respectively.

\[
\begin{align*}
\text{10} & \xrightarrow{\text{hv}} \text{11} & 33\% \\
& \quad \text{12} & 16\% & \quad \text{13} & 7\%
\end{align*}
\]
Therefore, at this stage of our synthetic work, we decided to first investigate the allene butenolide 15 as the photosubstrate (eq 3.2) because of its ready accessibility. Furthermore, cycloadduct 14, once formed, was expected to be an excellent model for further chemical transformation studies toward the right hand fragment 3 of solanoeclepin A. Chemistry of the real photocycloadduct 7 could be developed based on this model.

\[
\begin{align*}
&\text{14} \quad \text{AgOCOCF}_3 \quad \text{TIPSO} \quad \text{15} \\
&\text{Br} \quad \text{16} \quad \text{17}
\end{align*}
\]

The required allene 15 was prepared via Jefford’s coupling procedure\(^3\) between silyloxyfuran 16 and allene bromide 17. As presented in the previous chapter, an allyl iodide proved to be a good coupling partner under silver-mediated coupling reaction conditions (see section 2.2.1). However, the use of an allenylmethyl bromide such as 17 as the coupling component in this type of reaction, to our knowledge, had not been reported. We hoped that allene bromide 17 would react as a regular allyl bromide, thus allowing the nucleophilic substitution by the silyloxyfuran 16.

We started our synthetic work with the preparation of bromide 17 according to a literature procedure (eq 3.3).\(^4,5\) Treatment of the commercially available 2-butyn-1,4-diol (18) with SOCl\(_2\) in pyridine gave the corresponding 4-chloro-2-butyn-1-ol (19) which was reduced by lithium aluminum hydride to afford the desired 1,2-butadiene-4-ol (20) in reasonable yield.\(^4\) The alcohol (20) was subsequently converted into bromide 17 upon reaction with PBr\(_3\).\(^5\)

\[
\begin{align*}
&\text{18} \quad \text{SOCl}_2 \quad \text{pyridine} \quad \text{Cl} \quad \text{19} \\
&\text{LiAlH}_4 \quad \text{ether} \quad \text{OH} \quad \text{17} \\
&\text{PBr}_3 \quad 0 \degree \text{C to rt} \quad \text{Br} \quad \text{61%}
\end{align*}
\]

This three step procedure can be conveniently performed on large scale to give the desired allene (17) in an acceptable overall yield. The main drawback of this methodology is a fact that 4-chloro-2-butyn-1-ol (19) is a severe skin irritant which may cause serious allergic reactions. There is alternative method reported in the literature,\(^6\) but in our hand this was not so successful.

With the required bromide 17 in hand, we turned to the synthesis of its eventual coupling partner, the silyloxyfuran 16 as outlined in Scheme 3.3. The commercially available cyclic anhydride 21 was selectively reduced with NaBH\(_4\) in THF\(^7\) to give the known butenolide 22,\(^8\) which was then treated with TIPSO\(_2\)F and Hünig’s base\(^9\) in CH\(_2\)Cl\(_2\). In this way, the desired triisopropylsilyl dienolate 16 was cleanly obtained as colorless oil which was used for the next step without further purification. Upon treating a mixture of enol ether 16 and bromide 17 in dichloromethane with silver trifluoroacetate at -78 °C, the desired photochemistry precursor 15 was obtained in 64% overall yield from furanone 22. Two main byproducts could be isolated from this reaction, namely the parent butenolide 22 and an allenic trifluoroacetate, resulting from the reaction between bromide 17 and the
trifluoroacetate anion. If this is the case, the use of an excess of 17 with respect to silyloxyfuran 16 should increase the yield of the coupling reaction. However, the lack of substantial quantities of 17 hampered further study for optimizing the coupling reaction conditions. The success of this reaction shows the usefulness of bromide 17 as a coupling partner in Jefford’s procedure.

Scheme 3.3

With the allene butenolide 15 successfully synthesized, its intramolecular [2+2] photocycloaddition reaction was then investigated. The key photoreaction was carried out on a 50 mM solution of 15 in a 9:1 v/v acetonitrile/acetone mixture. Complete conversion of the starting material was observed after 5 h of irradiation. The $^1$H NMR spectrum of the crude material showed the formation of a single product, which was isolated as a crystalline solid (mp 125–127 °C) in 70% yield. The $^1$H NMR spectrum of the cyclized adduct clearly showed that it was the result of cycloaddition of the internal allene double bond in view of the presence of two singlets of an exocyclic methylene group (H-14) at 4.76 and 4.56 ppm (Fig. 3.1). In addition, the two singlets at 4.61 and 2.94 ppm correspond to the final hydrogen atoms of the lactone (H-9) and the cyclobutane ring (H-7), respectively. The structure of 14 was then proven by X-ray analysis (Fig. 3.2).

Figure 3.1 $^1$H NMR spectrum (6.0 - 0.5 ppm) of the photocycloadduct 14
Mechanistically, it has been accepted for photocycloadditions between alkenes and enones that the initial excitation of the enone is $\pi \rightarrow \pi^*$ triplet.\textsuperscript{10} This triplet species reacts with the double bond, with the first bond formation at C-β of the enone, leading to a triplet 1,4-diradical intermediate which, after spin inversion, closes to the product. This hypothesis has also been established for the photocycloadditions between allenes and enones.\textsuperscript{11} The origin of the regioselectivity in intermolecular\textsuperscript{12} and intramolecular\textsuperscript{11} photocycloadditions of such substrates have been recently discussed. Based on those studies, a possible mechanistic interpretation for the formation of the crossed adduct 14, obtained in the photocyclization of allene 15, is given in the following Scheme 3.4.

Scheme 3.4

Reaction of the excited $\alpha,\beta$–unsaturated lactone with the allene can lead, in principle, to the formation of three different triplet 1,4-diradicals: one contains an allylic moiety resulting from
bonding of the excited triplet enone to the central carbon of the allene (path a), one from bond formation to the internal carbon (path b), and one from the attack to the terminal carbon of the allene (path c). The 1,4-diradical intermediate II, containing the allylic fragment, is expected to be lower in energy than the other diradicals III and IV.\textsuperscript{12} After spin inversion, closure of the diradical intermediate II leads to the formation of two possible cycloadducts 14 and 23 while closure of III or IV leads only to adduct 24 or 25, respectively. Adducts 14 and 25 are called crossed products while 23 and 24 are known as straight products. Because reversions of 1,4-diradical intermediates to starting material may also occur, the distribution of the products is then interpreted as depending on the competition of the particular 1,4-diradicals between reversion to reactant and closure to products.

The formation of product 14 indicates that the excited lactone intermediate I initially attacks the central carbon of the allene moiety with the first bond formed to C-\(\beta\) of the lactone (path a). The process proceeds via a five-membered ring diradical intermediate II. This diradical intermediate, after spin inversion, closes to the crossed adduct 14. The straight cycloadduct 23 is not formed. The other two possible products 24 and 25, resulting from the addition of the excited enone intermediate I to the internal and terminal carbons of the allene moiety (path b and c, respectively) are not detected.

The regioselectivity observed in the photocycloaddition of allene butenolide 15 follows the empirical "rule of five"\textsuperscript{13} which states that formation of a five-membered ring is favored in the initial reaction of diradical I with an alkene. A six-membered ring is formed only if a five-membered ring is not possible. The low regioselectivity in the photoreaction of the homologous allene 10 with a penta-3,4-dienyl side chain reported by Coates (eq 3.1)\textsuperscript{2} may be explained by the fact that 5-membered ring formation in this case gives a less stable vinyl radical V (eq 3.4), so that other cyclization modes can compete.

\[
\begin{align*}
\text{hv} & \quad \text{O} \quad \text{O} \\
\text{O} & \quad \text{O} \\
10 & \quad \text{V} \quad \rightarrow \\
& \quad \text{11} (3.4)
\end{align*}
\]

The success of the photoreaction of 15 confirms the feasibility of our new concept of utilizing allene butenolides as photosubstrates. The compact tricyclic core, containing the exocyclic methylene group of the right hand substructure 3 of solanoeclepin A, e.g. cycloadduct 14, was successfully constructed in a single step based on a completely regioselective intramolecular [2+2] photocycloaddition of allene butenolide 15. Cycloadduct 14 contains the appropriate functional handles for introducing the bridgehead methyl and the hydroxyl group in the correct chemical arrangement, and especially, the cyclobutanone moiety. Further studies on functional group transformations of this cycloadduct model would, therefore, provide the basis for the complete synthesis of the right hand fragment 3, and hence, solanoeclepin A.

The highly interesting and promising results from the photocycloaddition of allene butenolide 15 also led us to study the intramolecular [2+2] photocycloaddition of several other models in order to acquire more knowledge on this process and assess its general synthetic utility.
3.3 Literature Review on the Intramolecular [2+2] Photocycloaddition of Cyclic α,β–Unsaturated Cycloalkenones with Allene Substituents

Conjugated cyclic enones substituted with a carbon chain with an α-allene moiety are interesting substrates for intramolecular [2+2] photocycloaddition. The ring size of the enone, and the length and the position of the side chain have significant effects on the regioselectivities. Substitutions on the enone ring and the side chain also strongly influence the stereochemical outcome of the reaction. Enantiopure allenes tethered to enones and enoates were reported to undergo stereoselective intramolecular photocycloadditions, with high levels of asymmetric induction derived exclusively from the allene chirality.

The first intramolecular [2+2] photocycloaddition of an allene connected to an enone was performed by Wiesner et al. in the synthesis of 12-epi-lycopodine. The bicyclic vinylogous imide was reported to give the straight adduct in 70% yield (eq 3.5). This high regioselectivity follows the empirical "rule of five".

![](image)

Dauben et al. also reported a straight (parallel) mode of cyclization in the intramolecular photocycloaddition of α,β-unsaturated cyclohexenones and (eq 3.6). Lengthening of the chain was found to cause loss of regioselectivity. The straight cycloadduct was formed as the sole product in the case of three carbon atoms separating the unsaturations. The degree of selectivity, however, decreased dramatically when the allene and the enone double bonds were separated by four carbon atoms although the straight adduct was still the main product.

![](image)

Interestingly, the opposite effect was observed in the intramolecular photocycloaddition of the analogous α,β–unsaturated cyclopentenones and (eq 3.7). Irradiation of gave a 3:1 mixture of adducts and while the homologue gave the straight adduct as the sole product. Apparently, these results show the importance of the ring size of the cycloalkenone for the regioselectivity of the photocycloaddition reaction. The "rule of five" appears to control the bonding order with initial bond formation between C-β of the enone and the internal carbon atom of the allene.
Loss of regioselectivity on increasing the chain length was also observed by Becker et al.\textsuperscript{14c} in the photocycloaddition of enones 38 and 39 bearing the allene substitute at the β–position (eq 3.8). Allene 38 gave only straight cycloadduct 40 in quantitative yield while the homologue 39 gave a 85:15 mixture of 41 and 43, respectively.

The same regioselectivity was observed by Carreira et al.\textsuperscript{16} in the intramolecular [2+2] photocycloaddition of a variety of enantiopure allenes connected to enones by three atom chains (eq 3.9). High levels of asymmetric induction were reported, controlled exclusively by the allene chirality.

It can be summarized at this point, concerning the regioselectivity in the intramolecular [2+2] photocycloaddition of allenes with enones, that α,β–unsaturated enones bearing at the β– or γ–position an allene-containing sidechain in which the allene is three or four carbons (or hetero atoms) away from the enone double bond, cyclize in a straight fashion. This mode of closure follows the empirical "rule of five". The length of the allenyl sidechain and the size of cycloalkenone affect the degree of regioselectivity. In the case of cyclohexenone, lengthening of the chain tether causes loss of regioselectivity while the opposite effect is observed in the case of cyclopentenone.

These literature precedents prompted us to explore the regioselectivity of the intramolecular [2+2] photocycloaddition of enones with allenes with the double bonds separated by two atoms,
either two carbon atoms or a carbon and a heteroatom. It was our hope that this study would not only expand the scope of the photocycloaddition of allenes, but also provide more information on our new concept for the construction of the compact tricyclic core of solanoeclepin A.

3.4 Preparation and Photocyclization of Cyclic \( \alpha,\beta \)-Unsaturated Carbonyl Compounds with Allenes

3.4.1 A \( \gamma \)-Substituted Butenolide

The high regioselectivity obtained in the case of allene 15 led us to investigate whether the simple butenolide 47 (eq 3.10) would give a similar result in the intramolecular photocycloaddition. Like allene 15, the preparation of butenolide 47 relied on Jefford’s coupling procedure between the commercially available silyloxyfuran 46 and bromide 17. According to this method, the desired allene butenolide 47 was isolated in 53% yield. A possible explanation for the modest yield of this coupling reaction is the undesired reaction of bromide 17 with the trifluoroacetate anion as seen before in the case of allene 15. The intramolecular photocycloaddition of butenolide 47 was then investigated. Irradiation of 47 at 300 nm for 1.5 h using acetone as a triplet sensitizer resulted exclusively in the expected crossed adduct 48 in 53% yield (eq 3.10). The starting material and decomposition were also observed along with the product under these unoptimized reaction conditions. Like in the case of 14, the exocyclic methylene moiety of 48 is readily assigned by two singlets at 4.60 and 4.55 ppm in the \( ^1 \)H NMR spectrum. The correct structure of 48 is fully verified by \( ^1 \)H NMR COSY and HETCOR experiments. Formation of the crossed adduct 48 again shows the great preference for 5-membered ring formation according to the "rule of five", as observed in the case of butenolide 15.

\[
\begin{align*}
\text{TMSO} &\quad \text{Br} &\quad \text{AgOCOCF}_3 \\
46 &\quad 17 &\quad \text{CH}_2\text{Cl}_2 \\
&\quad -78 \degree \text{C to rt} &\quad \text{MeCN/acetone} (9:1, v/v), 1.5 \text{ h} \\
\rightarrow &\quad 47 &\quad 53\% \\
\text{hv} &\quad 48 &\quad 53\% \\
\end{align*}
\]  
(3.10)

The structural motif of 48 is found in compound 51 (eq 3.11), the key intermediate for the synthesis of ABHxD-I, a potent mGluR agonist.\(^{18}\) In this synthesis, however, the bicyclo[2.1.1]hexane moiety of ketone 51 was constructed based on a Wolff rearrangement of diazoketone 50, which was in turn synthesized through a six step sequence, starting from the commercially available 5-norbornen-2-ol 49.

\[
\begin{align*}
\text{HO} &\quad 6 \text{ steps} &\quad \text{MeO} \\
49 &\quad \text{5-norbornen-2-ol} &\quad 50 \\
\rightarrow &\quad 51 &\quad 2 \text{ steps} \\
\end{align*}
\]  
(3.11)
3.4.2 A γ-Substituted α,β–Unsaturated Cyclohexenone

Our next substrate for investigation was the conjugated cyclohexenone 55 (eq 3.12) having the allene connected at C-4. This type of substrate has not been as widely applied in photocycloaddition as the C-2 and C-3 substituted derivatives. It was our interest to determine whether the "rule of five" would also regulate the process. Thus, the allene 55 was prepared in a straightforward fashion as depicted in eq 3.12.

\[
\begin{align*}
\text{O} & \xrightarrow{1) \text{LDA, -78 °C}} \text{OEt} \\
& \xrightarrow{2) \text{HCCCH}_2\text{Br}} \xrightarrow{(\text{HCHO})_n \text{DIPA, CuI}} \xrightarrow{1) \text{LiAlH}_4 \ 2) \text{HCl}} \text{OEt}
\end{align*}
\]

(3.12)

Starting from the commercially available enol ether 52, alkylation with propargyl bromide was accomplished under kinetic conditions using LDA at -78 °C to give the α′-alkylated product 53 in reasonable yield.\(^{19}\) Homologation of the ethynyl group to an allenyl function with addition of one carbon atom was conducted as previously described by Crabbé \textit{et al}.\(^{20}\) to give the desired allene 54 in acceptable yield. The ketone moiety of the intermediate 54 was then reduced with LiAlH\(_4\) to give the corresponding β-hydroxy enol ether which was subsequently hydrolyzed using aq HCl.\(^{21}\) In this way, the required cyclohexenone 55 was isolated in moderate yield.

Cyclization precursor 55 was then subjected to irradiation at 300 nm using acetone as sensitizer (Scheme 3.5). A complete conversion of the starting material was observed after 30 min and the expected crossed adduct 56 was formed as the exclusive regioisomer in very good yield. The formation of product 56 again indicates that the "rule of five" regulates the process. The reaction proceeds via a five-membered ring diradical intermediate VII, which subsequently cyclizes to the crossed adduct 56. As expected, the more strained and therefore less stable straight cycloaduct 57 is not formed. The structure of the crossed adduct 56 was established based on the basis of \(^1\text{H} \text{NMR NOE, COSY and HETCOR experiments.}

\textbf{Scheme 3.5}

\[
\begin{align*}
\text{O} & \xrightarrow{300 \text{ nm \ MeCN/Acetone (9:1, v/v)}} \text{O} \\
55 & \xrightarrow{hv} \xrightarrow{\text{VI}} \xrightarrow{\text{O}^*} \text{O}^* \\
\text{VI} & \xrightarrow{\text{VII}} \text{O} \\
56 & \xrightarrow{80\%} \text{VII} \\
57 & \text{(not observed)}
\end{align*}
\]
It can be concluded at this point that the allene moiety in compound 55 adds intramolecularly to the cyclohexenone double bond in very high regioselectivity. Only the crossed adduct is formed after the first bond formation. In line with the results obtained by Dauben, the "rule of five" appears to be superior if two or three carbon atoms separate the allene and the enone double bond.

3.4.3 A β-Substituted α,β-Unsaturated Cyclohexenone

In view of the high regioselectivity obtained with cyclohexenone 55, we wished to further investigate the effect of the position of the allene-containing sidechain on the regiochemical outcome of the intramolecular photocycloaddition. Towards this end, we examined the irradiation of α,β-unsaturated cyclohexenone 58 (eq 3.13). Attempts to prepare this photosubstrate by Becker et al.\textsuperscript{14c} were reported to be unsuccessful. Our synthetic plan for this photochemical precursor is presented in eq 3.13. Like the synthesis of allene 55, acid-catalyzed hydrolysis of β-hydroxyl enol ether\textsuperscript{21} 59 would give the required α,β-unsaturated cyclohexenone having the substituent at the C-3 position. The enol ether intermediate 59 could be prepared by reaction of the Grignard 60 with the commercially available enol ether 52.

Starting from the commercially available homopropargylic alcohol 61 (Scheme 3.6), hydroxyl group activation via methanesulfonation followed by displacement gave bromide 62 in modest yield. Treatment of bromide 62 with an excess of Mg in refluxing THF in the presence of a few drops of 1,2-dibromoethane for 2 h gave the desired Grignard 60 which was then added to enol ether 52 followed by hydrolysis using 2 N aqueous HCl to afford enone 63 in good yield.

The reaction temperature was found to be crucial for the successful preparation of the Grignard reagent 60. Only 30% yield of the desired unsaturated ketone 63 was achieved when 60 was prepared at lower temperature. Finally, desilylation of 63 using K\textsubscript{2}CO\textsubscript{3} in methanol effectively
liberated the free acetylene which was subsequently converted into the allene under Crabbé reaction conditions. This sequence gave the desired photosubstrate 58 in good yield.

With the desired allene 58 in hand, we turned to explore its photochemical behavior in an intramolecular fashion in order to compare the outcome with Becker’s results on the homologue 38 and also with that of allene 55, concerning the regioselectivity. Thus compound 58 was subjected to the photocycloaddition conditions using cyclohexane as solvent (eq 3.14). Complete conversion of the starting material was observed after 1 h of irradiation and, to our surprise, only the straight cycloadduct 65 was obtained. This cycloadduct proved to be rather unstable and decomposed slowly upon column chromatography. We reasoned that hydrogenation of the double bond of the photoprodut 65 would stabilize the system. Indeed, the saturated ketone 66 was produced although in an overall yield of only 27% over two steps. The tricyclic ketone 66 was found to be stable and amenable to further structural characterization based on 1H NMR COSY and HETCOR experiments, thereby providing proof for the correct structure of cycloadduct 65. The relative stereochemistry of 66 is unknown.

The previously described saturated ketone 66 was reported to be the sole product in the intramolecular [2+2] photocycloaddition of the analog 67 (eq 3.15). This straight mode of closure also follows the empirical “rule of five”.

Formation of 65 again indicates that diradical intermediate VIII cyclizes via bond formation to the central carbon of the allene moiety, following the “rule of five” (Scheme 3.7). This is a general trend as observed in Becker’s cases and allene 55. This reaction mode leads to formation of an allylic diradical intermediate IX but subsequent closure of this 1,4-diradical gave only the straight adduct 65. This is a surprising result as the straight adduct is considered to be more strained than the crossed adduct 68. The decomposition observed during purification of 65 points to the instability of this straight cycloadduct. This result suggests that further modeling studies by molecular mechanics need to be carried out in order to explain for the formation of the straight cycloadduct 65.
Similar to allene 58, the "rule of five" was found to control the photocycloaddition of the analogous homoallylic cyclohexanone 69 (eq 3.16). However, different from 58, five-membered ring formation in the case of 69 can lead only to the crossed product 70. The straight mode of closure was also observed giving 71 as the minor product.

In order to explore whether hetero atoms in the sidechains would affect the regioselectivity in the intramolecular [2+2] photocycloaddition, several cyclic enones in which the allenes are attached to C-3 of the enones separated by two atoms: one carbon and one nitrogen (or oxygen), were prepared and irradiated. When we started our studies, no precedent on the photoreaction of this type of allenic substrate, to our knowledge, had been reported yet.

### 3.4.4 β-Heteroatom Substituted α,β-Unsaturated Cyclohexenones

We began our studies with the preparation of the N-containing allene enone 75 as delineated in Scheme 3.8. Refluxing commercially available enol 72 and propargylamine in benzene under the typical Dean-Stark conditions gave the desired vinylpropargylamine 73 in good yield.

![Scheme 3.7](image-url)
The vinylogous amide was then protected as the tert-butyl carbamate. Use of an excess of (Boc)$_2$O was necessary to achieve high yield of N-Boc protected amine 74. Removal of the excess (Boc)$_2$O was efficiently accomplished by using inexpensive imidazole as reported by Hassner et al.\textsuperscript{25} Finally, homologation of the terminal alkyne moiety to the corresponding allene under the Crabbé reaction conditions\textsuperscript{20} provided the desired allene 75 in very good yield.

The oxygen analogue 77 was also efficiently prepared in a similar straightforward fashion as outlined in eq 3.17. Vinylpropargyl ether 76 was formed in good yield by reaction of 72 with propargylalcohol under the Dean-Stark conditions.\textsuperscript{24c} Homologation of the terminal alkyne group to an allenyl group eventually gave the allene 77 in an acceptable yield.

\[
\text{72} \xrightarrow{\text{pTsOH (cat)}} \text{76} \quad \text{78\%} \quad \text{76} \xrightarrow{(\text{CH}_2\text{O})_n, \text{DIPA, CuI}} \text{77} \quad \text{61\%}
\]

(3.17)

With the required precursors in hand, we set out to investigate the photochemical behavior of this type of substrates in the intramolecular [2+2] photocycloaddition. The first photoreaction was carried out on the allene 75. This is obviously an interesting precursor as Tamura et al.\textsuperscript{26} already reported the photocycloaddition of the vinylogous imide 78 (eq 3.18). The exclusively crossed mode of closure gave a ca. 1:1 mixture of two possible isomers 79 and 80.

\[
\text{78} \xrightarrow{\text{hv, ether}} \text{79} + \text{80} \quad (52:48)
\]

(3.18)

Irradiation of allene 75 at 300 nm for 25 min, using MeCN as solvent, resulted in the formation of a 75:17:8 mixture of three products (eq 3.19). The major product showed two doublets at 7.12 and 5.98 ppm in the $^1$H NMR spectrum with the characteristic ortho coupling constant of pyrrole (J = 3.4 Hz). The two minor cycloaducts showed four singlets at 4.69, 4.67, 4.54 and 4.42 ppm, which would come from the two exocyclic methylene moieties of the crossed adducts 82 and 83. Only the major and one of the two minor cycloaducts could be isolated upon column chromatographic purification. These two cycloaducts were crystalline solids and appeared, after recrystallization, suitable for crystal structure determinations by X-ray diffraction (figure 3.3). The crystal structures revealed that the major cycloaduct obtained in the photocycloaddition of allene 75 was, in fact, the pyrrole 81 (mp 119-121 °C) and one of the two minor products was the crossed adduct 82 (mp 103-104 °C), with a trans-fusion between the six- and the five-membered rings.

In view of similarity in chemical shifts between the two minor cycloaducts, as shown in $^1$H and $^{13}$C NMR spectra of the crude product after the photoreaction, we envisioned that the inseparable
minor adduct would be the *cis*-fused isomer \(83\), as observed by Tamura.\(^{26}\) If that were the case, a base induced epimerization should convert the less stable *cis*- isomer to the more stable *trans*-fused isomer.

\[
\begin{align*}
\text{MeCN, rt, 15 min} &
\begin{array}{c}
\text{hv (300 nm)} \\
\end{array} &
\begin{array}{c}
\text{MeCN, rt, 15 min} \\
\end{array} \\
\end{align*}
\]

\(75\) \quad \begin{array}{c}
\text{hv (300 nm)} \\
\end{array} \quad \begin{array}{c}
\text{MeCN, rt, 15 min} \\
\end{array} \\
\end{align*}

\begin{align*}
\text{O} &
\text{N} &
\text{Boc} \\
\text{h} &
\end{align*}

\begin{align*}
\text{O} &
\text{N} &
\text{Boc} \\
\text{h} &
\end{align*}

(3.19)

Figure 3.3 X-ray structures of (a) pyrrole \(81\) and (b) the crossed adduct \(82\)

To check if the *cis*-fused isomer \(83\) was formed, the crude product obtained after the photoreaction was treated with a catalytic amount of DBU in CH\(_2\)Cl\(_2\). This led to a clean mixture of pyrrole \(81\) together with only the crossed adduct \(82\), as shown in the crude \(^1\)H NMR spectrum (eq 3.20). Purification by column chromatography eventually provided the pyrrole \(81\) and the adduct \(82\) in yields of 70 and 15\%, respectively.

\[
\begin{align*}
\text{O} &
\text{N} &
\text{Boc} \\
\text{h} &
\end{align*}

\begin{align*}
\text{O} &
\text{N} &
\text{Boc} \\
\text{h} &
\end{align*}

(3.20)

In line with the results achieved with allene \(58\), and also with Tamura’s substrates,\(^{26}\) the formation of pyrrole \(81\) can be attributed to the initial formation of the straight adduct \(84\) (eq 3.21). This straight cycloadduct is expected to be unstable, due to the strained ring, and readily undergoes a retro-Mannich fragmentation to give the N-acyliminium ion intermediate \(85\). Subsequent proton transfer of the intermediate \(85\) provides the final pyrrole ring \(81\). The energy release of the strained cyclobutane in combination with the energy gain by resonance stabilization of the pyrrole is probably the driving force for this rearrangement.
The use of acetone as a sensitizer in the photoreaction of allene 75 was found much less effective. Only 17% of pyrrole 81 could be isolated after purification. The UV absorption spectrum of pyrrole 81 shows no significant absorption at 300 nm. This suggests that the decomposition observed in the photoreaction of allene 75 is likely due to the indirect excitation of pyrrole 81 by energy transfer from the excited acetone followed by bond cleavage of the resulting excited state of the pyrrole product.

For comparison with the results obtained on allene 75, allene 77 was also irradiated at 300 nm using a 9:1 mixture of CH$_3$CN/acetone as solvent. Complete conversion of starting material was observed after 3 h of irradiation. The $^1$H NMR spectrum of the crude product showed the formation of one major photocycloadduct along with unidentified adducts. The purification of the major adduct by column chromatography was quite difficult. Only 32% yield of the major product could be separated in pure form which was determined to be the furan 86 (Scheme 3.9). The formation of 86 is verified by the presence of two doublets at 7.17 and 6.17 ppm in the $^1$H NMR spectrum with the characteristic ortho coupling constant of furan (J=1.7 Hz).

Scheme 3.9

The formation of 86 from 77 is probably a consequence of a retro-aldol fragmentation of the straight cycloadduct 87 followed by proton transfer of the formed oxocarbenium 88 to provide the final aromatic furan ring. The poor yield of this photoreaction might be due to the presence of acetone, as already observed in the case of allene 75. Further studies may eventually improve the yield of this photoreaction. At this stage of our studies, however, it can be concluded that the straight mode of closure is preferred over the crossed fashion in the photoreaction of allene 77.

The photocycloaddition of the alkenyl analog 89 was already reported by Tamura et al.$^{26}$ (eq 3.22). Like allene 77, the "rule of five" was found to regulate the process leading only to the crossed product 90 in good yield.
In summary, the intramolecular [2+2] photocycloadditions of cyclohexenones with an allene substituent at C-3 as in 75 and 77 proceed regioselectively, with the first bond formation following the "rule of five". Subsequent closure of the five-membered diradical intermediates gives predominantly the straight cycloadducts. Heteroatom-induced fragmentations of the straight cyloadducts eventually give the corresponding pyrrole and furan. This result, apparently, confirms the utilities of allenes as useful substrates in the intramolecular [2+2] photocycloaddition.

3.5 Conclusions

This chapter describes the new concept of utilizing an allene butenolide in an intramolecular [2+2] photocycloaddition reaction to construct the compact tricyclic core, containing the bicyclo[2.1.1]hexanone skeleton of solanoeclepin A. The regioselective photocyclization of allene butenolide 15 exclusively led to the tetracyclic adduct 14 which contains appropriate substituents for further functional group transformations towards the right hand fragment 3. Furthermore, several other cyclic α,β-unsaturated carbonyl compounds with allene substituents were prepared and irradiated in order to acquire knowledge concerning the regioselectivity in the intramolecular photocycloaddition. The "rule of five" was found to be obeyed in most cases. These studies not only expand the scope of the intramolecular photocycloaddition but also provide the basis for our new strategy toward the synthesis of solanoeclepin A.

3.6 Acknowledgments

Jan Dijkink is gratefully acknowledged for the large scale preparation of allene bromide 17 and also for pioneering studies on the photocycloaddition of model 15. Ginger Lutteke, Ana Cristina Correia, Pauli Wrigstedt and Rana Al Hussainy are kindly acknowledged for their contributions to this chapter. Jan Fraanje and Kees Goubitz are kindly thanked for the crystal structure determination of cycloadduct 14. Dr. René de Gelder and Jan M. M. Smits (Radboud University Nijmegen) are kindly acknowledged for crystal structure determinations of pyrrole 81 and cycloadduct 82.

3.7 Experimental Section

General information. For general experimental details, see Section 2.6.

4-Bromo-buta-1,2-diene (17)

To alcohol 20 (4.26 g, 61 mmol) at 0 °C was added PBr₃ (2.1 mL, 0.37 equiv). The mixture was stirred at 0 °C for 15 min and at room temperature for an additional 15 min. The reaction mixture was poured onto ice and extracted with ether (6x20 mL). The combined
organic layers were washed with brine, dried over MgSO₄ and solvent was removed by distilling at atmospheric pressure. The product was distilled under reduced pressure (bp 49-55 °C/65 mbar) to afford bromide 17 (4.95 g, 61%) as a colorless liquid. ¹H NMR: 5.48 - 5.40 (m, 1 H), 4.94 - 4.91 (m, 2 H), 3.97 - 3.94 (m, 2 H). ¹³C NMR: 209.5, 89.1, 76.6, 29.7.

4,5,6,7-Tetrahydro-3H-isobenzofuran-1-one (22)

To a stirred suspension of NaBH₄ (950 mg, 25.1 mmol) in THF (70 mL) at 0 °C was added dropwise over 2 h a solution of 3,4,5,6-tetrahydrophthalic anhydride 21 (3.8 g, 25.0 mmol) in THF (100 mL). The reaction mixture was stirred at 0 °C for 1 h and at rt for another 1 h. The reaction mixture was cooled to 0 °C and acidified with 2 M HCl (until pH 3). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2 R 100 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ (300 mL) and brine (300 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (PE:EtOAc=2:1) afforded 22 (2.13 g, 15.4 mmol, 60%) as a colorless solid, mp 56-57 °C (lit. mp 53-54 °C). ¹H NMR: 4.67 (br s, 2 H), 2.30 (m, 2 H), 2.22 (m, 2 H), 1.75 (m, 4 H). ¹³C NMR: 174.1, 160.9, 126.0, 71.8, 23.3, 21.3, 21.2, 19.7. IR (CHCl₃): 1735, 1678.

Triisopropyl-(4,5,6,7-tetrahydro-isobenzofuran-1-yloxy)-silane (16)

To a stirred solution of lactone 22 (100 mg, 0.72 mmol) in CH₂Cl₂ (2 mL) at 0 °C was added dropwise triisopropylsilyl triflate (250 X L, 285 mg, 0.93 mmol) and diisopropylethylamine (251 X L, 186 mg, 1.44 mmol). The reaction mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with ice-cold saturated aqueous NH₄Cl (2 mL). The layers were separated and the aqueous phase was extracted with ether (3 R 10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄, and concentrated in vacuo to afford 16 as a colorless oil, which was used for the next step without further purification. ¹H NMR: 6.55 (s, 1 H), 2.46 (m, 2 H), 2.34 (m, 2 H), 1.63 (m, 4 H), 1.21 (m, 3 H), 1.07 (m, 18 H).

3-(Buta-2,3-dienyl)-4,5,6,7-tetrahydro-3H-isobenzofuran-1-one (15)

To a solution of the crude silyloxyfuran 16 and 1-bromobuta-2,3-diene (17) (144 mg, 1.08 mmol, 1.5 equiv) in CH₂Cl₂ (25 mL) at -78 °C was added silver trifluoroacetate (240 mg, 1.09 mmol). The reaction mixture was stirred at -78 °C for 20 min and then at -20 °C for 3 h and at rt overnight. The mixture was filtered through Celite® and the filtrate concentrated in vacuo. Purification by chromatography (PE:EtOAc=4:1) afforded 15 (85 mg, 0.45 mmol, 62% from 22) as a slightly yellow oil (Rf = 0.17). ¹H NMR: 5.00 (m, 1 H), 4.88 (m, 1 H), 4.70 (m, 2 H), 2.58 (m, 1 H), 2.31 (m, 1 H), 2.22 (m, 4 H), 1.74 (m, 4 H). ¹³C NMR: 209.3, 173.2, 162.7, 127.2, 83.2, 81.6, 75.2, 31.1, 23.1, 21.4 (2 C), 19.7. IR (neat): 2941, 2947, 1957, 1747, 1681. HRMS (FAB) calcld for C₁₂H₁₅O₂ (MH+) 191.1072, found 191.1076.

General procedure A for the intramolecular [2+2] photocycloadditions: The photoreaction was carried out in a Pyrex glass vessel with a Rayonet RPR 300 nm at room temperature. A solution of precursor in indicated solvent was degassed by bubbling argon through for 30 min. The solution was kept under argon and irradiated for the time indicated. The reaction was followed by monitoring the
UV absorption of the starting material on TLC. When complete conversion was observed, the solvent was removed in vacuo.

**Photocycloaddition product 14**

According to the general procedure A, solution of allene 15 (85 mg, 0.45 mmol) in acetonitrile/acetone (0.05 M, 9:1 v/v) was irradiated (300 nm) for 5 h to give 14 (60 mg, 0.32 mmol, 70%) as colorless crystals after column chromatography (PE:EtOAc=4:1) (Rf=0.40, mp 125-127 °C). 1H NMR: 4.76 (s, 1 H), 4.61 (d, J = 3.9 Hz, 1 H), 4.56 (s, 1 H), 2.94 (s, 1 H), 2.17 (br d, J = 13.8 Hz, 1 H), 2.10 (dd, J = 12.0, 4.1 Hz, 1 H), 1.87 (br d, J = 15 Hz, 1 H), 1.73 (dd, J = 12.0, 2.3 Hz, 1 H), 1.62 - 1.45 (m, 4 H), 1.35 (m, 1 H), 0.96 (m, 1 H). 13C NMR: 175.6, 150.8, 96.0, 79.6, 66.0, 53.9, 48.4, 36.6, 21.7, 21.1, 20.1, 19.3. IR (CHCl3): 2941, 1763, 1215 cm⁻¹. Elemental analysis: calcd for C12H14O2: C: 75.76%, H: 7.42%; found C: 75.65%, H: 7.40%.

**Crystallographic data for 14:** C12H14O2, M = 190.24, triclinic, a = 6.6969(4), b = 7.0489(6), c = 10.9328(7) Å, α = 77.964(6), β = 75.679(9), γ = 80.977(8)°, V = 250 K, space group P1, Z = 2, μ(Cu-Kα) = 0.70 mm⁻¹, 1806 observed unique reflections.

**5-(buta-2,3-dienyl)furan-2(5H)-one (47)**

To a suspension of silver trifluoroacetate (1.312 g, 5.83 mmol) in CH2Cl2 (11 mL) at –78 °C was added allenyl bromide 17 (0.55 mL, 5.83 mmol) followed by silyloxy furane 46 (0.75 mL, 4.479 mmol). The reaction mixture was stirred at –78 °C for 20 min and then at –20 °C for 3 h and at rt overnight. The mixture was filtered through Celite® and solvent was concentrated in vacuo. Purification by chromatography (PE:EtOAc=2:1) afforded the desired product 47 (429 mg, 70%) as a light yellow oil (Rf = 0.2). 1H NMR: 7.50 (dd, J = 1.4 Hz, J = 5.7 Hz, 1 H), 6.13 – 6.11 (m, 1 H), 5.11 – 5.03 (m, 2 H), 4.79 – 4.71 (m, 2 H), 2.51 – 2.40 (m, 2 H). 13C NMR: 209.4, 172.7, 155.6, 121.9, 83.5, 82.2, 75.8, 31.9. IR: 3026, 2924, 1957, 1769, 1602.

**Cycloadduct 48**

According to the general procedure A, solution of 47 (93 mg, 0.68 mmol) in CH3CN/acetone (9:1, v/v) (25 mL) was irradiated for 40 min to give cycloadduct 48 (49 mg, 53%) as a light yellow oil after column chromatography (PE:EtOAc=2:1) (Rf = 0.3). 1H NMR: 4.98 – 4.97 (m, 1 H), 4.60 (s, 1 H), 4.55 (s, 1 H), 3.62 – 3.59 (m, 1H), 3.29 – 3.28 (m, 1H), 2.97 – 2.96 (m, 1 H), 2.09 (dd, J = 4 Hz, J = 12 Hz, 1 H), 1.78 (dd, J = 2 Hz, J = 12 Hz, 1 H). 13C NMR: 173.8, 148.7, 94.8, 78.9, 59.0, 48.8, 46.1, 35.1. IR: 3100, 1766. HRMS (FAB) calcd for C8H9O2 (MH⁺) 137.0597, found 137.0612.

**3-Ethoxy-6-pro-2-ynyl-cyclohex-2-enone (53)**

To a solution of freshly prepared LDA (27.5 mmol of DIPA and 1 equiv of n-BuLi (1.6 M in hexane) in THF (50 mL) at –78 °C to rt, 15 min) at –78 °C was added dropwise over 1 h a solution of β-diketone enol ether 52 (3.5 mL, 25 mmol) in THF (3 mL). The resulting reaction mixture was stirred for 45 min and then solution of propargyl bromide (2.96 mL, 27.5 mmol) in THF (5 mL) was added. The reaction mixture was stirred at –78 °C for an additional 2 h and then at rt for 1 h and quenched by water (3 mL). The layers were separated
and the aqueous phase was extracted with ether (3x10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo}. Purification by chromatography (PE:EtOAc=1:1) afforded the desired product 53 (2.83 g, 64\%) as a slightly yellow oil.

\(^1\)H NMR: 5.34 (s, 1 H), 3.92 – 3.84 (m, 2 H), 2.78 (dt, \(J = 3\) Hz, \(J = 16\) Hz, 1 H), 2.55 – 2.26 (m, 5 H), 1.97 (t, \(J = 2.5\) Hz, 1 H), 1.88 – 1.81 (m, 1 H), 1.35 (t, \(J = 7\) Hz, 3 H). \(^{13}\)C NMR: 198.4, 177.2, 101.9, 82.2, 69.4, 64.2, 44.0, 28.5, 25.9, 18.9, 13.9. IR: 3308, 3012, 2944, 1642, 1605.

**General procedure B for the Crabbé reactions:** to a 0.07 M solution of the starting acetylenyl compounds in 1,4-dioxane was added DIPA (2 equiv), paraformaldehyde (2.5 equiv) and CuI (0.5 equiv). The reaction mixture was brought to reflux and stirred overnight. The reaction mixture was allowed to cool to room temperature and quenched with saturated aqueous NaHSO\(_4\). The mixture was diluted with water and extracted with CH\(_2\)Cl\(_2\). The combined organic layers were washed with brine, dried over MgSO\(_4\) and concentrated \textit{in vacuo}. The residue was purified by column chromatography.

**6-(buta-2,3-dienyl)-3-ethoxycyclohex-2-enone (54)**

According to the general procedure B, starting from \(\beta\)-diketone enol ether 53 (0.5 g, 2.8 mmol) gave 54 (0.36 g, 67\%) as a light yellow oil after column chromatography (PE:EtOAc=1:1). \(^1\)H NMR: 5.33 (s, 1 H), 5.13 – 5.06 (m, 1 H), 4.68 – 4.65 (m, 2 H), 3.92 – 3.86 (m, 2 H), 2.60 – 2.56 (m, 1 H), 2.45 – 2.41 (m, 2 H), 2.30 – 2.27 (m, 1 H), 2.13 – 2.09 (m, 2 H), 1.79 – 1.76 (m, 1 H), 1.35 (t, \(J = 7\) Hz, 3 H). IR: 3014, 1955, 1604.

**4-(buta-2,3-dienyl)cyclohex-2-enone (55)**

To a suspension of LiAlH\(_4\) (23 mg, 0.598 mmol) in ether (2 mL) at rt was added a solution of \(\beta\)-diketone enol ether 54 (150 mg, 0.78 mmol) in ether (1 mL). The resulting mixture was stirred at rt for 1 h and carefully quenched with saturated aqueous Na\(_2\)SO\(_4\) followed by acidification of the reaction media to pH 2 using 2 N aqueous solution of HCl. The resulting mixture was stirred for an additional 30 min. The layers were separated and the ether layer was washed with saturated aqueous NaHCO\(_3\) (3x10 mL), brine (10 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo}. Purification by chromatography (hexane:EtOAc = 1:1) afforded 55 as a slightly yellow oil (65 mg, 56\%). \(^1\)H NMR: 6.89 (d, \(J = 10\) Hz, 1 H), 6.00 (d, \(J = 10\) Hz, 1 H), 5.14 – 5.07 (m, 1 H), 4.74 – 4.71 (m, 2 H), 2.54 – 2.48 (m, 2 H), 2.40 – 2.37 (m, 1 H), 2.19 – 2.13 (m, 3 H), 1.77 – 1.73 (m, 1 H). \(^{13}\)C NMR: 209.0, 199.5, 153.8, 129.2, 86.8, 75.2, 36.7, 35.9, 33.1, 28.3.

**Cycloaduct 56**

According to the general procedure A, a solution of 55 (30 mg, 0.2 mmol) in CH\(_3\)CN/acetone (9:1, v/v) (25 mL) was irradiated for 30 min to give the crossed adduct 56 as a slightly yellow oil (24 mg, 80\%) after purification by column chromatography (pentane:ether=1:1). \(^1\)H NMR: 4.39 (s, 2 H), 2.75 (br, 1 H), 2.45 – 2.41 (m, 2 H), 2.10 – 2.05 (m, 1 H), 1.95 – 1.85 (m, 2 H), 1.55 – 1.40 (m, 1 H), 1.93 – 1.88 (m, 2 H), 1.67 – 1.61 (m, 1 H). \(^{13}\)C NMR (benzene): 207.4, 154.1, 91.5, 53.1, 52.6, 50.7, 35.2, 32.4, 29.0, 26.5. IR: 2937, 1694.
4-Bromo-but-1-ynyl)-trimethyl-silane (62)

To a solution of MsCl (8.2 mL, 104 mmol) in DCM (30 mL) was added a mixture of alcohol 61 (10 g, 70 mmol) and TEA (14.4 mL, 104 mmol). The resulting mixture was stirred for 20 h. The mixture was diluted with DCM, washed with water, brine, dried with MgSO₄ and solvent was evaporated in vacuo to give a sufficiently pure mesylate product as a red liquid (14.82 g, 95%) which was used for the next step without purification. ¹H NMR: 4.25 (t, J = 7 Hz, 2 H), 3.01 (s, 3 H), 2.65 (t, J = 7 Hz, 2 H), 0.11 (s, 9 H). ¹³C NMR: 100.5, 87.4, 67.2, 37.4, 20.8, -0.3.

To a solution of LiBr (23.28 g, 268 mmol) in acetone (70 mL) at 0 °C was added solution of the crude mesylate (14.82 g, 67 mmol) in acetone (120 mL). The mixture was stirred at rt for 19 h. After addition of water the solution was extracted with DCM (3×50 mL). The DCM layers were combined, washed with water (100 mL), brine (100 mL), dried over MgSO₄ and solvent was evaporated in vacuo to give the crude product which was distilled (44 °C, 2 mbar) to afford the pure product 62 as a colorless liquid (6.4 g, 46%). ¹H NMR: 3.42 (t, J = 7.5 Hz, 2 H), 2.77 (t, J = 7.5 Hz, 2 H), 0.15 (s, 9 H). ¹³C NMR: 103.0, 86.8, 29.0, 24.1. IR: 3008, 2960, 2926, 2171, 1663.

3-(4-Trimethylsilanyl-but-3-ynyl)-cyclohex-2-enone (63)

To a suspension of Mg turnings (0.61 g, 25.0 mmol) in THF (3 mL) was added 1,2-dibromoethane (8 µL). The reaction mixture was heated to reflux and the solution of 1,2-dibromoethane (0.4 mL) and bromide 62 (4.20 g, 20.5 mmol) in THF (6 mL) was added dropwise. The mixture was refluxed for 2 h and then cooled to 0 °C. To this mixture was added dropwise a solution of 3-ethoxy-2-cyclohexen-1-one 52 (2.96 mL, 20.5 mmol) in THF (4 mL). The reaction mixture was stirred at 0 °C for 20 min, then allowed to warm to rt and stirred overnight. Aqueous solution of HCl (2 M) was added in small portions until all excess Mg was dissolved (2 h). The mixture was stirred for an additional 1 h and then extracted with ether (3×20 mL). The combined organic layers were washed with saturated NaHCO₃ (3×15 mL) and brine (20 mL), dried with MgSO₄ and solvent evaporated in vacuo to give the crude product which was then purified by column chromatography (EtOAc:PE=1:2) to afford pure 63 (3.15 g, 70%) as a yellow oil (Rf = 0.3). ¹H NMR: 5.87 (s, 1 H), 2.41 (s, 4 H), 2.36 - 2.29 (m, 4 H), 2.01 - 1.95 (m, 2 H), 0.13 (m, 9 H). ¹³C NMR: 199.4, 163.5, 126.2, 104.9, 85.9, 37.1, 36.4, 29.3, 22.4, 17.8. IR: 3008, 2961, 2174, 1663.

3-But-3-ynyl-cyclohex-2-enone (64)

To a solution of 63 (3.15 g, 14.3 mmol) in methanol (50 mL) was added K₂CO₃ (1.98 g, 14.4 mmol) and the reaction mixture was stirred at rt for 4 h. The solution was concentrated in vacuo and then water (20 mL) was added. The aqueous layer was extracted with ether (3×20 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried with MgSO₄ and solvent evaporated in vacuo to afford enone 64 (1.99 g, 94%) as a yellow oil after purification by column chromatography. ¹H NMR: 5.92 (s, 1 H), 2.44 - 2.30 (m, 8 H), 2.04 - 1.98 (m, 3 H). ¹³C NMR: 199.4, 163.2, 126.1, 82.3, 69.4, 37.1, 36.2, 29.3, 22.4, 16.2. IR: 3672, 3308, 3012, 2928, 1663.
3-Penta-3,4-dienyl-cyclohex-2-enone (58)

According to the general procedure B, starting from 64 (0.2 g, 1.34 mmol), pure allene 58 was obtained (0.19 g, 71%) as a yellow oil after column chromatography (EtOAc:PE=5:4, Rf = 0.32). 1H NMR: 5.86 (s, 1 H), 5.12 - 5.05 (m, 1 H), 4.69 - 4.66 (m, 2 H), 2.35 - 2.26 (m, 6 H), 2.22 - 2.17 (m, 2 H), 2.00 - 1.95 (m, 2 H). 13C NMR: 208.3, 199.6, 165.1, 125.8, 88.5, 75.5, 37.1, 36.8, 29.5, 25.2, 22.5. IR: 3011, 2954, 2927, 1955, 1661.

Cycloadduct 65

According to procedure A, a solution of 58 (100 mg, 0.62 mmol) in cyclohexane (20 mL) was irradiated for 55 min. The crude product was first columned (EtOAc:PE=1:9) (Rf=0.21) and then flashed through silica gel using diethyl ether as eluent. The crude product 65 was subjected to the reduction step without further purification. 13C NMR (benzene): 208.8, 146.7, 118.4, 58.9, 52.6, 44.7, 38.0, 33.6, 32.7, 27.0, 21.3.

Octahydro-cyclopenta[1,4]cyclobuta[1,2]benzen-5-one (66)

To a solution of cycloadduct 65 in THF (2 mL) was added Pd/C (2 mol%) under hydrogen atmosphere. The mixture was stirred at rt for 3 h. The reaction mixture was then filtered and solvent evaporated in vacuo to give crude product which was purified by column chromatography to afford pure product 66 as a colorless liquid (28 mg, 27% over two steps). 1H NMR: 2.58 - 2.54 (m, 1 H), 2.48 - 2.45 (m, 1 H), 2.41 - 2.37 (m, 1 H), 2.19 – 1.98 (m, 4 H), 1.97 - 1.80 (m, 3 H), 1.64 - 1.54 (m, 5 H), 1.53 - 1.33 (m, 1 H). 13C NMR: 215.4, 49.8, 47.1, 40.2, 39.4, 39.3, 32.8, 32.7, 26.7, 24.8, 21.0.

5,5-Dimethyl-3-(2-propylamino)-2-cyclohexen-1-one (73)

To a solution of propargylamine (2.0 g, 36.3 mmol) in benzene (60 mL) was added 5,5-dimethyl-1,3-cyclohexanadione (72) (5.1 g, 36.3 mmol). The resulting mixture was brought to reflux and stirred overnight under the Dean-Stark conditions. The reaction mixture was concentrated in vacuo and the residue solid was recrystallized from EtOAc-PE to give 73 (5.0 g, 78%) as yellow crystals (mp 148-149 ºC). 1H NMR: 5.45 (br, 1 H), 5.14 (s, 1 H), 3.86 (q, J = 3 Hz, 2 H), 2.28 (t, J = 2.4 Hz, 1 H), 2.22 (s, 2 H), 2.18 (s, 2 H), 1.06 (s, 6 H). 13C NMR: 197.5, 163.8, 95.9, 78.8, 72.6, 50.5, 42.9, 33.1, 32.6, 28.5. IR: 3441, 3307, 1591.

tert-Butyl 5,5-dimethyl-3-oxocyclohex-1-enyl(prop-2-ynyl)carbamate (74)

To a suspension of 73 (1.0 g, 5.6 mmol) in CHCl3 (40 ml) was added (BOC)2O (2.4 g, 11.3 mmol) and DMAP (70 mg, 0.56 mmol). The resulting mixture was stirred for 1 h at room temperature. Then imidazole (0.40 g, 5.6 mmol) was added and the reaction mixture was stirred for 1 h. The reaction mixture was washed with 1N HCl (2x10 ml), saturated aqueous NaHCO3 (2x10 ml), dried over MgSO4 and concentrated in vacuo. The residue was recrystallized from n-hexane to afford 74 (1.2 g, 77%) as colorless crystals (mp 106-107 ºC). 1H NMR: 5.95 (s, 1 H), 4.31 (d, J = 2.4 Hz, 2 H), 2.62 (s, 2 H), 2.27 (t, J
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47 = 2.4 Hz, 1 H), 2.24 (s, 2 H), 1.52 (s, 9 H), 1.07 (s, 6 H). 13C NMR: 199.2, 159.9, 151.7, 114.9, 82.9, 78.2, 72.4, 50.3, 43.8, 38.7, 33.8, 27.9. IR: 3307, 1716, 1650.

tert-Butylbuta-2,3-dienyl-5,5-dimethyl-3-oxocyclohex-1-enylcarbamate (75)

According to procedure B, starting from 74 (0.5 g, 1.8 mmol) gave 75 (0.45 g, 85%) as a colorless oil after column chromatography (EtOAc:PE=1:1). Rf = 0.47.

1H NMR: 5.77 (1 H, s), 5.19 – 4.82 (m, 1 H), 4.82 - 4.79 (m, 2 H), 4.16 - 4.13 (m, 2 H), 2.59 (s, 2 H), 2.21 (s, 2 H), 1.48 (s, 9 H), 1.04 (s, 6 H). 13C NMR: 208.1, 199.0, 160.5, 152.0, 114.3, 86.8, 82.1, 77.4, 50.2, 47.5, 43.8, 33.7, 21.8. IR: 1736, 1694.

Crystal data for 75: C17H25NO3, M = 291.38, orthorhombic, a = 9.9168(4) Å, b = 11.1617(3) Å, c = 14.8053(7) Å, V = 1638.77(11) Å³, T = 293 K, space group P212121, Z = 4, C(Mo-Kα) = 0.08 mm⁻¹, 2405 observed unique reflections.

The faster moving compound was identified as the bicyclic pyrrole 81. Recrystallisation from n-hexane afforded pyrrole 81 (70 mg, 70%) as colorless crystals (mp 119-121 °C). 1H NMR: 7.12 (d, J = 3.4 Hz, 1 H), 5.98 (d, J = 3.4 Hz, 1 H), 3.07 (s, 2 H), 2.76 (t, J = 6.1 Hz, 2 H), 2.55 (t, J = 6.1 Hz, 2 H), 2.23 (s, 2 H), 1.57 (s, 9 H), 1.01 (s, 6 H). 13C NMR: 212.1, 149.4, 129.4, 124.9, 120.8, 110.7, 83.1, 52.8, 48.4, 48.4, 36.3, 35.9, 57.8, 21.8. IR: 1736, 1694.

Crystal data for 81: C17H25NO3, M = 291.38, triclinic, a = 6.7979(6), b = 11.2185(7), c = 11.6611(7) Å, α = 78.521(4), β = 79.840(6), γ = 89.451(5), V = 836.04(10) Å³, T = 208 K, space group P1, Z = 2, μ(Mo-Ka) = 0.079 mm⁻¹, 2619 observed unique reflections. HRMS (FAB) calcd for C17H26O3N (MH+) 292.1913, found 292.1902.

5,5-Dimethyl-3-prop-2-ynloxy-cyclohex-2-enone (76)

A mixture of 5,5-dimethyl-1,3-cyclohexanediene (72) (1 g, 7.13 mmol), propargyl alcohol (1.27 mL, 21.4 mmol) and pTsOH (1.6 g, 9.25 mmol) in benzene (50 mL) was refluxed for 1.5 h under Dean-Stark conditions. The reaction mixture was allowed to
cool to rt and saturated NaHCO₃ (25 mL) was added. The layers were separated and the aqueous phase was extracted with DCM (2x25 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Recrystallization from PE:EtOAc gave the product (998.4 mg, 78%) as colorless crystals (mp 50–52 ºC). ¹H NMR: 5.43 (s, 1 H), 4.66 (d, J = 2.4 Hz, 2 H), 2.57 (t, J = 2.4 Hz, 1 H), 2.30 (s, 2 H), 2.22 (s, 2 H), 1.07 (s, 6 H). ¹³C NMR: 199.1, 174.3, 102.2, 76.3, 55.8, 50.4, 42.3, 32.4, 28.0. IR: 3243, 2960, 1655, 1011.

3-Buta-2,3-dienyloxy-5,5-dimethyl-cyclohex-2-enone (77)
According to procedure B, starting from 76 (0.706 g, 3.918 mmol) gave allene 77 (0.46 g, 61%) as a brown oil after purification by column chromatography (PE:EtOAc=1:1) ¹H NMR: 5.35 (s, 1 H), 5.30 (q, J = 6.7 Hz, 1 H), 4.88 (dt, J = 2.3 Hz, J = 1.7 Hz, 2 H), 2.28 (s, 2 H), 2.20 (s, 2 H), 1.06 (s, 6 H). ¹³C NMR: 209.4, 199.2, 175.2, 101.8, 85.5, 76.5, 65.9, 50.5, 42.5, 32.4, 28.0. IR: 2957, 1957, 1703.

Photocycloadduct 86
According to general procedure A, solution of allene 77 (0.216 g, 1.12 mmol) in acetonitrile/acetone (9:1, v/v) (30 mL) was radiated for 3 h to give product 86 (65 mg, 32%) as a brown oil after column chromatography (PE:EtOAc=2:1). ¹H NMR: 7.18 (d, J = 1.7 Hz, 1 H), 6.17 (d, J = 1.6 Hz, 1 H), 2.72 (t, J = 2.5 Hz, 2 H), 2.57 (t, J = 2.5 Hz, 2 H), 2.56 (s, 2 H), 2.25 (s, 2 H), 0.98 (s, 6 H). ¹³C NMR: 212.3, 149.9, 140.1, 118.5, 111.6, 52.1, 46.2, 38.9, 36.0, 28.6, 20.9. IR: 2957, 2869, 1699.

3.8 References
Chapter 4

Further Chemistry with the Model Cycloadduct*

4.1 Introduction

The highly regioselective intramolecular [2+2] photocycloadditions between allenes and electron-poor alkenes separated by two carbon or heteroatoms as described in chapter 3 proved the feasibility of our new synthetic strategy toward the right hand fragment 3 of solanoeclepin A. The use of butenolide 4 as the photosubstrate allows a straightforward construction of the tricyclic core containing the bicyclo[2.1.1]hexane skeleton of 5 in good yield and with complete regioselectivity (Scheme 4.1). The cycloadduct 5 contains the appropriate handles for further functional group transformation studies with the exocyclic methylene group as a potential protective group of a ketone. Our next goal was, therefore, to develop efficient synthetic methodologies for completion of the synthesis of the model compound 6, containing the key structural features of the right hand fragment 3 of solanoeclepin A.

Scheme 4.1

The synthesis of 6 requires installing the angular methyl and the hydroxyl functions in the correct stereochemical arrangement. To that end, a reductive opening of the lactone moiety of the photocycloadduct 5 should be a feasible strategy. Especially, the completion of the model 6 also needs the critical conversion of the exocyclic methylene group into the corresponding ketone function. For this transformation, an ideal approach would involve the ozonolysis of the double bond, but this method was expected to be unproductive in line with our earlier studies (see section 2.3.1). Therefore, it was our intention to make use of a different oxidative cleavage procedure for the introduction of the cyclobutanone moiety. The highly strained nature of the tetracyclic ring system of 5 is expected to influence the introductions of the required functional groups in the synthesis of 6. It is desirable,

therefore, to establish an optimal order of functional group transformations. In other words, it was not clear beforehand whether the reductive opening of the lactone moiety to generate the angular methyl group, or the oxidative cleavage of the double bond should be conducted first. This model study should provide the basis for the synthesis of the right hand subunit 3, and hence, solanoeclepin A.

4.2 The Bridgehead Methyl Group

We initially considered possibilities of introducing the angular methyl and the hydroxyl groups upon reductive opening of the $\gamma$-butyrolactone moiety. The highly strained tricyclic carbon skeleton of the cycloadduct 5 was expected to be unstable under chemical transformations which involve radical or cation intermediates, due to cation or radical induced rearrangement. A process involving a carbanion intermediate might be convenient for the successful generation of the bridgehead methyl group. The Wolff-Kishner reduction, a well-known process proceeding via a carbanion intermediate, however, proved to be inefficient on the basis of our earlier work (see section 2.3.3). A modified procedure utilizing hydride reduction of a $p$-toluenesulfonylhydrazone also gave unsatisfactory results. A competitive radical pathway assumingly accounts for the failure of this reaction. Because of these experiences, we sought other methods which could efficiently convert the lactone moiety of the cycloadduct 5 into the corresponding angular methyl and hydroxyl functionalities.

4.2.1 Hydrodeamination Strategy

The reductive removal of an amino group, the hydrodeamination reaction (eq 4.1), is a well-known method for the preparation of alkanes from the corresponding amines. The reaction presumably proceeds via a $p$-tosylhydrazine intermediate 9 which is formed upon amination of the $p$-toluenesulfonamide 8. Subsequent in situ elimination of $p$-toluenesulfonic acid under basic conditions gives the diazene intermediate 10. Evolution of nitrogen from the diazene 10 finally affords the deamination product 12.

\[
\begin{align*}
R-NH_2 & \overset{TsCl}{\text{base}} \overset{1) NaH (2 equiv)}{\longrightarrow} R-NH-Ts \\
& \overset{2) NH_2Cl (xs)}{\longrightarrow} R-N-Ts \overset{1} {\overset{NH_2}{\longrightarrow}} R-N=N-H \overset{11} {\overset{-N_2}{\longrightarrow}} R^+ \overset{H^+}{\longrightarrow} RH
\end{align*}
\]

(4.1)

The use of chloroamine as an aminating agent was found to be more convenient than other reagents such as hydroxylamine $O$-sulfonic acid, or $O$-2,4-dinitrophenyloxylamine and $O$-mesitylenesulfonylhydroxylamine, in term of effectiveness, solubility in organic solvent and practical preparation. The ethereal chloroamine solution can easily be prepared in typical yield greater than 90% by buffering the sodium hypochlorite-ammonia reaction with ammonium chloride. The readily prepared $p$-toluenesulfonamide 8 can be best converted into the corresponding $p$-tosylhydrazine intermediate 9 using an excess of ethereal chloroamine solution and two equivalents of NaH. Under
these conditions, the elimination of the initially formed \( p \)-tosylhydrazine intermediate 9 occurs \textit{in situ} to afford the desired reduced product.

Although the reaction is known to work best for primary amines attached to primary carbons, a reasonable yield of the reduced product was also reported in the reductive deamination reaction of a hindered primary amine attached to a neopentyl carbon.\textsuperscript{1b} This precedent prompted us to explore the usefulness of this hydrodeamination methodology on cycloadduct 5, in an effort to generate the angular methyl group from the lactone moiety.

The preparation of the required starting material for the hydrodeamination reaction, the \( p \)-toluenesulfonamide 17, is presented in Scheme 4.2. The synthesis began with the ammonolysis of the \( \gamma \)-butyrolactone moiety of cycloadduct 5. The reaction was found to be best conducted in a sealed tube at 80 \( ^\circ \)C for 40 h using an excess of a 25\% aqueous solution of ammonia. In this way, the desired hydroxyamide 13 was isolated in 99\% yield as a white solid. The hydroxyl group was then protected as a TBS-silyl ether giving rise to the primary amide 14 in 73\% yield. The use of TBSOTf as the silylating agent was necessary to bring about the reaction although this silylating agent also affected, to some extent, the silylation of the amide moiety, leading to the disilylated byproduct. Less reactive silylating agents such as TBSCI only led to fully recovered starting hydroxy amide 13.

Scheme 4.2

The next step was the reduction of the primary amide moiety to the corresponding amine, the starting material for the hydrodeamination reaction. This functional group transformation was efficiently accomplished upon heating the solution of amide 14 with an excess of LiAlH\(_4\) in THF at reflux for 1 h leading to amine 15 in reasonable yield.\textsuperscript{2} Desilylation of the hydroxyl group had also occurred. Attempts to conduct the reduction step on the hydroxyamide 13 having a free hydroxyl group were unsuccessful. Only decomposition of the starting material 13 was observed. This is likely due to the deprotonation of the hydroxyl group by LiAlH\(_4\) followed by an alkoxide induced ring opening of the tricyclic core of amide 13 under these harsh conditions. This makes an extra protection step of the secondary hydroxyl group, therefore, unavoidable.

The crude amino alcohol 15 was then subjected to the tosylation conditions, using TsCl as a tosylating agent and pyridine as a base in CH\(_2\)Cl\(_2\). This led to the selective tosylation of the amine moiety in a yield of 60\% over two steps. Finally, the secondary alcohol was protected as a TBS-silyl
ether using the same conditions as applied for amide 13. A better yield was achieved in this case likely due to the presence of the bulky tosyl group which precludes silylation of nitrogen.

With the required p-toluenesulfonamide 17 in hand, we could eventually explore the feasibility of the hydrodeamination methodology for generating the angular methyl group. It is known that the in situ elimination of the diazene intermediate might occur via a radical mechanism, which assumingly accounts for the failure of the hydride reduction of the tosylhydrazone in our previous work (see section 2.3.3). The base catalyzed decomposition of the alkylidiazene to the corresponding hydrocarbon anion, however, can compete. It was our hope, therefore, that under basic conditions, the elimination of the diazene intermediate 19 (eq 4.2), once formed, to the methyl group would be the predominant reaction. Thus, treatment of a solution of 17 in DMF with 2 equiv of NaH followed by 2 equiv of chloroamine at 0 °C to room temperature for 2 h led to the complete disappearance of 17, as monitored by TLC. Unfortunately, unwanted decomposition of the starting material was found to occur as the main process along with formation of some desired product, as shown by 1H NMR. Eventually, less than 10% of the desired deamination product 20 could be isolated after column chromatography. The use of another base such as KHMDS did not improve the yield of the reaction. This poor result might be due to the potential competition of a radical pathway under the reaction conditions. The base catalyzed decomposition of the diazene 19 to the corresponding reduced product 20 does occur but is obviously not the predominant process. The failure of this reaction might also be attributed to the steric hindrance of p-toluenesulfonamide 17 which might hamper the amination step and hence the following step to form the required diazene intermediate so that other reaction pathways could compete.

\[
\text{NHTs NaH (2 equiv)} \xrightarrow{\text{DMF (2 equiv)}} \text{TsH - N}_2
\]

These unsatisfactory results indicate that a more efficient strategy needs to be developed for the successful generation of the required angular methyl group.

4.2.2 Reduction of Sulfonate Derivatives

In view of the failure of the hydrodeamination strategy, we devised an alternative route which made use of deoxygenation to reveal the angular methyl group (eq 4.3). Thus the lactone function of cycloadduct 5 was reduced to form the corresponding diol 21 in good yield using LiAlH₄ as the reducing agent. Much of the deoxygenation methodology available in the literature makes use of hydroxyl group activation via sulfonate ester formation followed by hydride displacement. For diol 21, an ideal strategy would be the selective monotosylation of the primary alcohol followed by hydride reduction to generate the angular methyl group.
Further Chemistry with the Model Cycloadduct

However, in previous studies, efforts for monotosylation of the model system 23 (Scheme 4.3) were unsuccessful. Only the cyclic ether 24 was formed in quantitative yield upon treatment of triol 23 with TsCl and pyridine. A logical explanation for the formation of tetrahydrofuran 24 is the displacement of the initially formed tosylate by the nearby secondary hydroxyl function. Attempts to convert the primary alcohol of the MOM-protected hydroxy acetonide 25 into the corresponding tosylate or iodide again met with failure. Only decomposition of the starting material was observed. It is likely that the MOM ether participates in the intramolecular substitution of the initially formed tosylate or iodide, leading to cation induced ring opening of the tricyclic skeleton of 25.

We verified those results with the attempted direct synthesis of the monotosylate from diol 21 by using tosyl chloride in pyridine followed by reduction. Indeed consumption of the starting material was observed but no trace of the reduced product could be detected. Therefore, a protection-deprotection sequence had to be followed as delineated in eq 4.4. The primary alcohol was selectively protected as a TBS-silyl ether followed by benzylation of the secondary alcohol to afford the intermediate 27 in quantitative yield over two steps. It was our hope that the more stable benzyl ether as the protective group for the secondary alcohol compared to the MOM ether could prevent undesired cyclic ether formation or cation induced rearrangement pathways.
At this stage it remained only to hydrolyze the primary silyl ether to liberate the hydroxyl group for the deoxygenation step. That was efficiently accomplished by utilizing a catalytic amount of camphorsulfonic acid in a 9:1 mixture of CH₂Cl₂ and MeOH to provide the primary alcohol 28 in good yield (eq 4.4).

With precursor 28 in hand, the reductive removal of the primary alcohol via the corresponding tosylate was then investigated. For this transformation the use of LiAlH₄ as the reducing agent is known to give best results with unhindered primary tosylates. With more hindered neopentyl alcohols, lithium triethylborohydride (Super-Hydride) in THF was found to be superior to conventional LiAlH₄ in both rate and selectivity for reduction versus attack of the metal hydride to the sulfur-oxygen bond to form the parent alcohol. Thus treatment of alcohol 28 with tosyl chloride in pyridine at room temperature for 20 h affected the tosylation of the hydroxyl group to form the tosylate 29 which was subjected to the reduction conditions without further purification (eq 4.5). No trace of the cyclic ether could be detected under the tosylation conditions. Gratifyingly, upon heating the solution of the crude tosylate 29 in THF at reflux in the presence of an excess of Super-Hydride for 1 h, the desired deoxygenation product 30 was formed in 66% overall yield over two steps. The parent alcohol 28, a possible side product, was not detected under these reaction conditions.

\[ \text{BnO} \quad \text{OH} \quad \overset{\text{TsCl}}{\longrightarrow} \quad \overset{\text{LiBH} \text{Et}_3}{\text{OTs}} \quad \overset{\text{THF reflux}}{\longrightarrow} \quad \text{BnO} \quad \text{Me} \]

The formation of the angular methyl group is evident from the presence of a singlet at 1.16 ppm besides the two singlets at 4.49 and 4.47 ppm of the exocyclic methylene moiety as shown in 1H NMR spectrum of 30.

The success of this deoxygenation process provided an efficient procedure for generating the angular methyl group, the required structural feature of the right hand substructure 3 of solanoeclepin A. Moreover, the secondary alcohol in the benzyl ether protected form was simultaneously put in place with the correct stereochemical arrangement. Although the extra protection-deprotection sequence appeared to be unavoidable, this methodology should be generally applicable for the synthesis of the right hand subunit 3 of solanoeclepin A at a later stage of the synthesis.

### 4.3 Cyclobutanone Formation

The successful reductive opening of the lactone moiety of the cycloadduct 5 encouraged us to investigate possibilities for conversion of the exocyclic methylene moiety into the corresponding cyclobutanone function. For this transformation, ozonolysis of the double bond would be an ideal approach but this method was expected to be unproductive in line with our earlier studies (see section 2.3.1). Therefore, an alternative ruthenium-based catalyzed oxidative cleavage procedure was
investigated. Unfortunately, attempts to cleave the olefin moiety of 30 or the cycloadduct 5 using a catalytic amount of RuCl₃ in conjunction with stoichiometric amounts of oxone or NaIO₄ as co-oxidant⁸ were totally unsuccessful (eq 4.6). Only decomposition of the starting material was observed. An osmium tetroxide-oxone⁹ promoted oxidative cleavage of the olefin also met with failure. These results indicate that a one-step procedure for the introduction of the cyclobutanone functionality is not feasible.

![Chemical structures](image)

(4.6)

We sought, therefore, an indirect procedure involving dihydroxylation of the double bond followed by oxidative cleavage of the formed vicinal diol. Addition of osmium tetroxide to olefins is known as the most selective and reliable process to give the corresponding diol moiety.¹⁰ The reaction occurs via the formation of an intermediate osmium(VI) ester complex 33 which could be hydrolyzed reductively to give insoluble osmium salts or oxidatively to regenerate osmium tetroxide and the vicinal diol 34 (eq 4.7).

![Chemical reactions](image)

(4.7)

In other words, the reduction of osmium tetroxide by unsaturated species can be performed either in stoichiometric or catalytic version. In its stoichiometric fashion, addition of pyridine to hydroxylation reactions is known to greatly facilitate the formation of the intermediate ester complex. Although the formed oxo(amine)osmium(VI) complexes tend to be more difficult to hydrolyze than the non-amine products, the reductive cleavage using bisulfite, hydrogen sulfide or lithium aluminum hydride is the most effective method for the stoichiometric use of osmium tetroxide with pyridine in cis-hydroxylation of alkenes. Alternatively, osmium tetroxide can be used catalytically in the presence of a secondary oxidant which oxidizes the intermediate osmium(VI) ester complex to regenerate the tetroxide for further reaction with the alkene substrate. Various stoichiometric oxidants have been used for the Os(VI) → Os(VIII) reoxidation step in the catalytic cycle. The most effective and widely used co-oxidants are 4-methylmorpholine N-oxide (NMO), potassium ferricyanide, tert-butyl hydroperoxide, sodium periodate and sodium hypochlorite.

Although stoichiometric oxidations of alkenes by osmium tetroxide usually give better yields of diol products and, especially, are more conveniently applicable for small-scale reactions, the catalytic version is found to be more desirable in terms of cost and toxicity of the osmium tetroxide. With respect to that concern, our first effort started with the dihydroxylation of the exocyclic methylene group using a catalytic amount of osmium tetroxide in conjunction with NMO as the co-
oxidant. For that purpose, either the cycloadduct 5 or the deoxygenation product 30 was expected to be a good study model. Moreover, because steric hindrance might affect the yield of the catalytic cis-dihydroxylation of alkenes, we planned to examine whether the dihydroxylation reaction could be best conducted in the presence or absence of the lactone moiety. Thus, treatment of cycloadduct 5 with catalytic amount of OsO₄ and stoichiometric amount of NMO at room temperature for 20 h led to the formation of a single diol 35 in 68% yield (eq 4.8). From ¹H NMR NOE measurements it was clear that the dihydroxylation had taken place from the more open endo face of the alkene. Unfortunately, oxidative cleavage of diol 35 using NaIO₄ as the oxidant appeared to be a difficult process giving only decomposition of the starting diol 35.

\[
\begin{align*}
\text{OsO}_4 \text{(cat)} & \quad \text{NMO} \\
\text{butanol/water/acetone} & \quad (5:1.5:1, \text{v/v/v}) \\
\text{68%} \\
\end{align*}
\]

A plausible explanation for the failure of the oxidative cleavage step is that the strained nature of the compact tetracyclic carbon skeleton causes instability of the product 36 which leads to decomposition once it is formed. If this is the case, the opening of the lactone moiety would prevent this undesired event. On the basis of this consideration, we took the deoxygenation product 30 as a substrate for our study on the conversion of the exocyclic methylene cyclobutane into the corresponding cyclobutanone function. Unfortunately, treatment of olefin 30 with a catalytic amount of osmium tetroxide and NMO, the same conditions as applied for the cis-dihydroxylation of the cycloadduct 5, only led to recovered starting material. No trace of the desired vicinal diol product could be detected. Attempts to increase the catalyst loading or the reaction temperature did not give any improvement. Finally we found out that the osmium-mediated dihydroxylation was only productive with a stoichiometric amount of osmium tetroxide in a 1:1 mixture of pyridine and water at 65 °C (eq 4.9). In this way a single diol 37 was obtained in 60% yield, based on 70% conversion of the starting material.

\[
\begin{align*}
\text{OsO}_4 (1.5 \text{ equiv}) & \quad \text{pyridine/water} \\
(1:1, \text{v/v}) \\
\text{60% (70% conversion)} \\
\end{align*}
\]

Like in the case of the cycloadduct 5, dihydroxylation of 30 took place from the endo face of the alkene as proven by ¹H NMR NOE measurements. However, different from the cycloadduct 5 where the endo face is more open, the benzyl ether and the methyl group in 30 push the ethane bridge towards the alkene, then reducing its accessibility for osmium tetroxide. As a result, harsher
conditions in the form of a stoichiometric amount of osmium tetroxide in pyridine at higher temperature appear to be required to affect the dihydroxylation of the double bond.

Interestingly, treatment of diol 37 with 2 equiv of NaIO4 in a 1:1 mixture of acetone/water at 0 °C for 1 h led to the cleavage of the vicinal diol moiety to give the desired cyclobutanone 31 in 47% yield (eq 4.10). The ring strain of the tricyclic core containing the bicyclo[2.1.1]cyclohexanone moiety is expected to have a pronounced effect on the stability of 31. This might account for the modest yield of the oxidative cleavage of diol 37.

\[
\begin{align*}
\text{BnO} \quad \text{OH} \quad \text{OH} & \quad \text{NaIO}_4 \text{ (2 equiv)} \quad \text{acetone/water} \quad \text{(1:1, v/v)} \quad \text{BnO}^\text{Me} \quad \text{Me} \\
37 & \quad \text{OH} \quad \text{BnO} \\
\text{BnO} \quad \text{Me} & \quad \text{H}_2 \text{(1 atm)} \quad 10\% \text{ Pd/C} \quad \text{ethanol} \\
31 & \quad \text{OBn} \\
\text{47\%} & \quad \text{6} \\
\text{OH} & \quad \text{BnO} \\
\text{44\%} & \quad \text{44\%}
\end{align*}
\]

Remarkably, upon exposure of the ethanol solution of diol 31 to hydrogen in the presence of 10% Pd/C at 0 °C, hydrogenolysis of the benzyl ether took place to afford the desired alcohol 6 in modest yield as a crystalline solid (mp 103–106 °C, IR ν 1798 and 1766 cm⁻¹). The 1H NMR spectrum of 6 shows one singlet at 1.31 ppm which corresponds to the angular methyl group beside the singlet at 2.63 ppm of the final hydrogen on the cyclobutanone. To our surprise, the rather strained β-hydroxyketone appeared to be quite stable although its stability in aqueous medium at different pH was not studied. The structure of product 6 was then proven by X-ray structural determination (figure 4.1).

The success of this synthetic sequence verifies our speculations on the failure of the oxidative cleavage of the vicinal diol 35. Obviously, the conformationally rigid nature of the γ-butyrolactone moiety, on one hand facilitates the dihydroxylation process but, on the other hand, hampers the
formation of the cyclobutanone function. The conformational consequences of the opening of the lactone moiety are, therefore, critical for the successful formation of the cyclobutanone, although this requires a stoichiometric use of OsO₄ to bring about the dihydroxylation of the double bond. Apparently, subtle steric and strain effects play a crucial role in the chemistry of the compact skeleton of the carbotricyclic structures.

We also investigated the hydrogenolysis process at an earlier stage in an effort to increase the yield of the cyclobutanone formation sequence. It is known that hydrogenolysis of benzyl ether can be conducted in the presence of free hydroxyl groups, and NaIO₄ can selectively cleave a vicinal diol moiety into the corresponding ketone, leaving the free hydroxyl group intact. It is desirable to remove the benzyl ether as soon as possible. Thus, vicinal diol 37 was subjected to the hydrogenolysis conditions as utilized for ketone 31, followed by oxidative cleavage using NaIO₄ as the oxidant. In this way, better yields were indeed achieved as shown in eq 4.11.

\[
\text{NaIO}_4 \text{ (2 equiv)} \quad \text{acetone/water (1:1, v/v)} \quad \text{H}_2 \text{ (1 atm)} \quad 10\% \text{ Pd/C} \quad \text{ethanol} \quad \text{MeOH} \\
37 \quad \rightarrow \quad 38 \quad 65\% \\
38 \quad \rightarrow \quad 6 \quad 67\%
\]

It can be concluded at this point that the cyclobutanone function can be efficiently generated from the exocyclic methylene moiety based on a two step sequence involving the dihydroxylation of the double bond followed by oxidative cleavage of the formed vicinal diol. The highly strained rigid nature of the bicyclo[2.1.1]cyclohexanone framework renders its formation only possible if there is no lactone moiety. That is, the reductive opening of the lactone moiety has to be carried out prior to the cyclobutanone formation although a stoichiometric use of OsO₄ and pyridine at high temperature is then needed for the dihydroxylation to occur.

In order to reduce the amount of OsO₄ used for the dihydroxylation of the double bond, an alternative synthetic route is depicted in eq 4.12.

According to this route, the vicinal diol 35, which was formed via the osmium catalyzed dihydroxylation of the cycloadduct 5, could be then protected as an acetonide ring to give the intermediate 39. Reductive opening of the γ-butyrolactone would be then carried out to afford the desired deoxygenation product 40. Deprotection of the diol moiety followed by oxidative cleavage of the formed vicinal diol could finally provide the required cyclobutanone 41. This synthetic route,
therefore, not only takes advantage of the lactone moiety in facilitating the dihydroxylation step in a catalytic fashion, but would also make the subsequent oxidative cleavage possible. This synthetic route was indeed investigated for the functionalization of the fully substituted photocycloadduct toward the right hand subunit 3. This study will be described in chapter 6.

It can be concluded that the functional group transformation studies on the model photocycloadduct 5 reveal the possibilities for introducing the key structural features of the right-hand fragment 3 of solanoeclepin A. These synthetic strategies should be generally applicable for the completion of the right hand substructure 3, and hence, solanoeclepin A.

4.4 Conclusions

This chapter describes the studies on the functional group transformations of the photocycloadduct 5 to introduce the key structural features of solanoeclepin A. Starting from the photocycloadduct 5, a six-step sequence efficiently put in place the angular methyl and the hydroxyl groups in the correct stereochemical arrangement. The subsequent three-step transformation afforded the most intricate tricyclic substructure of solanoeclepin A containing the bicyclo[2.1.1]cyclohexanone moiety. This major breakthrough provides the basis for the complete synthesis of the right-hand substructure 3 and hence solanoeclepin A.

4.5 Acknowledgements

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4.6 Experimental Section

General information. For general experimental details, see Section 2.6.

**Synthesis of amide 13**

A mixture of lactone 5 (197 mg, 1.04 mmol) and 25% aqueous NH₄OH (10 mL) in a sealed tube was heated at 80 °C for 40 h. The formed clean solution was cooled to rt and extracted with ether and pentane. The combined organic layers were concentrated *in vacuo* to afford the amide 13 (223 mg, 99%) as white crystals. ^1^H NMR: 5.61 - 5.55 (br, 2 H), 4.63 (s, 1 H), 4.49 (s, 1 H), 3.91 (dd, J = 3 Hz, J = 8 Hz, 1 H), 2.84 (s, 1 H), 2.33 (dd, J = 8 Hz, J = 12 Hz, 1 H), 2.04 - 1.92 (m, 3 H), 1.76 - 1.50 (m, 4 H), 1.49 - 1.35 (m, 1 H), 1.34 - 1.25 (m, 1 H). ^13^C NMR: 180.1, 152.6, 95.7, 71.9, 62.2, 51.9, 51.7, 38.1, 31.2, 21.6, 21.1, 20.2. IR: 3360, 3175, 1659.

**Synthesis of amide 14**

To a stirred solution of crude amide 13 (60 mg) in DMF (5 mL) at 0 °C was added drop wise TBSOTf (90 µL, 1.3 equiv) and pyridine (95 µL, 4 equiv). The reaction
mixture was stirred at 0 °C for 2 h, quenched by saturated aqueous NaHCO₃ (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×7 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (PE:EtOAc=2:1) afforded amide 14 (68 mg, 40% from 5) as white solid. *(Rf = 0.25)*. ¹H NMR: 6.55 - 6.25 (br, 1 H), 5.50 - 5.25 (br, 1 H), 4.64 (s, 1 H), 4.45 (s, 1 H), 3.99 (dd, J = 3 Hz, J = 7 Hz, 1 H), 2.94 (s, 1 H), 2.21 - 2.16 (m, 1 H), 2.07 (d, J = 12 Hz, 1 H), 1.87 (td, J = 3 Hz, J = 14 Hz, 1 H), 1.73 - 1.52 (m, 6 H), 1.51 - 1.38 (m, 1 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H). ¹³C NMR: 178.7, 153.0, 95.7, 72.8, 62.0, 51.1, 38.0, 31.0, 25.6, 21.8, 21.1, 20.6, 17.9, -5.0, -5.3. IR: 1672.

**Synthesis of amine 15**

To a solution of amide 14 (16 mg, 0.049 mmol) in THF (1 mL) at 0 °C was added drop wise LiAlH₄ (1M in THF, 0.5 mL, 10 equiv). The reaction mixture was brought to reflux for 1 h and carefully quenched with EtOAc. Saturated aqueous Na₂SO₄ (10 drops) was then added and the mixture was stirred for 1 h. After addition of more solid Na₂SO₄ the mixture was filtered through Celite® and concentrated in vacuo. The crude amine 15 was used for the next step without purification. ¹H NMR: 4.5 (s, 1 H), 4.3 (s, 1 H), 3.9 (d, J = 7 Hz, 1 H), 3.2 (d, J = 14 Hz, 1 H), 2.9 (d, J = 14 Hz, 1 H), 2.6 (s, 1 H), 2.2 - 2.1 (m, 1 H), 2.0 - 1.0 (m, 9 H).

**Synthesis of sulfonamide 16**

To a solution of crude 15 in CH₂Cl₂ (1 mL) at 0 °C was added TsCl (10.6 mg, 1.2 equiv) and pyridine (0.5 mL). The reaction mixture was allowed to warm to rt and stirred overnight. Aqueous solution of citric acid (2%, 1 mL) was added and the mixture was stirred for additional 30 min. The resulting mixture was poured into water. The layers were separated and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (15 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (PE:EtOAc=2:1) afforded 16 (10.2 mg, 60% two steps) as white crystals. *(Rf=0.2)*. ¹H NMR: 7.7 (d, J = 8 Hz, 2 H), 7.3 (d, J = 8 Hz, 2 H), 4.5 (s, 1 H), 4.4 (t, J = 6 Hz, 1 H), 3.9 (dd, J = 8 Hz, J = 2 Hz, 1 H), 3.6 (dd, J = 7 Hz, J = 13 Hz, 1 H), 2.9 (dd, J = 6 Hz, J = 12 Hz, 1 H), 2.6 (s, 1 H), 2.4 (s, 3 H), 2.1 - 2.0 (m 1 H), 1.7 - 1.3 (m, 10 H). ¹³C NMR: 154, 143, 136, 129, 127, 95, 72, 62, 49, 43, 42, 35, 29, 21.4, 21.33, 21.31, 20. IR: 3520, 3282.

**Synthesis of sulfonamide 17**

To a stirred solution of sulfoamine 16 (72 mg, 0.2 mmol) in DMF (5 mL) at 0 °C was added drop wise TBSOTf (0.6 mL, 1.2 equiv) and pyridine (0.7 mL, 4 equiv). The reaction mixture was stirred at 0 °C for 2 h and quenched by saturated aqueous NaHCO₃ (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (PE:EtOAc=4:1) afforded 17 (82 mg, 89%) as white solid. *(Rf = 0.38)*. ¹H NMR: 7.71 (d, J = 8 Hz, 2 H), 7.27 (d, J = 8 Hz, 2 H), 4.54 (s, 1 H), 4.35 (s, 1 H), 4.28 (t, J = 6 Hz, 1 H), 3.84 (dd, J = 2 Hz, J = 7 Hz, 1 H), 3.68 (ddd, J = 1.4 Hz, J = 7 Hz, J = 13 Hz, 1 H), 2.85 (d, J = 6 Hz, J = 13 Hz, 1 H), 2.60 (s, 1 H), 2.41 (s, 3 H), 2.04 (ddd, J = 1.4 Hz, J = 7.5 Hz, J = 12 Hz, 1 H), 1.79 - 1.20 (m, 8 H), 0.79 (s, 9 H), -0.01 (s, 3 H), -0.03 (s, 3 H). ¹³C NMR: 154.9, 142.8, 136.8,
Reduction product 20

**Ethereal chloroamine:** ammonium chloride (0.707 g, 13.2 mmol) was added to a 2.0 M aqueous ammonia solution (4.35 mL, 8.7 mmol) and the mixture was cooled in an ice bath. To this cooled mixture was added dropwise 5.25% (0.76 M) aqueous sodium hypochlorite (commercial bleach) (18.8 mL, 14.3 mmol) over 15 min and the mixture was stirred for an additional 15 min at 0 °C. The aqueous solution was extracted with ice-cold ether (30 mL) and then with another portion of cold ether (15 mL). The combined organic layers were dried with CaCl$_2$ at -10 °C for 30 min. An aliquot of the ethereal chloroamine solution could be iodometrically titrated using potassium iodide and sodium thiosulfate to accurately determine the chloroamine concentration in the organic solution. The typical yield of chloroamine in solution using this procedure was about 6.0 mmol.

**Hydrodeamination:** To the solution of sulfonamide 17 (100 mg, 0.225 mmol) in DMF (5 mL) at 0 °C was added NaH (60 wt% dispersion in mineral oil, 45 mg, 2 equiv). The mixture was then stirred at 0 °C for 1 h and a solution of chloroamine (3.5 mL, 2 equiv) was slowly added. The reaction mixture was allowed to warm to rt over 2 h. The layers were separated and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO$_4$ and concentrated in vacuo. Purification by chromatography (pentane) afforded 20 as a colorless oil ($R_f = 0.55$). $^1$H NMR: 4.47 (s, 1 H), 4.30 (s, 1 H), 3.85 (dd, $J = 2.5$ Hz, $J = 6$ Hz, 1 H), 2.46 (s, 1 H), 2.04 (ddd, $J = 1.5$ Hz, $J = 7$ Hz, $J = 11$ Hz, 1 H), 1.84 - 1.73 (m, 2 H), 1.57 - 1.39 (m, 7 H), 1.09 (s, 3 H), 0.88 (s, 9 H) 0.02 (s, 3 H), 0.01 (s, 3 H). $^{13}$C NMR: 157.6, 93.4, 72.8, 61.1, 52.0, 41.2, 36.9, 34.2, 25.5, 22.1, 21.8, 20.1, 17.7, 16.1, -4.9, -5.2.

7a-Hydroxymethyl-8-methylene-octahydro-1,3a-methano-inden-3-ol (21)

To a 1 M solution of LiAlH$_4$ in THF (6.5 mL, 5 equiv) at rt was added a solution of lactone 5 (250 mg, 1.315 mmol) in THF (5 mL). The resulting mixture was stirred at rt for 30 min and carefully quenched with EtOAc. Saturated aqueous Na$_2$SO$_4$ (10 drops) was then added and the mixture was stirred for 1 h. After addition of more solid Na$_2$SO$_4$ the mixture was filtered through Celite® and concentrated in vacuo. Purification by chromatography (EtOAc) afforded diol 21 as a colorless solid (189 mg, 74%). $R_f = 0.30$, mp 110-114 °C. $^1$H NMR (methanol): 4.53 (s, 1 H), 4.35 (s, 1 H), 4.23 (dd, $J = 11.9$, 1.8 Hz, 1 H), 3.88 (dd, $J = 7.6$, 2.6 Hz, 1 H), 3.46 (d, $J = 11.9$ Hz, 1 H), 2.65 (s, 1 H), 2.10 (ddd, $J = 11.8$, 7.8, 1.7 Hz, 1 H), 2.03 (br d, $J = 13.4$ Hz, 1 H), 1.89 – 1.85 (m, 1 H), 1.67 - 1.50 (m, 6 H), 1.30 – 1.26 (m, 1 H). $^{13}$C NMR (methanol): 158.0, 94.5, 73.3, 63.5, 60.3, 51.3, 47.1, 36.6, 28.8, 23.0, 22.8, 21.6. IR (neat): 3397, 2934, 1690.

7a-(tert-Butyl-dimethyl-silyloxy)methyl-8-methylene-octahydro-1,3a-methano-inden-3-ol

To a stirred solution of diol 21 (158 mg, 0.81 mmol) in DMF (5 mL) at rt was added tert-butyldimethylsilyl chloride (182 mg, 1.5 equiv) and imidazole (386 mg, 7 equiv). The reaction mixture was stirred for 5 h and diluted with EtOAc (10 mL). The organic phase was washed with 2% aqueous solution of citric acid (10 mL), water (10 mL), and brine (10 mL),...
dried over MgSO₄ and concentrated in vacuo to provide 273 mg (0.88 mmol) crude silyl-protected alcohol as a colorless oil. The crude silyl ether was used for the next step without further purification.

**1H NMR:** 4.51 (s, 1 H), 4.34 (s, 1 H), 3.94 – 3.80 (m, 2 H), 3.74 (d, J = 10.9 Hz, 1 H), 3.12 (d, J = 6.8 Hz, 1 H), 2.61 (s, 1 H), 2.14 (ddd, J = 12.0, 7.6, 1.6 Hz, 1 H), 1.86 – 1.72 (m, 3 H), 1.67 – 1.48 (m, 5 H), 1.35 – 1.27 (m, 1 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H). 13C NMR: 156.2, 93.7, 72.6, 63.8, 62.4, 50.4, 45.1, 36.5, 30.8, 25.7, 21.9, 21.5, 20.7, 18.0, -5.6, -5.8. IR (neat): 3400, 2930, 1684 (w), 1254, 1080.

**To a solution of the above crude alcohol (273 mg, 0.88 mmol) in THF (5 mL) at rt was added benzyl bromide (0.2 mL, 288 mg, 1.68 mmol), and sodium hydride (60 wt.% dispersion in mineral oil, 80 mg, 2 equiv). The resulting mixture was stirred at rt for 30 min. Tetra-n-butylammonium iodide (cat) was added and stirring was continued overnight. The reaction was quenched with icewater. The layers were separated and the aqueous phase extracted with ether (3×10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄, and concentrated in vacuo to afford 27 as a colorless oil after chromatographic purification (290 mg, 0.73 mmol, 90% from 21). 1H NMR: 7.35 - 7.24 (m, 5 H), 4.56 (d, J = 12.2 Hz, 1 H), 4.52 (s, 1 H), 4.48 (d, J = 12.2 Hz, 1 H), 4.34 (s, 1 H), 4.23 (dd, J = 10.8, 1.7 Hz, 1 H), 3.69 (dd, J = 7.3, 2.7 Hz, 1 H), 3.47 (d, J = 10.8 Hz, 1 H), 2.68 (s, 1 H), 2.09 – 2.00 (m, 2 H), 1.87 (dd, J = 11.5, 1.9 Hz, 1 H), 1.64 - 1.46 (m, 6 H), 1.25 - 1.20 (m, 1 H), 0.88 (s, 9 H), 0.02 (s, 6 H). 13C NMR (200 MHz): 156.2, 139.0, 128.2 (2 C), 127.23, 127.18 (2 C), 94.0, 79.8, 72.1, 61.4, 59.7, 49.9, 46.2, 33.7, 26.9, 26.0, 21.9, 21.7, 21.1, 18.3, -5.31, -5.33. IR (neat): 2929, 1687, 1452.

**Toluene-4-sulfonic acid 3-benzyloxy-8-methylene-hexahydro-1,3a-methano-inden-7a-yl methyl ester (29)**

To a stirred solution of alcohol 28 (185 mg, 0.65 mmol, 84%) after chromatography (hexane:EtOAc=3:1). Rf = 0.26. 1H NMR: 7.34 - 7.26 (m, 5 H), 4.63 (d, J = 11.9 Hz, 1 H), 4.55 (s, 1 H), 4.48 (d, J = 11.9 Hz, 1 H), 4.37 (s, 1 H), 3.93 (d, J = 11.9 Hz, 1 H), 3.81 - 3.76 (m, 2 H), 2.66 (s, 1 H), 2.11 (br s, 1 H), 2.05 (ddd, J = 11.9, 7.1, 1.6 Hz, 1 H), 1.97 (br d, J = 11 Hz, 1 H), 1.90 - 1.48 (m, 8 H). 13C NMR: 155.3, 138.1, 128.2 (2 C), 127.4, 127.2 (2 C), 94.2, 79.5, 71.2, 63.7, 61.8, 49.8, 45.6, 33.6, 30.8, 21.8, 21.5, 21.2. IR (neat): 3370, 2930, 1687, 1452.

**Toluene-4-sulfonic acid 3-benzyloxy-8-methylene-hexahydro-1,3a-methano-inden-7a-yl methanol (28)**

To a stirred solution of the above silyl ether 27 (312 mg, 0.78 mmol) in CH₂Cl₂/MeOH (9:1 v/v) (5 mL) at rt was added camphorsulphonic acid (60 mg, 0.3 equiv). The reaction mixture was stirred at rt for 3 h and quenched with saturated aqueous NaHCO₃ (5 mL). The layers were separated and the aqueous phase extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, and concentrated in vacuo to give alcohol 28 as a slightly yellow oil (185 mg, 0.65 mmol, 84%) after chromatography (hexane:EtOAc=3:1). Rf = 0.26. 1H NMR: 7.34 - 7.26 (m, 5 H), 4.63 (d, J = 11.9 Hz, 1 H), 4.55 (s, 1 H), 4.48 (d, J = 11.9 Hz, 1 H), 4.37 (s, 1 H), 3.93 (d, J = 11.9 Hz, 1 H), 3.81 - 3.76 (m, 2 H), 2.66 (s, 1 H), 2.11 (br s, 1 H), 2.05 (ddd, J = 11.9, 7.1, 1.6 Hz, 1 H), 1.97 (br d, J = 11 Hz, 1 H), 1.90 - 1.48 (m, 8 H). 13C NMR: 155.3, 138.1, 128.2 (2 C), 127.4, 127.2 (2 C), 94.2, 79.5, 71.2, 63.7, 61.8, 49.8, 45.6, 33.6, 30.8, 21.8, 21.5, 21.2. IR (neat): 3370, 2930, 1687, 1452.
layers were washed with water (30 mL), brine (30 mL), dried over MgSO₄, and concentrated in vacuo to afford the crude tosylate 29 as a colorless oil (341 mg, 0.78 mmol), that was used for the next step without further purification. ¹H NMR: 7.73 (d, J = 8.3 Hz, 2 H), 7.37 – 7.21 (m, 7 H), 4.77 (dd, J = 10.5, 1.9 Hz, 1 H), 4.58 (s, 1 H), 4.42 (d, J = 12.0 Hz, 1 H), 4.38 (s, 1 H), 4.32 (d, J = 12.0 Hz, 1 H), 3.92 (d, J = 10.5 Hz, 1 H), 3.64 (dd, J = 7.3, 2.5 Hz, 1 H), 2.71 (s, 1 H), 2.41 (s, 3 H), 1.98 – 1.90 (m, 2 H), 1.67 – 1.41 (m, 7 H), 1.06 – 1.00 (m, 1 H). ¹³C NMR: 154.4, 144.2, 138.3, 132.8, 129.5 (2 C), 128.1 (2 C), 127.8 (2 C), 127.2, 126.9 (2 C), 95.3, 78.8, 70.7, 68.7, 62.2, 49.7, 44.0, 44.0, 33.0, 26.8, 21.4, 21.3, 21.0, 20.6. IR (CHCl₃): 2939, 1696, 1598, 1452, 1356, 1175. HRMS (FAB) calcd for C₂₆H₃₁O₄S (MH⁺) 439.1943, found 439.1945.

3-Benzyloxy-7a-methyl-8-methylene-octahydro-1,3a-methano-indene (30)

Lithium triethylborohydride (1 M in THF, 3 mL, 4 equiv) was added to a solution of the above tosylate 29 in THF (10 mL) at 0 °C. The reaction mixture was brought to reflux for 1 h and then cooled to 0 °C. The reaction was quenched with icewater and the layers were separated. The aqueous layer was extracted with ether (3×10 mL). The combined organic layers were washed with 3 N aqueous NaOH (10 mL) and 30% aqueous H₂O₂ (10 mL), water (30 mL), brine (30 mL), dried over MgSO₄, and concentrated in vacuo to provide 30 (142 mg, 0.53 mmol, 66% from 28) as a colorless oil after chromatography (hexane:EtOAc=20:1). Rf = 0.50. ¹H NMR: 7.36 – 7.24 (m, 5 H), 4.58 (d, J = 12.3 Hz, 1 H), 4.49 (s, 1 H), 4.47 (d, J = 12.3 Hz, 1 H), 4.33 (s, 1 H), 3.69 (dd, J = 7.3, 2.8 Hz, 1 H), 2.51 (s, 1 H), 2.02 (ddd, J = 11.4, 7.3, 1.6 Hz, 1 H), 1.91 – 1.81 (m, 2 H), 1.66 – 1.42 (m, 6 H), 1.28 – 1.20 (m, 1 H), 1.16 (s, 3 H). ¹³C NMR: 157.0, 139.1, 128.0 (2 C), 127.0, 126.9 (2 C), 93.7, 79.8, 71.0, 61.0, 51.8, 41.2, 34.1, 33.8, 22.2, 21.8, 20.6, 16.4. IR (neat): 2931, 2857, 2860, 1686, 1455, 1355, 867. HRMS (FAB) calcd for C₁₉H₂₅O (MH⁺) 269.1905, found 269.1908.

3-Benzyloxy-8-hydroxymethyl-7a-methyl-octahydro-1,3a-methano-inden-8-ol (37)

To a stirred solution of 30 (113 mg, 0.42 mmol) in pyridine/water (1:1, v/v, 5 mL) at rt was added OsO₄ (161 mg, 0.63 mmol, 1.5 equiv). The reaction mixture was heated to 65 °C, stirred for 6 h at this temperature and then cooled to rt. Saturated aqueous NaHSO₃ (10 mL) and solid Na₂SO₃ (50 mg) were added and the resulting mixture was stirred for 30 min. The layers were separated and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were washed with saturated aqueous NaHSO₃ (30 mL), water (30 mL), brine (30 mL), dried over MgSO₄, and concentrated in vacuo to afford the crude product. Chromatographic purification (hexanes:EtOAc=1:1) gave residual starting material (26.0 mg, 0.097 mmol) and diol 37 (55.6 mg, 0.18 mmol, 60% yield, based on 73% conversion) as a colorless oil. Rf = 0.37. ¹H NMR: 7.36 – 7.23 (m, 5 H), 4.62 (d, J = 12.3 Hz, 1 H), 4.50 (d, J = 12.3 Hz, 1 H), 4.38 (br d, J = 11 Hz, 1 H), 4.25 (br d, J = 11 Hz, 1 H), 4.15 (dd, J = 7.1, 2.2 Hz, 1 H), 3.15 (s, 1 H), 2.29 (s, 1 H), 2.24 – 2.11 (m, 1 H), 2.08 – 2.07 (m, 1 H), 1.92 – 1.91 (m, 2 H), 1.67 – 1.60 (m, 4 H), 1.46 – 1.32 (m, 3 H), 1.20 (s, 3 H). ¹³C NMR: 139.3, 128.0 (2 C), 126.9 (3 C), 81.0, 80.8, 71.5, 67.8, 58.3, 48.3, 38.7, 33.0, 32.4, 22.0, 21.7, 21.2, 20.4. IR (neat): 3400, 2926, 1453, 1274, 1073.

8-Hydroxymethyl-7a-methyl-octahydro-1,3a-methano-indene-3,8-diol (38)

A mixture of benzyl ether 37 (48 mg, 0.159 mmol) and pre-equilibrated 10% Pd/C (40 mg) in ethanol (2 mL) was treated with hydrogen at rt and atmospheric pressure for
30 min. The mixture was filtered and the filtrate was evaporated to yield the desired triol 38 (22 mg, 0.104 mmol, 65%) as a colorless oil after chromatographic purification (EtOAc). \( R_f = 0.30 \). \(^1\)H NMR (CD\textsubscript{3}OD): 4.36 – 4.32 (m, 1 H), 4.33 (d, \( J = 11.5 \) Hz, 1 H), 4.1 (d, \( J = 11.5 \) Hz, 1 H), 2.3 – 2.27 (m, 2 H), 2.24 (s, 1 H), 1.7 (dd, \( J = 1 \) Hz, \( J = 11 \) Hz, 1 H), 1.66 – 1.4 (m, 7 H), 1.16 (s, 3 H). \(^{13}\)C NMR: 81.0, 73.9, 67.8, 58.0, 48.4, 38.6, 34.6, 33.2, 22.0, 21.35, 21.31, 19.9. IR (neat): 3400, 2932, 1058.

3-Hydroxy-7a-methyl-octahydro-1,3a-methano-inden-8-one (6)

To a stirred solution of the above triol 38 (22 mg, 0.104 mmol) in acetone/water (1:1, \( v/v \), 2 mL) at 0 °C was added NaIO\(_4\) (45 mg, 2 equiv). The resulting mixture was allowed to warm up to rt and stirred for 30 min. Most of the acetone was evaporated \textit{in vacuo}. The residue was dissolved in EtOAc (5 mL) and the organic phase washed with brine (5 mL) and concentrated \textit{in vacuo} to provide cyclobutanone 6 as a colorless solid after chromatography purification (hexanes:EtOAc=4:1). \( R_f = 0.10 \). Recrystallization (diisopropyl ether) gave colorless crystals (12 mg, 0.067 mmol, 64%), mp 103-106 °C. \(^1\)H NMR: 4.08 (dd, \( J = 7.8, 2.8 \) Hz, 1 H), 2.63 (s, 1 H), 2.28 (ddd, \( J = 12.7, 7.8, 1.5 \) Hz, 1 H), 2.00 (ddd, \( J = 12.7, 3.0, 1.6 \) Hz, 1 H), 1.87 (br s, 1 H), 1.8 – 1.2 (m, 8 H), 1.31 (s, 3 H). \(^{13}\)C NMR: 202.8, 70.0, 67.9, 61.0, 36.1, 35.3, 32.4, 22.2, 21.3, 18.8, 14.2. IR (neat): 3430, 2938, 1798, 1766.

Crystallographic data for (6): \( \text{C}_{11}\text{H}_{16}\text{O}_2 \), \( M = 180.24 \), monoclinic, \( a = 7.0166(3) \) Å, \( b = 10.5703(6) \) Å, \( c = 13.7222(13) \) Å, \( \beta = 102.880(5)° \), \( V = 992.13(12) \) Å\(^3\), \( T = 295 \) K, space group \( P2_1/n \), \( Z = 4 \), \( C(\text{Cu-K}) = 0.65 \) mm\(^{-1}\), 1743 observed unique reflections.

Synthesis of diol 35

To a stirred solution of lactone 5 (116 mg, 0.61 mmol) in \( n \)-butanol/water/acetone (5 mL, 5.0/1.5/1.0, \( v/v/v \)) was added \( N \)-methylmorpholine-\( N \)-oxide (142 mg, 2 equiv) and OsO\(_4\) (1.55 mg, 1 mol %) at rt. The reaction mixture was stirred overnight and quenched with saturated aqueous Na\(_2\)S\(_2\)O\(_3\) (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3x10 mL). The combined organic layers were washed with saturated aqueous Na\(_2\)S\(_2\)O\(_3\) (30 mL), water (30 mL), brine (30 mL), dried over MgSO\(_4\), and concentrated \textit{in vacuo} to afford diol 35 (81 mg, 0.36 mmol, 59%) as an oil after chromatography (EtOAc). \( R_f = 0.34 \). \(^1\)H NMR: 4.67 (dd, \( J = 4.2, 1.2 \) Hz, 1 H), 4.32 (d, \( J = 10.8 \) Hz, 1 H), 4.20 (d, \( J = 10.8 \) Hz, 1 H), 3.37 (br s, 1 H), 2.81 (s, 1 H), 2.76 (dd, \( J = 11.9, 4.3 \) Hz, 1 H), 2.35 (dd, \( J = 14.6, 3.7 \) Hz, 1 H), 2.07 (br s, 1 H), 1.90 - 1.76 (m, 2 H), 1.72 - 1.68 (m, 1 H), 1.61 – 1.57 (m, 1 H), 1.48 - 1.39 (m, 2 H), 1.27 – 1.13 (m, 1 H), 1.07 – 0.95 (m, 1 H). \(^{13}\)C NMR: 178.0, 82.0, 79.6, 64.7, 62.5, 49.7, 47.1, 34.0, 22.6, 21.3, 20.5, 18.5. IR (neat): 3450, 2936, 1749.

Synthesis of cyclobutanone 31

To a stirred solution of diol 37 (16 mg, 0.05 mmol) in acetone/water (1:1, \( v/v \)) (2 mL) at rt was added NaIO\(_4\) (23 mg, 2 equiv). The reaction mixture was stirred at rt for 1 h and most of acetone was then evaporated (bath temperature: 30 °C). The residue was dissolved in EtOAc (10 mL) and the organic phase was washed with water (10 mL), brine (10 mL) and concentrated \textit{in vacuo} to provide cyclobutanone 31 (47%) as a colorless oil after chromatography purification (PE:EtOAc=4:1). \( R_f = 0.38 \). \(^1\)H NMR: 7.3 - 7.2 (m, 5 H), 4.6 (d, \( J = 12 \) Hz, 1 H), 4.5 (d, \( J = 12 \) Hz, 1 H).
Further Chemistry with the Model Cycloadduct

Hz, 1 H), 3.8 (dd, J = 3 Hz, J = 7 Hz, 1 H), 2.6 (s, 1 H), 2.2 (ddd, J = 1 Hz, J = 7 Hz, J = 12 Hz, 1 H), 2.05 (ddd, J = 1.5 Hz, J = 3 Hz, J = 12 Hz, 1 H), 1.8 - 1.7 (m, 2 H), 1.68 - 1.6 (m, 1 H), 1.59 - 1.56 (m, 2 H), 1.53 - 1.34 (m, 3 H), 1.33 (s, 3 H). 13C NMR: 202.7, 138.2, 128.1, 127.3, 127.0, 74.3, 70.8, 69.9, 60.9, 35.9, 35.4, 30.7, 22.3, 21.2, 19.5, 14.4. IR: 2937, 2863, 1782, 1045. HRMS (FAB) calcd for C18H23O2 (MH+) 271.1698, found 271.1706.

4.7 References


Chapter 5
Intramolecular [2+2] Photocycloadditions of Substituted Allene Butenolides

5.1 Introduction

As described in previous chapters, the intramolecular [2+2] photocycloaddition of allene butenolide 1 gave exclusively cycloadduct 2 in good yield (Scheme 5.1). Further functional group transformations on the cycloadduct 2 eventually led to the tricyclic compound 5 containing the bicyclo[2.1.1]cyclohexanone moiety, the key structural feature of the right hand fragment 3 of solanoeclepin A.

Scheme 5.1

![Scheme 5.1 diagram]

The synthesis of the right hand substructure 3, and hence solanoeclepin A, however, requires the final hydrogen of the cyclobutanone ring in 5 to be replaced by a cyclopropanecarboxylic acid function. In addition, the vinyl triflate moiety, the functional handle for connecting the right- and the left-hand fragments of solanoeclepin A, needs to be installed on the six-membered ring. To this end, the use of the highly substituted allene butenolide 7 as the substrate in the key intramolecular [2+2] photocycloaddition would be a usable strategy. The allene 7 contains a ketone protected as a dioxolane which should be converted into the critical ester vinyl triflate moiety at a later phase of the synthesis. For the introduction of a cyclopropanecarboxylic acid moiety, a hydroxymethyl group (R = CH₂OPG, PG=protective group) would be the substituent of choice. As there was no literature precedent on the photocycloaddition of highly substituted butenolides, we decided to initially investigate the photocycloaddition of several models of 7 (R = SiMe₃, SiMe₂Ph, CH₃CO₂Et, n-Bu) in order to probe whether the photocycloaddition would proceed well with substituted allene butenolides. This model study will be followed by the successful synthesis of the "real" allene butenolide (R = CH₂OPG) and its satisfactory photocycloaddition. These results will be described in this chapter.
5.2. Photocycloaddition of the Substituted Allene Butenolide Models

Our synthetic plan toward the required butenolide 8 is shown in eq 5.1. Similar to the synthesis of the model butenolide described in chapter 3, the substituted allene butenolide 8 should be conveniently accessible based on Jefford’s coupling procedure between silyloxyfuran 10 or 11 and the substituted allenylmethyl bromide 9. The straightforward synthesis of 10 and 11 has been successfully carried out in our previous work as presented in chapters 2 and 3, respectively. Therefore, several substituted allenylmethyl bromides 9 (R₂= SiMe₃, SiMe₂Ph, CH₂CO₂Et, n-Bu) were prepared and allowed to couple with either silyloxyfuran 10 or 11. The resulting coupling products were then irradiated in order to examine their potential as photosubstrates in the intramolecular [2+2] photocycloaddition.

\[
\begin{align*}
\text{R}_1 & \quad \text{Br} \quad \text{R}_2 \\
\text{O} & \quad \text{O} \\
\text{TIPSO} & \quad \\
(5.1)
\end{align*}
\]

5.2.1 Preparation and Cyclization of Trimethylsilyl-Substituted Allene Butenolide

Our first model was the allene butenolide 12 having a dimethylphenylsilyl substituent on the allene moiety (eq 5.2). It is known that a dimethylphenylsilyl group is a potential synthetic equivalent for a hydroxyl function.¹ It was our hope, therefore, that this silyl group could serve as a stable functional group that would enable the introduction of a cyclopropanecarboxylic acid moiety at a later phase of our synthesis.

\[
\begin{align*}
\text{R} & \quad \text{Br} \\
\text{O} & \quad \text{O} \\
\text{TIPSO} & \quad \\
(5.2)
\end{align*}
\]

The butenolide 12 was expected to derive from the readily prepared furanolate 11 (chapter 3) and the allenic bromide 14. Several useful methods have been developed for the synthesis of substituted allenes.² One of the most common methods is the reaction of Grignard reagents with propargyl sulfonate derivatives catalyzed by cuprous bromide or iodide. Based on this methodology, we decided to initially prepare an analogue of allene 14, e.g. the known allene 15³ (eq 5.2) because of the commercial availability of the Grignard reagent (trimethylsilyl)methylmagnesium chloride.
Starting from the commercially available 2-butyn-1,4-diol (16), a reasonable yield of the monobenzoylation product 17 was obtained using benzoyl chloride and pyridine (Scheme 5.2). Treatment of 17 with methanesulfonyl chloride and triethylamine produced the desired mesylate 18 which subsequently reacted with (trimethylsilyl)methylmagnesium chloride in the presence of copper bromide and lithium bromide to afford allenylmethylsilane 19 in a modest yield. The benzoyl group was then saponified using K$_2$CO$_3$ in MeOH/H$_2$O to give the corresponding allenic alcohol 20. Finally, mesylation of the hydroxyl group followed by substitution with LiBr provided the desired allenylmethyl bromide 15 in excellent yield.

**Scheme 5.2**

With the required allenylmethyl bromide 15 in hand, the next step was to couple it with silyloxyfuran 11 (eq 5.3). Thus, mixing 15 with silver trifluoroacetate in CH$_2$Cl$_2$ at -78 °C followed by addition of furanolate 11 led to the formation of allene butenolide 13 in 29% yield along with unidentified byproducts. The low yield of this reaction indicates that the trimethylsilyl group is not well tolerated by the reaction conditions although further optimization has not yet been investigated.

Our next goal was to examine whether the photocycloaddition reaction of the allene butenolide 13 would proceed as well as the unsubstituted analogue. Thus, butenolide 13 was subjected to irradiation at 300 nm, using a 9:1 mixture of acetonitrile and acetone as the solvent (eq 5.4).

---

### References

1. TIPSO
2. Br
3. Me$_3$Si
4. AgOCOCF$_3$
5. CH$_2$Cl$_2$
6. -78 °C to rt
7. O
8. O
9. MeCN/acetone (9:1, v/v)
10. 35 min
Complete conversion of the starting material was observed after 35 min. Only one product was formed along with decomposition as shown in 1H NMR of the crude photocycloadduct. Purification by column chromatography finally gave 65% yield of a crystalline compound which was assigned as the desired crossed adduct 21, in view of the presence of the AB system (J = 0.6 Hz) in 1H NMR spectrum which corresponds to the exocyclic methylene group at 4.68 and 4.52 ppm.

The success of this photocycloaddition confirms the utility of the allene butenolide 13 in the intramolecular photocycloaddition. The trimethylsilyl substituent on the allene moiety is, in fact, tolerated by the photoreaction conditions and has no effect on the regiochemical outcome of the reaction. This result prompted us to prepare the required butenolide 12 having the dimethylphenylsilyl group, a potential synthetic equivalent for a hydroxyl function (eq 5.2). The preparation of the allenic bromide 14 is presented in eq 5.5. The Grignard reagent formed in situ from dimethylphenylmethyl chloride underwent transmetallation with copper bromide to form the corresponding magnesium organocuprate which was reacted with mesylate 22 to produce the desired allenylsilane 23 in good yield. Subsequent hydrolysis of the acetyl group followed by mesylation and substitution of the formed hydroxyl function finally afforded the required allenylmethyl bromide 14 in excellent yield.

\[
\text{Mg} \quad \text{PhMe}_2\text{SiCH}_2\text{Cl} \\
\text{LiBr, CuBr} \quad \text{HMPA, THF} \\
-78 \degree C \text{ to rt} \\
\rightarrow \\
\text{OAc} \\
\text{SiMe}_2\text{Ph} \\
\text{OAc}
\]

The allenic bromide 14 was then subjected to the silver-mediated coupling reaction conditions with silyloxyfuran 11 as the other coupling partner (eq 5.6). Unfortunately, the desired butenolide 12 was formed in very low yield along with extensive decomposition of the starting allenic bromide as shown in the 1H NMR spectrum of the crude product.

\[
\text{TIPSO} \\
\text{PhMe}_2\text{Si} \\
\text{Br} \\
\text{AgOOCOCF}_3 \\
\text{CH}_2\text{Cl}_2 \\
-78 \degree C \text{ to rt} \\
\rightarrow \\
\text{O} \\
\text{SiMe}_2\text{Ph} \\
\text{O} \\
\text{O} \\
\text{OAc}
\]

Purification by column chromatography did not give sufficiently pure coupling product for further characterization. This result strongly points to the instability of the allylsilane under Jefford’s coupling reaction conditions as already observed in the case of allene 13 (eq 5.3). These unsatisfactory results prompted us to seek for other methods which would allow the synthesis of the required substituted allene butenolide, the key photoprecursor in our total synthesis.

5.2.2 Preparation and Cyclization of an Ester-Substituted Allene Butenolide
In an effort to explore whether the photocycloaddition would proceed satisfactorily with other substituted allene butenolides, we turned to the synthesis of allene 26 having an ethyl ester substituent as depicted in eq 5.7. By using carefully controlled conditions the orthoester Claisen rearrangement starting from 2-butyne-1,4-diol (16) could be directed to occur only once to a considerable extent so that the pure hydroxyester 25 could be prepared in 28% yield.4 From 25 bromide 26 was readily obtained in excellent yield as a stable compound through mesylation of the hydroxyl group followed by substitution.

\[
\begin{align*}
\text{HO} & \xrightarrow{\text{MeC(OEt)3, EtCO2H (cat)}} \text{CO2Et} \\
\text{16} & \rightarrow 25 \text{ (28\% yield)} \\
& \xrightarrow{1) \text{MsCl, TEA, 120 °C}} \text{26 (62\% (two steps))}
\end{align*}
\]

The silver-mediated coupling of the allenic bromide 26 with silyloxyfuran 11 was then carried out under the same conditions as described for allene 15. This led to the formation of butenolide 27 in a moderate yield, likely due to the sensitivity of the allenic starting material under these unoptimized reaction conditions (eq 5.8). Butenolide 27 was then irradiated for 35 min under normal conditions, using acetone as the sensitizer. Interestingly, the photocycloaddition cleanly gave a single regioisomer which was assigned as the crossed cycloadduct 28 albeit in a moderate yield.

\[
\begin{align*}
\text{TIPSO} & \xrightarrow{\text{AgOCOCF3, CH2Cl2, -78 °C to rt}} \text{CO2Et} \\
11 & \rightarrow 26 \\
& \xrightarrow{\text{hv, MeCN/acetone (9:1, v/v), 35 min}} 27 \text{ (48\% yield)} \\
& \xrightarrow{\text{28 \text{ (40\% yield)}}}
\end{align*}
\]

Although the reaction conditions need to be optimized in order to secure a satisfactory yield, it can be concluded at this point that the ester group, like the trimethylsilyl moiety, appears to have little effect on the regioselectivity of the photocycloaddition.

In line with the results obtained with the model unsubstituted butenolide as described in chapter 3, the rate of cyclization of the more substituted butenolides 13 and 27 is higher than that of the unsubstituted analogue. The ease of these cycloadditions leading to the tricyclic framework containing three quaternary centers in a highly compact setting is noteworthy.

### 5.2.3 Preparation and Cyclization of an n-Butyl Substituted Allene Butenolide

The results achieved with the allene butenolides having substituents on the allene moieties prompted us to investigate whether the same result could be obtained in the photocycloaddition of more highly substituted allene butenolides, bearing two substituents both on the allene and the
cyclohexene moieties. Toward that end, we decided to prepare the \(n\)-butyl substituted allenic bromide 29 (eq 5.9) in a similar fashion as described for the allene 14. The known mesylate 22 was allowed to react with the \(in\ situ\) formed magnesium organocuprate leading to sufficiently clean formation of the corresponding \(n\)-butyl-substituted allene 30 which was used for the next step without purification. The same sequence as for allene 14 was then followed which eventually led to the required allenic bromide 29 in good yield.

\[
\begin{align*}
\text{OAc} & \quad \text{n-BuMgCl} \quad \text{LiBr, CuBr} \\
\text{MsO} & \quad \text{HMPA, THF} \quad -78 \, ^\circ\text{C to rt} \\
\text{OAc} & \quad \rightarrow \\
\text{Bu} & \quad \rightarrow \\
\text{Br} & \quad (5.9)
\end{align*}
\]

The use of \(n\)-butylmagnesium chloride appears to be crucial for the successful formation of allene 30. It was found in our earlier work that reaction of methylmagnesium bromide with 22 under the same reaction conditions mainly led to the substitution of the mesylate group by the bromide.

The coupling reaction between allene 29 and silyloxyfuran 10 was then carried out. Mixing 29 with silver trifluoroacetate in CH\(_2\)Cl\(_2\) followed by addition of silyloxyfuran 10 at \(-78\) °C led to the formation of allene butenolide 31 in 60% yield (eq 5.10). Interestingly, when butenolide 31 was irradiated at 300 nm for 30 min, using a 9:1 mixture of acetonitrile and acetone as the solvent, the desired crossed photocycloadduct 32 was formed as a single product in excellent yield.

\[
\begin{align*}
\text{O} & \quad \text{TIPSO} \\
\text{Br} & \quad \text{O} \\
\text{Bu} & \quad \text{O} \\
\text{AgOCOCF}_3 & \quad \text{Bu} \\
\text{CH}_2\text{Cl}_2 & \quad -78 \, ^\circ\text{C to rt} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{Bu} \\
\text{MeCN/acetone} & \quad \text{30 min} \\
\text{32} & \quad 81\%
\end{align*}
\]

The success of the photocycloaddition of the model 31 indicates that the acetal protective group of the ketone is in fact tolerated by the reaction conditions. This result proves the feasibility of utilizing the photosubstrate 7 in the key photocycloaddition step of our synthetic strategy toward the right hand fragment of solanoeclepin A (Scheme 5.1). The acetal protected ketone is expected to be a good functional group for the crucial installation of the vinyl triflate, the functional handle for connecting the left- and the right-hand fragments of the natural product. Our next goal was, therefore, to prepare the required allene butenolide bearing a suitable functional group on the allene moiety which could serve as a handle for incorporating a cyclopropane carboxylic acid moiety. To meet that requirement, R in the butenolide photosubstrate 7 should be a hydroxymethyl group. Our synthesis was then set to prepare this crucial substituted allene butenolide.

5.3 Preparation and Photocycloaddition of the "Real" Butenolide
The synthetic strategy toward the key intermediate 33 (eq 5.11) requires the preparation of the allenylmethyl bromide 34. To prepare this allene we planned to make use of the Baylis-Hillman reaction\(^5\) to install the hydroxymethyl group onto the α-allenic ester 35. The synthesis, therefore, started with the preparation of ester 35.

\[\text{Baylis-Hillman} \quad \text{OPG} \quad + \quad \text{Br} \quad \rightarrow \quad \text{TIPS-OPG} \quad \text{CO}_2\text{R} \quad \text{35}\]  

The acylation of Wittig reagents is the most convenient method for the preparation of allenes substituted with electron-withdrawing substituents. Lange et al.\(^6\) reported an efficient synthesis of α-allenic esters via the reaction of resonance-stabilized ylides with acid chlorides in the presence of triethylamine. Based on this methodology, the required α-allenic benzyl ester 37 was prepared in an excellent yield starting from the commercially available triphenylphosphorane 36 (Scheme 5.3). A Wittig type mechanism is suggested for this reaction between ylide 36 with the ketene formed \textit{in situ} by dehydrochlorination of the acid chloride by triethylamine. This clean and mild reaction was reliably conducted on 50 gram scale with a yield up to 80%.

Scheme 5.3

The next step was the introduction of the hydroxymethyl group to C-α of the allenic ester 37. For this purpose, our initial attempt relied on the reaction of 37 with paraformaldehyde in the presence of n-butyllithium at -78 °C.\(^7\) Unfortunately, only decomposition of the starting allene was observed and no trace of the required aldol adduct could be detected. Therefore, we turned to a mild tertiary amine-catalyzed condensation with formaldehyde. This reaction is normally referred to as the Baylis-Hillman reaction,\(^5\) the reaction of an electron-deficient alkene with an aldehyde catalyzed by a
tertiary amine or phosphine. Among the popular tertiary amines or phosphines, 1,4-diazabicyclo[2.2.2]octane (DABCO) is the most frequently used catalyst for this reaction. While numerous papers concerning the use of α,β-unsaturated carbonyl compounds in the Baylis-Hillman reaction have been published, the use of allenic esters is less documented. The coupling reaction with a variety of aldehydes catalyzed by DABCO is a good method for preparation of α-(hydroxyalkyl) allenic esters, but formaldehyde has not yet been used. For our goal of introducing a hydroxy methyl group onto the allene 37 via the Baylis-Hillman procedure, we decided to explore the utility of formaldehyde as the electrophile. Thus, our initial effort made use of an aqueous solution of formaldehyde, generated in situ from paraformaldehyde and aqueous phosphoric acid, as the source of the electrophile and DABCO as the catalyst. Disappointingly, only decomposition of the starting allene was observed under these reaction conditions. The use of excess of paraformaldehyde and 20 mol% of DABCO in THF, fortunately, turned out to be superior (Scheme 5.3). In this way, the required α-(hydroxymethyl) allene 38 was efficiently isolated in 60% yield along with 28% yield of the recovered starting allene 37.

Mechanistically, the reaction is believed to be initiated by the Michael type nucleophilic addition of the tertiary amine (DABCO) to the central carbon of the allene resulting in the transient zwitterionic enolate II, which subsequently attacks formaldehyde to produce the zwitterionic III. Proton migration followed by elimination of the tertiary amine gives the final substituted allene 38.

The temperature and the reaction time were found to influence dramatically the yield of the Baylis-Hillman reaction of allene 37. The reaction is best started at -10 °C and continued at about 18 °C for 1.5 h. These optimized conditions resulted in a clean mixture of the allene product 38 and the starting allene 37, which could be easily separated by column chromatography. Higher temperature or longer reaction time led to lower yields of both product and starting material. It is noteworthy that, starting from commercially available phosphorane 36, this two step procedure provides an efficient mean for the preparation of the highly substituted and novel allene 38. Allene 38 not only serves as the critical building block in our total synthesis but could also be a useful structural element for the synthesis of allene containing natural products.

The synthesis of the target bromide required protection of the hydroxyl group of allene 38. The stable TIPS–silyl ether was our first choice due to the observed tolerance of an alkylsilyl-containing photosubstrate 13 under photocycloaddition conditions (eq 5.4). Thus, treatment of allene 38 with triisopropylsilyl trifluoromethanesulfonate in the presence of triethylamine followed by reduction of the ester moiety using DIBAL-H produced allene 39 in good yield (eq 5.12). A two step sequence involving mesylation followed by substitution finally converted the hydroxy moiety of the allene 39 into the required allenylmethyl bromide 40 in excellent yield.
With the desired allene 40 in hand, we could eventually explore its utility in the coupling reaction with the silyloxyfuran 10. Unfortunately, treatment of allene 40 with silver trifluoroacetate in CH$_2$Cl$_2$ at -78 °C followed by furanolate 10 afforded the desired allene butenolide 41 in low yield (eq 5.13). In line with our experience with allenes 14 and 15, this result indicates that neither alkylsilane nor alkylsilyl ether substituted allenic bromide appears to be tolerated by the rather Lewis acidic coupling reaction conditions.

In contrast to the unsatisfactory results obtained from the coupling reaction, the allene butenolide 41 shows its potential as a useful substrate in the intramolecular photocycloaddition. Upon irradiation of 41 at 300 nm for 15 min, the desired crossed photocycloadduct 42 was isolated in good yield as a single product (eq 5.13). The cycloadduct 42 contains important functional groups for further elaboration toward the right hand fragment 3 of solanoeclepin A.

We then searched for an allenic bromide with a more stable protective group for the hydroxyl moiety. A methoxymethyl (MOM) group was expected to be tolerated by the coupling conditions. Thus, the MOM-protected allene 43 was prepared as presented in eq 5.14. Treatment of allene 38 with MOMCl in CH$_2$Cl$_2$ in the presence of diisopropylethylamine$_{12}$ as a base followed by reduction of the ester moiety using DIBAL-H$_{11}$ provided the MOM-protected allene 43 in a moderate yield. A normal two step conversion eventually converted 43 into the corresponding allenylmethyl bromide 44 in reasonable overall yield.

Unfortunately, subjection of allene 44 to the silver-mediated coupling reaction conditions led only to decomposition of the starting allene. No trace of the desired coupling product 45 could be detected (eq 5.15).
This result must be ascribed to the low stability of the MOM-ether under the reaction conditions as observed previously for the silicon protective group. Therefore, an even more stable protective group is required for the success of this coupling reaction.

We then decided to use a benzyl ether group as the protective group for the hydroxyl moiety of allene 38. This robust protecting group is known to be tolerated by a variety reaction conditions and it can be efficiently removed via catalytic hydrogenolysis as described in our previous work (chapter 4) or with sodium in liquid ammonia. Thus, the hydroxyl group of allene 38 was benzylated under mildly acidic conditions using benzyl trichloroacetimidate 13 and TMS-OTf as the catalyst (eq 5.16). Reduction of the ester moiety followed by mesylation and substitution of the resulting alcohol gave the corresponding allenic bromide 47 in 37% yield over three steps. The modest yield of this sequence is likely due to the low efficiency of the reduction step which appeared to be strongly dependent upon the temperature, the reaction time and the amount of DIBAL-H used.

With the required allene bromide 47 in hand, its coupling reaction with silyloxyfuran 10 was then carried out. Mixing allene 47 with the triisopropylsil dianolate 10 in CH₂Cl₂ and then treated at -78 °C with silver trifluoroacetate led to the desired allene butenolide 48 in 60% yield (eq 5.17). The reasonable yield of this coupling reaction should allow the preparation of sufficient quantities of the required photosubstrate 48, the key intermediate for constructing the tricyclic core of the natural product.

The key photocycloaddition was then investigated. Acetone sensitized irradiation of butenolide 48 at 300 nm for 1 h, using acetonitrile as the solvent resulted in the desired crossed cycloadduct 49 in low yield along with extensive decomposition of the starting material. Further investigation on the photocycloaddition reaction revealed that the cyclization of butenolide 48 could be best conducted in a 9:1 mixture of benzene and acetone as the solvent (eq 5.18). Under such optimized conditions the photocycloadduct 49 was cleanly isolated in 60% yield as a stable colorless oil (IR ν 1770 cm⁻¹). The ¹H NMR spectrum of the cycloadduct 49 shows two singlets at 4.78 and 4.76 ppm (Fig 5.1) which clearly correspond to the exocyclic methylene moiety (H-14) as observed previously in our model study (chapter 3).
Intramolecular [2+2] Photocycloadditions of Substituted Allene Butenolides

Figure 5.1 $^1$H NMR spectrum (7.60-1.40 ppm) of the photocycloadduct 49

This successful photocycloaddition allows construction of the exocyclic methylene containing tricyclic core of the right hand fragment of solanoeclepin A in one step with high yield and high regioselectivity. The ease of the cycloaddition leading to the three quaternary centers in a highly compact setting is noteworthy. The photocycloadduct 49 contains the required functional handles for further elaboration toward the right hand substructure 3 of the natural product. Application of the chemistry developed previously for the model (chapter 4) on the photocycloadduct 49 could generate the angular methyl and the cyclobutanone functions. The benzyl ether could serve as a handle for incorporating a cyclopropane carboxylic acid moiety at a later phase of the synthesis. The critical installation of the vinyl triflate from the ketone could eventually accomplish the right hand substructure 3, and hence, solanoeclepin A.

5.4 Conclusions

Preparation and photocycloaddition of several models of highly substituted allene butenolides have been described in this chapter. This model study further illustrates the potential of allenes as the substrates in the intramolecular [2+2] photocycloaddition reaction presented in chapter 3. The successful synthesis of the "real" allene butenolide 48 and its satisfactory intramolecular [2+2]
photocycloaddition allow assembling the tricyclic core containing the bicyclo[2.1.1]cyclohexane keleton of the cycloadduct 49 in good yield and with complete regioselectivity. The cycloadduct 49 contains the key structural features and the required functional handles for further elaboration toward the right hand substructure 3 of solanoeclepin A.

5.5 Acknowledgements

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5.6 Experimental Section

General information. For general experimental details, see Section 2.6.

4-Hydroxybut-2-ynyl benzoate (17)

To a solution of diol 16 (5g, 58.1 mmol) in CH2Cl2 (400 mL) at 0 °C was added pyridine (4.7 mL, 58.1 mmol) and benzoyl chloride (6.75 mL, 58.1 mmol). The reaction mixture was stirred overnight, quenched with ethanol and part of solvent was removed. Water (100 mL) was added and the water layer was extracted with EtOAc (2x100 mL) and the combined organic layers were washed with brine (200 mL), dried over MgSO4 and concentrated in vacuo. Purification by chromatography (PE:EtOAc=2:1) afforded alcohol (17) (6.6 g, 60%). 1H NMR: 8.06 (dd, J = 8.2 Hz, J = 1.1 Hz, 2 H), 7.59 (t, J = 7 Hz, 1 H), 7.47 – 7.43 (m, 2 H), 4.97 (t, J = 2 Hz, 2 H), 4.33 (t, J = 2 Hz, 2 H), 1.82 (br, 1 H).

4-(Methylsulfonyloxy)but-2-ynyl benzoate (18)

To a solution of alcohol 17 (2.39 g, 12.5 mmol) in in CH2Cl2 (50 mL) at 0 °C was added TEA (2.6 mL, 16.75 mmol) and MsCl (1.06 mL, 13.75 mmol). The reaction mixture was stirred for 35 min at 0 °C and allowed to warm to rt and stirred for an additional 5 min. Water (50 mL) was added and the aqueous phase was extracted with ether (3x40 mL). The combined organic layers were washed with brine (100 mL), dried over MgSO4 and concentrated in vacuo. Purification by chromatography (CH2Cl2) afforded alcohol 18 (1.64 g, 49%). 1H NMR: 8.04 (dd, J = 8.2 Hz, J = 1.1 Hz, 2 H), 7.58 (t, J = 7 Hz, 1 H), 7.50 – 7.40 (m, 2 H), 4.97 (t, J = 1.6 Hz, 2 H), 4.90 (t, J = 1.6 Hz, 2 H), 3.13 (s, 3 H).

2-((Trimethylsilyl)methyl)buta-2,3-dienyl benzoate (19)

To a suspension of CuBr (157.8 mg, 1.1 mmol) and LiBr (955 mg, 1.1 mmol) in THF (2 mL) at -78 °C was added TMSCH2MgCl (1.0 M solution in ether, 1.1 mL). After stirring for 15 min, HMPA (0.55 mL) was added followed by a solution of 18 (290 mg, 1.08 mmol) in THF (1 mL). The resulting mixture was warmed slowly to rt and stirred for an
additional 30 min. Saturated aqueous NH₄Cl was added (3 mL) and the aqueous phase was extracted with PE (3x10 mL). The combined organic layers were washed with water (25 mL), brine (25 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (PE:EtOAc=9:1) afforded 19 (122 mg, 43%). ¹H NMR: 8.06 (dd, J = 7.8 Hz, J = 1.3 Hz, 2 H), 7.56 (t, J = 7.4 Hz, 1 H), 7.46 – 7.42 (m, 2 H), 4.81 – 4.78 (m, 2 H), 4.73 (t, J = 2.7 Hz, 2 H), 1.41 (t, J = 2.6 Hz, 2 H), 0.08 (s, 9 H).

2-((Trimethylsilyl)methyl)buta-2,3-dien-1-ol (20)

To a solution of K₂CO₃ (64 mg, 0.46 mmol) in water (1 mL) at rt was added a solution of 19 (120 mg, 0.46 mmol) in methanol (2 mL). The resulting mixture was stirred for 60 min. Part of the solvent was removed and the suspension was diluted with brine (5 mL). The aqueous phase was extracted with ether (3x5 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (CH₂Cl₂) afforded 20 (44 mg, 61%). ¹H NMR: 4.88 – 4.85 (m, 2 H), 3.96 (s, 2 H), 1.32 (t, J = 2.5 Hz, 2 H), 0.05 (s, 9 H). ¹³C NMR: 204.2, 101.7, 78.1, 63.6, 17.2, -1.50. IR: 3333, 1954.

Trimethyl(2-((methylsulfonylmethoxy)methyl)buta-2,3-dienyl)silane (15)

To a stirred solution of MsCl (180 mg, 1.6 mmol) in CH₂Cl₂ (1 mL) at 0 °C was added a solution of 20 (167.5 mg, 1.07 mmol) and TEA (0.22 mL, 1.6 mmol) in CH₂Cl₂ (3 mL). The resulting mixture was allowed to warm to rt and stirred for 30 min. The reaction was diluted with CH₂Cl₂ (10 mL). The layers were separated and the organic layer was washed with water (10 mL), brine (10 mL), dried over MgSO₄ and concentrated in vacuo to afford the corresponding mesylate (238 mg) which was used for the next step without purification. ¹H NMR: 4.85 – 4.83 (m, 2 H), 4.64 (t, J = 2 Hz, 2 H), 3.02 (s, 3 H), 1.41 (t, J = 2.7 Hz, 2 H), 0.08 (s, 9 H). To the solution of LiBr (354.3 mg, 4.08 mmol) in acetone (2 mL) at 0 °C was added a solution of the above mesylate (238 mg, 1.02 mmol) in acetone (2 mL). The resulting mixture was allowed to warm to rt and stirred for 30 min. After adding water (3 mL) the layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3x5 mL). The combined organic layers were washed with brine (15 mL), dried over MgSO₄ and concentrated in vacuo to afford the allenic bromide 15 (213 mg, 95%). ¹H NMR: 4.75 – 4.73 (m, 2 H), 3.89 (t, J = 1.6 Hz, 2 H), 1.48 (t, J = 2.7 Hz, 2 H), 0.06 (s, 9 H). ¹³C NMR: 204.2, 98.6, 75.9, 38.1, 18.5, -1.4.

General procedure A for Jefford’s coupling reaction

A mixture of silver trifluoroacetate (1.2 equiv), molecular sieves and allenic bromide (1.2 equiv) in CH₂Cl₂ (0.3 M) was stirred for 10 min at -78 °C before adding a solution of furanolate (1 equiv) in CH₂Cl₂ (0.3 M). The resulting mixture was stirred at -78 °C for 20 min and at -20 °C for additional 2 h and then at rt overnight. The reaction mixture was filtered through Celite® and solvent evaporated in vacuo. The coupling product was purified by column chromatography.

General procedure B for the [2+2] photocycloaddition reactions

The photoreaction was carried out in a Pyrex glass vessel with a Rayonet RPR 3000 Å at room temperature. A solution of the precursor in the indicated solvent was degassed by bubbling argon.
through for 30 min. The solution was kept under argon and irradiated for the time indicated. The reaction was followed by monitoring the UV absorption of the starting material on TLC. When complete conversion was observed, the solvent was removed in vacuo.

3-(2-((Trimethylsilyl)methyl)buta-2,3-dienyl)-4,5,6,7 tetrahydroisobenzofuran-1(3H)-one (13)

According to the procedure A, allenic bromide 15 (105 mg, 0.48 mmol) gave the allene butenolide 13 (38 mg, 29%) after purification (pentane:CH₂Cl₂= 7:3 then CH₂Cl₂). ¹H NMR: 4.94 (t, J = 5.8 Hz, 1 H), 4.74 – 4.65 (m, 2 H), 2.36 - 2.20 (m, 6 H), 1.78 – 1.71 (m, 4 H), 1.40 – 1.31 (m, 2 H), 0.04 (s, 9 H).

Photocycloadduct 21

According to procedure B, allene butenolide 13 (29 mg, 0.1 mmol) in acetonitrile/acetone (9:1, v/v) (25 mL) gave 21 (18 mg, 65%) after purification (PE:DCM=1:1) as a solid compound (Mp 70-72 °C). ¹H NMR: 4.68 (d, J = 0.6 Hz, 1 H), 4.60 (d, J = 4.1 Hz, 1 H), 4.52 (d, J = 0.6 Hz, 1 H), 2.03 (dd, J = 11.8, 4.2 Hz, 1 H), 2.05 – 2.01 (m, 1 H), 1.89 (d, J = 15 Hz 1 H), 1.69 (d, J = 11.8 Hz, 1 H), 1.64 - 1.24 (m, 5 H), 1.05 - 0.87 (m, 1 H), 0.99 (d, J = 15.1 Hz, 1 H), 0.87 (d, J = 15.1 Hz, 1 H), 0.03 (s, 9 H). ¹³C NMR: 175.7, 155.9, 93.5, 80.4, 64.1, 58.1, 56.5, 41.1, 21.5, 20.1, 19.4, 19.3, 14.5, -0.1. IR (CHCl₃): 1760, 1693, 1324, 1251. HRMS (FAB) calcd for C₁₆H₂₄O₂Si (MH⁺) 277.1624, found 277.1615.

2-((Dimethyl(phenyl)silyl)methyl)buta-2,3-dienyl acetate (23)

A solution (1 mL) of (chloromethyl)dimethyl phenylsilane (1.34 mL, 11 mmol) in ether (10 mL) was added to Mg (264 mg, 11 mmol). The reaction was started with one drop of dibromomethane after which the reaction mixture was brought to reflux with continuing addition of the rest of the (chloromethyl)dimethyl phenylsilane solution. The reaction mixture was refluxed for 1 h to obtain an almost clear solution. A mixture of CuBr (1.573 g, 11 mmol) and LiBr (957 mg, 11 mmol) was heated at 150 °C/1 mmHg for 1 h and then cooled to rt under argon. THF (20 mL) was added and the resulting clear, light green solution was stirred for 15 min at rt, then cooled to -78 °C. To this solution was added dropwise the above prepared Grignard solution. The brown suspension was stirred at -78 °C for 15 min and then HMPA (5 mL) was added dropwise. To this reaction mixture was added dropwise a solution of 22 (2.06 g, 10 mmol) in THF (5 mL). The colorless solution was slowly warmed to rt and stirred for 14 h. Sat. NH₄Cl was added. The mixture was extracted with pentane (4x20 mL). The combined organic layers were subsequently washed with water (2x60 mL), brine (60 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (EtOAc:PE=1:9) afforded 23 (1.963 g, 75%). ¹H NMR: 7.54 - 7.33 (m, 5 H), 4.72 - 4.69 (m, 2 H), 4.37 (t, J = 2.6 Hz, 2 H), 2.03 (s, 3 H), 1.58 (t, J = 2.6 Hz, 2 H), 0.27 (s, 6 H).
Intramolecular [2+2] Photocycloadditions of Substituted Allene Butenolides

2-((Dimethyl(phenyl)silyl)methyl)buta-2,3-dien-1-ol

To a solution of 23 (1.963 g, 7.55 mmol) in MeOH (10 mL) was added solution of K₂CO₃ (1.04 g) in H₂O (1 mL). The mixture was stirred at rt for 30 min. The solvent was evaporated. The residue was dissolved in ether, dried over MgSO₄ and concentrated in vacuo. The residue (1.593 g, 97%) was pure enough to use for the next step without purification. ¹H NMR: 7.53 - 7.50 (m, 2 H), 7.36 - 7.34 (m, 3 H), 4.83 - 4.80 (m, 2 H), 3.85 (t, J = 3.3 Hz, 2 H), 1.57 (t, J = 2.5 Hz, 2 H), 0.34 (s, 6 H).

(2-(Bromomethyl)buta-2,3-dienyl)dimethyl(phenyl)silane (14)

To a stirred solution of 2-((dimethyl(phenyl)silyl)methyl)buta-2,3-dien-1-ol (1.593 g, 7.32 mmol) in CH₂Cl₂ (20 mL) at 0 °C was added triethylamine (1.53 ml, 1.5 equiv) and freshly distilled MsCl (0.85 ml, 1.5 equiv). The reaction mixture was stirred at rt for 1 h. After diluting with CH₂Cl₂, the mixture was washed with water (2x30 mL), dried over MgSO₄ and concentrated in vacuo. The reaction mixture was stirred at rt for 1 h. Water and CH₂Cl₂ were added. The water layer was extracted with CH₂Cl₂ (2x40 mL). The combined organic layers were washed with water, dried over MgSO₄ and evacuated in vacuo. Purification by chromatography (PE) afforded 14 (1.875 g, 91%). ¹H NMR: 7.54 - 7.51 (m, 2 H), 7.37 – 7.34 (m, 3 H), 4.70 - 4.69 (m, 2 H), 3.82 (t, J = 1.6 Hz, 2 H), 1.74 (t, J = 2.6 Hz, 2 H), 0.36 (s 6 H).

Ethyl 3-(hydroxymethyl)penta-3,4-dienoate (25)

Triethyl orthoacetate (47.1, 290 mmol), 1,4-butynediol (5.0 g, 58.1 mmol) and propionic acid (1.0 mL) were heated at 110 °C for 2 h and then the temperature raised to 125 °C while the ethanol liberated was allowed to distill out of the reaction mixture over 4 h. The mixture was kept at 125 °C for 18 h under positive nitrogen pressure and cooled to room temperature. The mixture was cooled in an ice bath and a mixture of THF (22 mL) and aqueous 2 N HCl was added dropwise over 30 min. After coming to room temperature over 30 min volatiles were removed in vacuo keeping the bath temperature at 40 °C. The residue was taken up in dichloromethane (50 mL), washed with water, saturated sodium bicarbonate and dried over anhydrous sodium sulfate. Concentration afforded a brown oil consisting primarily of diethyl 3,4-bismethyleneadipate and the desired hydroxyallenic ester in a ratio of 2:3. Flash chromatography (EtOAc:hexanes=1:1) afforded pure ethyl 3-(hydroxymethyl)penta-3,4-dienoate (25) (2.54 g, 28% yield). ¹H NMR: 4.88 (quintet, J = 2.4 Hz, 2 H), 4.20 - 4.14 (m, 4 H), 3.12 (t, J = 2.3 Hz, 2 H), 2.17 (t, J = 6.1 Hz, 1 H), 1.27 (t, J = 7.1 Hz, 3 H). IR (neat): 3420, 1960, 1737 consistent with the spectra previously described for this compound.¹⁴ ¹³C NMR: 206.8, 171.8, 97.3, 77.2, 63.3, 61.1, 35.9, 14.2.

Ethyl 3-(bromomethyl)penta-3,4-dienoate (26)

A mixture of ethyl 3-(hydroxymethyl)penta-3,4-dienoate 25 (700 mg, 4.48 mmol) and Et₃N (680 mg, 6.72 mmol), dissolved in CH₂Cl₂ (12 mL), was added to a solution of methanesulfonyl chloride (770 mg, 6.72 mmol) in CH₂Cl₂ (2 mL) at 0 °C.
The stirred mixture was allowed to warm up to room temperature over 1 h. Then more CH₂Cl₂ was added to the mixture, which was then washed with water and saturated aqueous NaHCO₃, and dried with Na₂SO₄. A crude oil was obtained upon concentration (960 mg, 4.10 mmol, 91%). LiBr (1.42 g, 16.4 mmol) in acetone (10 mL) was added to this crude mesylate dissolved in acetone (5 mL) at 0 °C. The mixture was allowed to come to room temperature and stirred for 45 min. It was concentrated, diluted with CH₂Cl₂, and washed with water, 2 N HCl, and NaHCO₃. It was then dried over Na₂SO₄ and concentrated to afford a brown oil (607 mg, 68%). ¹H NMR: 4.88 (m, 2 H), 4.20 - 4.15 (m, 4 H), 3.19 (t, J = 2.3 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H). ¹³C NMR: 208.4, 170.5, 95.6, 77.1, 60.9, 35.6, 34.6, 14.2. IR (neat): 2983, 1956, 1736.

**Ethyl 3-((3-oxo-1,3,4,5,6,7-hexahydroisobenzofuran-1-yl)methyl)penta-3,4-dienoate (27)**

According to procedure A, allene bromide 26 (241 mg, 1.10 mmol) and dienol silyl ether 11 (1 mmol) afforded 133 mg of 27 (0.48 mmol, 48%) as a colorless oil (not completely pure) after purification by flash column chromatography (hexanes:EtOAc 2:1, with 1% of Et₃N). ¹H NMR: 4.95 (br s, 1 H), 4.81 (m, 2 H), 4.14 (q, J = 7.1 Hz, 2 H), 3.08 (br d, J = 16.1 Hz, 1 H), 3.04 (br d, J = 16.1 Hz, 1 H), 2.60 (tdd, J = 3.1, 4.1, 15.4 Hz, 1 H), 1.60 - 2.33 (m, 9 H), 1.26 (t, J = 7.1 Hz, 3 H).

**Photocycloadduct 28**

According to procedure B, allene butenolide 27 (133 mg, 0.48 mmol) was irradiated for 4.5 h which gave 28 (53 mg, 40%) as a colorless oil after chromatography (hexanes:EtOAc:1:2). Rf = 0.40. ¹H NMR: 4.72 (d, J = 0.8 Hz, 1 H), 4.63 (d, J = 4.1 Hz, 1 H), 4.60 (d, J = 0.8 Hz, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 2.68 - 2.59 (AB-quartet, J = 15.7 Hz, 2 H), 2.13 (dd, J = 11.9, 4.1 Hz, 1 H), 2.09 (m, 1 H), 1.90 (m, 1 H), 1.85 (d, J = 11.9 Hz, 1 H), 1.65-1.25 (m, 5 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.02 (m, 1 H). ¹³C NMR: 174.7, 169.7, 152.5, 94.6, 79.8, 64.5, 60.8, 55.4, 54.9, 39.8, 31.4, 21.3, 20.1, 19.3, 19.2, 13.9. IR (CHCl₃): 1772, 1731, 1329, 978. HRMS (FAB) calcd for C₁₆H₂₀O₄ (MH⁺) 277.1440, found 277.1443.

**2-Vinylidenehexyl acetate (30)**

LiBr (5.63 g, 64.8 mmol) and CuBr (9.3 g, 64.8 mmol) were dried under vacuum (2 mmHg) at 150 °C for 2 h. THF (130 mL) was added at rt and the mixture was stirred for 15 min and then allowed to cooled to -78 °C. To this mixture was added n-butylmagnesium chloride (2 M solution in THF, 35 mL). After stirring for 15 min, HMPA (32 mL) was added followed by a solution of 22 (12.15 g, 59 mmol) in THF (10 mL). The resulting mixture was slowly warmed up to rt for 20 min and stirred for additional 30 min at rt. Sat. NH₄Cl (100 mL) was added and the mixture was filtered through Celite®. The filtrate was extracted with pentane (3×150 mL). The combined organic layers were washed with water (200 mL), brine (200 mL), dried over over MgSO₄ and concentrated in vacuo to afford 30 which was used for the next step without purification. ¹H NMR: 4.80 (m, 2 H), 4.54 (t, J = 2.3 Hz, 2 H), 2.07 (s, 3 H), 1.99 (m, 2 H), 1.95 - 1.20 (m, 4 H), 0.89 (t, J = 2.7 Hz, 3 H).
2-Vinylidenehexan-1-ol
To a solution of K₂CO₃ (12.23 g, 88.5 mmol) in water (100 mL) was added a solution of crude 30 (9.92 g, 59 mmol) in methanol (100 mL). The resulting mixture was stirred at rt for 2 days and part of the solvent was distilled off using a cold trap at -78 °C. To the resulting white suspension was added brine (100 mL) and the aqueous phase was extracted with pentane (3×100 mL). The combined organic layers were washed with water (200 mL), brine (200 mL), dried over MgSO₄ and concentrated using the above described distillation (25 °C, 100 mmHg) to afford 2-vinylidenehexan-1-ol (5.288 g, 71% from 22) as a yellow oil after column chromatography (pentane:ether=8:2). ¹H NMR: 4.87 (m, 2 H), 4.05 (t, J = 3 Hz, 2 H), 2.01 (m, 2 H), 1.50 – 1.25 (m, 4 H), 0.91 (m, 3 H).

3-(Bromomethyl)hepta-1,2-diene (29)
To a solution of 2-vinylidenehexan-1-ol (1 g, 7.93 mmol) and TEA (1.32 mL, 9.51 mmol) in CH₂Cl₂ (40 mL) at 0 °C was added solution of MsCl (0.736 mL, 9.51 mmol) in CH₂Cl₂ (8 mL). The resulting mixture was stirred at rt for 1 h and then CH₂Cl₂ (40 mL) was added. The organic phase was washed with sat. NH₄Cl (100 mL), water (100 mL), brine (100 mL), dried over MgSO₄ and solvent was distilled off using a cold trap at -78 °C to afford the corresponding mesylate which was used for the next step without purification. ¹H NMR: 4.88 (m, 2 H), 4.71 (t, J = 2 Hz, 2 H), 3.02 (s, 3 H), 2.07 (m, 2 H), 1.47 – 1.33 (m, 4 H), 0.90 (m, 3 H).

To a solution of lithium bromide (2.75 g, 31.7 mmol) in acetone (15 mL) at 0 °C was added solution of the above mesylate (1.62 g, 7.93 mmol) in acetone (5 mL). The resulting mixture was stirred at 0 °C for 30 min and then water (5 mL) was added. The mixture was extracted with pentane (3×10 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over MgSO₄ and concentrated using the above described distillation to afford 29 (1.17 g, 78% from 2-vinylidenehexan-1-ol) after column chromatography (pentane). ¹H NMR: 4.79 (m, 2 H), 4.02 (s, 2 H), 2.12 (m, 2 H), 1.46 – 1.31 (m, 4 H), 0.90 (m, 3 H). ¹³C NMR: 206.9, 101.2, 76.5, 46.9, 35.6, 29.1, 22.1, 13.7. IR: 2958, 1953.

Coupling product 31
According to procedure A, allene 29 (709 mg, 3.75 mmol) gave the coupling product 31 (452.5 mg, 60%) after purification (PE:EtOAc=2:1). ¹H NMR: 4.96 (m, 1 H), 4.74 (m, 2 H), 4.01 (m, 4 H), 2.53 – 2.43 (m, 4 H), 2.32 (m, 2 H), 1.97 (m, 2 H), 1.83 (m, 2 H), 1.4 – 1.22 (m, 4 H), 0.9 (m, 3 H).

Photocycloadduct 32
According to procedure B, butenolide 31 in acetonitrile/acetone (9:1, v/v) was irradiated for 30 min giving rise to cycloadduct 32 (41.5 mg, 81%) as a brown oil after purification (PE:EtOAc=3:1). ¹H NMR: 4.76 (d, J = 2 Hz, 1 H), 4.63 (d, J = 4 Hz, 1 H), 3.93 (m, 4 H), 2.10 – 1.95 (m, 4 H), 1.83 – 1.61 (m, 4 H), 1.50 – 1.10 (m, 6 H), 0.88 (t, 3 H). ¹³C NMR: 175.4, 154.2, 108.4, 95.8, 80.3, 64.8, 64.5, 63.9, 58.4, 55.2, 39.5, 30.9, 29.5, 29.3, 26.9, 25.9, 22.8, 17.3, 13.7.
Benzyl buta-2,3-dienoate (37)

Benzyl(triphenylphosphoranylidene)acetate (50.42 g, 123 mmol) was dissolved in CH₂Cl₂ (400 mL) in a three-necked, round-bottomed flask under nitrogen. The solution was stirred at rt as solution of Et₃N (12.42 g, 1 equiv) in CH₂Cl₂ (100 mL) was added dropwise (10 min). After 10 min, CH₃COCl (9.66 g, 1 equiv) in CH₂Cl₂ (100 mL) was added dropwise over a period of 20 min. Stirring was continued for an additional 30 min, after which the clear, yellow mixture was evaporated on a rotary evaporator at reduced pressure. A portion of PE (800 mL) was added to the residue and the slurry was allowed to stand for 2 h while it was shaken periodically to facilitate solidification. The precipitate was removed by filtration and the filter was washed with PE (2×50 mL). The filtrates were combined and the solvent was evaporated. Purification by chromatography (PE:EtOAc=4:1) afforded the desired product (17.46 g, 82 %) as a colorless oil. Rf = 0.43. ¹H NMR: 7.37 – 7.31 (m, 5 H), 5.68 (t, J = 6.5 Hz, 1 H), 5.23 (d, J = 6.5 Hz, 2 H), 5.19 (s, 2 H). ¹³C NMR: 215.8, 165.2, 135.7, 128.3, 128.0, 127.9, 87.6, 79.2, 66.3. IR: 1969, 1716, 1259, 1155, 855.

Benzyl 2-(hydroxymethyl)buta-2,3-dienoate (38)

To a suspension of paraformaldehyde (95%, 535 mg, 5 equiv) (pre-dried under vacuum at 50 °C for 30 min) in THF (10 mL) at –10 °C was added dropwise a solution of DABCO (pre-dried on the oil pump for 30 min) (76 mg, 0.2 equiv) in THF (5 mL) followed by a solution of allenic ester (590 mg, 3.39 mmol) in THF (5 mL). The reaction mixture was allowed to warm to 18 °C and stirred for 1.5 h. The reaction was quenched by saturated aqueous NH₄Cl (10 mL). The layers were separated and the aqueous phase was extracted with ethylacetate (3×10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (PE:EtOAc=1.5:1) afforded the desired product (416 mg, 60 %) as slightly brown oil along with the starting allene (28%). Rf = 0.25. ¹H NMR: 7.35 – 7.25 (m, 5 H), 5.26 (s, 2 H), 5.22 (s, 2 H), 4.34 (s, 2 H), 2.50 (s, br s, 1 H). ¹³C NMR: 213.0, 166.4, 135.5, 128.3, 128.0, 127.7, 99.5, 79.8, 66.5, 60.7. IR: 3407, 1966, 1708, 1262, 1027, 854.

2-Triisopropylsilanyloxymethyl-buta-2,3-dienoic acid benzyl ester

To a solution of allenyl methyl alcohol (350 mg, 1.71 mmol) in CH₂Cl₂ (20 mL) at 0 °C was added TIPSOTf (0.7 mL, 1.5 equiv) followed by Et₃N (260 mg, 1.5 equiv). The reaction mixture was stirred 0 °C for 1 h. The reaction was quenched by saturated aqueous NaHCO₃ (20 mL). The layers were separated and the aqueous phase was extracted with ether (3×20 mL). The combined organic layers were washed with brine (60 mL), dried over MgSO₄ and concentrated in vacuo. Purification by chromatography (PE:EtOAc=15:1) afforded the desired product (484 mg, 79 %) as a colorless oil (Rf = 0.3). ¹H NMR: 7.35 – 7.29 (m, 5 H), 5.26 (t, J = 3 Hz, 2 H), 5.20 (s, 2 H), 4.47 (t, J = 3 Hz, 2 H), 1.25 – 1.01 (m, 21 H). ¹³C NMR: 213.5, 165.6, 135.8, 128.2, 127.8, 127.6, 101.4, 80.6, 66.2, 59.7, 17.7, 17.1. IR (neat): 2943, 2865, 1969, 1712, 1258, 1064.

2-((Triisopropylsilyloxy)methyl)buta-2,3-dien-1-ol (39)

To a stirred solution of allenic ester (214 mg, 0.59 mmol) in dried toluene (8 mL) at –78 °C was added DIBAL-H (1.5 M in toluene) (1.2 mL, 3 equiv). The reaction mixture was stirred at –78 °C for 1 h and carefully quenched with EtOAc at 0 °C.
Intramolecular [2+2] Photocycloadditions of Substituted Allene Butenolides

Saturated aqueous solution of Na$_2$SO$_4$ (0.5 mL) was added and the resulting mixture was stirred for 1 h. After adding solid Na$_2$SO$_4$, the mixture was filtered through Celite$^6$ and the filtrate was concentrated in vacuo. Purification by chromatography (PE:EtOAc=5:1) afforded the desired product 39 (91.5 mg, 61%) as a colorless oil ($R_f = 0.26$). $^1$H NMR: 4.86 – 4.84 (m, 2 H), 4.40 – 4.39 (m, 2 H), 4.27 – 4.24 (m, 2 H), 2.32 (t, $J = 6$ Hz, 1 H), 1.31 – 1.01 (m, 21 H). $^{13}$C NMR (benzene): 206.1, 104.53, 77.37, 64.2, 62.78, 18.0, 12.8. IR: 3396, 2943, 2866, 1961.

(2-(Bromomethyl)buta-2,3-dienyloxy)triisopropylsilane (40)

To a solution of MsCl (1.54 mL, 1.5 equiv) in CH$_2$Cl$_2$ (30 mL) at 0 °C was added a solution of 39 (3.345 g, 13.06 mmol) in CH$_2$Cl$_2$ (8 mL) followed by Et$_3$N (2.73 mL, 1.5 equiv). The reaction mixture was allowed to warm to rt and stirred for 30 min. CH$_2$Cl$_2$ (10 mL) was added and the organic phase was washed with water (30 mL), brine (30 mL), dried over MgSO$_4$ and concentrated in vacuo to afford the crude mesylate which was used for the next step without purification. $^1$H NMR: 4.95 (t, $J = 2$ Hz, 2 H), 4.83 (t, $J = 1.8$ Hz, 2 H), 4.33 (t, $J = 2$ Hz, 2 H), 3.02 (s, 3 H), 1.14 – 1.03 (m, 21 H).

To a stirred solution of LiBr (4.46 g, 4 equiv) in acetone (20 mL) at 0 °C was added a solution of the above crude mesylate in acetone (20 mL). The reaction mixture was stirred at rt for 30 min then water was added. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 20 mL) and the combined organic layers were washed with brine (60 mL), dried over MgSO$_4$ and concentrated in vacuo to give allenyl methyl bromide 40 (2.91 g, 70% from 39) as a colorless oil after purification (PE:EtOAc=2:1). $R_f = 0.6$. $^1$H NMR (benzene): 4.51 – 4.49 (m, 2 H), 4.35 (t, $J = 2.4$ Hz, 2 H), 3.97 – 3.96 (m, 2 H), 1.10 – 1.01 (m, 21 H). $^{13}$C NMR (benzene): 207.3, 102.8, 77.7, 62.6, 31.8, 18.8, 12.9. IR (neat): 2943, 2866, 1955.

TIPS-substituted allenyl butenolide 41

According to procedure A, allene bromide 40 (1.3 g, 1.5 equiv) gave butenolide 41 (260 mg, 22 %). $^1$H NMR: 5.01 – 4.98 (m, 2 H), 4.83 – 4.75 (m, 2 H), 4.23 (qt, $J = 12$ Hz, $J = 2.5$ Hz, 2 H), 4.00 (br s, 4 H), 2.60 – 2.34 (m, 6 H), 1.86 – 1.77 (m, 2 H), 1.13 – 0.87 (m, 21 H). $^{13}$C NMR (in Benzene): 172.2, 160.9, 127.6, 108.7, 99.6, 80.8, 77.6 (not seen in CDCl$_3$), 65.4, 65.19, 65.18, 53.9, 53.2, 32.4, 31.4, 20.0, 18.8, 12.9. IR (neat): 2944, 2867, 1960, 1758.

Photocycloadduct 42

According procedure B, butenolide 41 (260 mg, 0.599 mmol) in acetonitrile:acetone (9:1, v/v) (30 mL) was irradiated for 15 min which gave 42 (155 mg, 60%) as a colorless oil after purification (PE:EtOAc=4:1). $R_f = 0.23$. $^1$H NMR: 4.77 (s, 2 H), 4.63 (d, $J = 4$ Hz, 1 H), 3.96 – 3.85 (m, 6 H), 2.16 – 2.10 (m, 2 H), 2.03 (dd, $J = 14$ Hz, $J = 1.6$ Hz, 1 H), 1.91 – 1.8 (m, 3 H), 1.65 – 1.61 (m, 1 H), 1.42 (td, $J = 4$ Hz, $J = 14$ Hz, 1 H), 1.10 – 0.99 (m, 21 H). $^{13}$C NMR: 174.5, 151.6, 108.4, 96.6, 79.8, 65.1, 64.4, 63.8, 59.1, 59.0, 54.5, 38.7, 30.8, 29.1, 17.7, 17.3, 11.6. IR: 2944, 2865, 1779, 1111.
3-(Bromomethyl)-4-(methoxymethoxy)buta-1,2-diene (44)

See the procedure described for the synthesis of allene 40. \(^1\)H NMR: 4.91 – 4.89 (m, 2 H), 4.65 (s, 2 H), 4.21 – 4.20 (m, 2 H), 4.09 – 4.08 (m, 2 H), 3.39 (s, 3 H).

2-Benzylxoymethybuta-2,3-dienoic acid benzyl ester (46)

To a solution of allenyl methyl alcohol 38 (364 mg, 1.78 mmol) in CH\(_2\)Cl\(_2\) (15 mL) at 0 °C was added benzyl trichloroacetimidate (0.34 mL, 1 equiv) followed by TMSOTf (64 \(\mu\)L, 0.2 equiv). The reaction mixture was allowed to warm to rt and stirred overnight. Solvent was then evaporated under reduced pressure. PE/Et\(_2\)O (6:1) (20 mL) was added to the residue and the slurry was filtered through a plug of silica gel to remove the formed trichloroacetamide. The silica gel was washed with PE/Et\(_2\)O (6:1) (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaHCO\(_3\) (30 mL), brine (30 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo}. Purification by chromatography (PE:EtOAc=5:1) afforded the desired product 46 (312 mg, 60 %) as a colorless oil (R\(_f\) = 0.3). \(^1\)H NMR: 7.39 – 7.27 (m, 10 H), 5.27 (t, J = 2 Hz, 2 H), 5.22 (s, 2 H), 4.57 (s, 2 H), 4.28 (t, J = 2 Hz, 2 H). IR (neat): 1965, 1708, 1260, 1070.

2-Benzylxoymethybuta-2,3-dien-1-ol

To a stirred solution of allenyl ester 46 (1.6 g, 5.44 mmol) in dried CH\(_2\)Cl\(_2\) (60 mL) at -78 °C was added DIBAL-H (1.5 M in toluene) (11 mL, 3 equiv). The reaction mixture was stirred at -78 °C for 2 h and carefully quenched with EtOAc at 0 °C. Saturated aqueous solution of Na\(_2\)SO\(_4\) (0.5 mL) was added and the resulting mixture was stirred for 1 h. After adding solid Na\(_2\)SO\(_4\), the mixture was filtered through Celite® and the filtrate was concentrated \textit{in vacuo}. Purification by chromatography (PE:EtOAc=2:1) afforded a mixture of the desired 2-Benzylxoymethybuta-2,3-dien-1-ol contaminating with benzyl alcohol (803 mg) as a colorless oil (R\(_f\) = 0.23) which was used for the next step without further purification. \(^1\)H NMR: 7.50 – 7.25 (m, 5 H), 4.95 – 4.80 (m, 2 H), 4.54 (s, 2 H), 4.25 (br, 2 H), 4.20 – 4.10 (m, 2 H). IR (neat): 3357, 1957, 1072, 1018.

(2-Bromomethyl-buta-2,3-dienyloxymethyl)-benzene (47)

To a solution of MsCl (0.5 mL, 1.5 equiv) in CH\(_2\)Cl\(_2\) (30 mL) at 0 °C was added a solution of the above mixture of 2-benzyloxymethyl-buta-2,3-dien-1-ol and benzyl alcohol (803 mg) in CH\(_2\)Cl\(_2\) (15 mL) followed by Et\(_3\)N (0.9 mL, 1.5 equiv). The reaction mixture was stirred at 0 °C for 30 min. CH\(_2\)Cl\(_2\) (10 mL) was added and the organic phase was washed with water, brine (30 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo} to afford the crude mesylate (1.24 g) which was used for the next step without purification.

To a stirred solution of LiBr (432 mg, 4 equiv) in acetone (10 mL) at 0 °C was added a solution of the crude mesylate (1.24 g) in acetone (10 mL). The reaction mixture was stirred at rt for 30 min then water was added. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) and the combined organic layers were washed with brine (20 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo} to give alleny methyl bromide 47 (516 mg, 37% from 46) as a colorless oil after purification (PE and then PE:EtOAc=7:1). R\(_f\) = 0.43. \(^1\)H NMR: 7.35 - 7.27 (m, 5 H), 4.90 (t, J = 2 Hz, 2 H), 4.53 (s, 2 H), 4.18 (t, J = 2 Hz, 2 H), 4.10 (t, J = 2 Hz, 2 H). \(^1\)C NMR: 207.5, 137.6, 128.2, 127.6, 127.5, 98.6, 76.9, 72.0, 67.6, 31.3. IR: 2857, 1951, 1207, 1071.
Benzyl-substituted allenyl butenolide 48

According to procedure A, allenyl methyl bromide 47 gave the coupling product 48 after purification by chromatography (PE:EtOAc=1:1) (Rf = 0.28). ¹H NMR: 7.35 - 7.26 (m, 5 H), 4.96 (br s, 1 H), 4.86 - 4.80 (m, 2 H), 4.49 (s, 2 H), 4.08 - 4.00 (m, 2 H), 3.99 - 3.95 (br s, 4 H), 2.58 - 2.50 (m, 2 H), 2.46 - 2.36 (m, 3 H), 2.35 - 2.29 (m, 1 H), 1.84 - 1.78 (m, 2 H). ¹³C NMR: 207.1, 172.0, 160.9, 137.7, 128.2, 127.6, 127.5, 126.2, 107.5, 95.2, 80.3, 70.2, 71.6, 70.9, 64.5, 34.2, 31.9, 30.4, 18.7. HRMS (FAB) calcd for C₂₂H₂₅O₅ (MH⁺) 369.1700, found 396.1698. IR (neat): 2888, 1957, 1752, 1063.

Photocycloaddition product 49

According to procedure B, solution of allene 48 in benzene/acetone (9:1, v/v) was irradiated (300 nm) for 1 h to give 49. Purification by chromatography (PE:EtOAc=2:1) afforded the cyclized adduct (Rf = 0.28). ¹H NMR: 7.35 - 7.27 (m, 5 H), 4.78 (s, 1 H), 4.76 (s, 1 H), 4.65 (d, J = 4, 1 H), 4.48 (s, 2 H), 3.96 - 3.83 (m, 4 H), 3.67 (d, J = 10.5 Hz, 1 H), 3.62 (d, J = 10.5 Hz, 1 H), 2.17 - 2.02 (m, 3 H), 1.91 - 1.80 (m, 3 H), 1.65 - 1.60 (m, 1 H), 1.4 (td, J = 4 Hz, J = 14 Hz, 1 H). ¹³C NMR: 174.6, 151.3, 137.7, 128.2, 127.4, 127.2, 108.3, 96.8, 79.9, 73.0, 65.4, 65.2, 64.4, 63.8, 57.3, 54.9, 39.0, 30.8, 29.1, 17.4. HRMS (FAB) calcd for C₂₂H₂₅O₅ (MH⁺) 369.1697, found 369.1703. IR: 2949, 2880, 1770, 1111.

References

Chapter 6
Further Chemistry towards the Right-Hand Substructure of Solanoeclepin A

6.1 Introduction

As described in chapter 5 the highly substituted allene butenolide 6 has been successfully prepared through a seven-step transformation starting from the commercially available triphenylphosphorane 4 (Scheme 6.1). This sequence involves the key introduction of the hydroxymethyl group onto the C-α of the allenic ester via the Baylis-Hillman reaction to provide the novel ester 5.

Scheme 6.1

The key intramolecular [2+2] photocycloaddition of allene butenolide 6 proceeds satisfactorily leading exclusively to the cycloadduct 7 in good yield. This photocycloaddition reaction efficiently assembles the tricyclic core, the distinctive structural feature of the right hand fragment 3, in a single step. Furthermore, the photocycloadduct 7 contains the important functional handles for further elaboration towards the right hand substructure 3. The remaining task, therefore, is to further functionalize the key intermediate 7 to reach the fragment 3 and hence, the ultimate target natural product. To that end, application of the previously developed chemistry of the model (chapter 4) for the cycloadduct 7 should affect the generation of the angular methyl and the cyclobutanone functions. The benzyl ether would serve as a handle for incorporating a cyclopropanecarboxylic acid moiety at a later phase of the synthesis. The critical installation of the vinyl triflate from the ketone moiety should eventually accomplish the right hand substructure 3, and hence, solanoeclepin A.
6.2 Generation of the Bridgehead Methyl Group

Our first goal was to investigate whether the angular methyl group could be conveniently generated based on the previously developed chemistry of the model (chapter 4). On the basis of that model study, concerning the osmium-induced dihydroxylation of the double bond, we envisioned that the dihydroxylation of the exocyclic methylene group of the cycloadduct 7 should be best conducted prior to the reductive opening of the lactone moiety. The lactone ring would render the endo-face of the double bond sufficiently accessible for the osmium tetroxide. As a result, a catalytic amount of the osmium tetroxide should bring about the dihydroxylation process. Based on this consideration, we started our synthetic work with the preparation of the intermediate 9 as presented in eq 6.1. In fact, subjection of the cycloadduct 7 to the osmium-catalyzed dihydroxylation conditions, using 50 mol% of OsO₄ in conjunction with an excess of NMO led to a remarkably clean formation of the desired vicinal diol 8 in good yield.

\[
\text{OsO}_4 (50 \text{ mol\%}) \quad \text{NMO} \\
\text{t-BuOH/H}_2\text{O/acetone} (5:1.5:1, v/v/v) \\
\text{PPTS (cat)} \quad \text{acetone}
\]

(eq 6.1)

Although ¹H NMR NOE measurements have not been carried for the diol product 8, the dihydroxylation of 7 most likely takes place from the endo face of the alkene in line with our previous results obtained with the model study (chapter 4).

The vicinal diol moiety of 8 is expected to be a good synthetic equivalent of a ketone function. An oxidative cleavage method using sodium periodate should affect this transformation at a later phase of our synthetic work. Therefore, it was required at this stage to protect this diol moiety. For that purpose, an acetal linkage was most likely the best choice. It is known that the selective hydrolysis of a dioxolane in the presence of an acetonide moiety is possible by using a catalytic amount of acid and an excess of acetone.

Thus diol 8 was acetalized using 2,2-dimethoxypropane with p-toluenesulfonic acid as the catalyst. In this way, the compact tetracyclic framework of compound 9 containing the five-membered acetonide ring was isolated in excellent yield. This strained polycyclic system is stable and is expected to be a good precursor for the subsequent chemical transformation to generate the bridgehead methyl and the hydroxyl functions. Towards that end, the reductive opening of the lactone moiety using LiAlH₄ was carried out giving rise to the corresponding diol in excellent yield (eq 6.2). This reduction reaction successfully puts in place the required secondary alcohol and sets the stage for the deoxygenation of the primary alcohol to generate the angular methyl group. For this transformation a protection-deprotection sequence had to be followed based on earlier experience (chapter 4). Thus, the primary hydroxyl group was selectively silylated using t-butyldimethylsilyl chloride and imidazole in DMF leading to silyl ether 10 in good yield. The stable MOM group was then thought to be a suitable
protective group for the secondary hydroxyl moiety thus preventing the formation of the undesired cyclic ether. Treatment of 10 with MOMCl and DIPEA gave the fully protected intermediate in quantitative yield. Finally, deprotection of the silyl ether with TBAF at 50 °C successfully released the primary alcohol, providing compound 11 in excellent yield.

The reductive deoxygenation reaction was then investigated. Treatment of alcohol 11 with an excess of p-toluenesulfonyl chloride and pyridine at room temperature for 20 h led to the formation of the desired tosylate 12 in reasonable yield (eq 6.3). The 1H NMR spectrum of 12 shows two characteristic singlets at 4.42 and 3.26 ppm, which correspond to the MOM-ether, and one singlet at 2.41 ppm of the tosylate methyl group. The starting alcohol 11 was also recovered under these unoptimized reaction conditions. Unfortunately, when heating tosylate 12 under reflux in THF with an excess of Super-Hydride, a 1:1.4 mixture of the desired product 13 and the cyclic furan 14, respectively, was formed as indicated in the 1H NMR spectrum of the crude product (eq 6.3). The angular methyl group of product 13 is clearly apparent as a singlet at 1.18 ppm in the 1H NMR spectrum. In addition, the two singlets at 4.45 and 3.36 ppm prove the presence of the MOM-ether. These characteristic signals are not observed in the 1H NMR of 14.

The formation of the cyclic ether 14 indicates the potential of the proximate MOM ether to participate in an intramolecular substitution of the formed tosylate, as observed in our previous study. Therefore, we turned to the use of a benzyl ether protective group for the secondary alcohol of the intermediate 10. This more stable protective group was found to give good results in the case of the model study (chapter 4). Thus, the hydroxyl group of 10 was benzylated using benzyl bromide and sodium hydride in THF, in the presence of tetrabutylammonium iodide as the phase transfer catalyst (eq 6.4). This led to the fully protected intermediate in good yield. Subsequent desilylation with TBAF at 50 °C gave 15 which was subjected to the tosylation conditions using p-toluenesulfonyl chloride and pyridine. Unfortunately, the benzyl ether function proved to be better compared to the
MOM ether in taking part in the intramolecular substitution of the formed tosylate. As a result, the desired tosylate 16 was formed along with the cyclic ether 14.

\[ \text{MOM ether} + \text{tosylate} \rightarrow \text{tosylate 16} + \text{cyclic ether 14} \]

The potential of the benzyl ether to participate in the cyclization process was further confirmed on heating tosylate 16 in THF in the presence of Super-Hydride. This led mainly to the formation of the cyclic ether 14 along with decomposition of the starting tosylate 16. Only a trace of the desired deoxygenation product 17 could be detected.

Comparison with the results obtained with the model study (chapter 4) in which the benzyl ether was successfully employed, the ease of the closure in the case of 16 might be the result of the strain increase by the acetonide ring. This might push the benzyl ether and the tosylate groups close enough so that they could react intramolecularly leading to the cyclized product. If this is the case, the absence of the acetonide ring would prevent the formation of the undesired cyclic ether 14. In order to verify this speculation, we decided to take the cycloadduct 7 as the precursor for the study of generating the angular methyl group.

Our study began with the reductive opening of the lactone moiety of 7 using lithium aluminum hydride as the reducing agent to provide diol 18 in good yield (eq 6.5). The same protection-deprotection sequence was followed which eventually gave the desired intermediate 19 in excellent yield.

With the key intermediate 19 in hand, we could eventually explore whether the acetonide ring plays a role in the failure of the reductive cleavage of tosylate 16. Therefore, tosylation of the primary hydroxyl moiety of 19 was conducted under the same reaction conditions described for 15 to afford the desired tosylate 20 in excellent yield (eq 6.6). The starting alcohol 19 was also recovered under these reaction conditions. The increased steric hindrance of the compound 19 compared to that of the model cycloadduct described in chapter 4 might be responsible for the slower reaction rate of the tosylation reaction. Heating the reaction at 50 °C indeed increased the reaction conversion but also led to the formation of the undesired cyclic ether.
Interestingly, upon heating at reflux a solution of tosylate 20 in THF in the presence of an excess of Super-Hydride for 6 h, the desired deoxygenation product 21 was formed in reasonable yield as a stable colorless oil (eq 6.6). The $^1$H NMR spectrum of the product shows clearly the formation of the angular methyl group in view of the presence of a singlet at 1.25 ppm. In addition, the presence of the exocyclic methylene group was fully verified by the two singlets at 4.63 and 4.56 ppm. Less than 10% of the cyclic ether was obtained. Again, the slower reaction rate of the reduction of tosylate 20 might be attributed to its steric hindrance compared to that of the model system as described in chapter 4.

In an effort to increase the productivity of the sulfonylation-reduction sequence to generate the bridgehead methyl group, we examined an alternative strategy involving the reduction of the mesylate derivative (eq 6.7). By treating alcohol 19 with MsCl and triethylamine in CH$_2$Cl$_2$ at 0 °C for 30 min, a complete conversion of the hydroxyl function into the corresponding mesylate was obtained. The sufficiently clean mesylate 22 was then heated under reflux in THF in the presence of Super-Hydride for 3 h leading to the desired product 21 in reasonable yield. The undesired cyclic ether was also isolated in less than 10% after the reduction of the mesylate 22.

Although the yield of the final product 21 achieved via the reduction of the mesylate 22, was not much better compared to that of the tosylate derivative, the ease of preparation of the mesylate 22 is noteworthy.

The successful reductions of 20 and 22 indicate that the conformationally rigid acetonide moiety indeed plays an important role in the failure of the hydride reduction of tosylates 12 and 16 (eq 6.3 and 6.4, respectively). It is likely that the acetonide ring stimulates the closure to occur by pushing the benzyl ether (or the MOM) towards the tosylate group so that they could react intramolecularly to form the cyclic ether. The ease of this closure might be attributed to the ability of the benzyl ether (and the MOM) in stabilizing the developed positive charged resulting from the attack of the benzyl ether (or the MOM) to the formed tosylate (eq 6.8). If this is the case, the use of an electron withdrawing protective group such as the $p$-chlorobenzyl ether for the secondary alcohol function would prevent this problem. Although this synthetic strategy has not yet been carried out due to the lack of material,
it can be concluded at this point that subtle steric and strain effects play a crucial role in the chemistry of the compact skeleton of the carbotricyclic structures.

\[
\text{Scheme 6.8}
\]

6.3 Cyclobutanone Formation

The successfully reductive opening of the lactone moiety of the cycloadduct 7 led to the intermediate 21 containing the angular methyl and the benzyl protected secondary alcohol in the correct stereochirical arrangement. The next goal was to explore the possibility of converting the exocyclic methylene moiety of 21 into the corresponding cyclobutanone function. Our initial attempt relied on the oxidative cleavage of the vicinal diol although we anticipated at this stage that the dihydroxylation of 21 would be more difficult compared to that for the cycloadduct 7 (eq 6.1).

Indeed, subjection of olefin 21 to the successful conditions applied for the model (see section 4.3), using 1.5 equiv of OsO\(_4\) in pyridine at 60 °C for 20 h did not give the desired vicinal diol 24 (eq 6.9). Only the starting olefin 21 was fully recovered. Increase of the reaction temperature or the reaction time led only to decomposition of the starting material.

\[
\text{Scheme 6.9}
\]

Attempts to use other conditions such as the OsO\(_4\)-catalyzed oxidative cleavage of the double bond using NaIO\(_4\) in the presence of 2,6-lutidine\(^3\) or the OsO\(_4\)-catalyzed dihydroxylation in acidic media\(^4\) just met with failure. In all cases, only the starting olefin 21 was fully recovered. These results are most likely due to steric and strain effects of the angular methyl and the benzyl ether groups which might cause the endo face of the double bond more hindered by pushing the ethane bridge towards the double bond.

Because of these unsatisfactory results, we sought for an alternative method for the dihydroxylation of 21. For this purpose, the epoxidation of the double bond using organic peroxycarboxylic acids followed by ring opening of the formed epoxide would be a possible strategy. As a peroxy acid is known to have relatively low steric requirements, the use of \(m\)-chloroperbenzoic (MCPBA) should bring about the epoxidation of the sterically hindered olefin 21. Indeed, treatment of
olefin 21 with MCPBA in CH₂Cl₂ buffered with Na₂HPO₄ afforded the epoxide 26 in good yield (eq 6.10).³ The stereochemistry of 26 has not yet been determined but the oxygen is most likely at the endo face.

Unfortunately, efforts to open the epoxide ring of 26 using sodium or cesium acetate in DMF/water at 90 °C were totally unsuccessful. Only the epoxide 26 but no trace of 27 could be observed (eq 6.10). Addition of Lewis acids such as BF₃.OEt₂ or B(C₆F₅)₃ to enhance the reactivity of the epoxide moiety⁶ or direct oxidative cleavage of the epoxide function to form the corresponding ketone⁷ would be a possible solution to achieve the cyclobutanone function.

Although that synthetic strategy has not yet been conducted in order to reach the cyclobutanone function, it can be concluded at this point that steric and strain effects indeed control the chemistry of the compact skeleton of the tricyclic structures. The presence of the lactone moiety in fact facilitates the dihydroxylation of the double bond, and hence the subsequent cyclobutanone formation. On the other hand, the generation of the angular methyl group appears to work best with the double bond intact. Thus, it is reasonable to expect that the installation of the vinyl triflate on the six-membered ring, which has not yet been carried out before in our synthetic work, might also be affected by those subtle steric and strain effects. The complete synthesis of the right-hand fragment 3, and hence solanoeclepin A, therefore requires an optimized order of functional group transformations.

6.4 The Connection Handle

The introduction of a cyclopropanecarboxylic acid moiety has been investigated previously with the model (chapter 2). Therefore, it was our interest at this stage of the synthesis to explore the possibility of installing the β-ketoester derived vinyl triflate on the cyclohexyl moiety of the intermediate 21 to form 28 (Scheme 6.2). Once formed, it would be interesting to perform the chromium-mediated⁸ coupling between 28 and the left-hand fragment (2) of solanoeclepin A to give the coupling product 29. This study would not only prove the feasibility of our synthetic strategy toward the natural product, but also provides the basis for establishing the optimal order of functional group transformations.
6.4.1 Regioselective Carbomethoxylation

We started our study with the effort to achieve the regioselective carbomethoxylation of ketone 30 to form 31 (eq 6.11). It was expected that the C-2 hydrogen atoms adjacent to the quaternary carbon of the cyclobutane ring of ketone 30 would be more acidic compared to that at the C-4 position. Therefore, the preferential removal of the C-2 proton would be possible by using a strong base such as lithium hexamethyldisilazide (LHMDS) at low temperature. Subsequent C-acylation of the formed lithium enolate with methyl cyanoformate (Mander’s reagent) would eventually produce the desired β-enol ester 31.

Thus, the ethylene acetal moiety of 21 was hydrolyzed using 30 mol% of p-toluenesulfonic acid in acetone at 50 °C (eq 6.12). These unoptimized reaction conditions gave the desired ketone 30 in 74% yield. Unfortunately, treatment of ketone 30 with LHMDS in THF at -78 °C followed by addition of Mander’s reagent led to a complex mixture of products which could not be separated by column chromatography.
This result indicates that the enolization of the ketone moiety of 30 followed by carbomethoxylation of the formed lithium enolate proceeds unselectively. For the desired regioselective installation of the β-enol ester moiety of 31, we then planned to make use of a possible directing effect of the neighboring hydroxyl substituent. Thus, the two benzyl protecting groups of 21 need to be removed. For this task, catalytic hydrogenolysis is most likely inapplicable due to the presence of the double bond. Fortunately, the use of sodium in liquid ammonia at -78 °C turned out to be a good procedure which cleanly released the diol moiety, leading to 32 in excellent yield (eq 6.13). Subsequent hydrolysis of the acetal group, using the same conditions as applied for compound 21, efficiently afforded ketone 33.

The primary hydroxyl moiety of 33 was then selectively protected as the silyl ether using TBSCI and imidazole in DMF providing the required intermediate 34 in good yield (eq 6.14). Disappointingly, no improvement was observed when treating 34 with LHMDS at -78 °C followed by Mander's reagent. Similar to the case of 30, a complex mixture of products was formed which could not be isolated by chromatography.

The concept of intramolecular carbomethoxylation was then investigated (eq 6.15). We envisioned prior conversion of the secondary hydroxyl moiety of 34 into the corresponding carbonate 35. Upon treating 35 with a base, the methoxycarbonyl group would direct the enolization of the ketone moiety through an intramolecular carbomethoxylation leading to the desired product 37. Based on this strategy, ketone 35 was prepared and subsequently subjected to the reversible enolization conditions, using t-BuOLi as a base in a 1:1 mixture of t-BuOH and hexane. Unfortunately, only the parent alcohol 34 was recovered after the reaction along with decomposition. This is probably due to the unreachable distance between the methoxy carbonyl group and the formed enolate so that they can not react intramolecularly. Because of that we decided to prepare compound 36 with the hope that the longer side chain of 36 would facilitate its intramolecular approach to the enolate, although the extra carbonyl group would hamper the formation of the required vinyl triflate. Disappointingly, subjection of 36 to the same conditions as applied for 35 again gave only the starting.
alcohol 34 along with decomposition. These results proved the infeasibility of the concept of intramolecular carbomethoxylation for compound 34.

As presented earlier in this chapter the subtle steric and strain effects play a crucial role in the chemistry of the compact skeleton of the carbotricyclic structure. We turned, therefore, to investigate the possibility of introducing the vinyl triflate moiety at an earlier stage, before the reductive opening of the lactone moiety. Thus, we took the cycloadduct 39 (chapter 5) as our model study due to its availability from our previously synthetic work (Scheme 6.3). Hydrolysis of the acetal moiety of 39 was accomplished using a catalytic amount of p-TsOH in acetone, leading to ketone 40 in good yield. Interestingly, upon treatment of 40 with LHMDS at -78 °C followed by Mander’s reagent, trimethylsilyl enol ether 41 was obtained in good yield as a single product.

Scheme 6.3

![Scheme 6.3](image)

The 1H NMR spectrum of 41 shows two singlets at 4.91 and 0.18 ppm which correspond to the vinyl hydrogen and the TMS group, respectively. The two characteristic singlets at 4.62 and 4.57 ppm prove the presence of the exocyclic methylene moiety. In addition, the assigned regiochemistry of 41 was based on the presence of two multiplets in the range from 2.25 to 1.75 ppm, which correspond to the four hydrogen atoms on the six-membered ring of 41. There would be two AB systems in this region in the spectrum of 42. The correct structure of 41 was then fully confirmed by 1H NMR COSY and HETCOR experiments.

The complete regioselectivity obtained in the case of 40 might be a consequence of the presence of the lactone moiety. This ring might render the C-2 position of the ketone function less hindered so that the removal of the expected more acidic C-2 proton becomes a predominant process.
A plausible explanation for the formation of 41 is that the excess LHMDS reacts with Mander’s reagent to form the corresponding methyl bis(trimethylsilyl)carbamate (III) (eq 6.16). The silyl carbamate III then functions as a silylating agent which reacts with the lithium enolate to form the O-silylated product 41. If this is the case, the use of LDA as a base might prevent the formation of trimethylsilyl enol ether 41. An alternative strategy is the cleavage of enol trimethylsilyl ether 41 by methyllithium to regenerate the lithium enolate which can be trapped by Mander’s reagent to form the desired β-enol ester. This strategy requires the lactone moiety of 40 to be protected and a methyl acetal should be the protective group of choice.

$$\text{Li}_2\text{N}_2\text{SiMe}_3 + \text{MeO}_2\text{CN} \rightarrow \text{MeO}_2\text{N}_2\text{SiMe}_3$$

Based on this consideration, our effort was then focused on the key intermediate 7. Thus, the lactone function was reduced with DIBAL-H to form the corresponding lactol 43 in good yield as a single diastereoisomer (eq 6.17). The yield of lactol 43 was found to be strongly dependent on the temperature, the reaction time and the amount of DIBAL-H used. Overreduction to the corresponding diol was the main side reaction.

$$\text{RO}_2\text{O}_2\text{OBn} \xrightarrow{\text{DIBAL-H}} \text{HO}_2\text{OBn} \xrightarrow{(\text{MeO})_3\text{CH}} \text{RO}_2\text{O}_2\text{OBn}$$

The lactol moiety of 43 was then efficiently protected as a methyl acetal using trimethyl orthoformate in the presence of a catalytic amount of PPTS, leading to 44 in excellent yield as a 3:1 mixture of two diastereoisomers. The formation of the two diastereoisomers of 44 under these acidic conditions is unavoidable as the reaction involves an oxocarbenium intermediate. Although it was easy at this stage to separate these two isomers by column chromatography, it was more convenient, however, to use 44 as a mixture for the next acid-catalyzed hydrolysis step. Thus, treatment of the mixture of 44 with 5 mol% of pTsOH in acetone at 50 °C for 3 h led to the formation of ketone 45 and 46 in 42 and 20% yield, respectively, along with 22% of the hydrolyzed byproduct 47 (eq 6.18).
The $^1$H NMR spectrum of \( \text{45} \) clearly shows a singlet at 2.60 ppm which corresponds to the two C-2 hydrogen atoms of the carbonyl moiety. These two protons give an AB system at 2.60 and 2.57 ppm (\( J = 14 \text{ Hz} \)) in the $^1$H NMR of \( \text{46} \). The correct structure of the major product \( \text{45} \) was then fully established by $^1$H NMR COSY, NOE and HETCOR measurements. These results, therefore, undoubtedly prove the correct structure of \( \text{46} \).

With the required ketones \( \text{45} \) and \( \text{46} \) in hand, we then examined whether the same regioselective enolization would occur as observed in the case of \( \text{40} \). Interestingly, treatment of \( \text{45} \) with LHMDS at -78 °C followed by Mander's reagent led to the formation of an inseparable 5:1 mixture of \( \text{48} \) and \( \text{49} \), respectively, in 79% yield along with 16% of TMS-enol ether \( \text{50} \) (Scheme 6.4). The $^1$H NMR spectrum of the mixture of \( \text{48} \) and \( \text{49} \) shows the presence of two singlets at 12.37 and 12.44 ppm in a ratio of 5:1 which are expected to correspond to the two characteristic hydroxyl groups of the enol ester \( \text{48} \) and \( \text{49} \), respectively. The complete regiochemistry of the TMS-enol ether \( \text{50} \) was assigned by comparison its $^1$H NMR spectrum with that of \( \text{41} \). More interestingly, by treatment of \( \text{50} \) with methyllithium in ether at -78 °C followed by Mander's reagent, a single $\beta$-enol ester was obtained in 59% yield which was determined to be compound \( \text{48} \) based on $^1$H NMR COSY and HETCOR measurements. This result strongly points to the predominant formation of the major regioisomer \( \text{48} \) over the undesired \( \text{49} \) from ketone \( \text{45} \).

In order to explore whether the base would play a role in the regioselective enolization of \( \text{45} \), lithium diisopropylamide (LDA) was used instead of LHMDS. In fact, the relatively less hindered and more basic LDA changes the regioselectivity of the reaction. A (1.6:1) mixture of \( \text{48} \) and \( \text{49} \), respectively, was formed on treatment of \( \text{45} \) with LDA followed by Mander's reagent. No trace of the TMS-enol ether \( \text{50} \) could be detected under these conditions.

These results indicate that the C-2 position of the ketone moiety of \( \text{45} \) appears to be less hindered than the C-4. This might be ascribed to the steric contribution of the acetal moiety. If this is the case, the isomer \( \text{46} \) would give a different result compared to that of \( \text{45} \). Indeed, when compound \( \text{46} \) was subjected to the same reaction conditions as applied for \( \text{45} \), using LHMDS as the base, the desired $\beta$-enol ester \( \text{51} \) was formed in 48% as a single regioisomer along with 14% of the TMS-enol ether \( \text{52} \), based on 11% of the recovered ketone \( \text{46} \) (Scheme 6.5). Treatment of TMS-enol ether \( \text{52} \) with
MeLi in ether at -78 °C to -5 °C for 2 h followed by Mander's reagent successfully gave 51 in 34% yield. The starting silyl ether 52 was also recovered under these unoptimized conditions.

Scheme 6.5

It can be concluded at this point that, in addition to the expected higher acidity of the C-2 protons compared to that of the C-4 of the ketone, the steric effect of the acetal moiety in fact plays an important role in obtaining the desired regioselective carbomethoxylation of 45 and 46. In the case of compound 45 the methoxy group of the acetal moiety is pointing away from the C-4 position of the ketone. As a result, removal of the C-4 proton takes place to some extent if LHMDS is used as a base. This trend becomes more important when a relatively less hindered and more basic LDA is used. In contrast, the methoxy moiety in ketone 46 is pointing towards the C-4 of the ketone thereby efficiently shielding this position from the attack of a base. As a result, the removal of the more acidic and less hindered C-2 proton takes place exclusively leading to the desired β-enol ester 51.

It remains unclear why under the same reaction conditions ketone 40 gives TMS-enol ether 41 as the sole product while ketones 45 and 46 give this type of product as minor components along with the major β-enol esters 48 and 51, respectively. However, it can be concluded that the presence of the lactone ring or the acetal plays a crucial role for obtaining the desired β-enol ester, the key functional group for the coupling with aldehyde (2).

6.4.2 Vinyl Triflate Formation and the Coupling Reaction

With the desired β-enol esters in hand, their conversions into the corresponding vinyl triflates were then investigated. For this transformation, the use of triflic anhydride in CH₂Cl₂ at -78 °C to room temperature in the presence of DIPEA₁⁴ appears to be superior compared to the conditions using KHMDS and PhN(SO₂CF₃)₂. Under these conditions enol ester 48 (5:1 mixture with 49) was successfully converted into the desired vinyl triflate 53 in good yield as almost 9:1 mixture with the other stereoisomer (eq 6.19).
The successful preparation of the required vinyl triflate 53 set the stage for its coupling reaction with the left-hand fragment (2) of solanoeclepin A. Towards that end, we planned to make use of the well-known chromium(II)/nickel(II) mediated coupling procedure.\(^8\) In previous studies\(^15\) we examined the feasibility of this methodology by conducting the coupling reaction of the left-hand subunit (2) with the model vinyl triflate 54 (Scheme 6.6). The reaction was found to proceed satisfactorily using an excess of CrCl\(_2\) and a catalytic amount of NiCl\(_2\) to provide the coupling products in good yield as a 69:31 mixture of two diastereomers. Subsequent functional group transformation successfully converted the desired isomer 55 into the tetracyclic left-hand substructure (57) of solanoeclepin A.

**Scheme 6.6**

\[
\begin{align*}
\text{O} & \quad \text{EtO} & \quad \text{TfO} \\
\text{Me} & \quad \text{Me} & \quad \text{TBDPSO} \\
\text{O} & \quad \text{O} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{Me} & \quad \text{O} \\
\text{TBDPSO} & \quad \text{54} & \quad \text{55} \\
\text{CrCl}_2 (4 \text{ equiv}) & \quad \text{NiCl}_2 (\text{cat}) & \quad \text{DMF, 50 °C, 18 h} \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{TBDPSO} \\
\text{O} & \quad \text{O} & \quad \text{57} \\
\end{align*}
\]

Therefore, it was our interest at this stage of the synthesis to examine whether the chromium-mediated coupling reaction would be still applicable for the highly substituted vinyl triflate 53 and the left-hand fragment (2). Thus, the aldehyde (2) was mixed with the vinyl triflate 53 (1.5 equiv) in DMF in the presence of 5 equiv of CrCl\(_2\) and a catalytic amount of NiCl\(_2\) (eq 6.20). Unfortunately, no trace of the desired coupling product 58 could be detected after running the reaction at 50 °C for 20 h.

\[
\begin{align*}
\text{O} & \quad \text{MeO} & \quad \text{O} \\
\text{MeO} & \quad \text{TBDPSO} & \quad \text{53} \\
\text{53: R}_1 = \text{H}, R_2 = \text{OMe} & \quad (9:1 \text{ mixture}) & \quad \text{(6.20)} \\
\end{align*}
\]

Besides the recovered aldehyde, the byproduct formed after the reaction was the reduced product 61 (Scheme 6.7) in view of the presence of a double doublet at 7.18 ppm (J=2.0, 4.0 Hz) in \(^1\)H NMR which corresponds the β-hydrogen atom of the α,β-unsaturated ester moiety. The structure of 61 was then informed based on \(^1\)H NMR COSY and HETCOR measurements.
Further Chemistry towards the Right-Hand Substructure of Solanoe克莱pin A

Scheme 6.7

The formation of 61 might be a consequence of the steric hindrance of either the chromium species 60 (Scheme 6.7) or the aldehyde (2) which might hamper their approach towards each other. As a result, the reduced product 61 is formed under the aqueous workup conditions. Attempts to increase the amount of CrCl2 or the reaction temperature just gave the same results.

In order to verify this speculation, we decided to perform the chromium-mediated coupling reaction of vinyl triflate 53 with the simple cyclohexanecarboxaldehyde (62) (eq 6.21). Thus, vinyl triflate 53 (1.5 equiv) was subjected to the same coupling conditions as presented in eq 6.20, using (62) (1 equiv) as the electrophilic component. Interestingly, the coupling product 63 was formed in 30% yield based on vinyl triflate 53 as a stable colorless oil along with unidentified products.

The 1H NMR spectrum of 63 shows a broad singlet at 4.75 ppm which corresponds to the \( \gamma \)-hydrogen atom of the \( \gamma \)-butyrolactone moiety. This proton shows a long range coupling pattern with protons of the cyclohexane moiety as indicated in 1H NMR COSY measurement. In addition, the R1-hydrogen and the exocyclic methylene group give three singlets at 4.88, 4.69 and 4.46, respectively, beside the doublet at 4.85 ppm (J = 3.6 Hz) of the final hydrogen of the methyl lactol moiety.

This result along with the results obtained with the model study (Scheme 6.6) indicate that steric effect in fact plays a crucial role for the failure of the coupling reaction between vinyl triflate 53 and the aldehyde (2) (eq 6.20). Increase of the reaction time or the aid of an amine additive might be a possible strategy for the success of this reaction; otherwise a more efficient coupling procedure is required.
Chapter 6

6.5 Conclusions

The study on the functionalization of the key intermediate 7 towards the right-hand fragment 3 of solanoeclepin A is described in this chapter. This study reveals that the subtle steric and strain effects, in fact, control the chemistry of the compact skeleton of the carbocyclic structures. Reductive opening of the lactone moiety followed by the sulfonylation-hydride reduction sequence successfully puts in place the angular methyl and the secondary hydroxyl groups in the correct stereochemistry arrangement. This process appears to proceed best with the exocyclic double bond intact. Nevertheless, the successful dihydroxylation of this double bond is greatly facilitated by the presence of the lactone ring. The crucial role of the lactone function is further illustrated through the successful introduction of the desired β-enol esters onto ketones 45 and 46. The chromium-mediated coupling reaction of the β-enol ester derived vinyl triflate 53 with cyclohexanecarboxaldehyde proceeds well to give the coupling product. However, this methodology appears unsuccessful when applied to the coupling reaction of 53 with the left-hand subunit (2) of the natural product. This failure is ascribed to steric hindrance of these two coupling components. Further investigations are, therefore, required in order to reach the right-hand fragment 3 and hence solanoeclepin A.

6.6 Acknowledgements

Jan Dijkink is gratefully acknowledged for the preparation of photocycloadduct 7 and lactol 44 in large scale. Jan Geenevasen is kindly thanked for NMR experiments.

6.7 Experimental Section

General information. For general experimental details, see Section 2.6.

Synthesis of diol 8

To a stirred solution of 7 (325 mg, 0.88 mmol) in t-BuOH/H2O/acetone (5/1.5/1) (18 mL) at rt was added OsO4 (112 mg, 50 mol %) and NMO (206 mg, 2 equiv). The reaction mixture was stirred overnight and quenched with saturated aqueous Na2S2O3 (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous Na2S2O3 (60 mL), water (60 mL), brine (60 mL), dried over MgSO4 and concentrated in vacuo to afford diol 8 (205 mg, 70% conversion, 82% yield) as a colorless oil after chromatography purification (EtOAc). Rf = 0.34. 1H NMR: 7.38 – 7.25 (m, 5 H), 4.63 (d, J = 4 Hz, 1 H), 4.50 (d, J = 12 Hz, 1 H), 4.45 (d, J = 12 Hz, 1 H), 3.99 – 3.73 (m, 5 H), 3.65 (br s, 1 H), 3.64 (d, J = 11 Hz, 1 H), 3.54 (d, J = 11 Hz, 1 H), 3.46 (br s, 1 H), 2.80 (dd, J = 4 Hz, J = 12 Hz, 1 H), 2.34 – 2.28 (m, 2 H), 1.97 (dd, J = 1.6 Hz, J = 15 Hz, 1 H), 1.85 (d, J = 15 Hz, 1 H), 1.73 (d, J = 15 Hz, 1 H), 1.35 – 1.25 (m, 3 H). 13C NMR: 176.8, 137.2, 128.3, 127.8, 127.4, 108.6, 81.6, 81.2, 73.5, 67.0, 64.8, 64.4, 63.7, 62.9, 57.0, 52.2, 36.9, 30.4, 29.0, 20.2. IR (neat): 3481, 1772, 1074, 948. HRMS (FAB) calcd for C22H27O7 (MH+) 403.1751, found 403.1747.
Further Chemistry towards the Right-Hand Substructure of Solanoeclepin A

Synthesis of acetonide 9
To a stirred solution of diol 8 (344 mg, 0.857 mmol) in acetone (20 mL) at rt was added 2,2-dimethoxypropane (1.1 mL, 10 equiv) and PPTS (cat). The reaction mixture was stirred at rt overnight, quenched by saturated aqueous NaHCO$_3$ (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO$_4$ and concentrated in vacuo to afford the desired acetonide 9 (360 mg, 95%) as a colorless oil after purification (PE:EtOAc=2:1). R$_f$ = 0.26. $^1$H NMR: 7.36 - 7.25 (m, 5 H), 4.79 (d, J = 10 Hz, 1 H), 4.58 (d, J = 12 Hz, 1 H), 4.50 (d, J = 12 Hz, 1 H), 4.45 (d, J = 12 Hz, 1 H), 4.37 (d, J = 10 Hz, 1 H), 3.98 - 3.83 (m, 4 H), 3.65 (d, J = 11 Hz, 1 H), 3.57 (d, J = 11 Hz, 1 H), 2.62 (dd, J = 4 Hz, J = 12 Hz, 1 H), 2.23 (dt, J = 14 Hz, J = 4 Hz, 1 H), 1.95 (dd, J = 15 Hz, 1 H), 1.83 (dd, J = 15 Hz, 1 H), 1.76 (dd, J = 4 Hz, J = 14 Hz, 1 H), 1.67 (d, J = 14 Hz, 1 H), 1.47 (d, J = 12 Hz, 1 H), 1.38 (dd, J = 4 Hz, J = 14 Hz, 1 H), 1.32 (s, 3 H), 1.30 (s, 3 H). $^{13}$C NMR: 176.3, 137.7, 128.1, 127.4, 127.2, 108.0, 106.4, 87.0, 81.3, 73.1, 66.3, 64.6, 64.5, 63.7, 62.4, 57.5, 36.7, 30.9, 28.8, 26.1, 25.8, 18.7. HRMS (FAB) calcd for C$_{25}$H$_{31}$O$_7$ (MH$^+$) 443.2064, found 443.2076. IR (neat): 2984, 1775, 1064.

Synthesis of diol
To a stirred solution of LiAlH$_4$ (1 M in THF) (2.4 mL, 5 equiv) in THF (5 mL) at 0 °C was added a solution of acetonide 9 (210 mg, 0.475 mmol) in THF (5 mL). The reaction mixture was warmed to rt, stirred for 1 h and carefully quenched by EtOAc. Saturated aqueous Na$_2$SO$_4$ (0.5 mL) was added and the resulting mixture was stirred for 1 h. After adding solid Na$_2$SO$_4$, the mixture was filtered through Celite® and the filtrate was concentrated in vacuo. Purification by chromatography (EtOAc) afforded the desired product (205 mg, 96%) as a colorless oil (Rf = 0.4). $^1$H NMR: 7.37 - 7.28 (m, 5 H), 5.10 (d, J = 7 Hz, 1 H), 4.56 (d, J = 9.6 Hz, 1 H), 4.53 (d, J = 9.6 Hz, 1 H), 4.32 - 4.28 (m, 2 H), 4.01 - 3.95 (m, 3 H), 3.93 - 3.89 (m, 2 H), 3.58 (d, J = 7.6 Hz, 1 H), 3.43 - 3.38 (m, 1 H), 3.37 (d, J = 7.6 Hz, 1 H), 2.28 (dd, J = 6 Hz, J = 9.6 Hz, 1 H), 2.22 - 2.15 (m, 2 H), 1.88 (d, J = 12 Hz, 1 H), 1.78 - 1.68 (m, 2 H), 1.73 (d, J = 12 Hz, 1 H), 1.71 - 1.42 (m, 1 H), 1.27 (s, 3 H), 1.26 (s, 3 H). $^{13}$C NMR: 136.9, 128.3, 127.7, 127.5, 109.6, 104.7, 87.9, 73.4, 72.4, 65.9, 65.2, 64.5, 63.6, 61.1, 60.4, 56.5, 45.6, 37.5, 30.5, 30.3, 25.9, 25.7, 20.9. IR (neat): 3419, 2934, 1060. HRMS (FAB) calcd for C$_{25}$H$_{35}$O$_7$ (MH$^+$) 447.2377, found 447.2395.

Synthesis of silyl ether 10
To a solution of diol (197 mg, 0.44 mmol) in DMF (5 mL) at rt was added TBSCl (99 mg, 1.5 equiv) and imidazole (209 mg, 7 equiv). The reaction mixture was stirred overnight and quenched by saturated aqueous NaHCO$_3$ (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO$_4$ and concentrated in vacuo to afford the desired silyl ether 10 (180 mg, 73%) as a slightly yellow oil after purification (PE:EtOAc=3:1). R$_f$ = 0.2. $^1$H NMR: 7.33 - 7.22 (m, 5 H), 5.10 (d, J = 7 Hz, 1 H), 4.56 (d, J = 9.6 Hz, 1 H), 4.53 (d, J = 9.6 Hz, 1 H), 4.32 - 4.28 (m, 2 H), 4.01 - 3.95 (m, 3 H), 3.93 - 3.89 (m, 2 H), 3.58 (d, J = 7.6 Hz, 1 H), 3.43 - 3.38 (m, 1 H), 3.37 (d, J = 7.6 Hz, 1 H), 2.28 (dd, J = 6 Hz, J = 9.6 Hz, 1 H), 2.22 - 2.15 (m, 2 H), 1.88 (d, J = 12 Hz, 1 H), 1.78 - 1.68 (m, 2 H), 1.73 (d, J = 12 Hz, 1 H), 1.71 - 1.42 (m, 1 H), 1.27 (s, 3 H), 1.26 (s, 3 H). $^{13}$C NMR: 136.9, 128.3, 127.7, 127.5, 109.6, 104.7, 87.9, 73.4, 72.4, 65.9, 65.2, 64.5, 63.6, 61.1, 60.4, 56.5, 45.6, 37.5, 30.5, 30.3, 25.9, 25.7, 20.9. IR (neat): 3419, 2934, 1060. HRMS (FAB) calcd for C$_{25}$H$_{35}$O$_7$ (MH$^+$) 447.2377, found 447.2395.
3 H). $^{13}$C NMR: 138.6, 127.9, 127.06, 127.04, 109.7, 104.7, 88.8, 73.0, 72.7, 68.0, 65.5, 64.5, 64.4, 63.6, 61.2, 57.2, 44.6, 38.2, 30.8, 30.5, 26.2, 25.7, 25.6, 24.6, 17.8, -5.6, -5.9. IR (neat): 3463, 2952, 1065.

**Synthesis of MOM-protected silyl ether**

To a stirred solution of alcohol 10 (163 mg, 0.29 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C was added MOMCl (44 µL, 2 equiv) and DIPEA (0.26 mL, 5 equiv). The mixture was warmed to rt and stirred overnight and quenched by saturated aqueous NaHCO$_3$ (10 mL). The layers were separated and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO$_4$ and concentrated in vacuo to afford the desired product (170 mg, 97%) as a colorless oil after purification (PE:EtOAc=4:1). R$_f$ = 0.33. $^1$H NMR: 7.31 – 7.21 (m, 5 H), 5.16 (d, J = 9 Hz, 1 H), 4.66 (d, J = 6.5, 1 H), 4.57 (d, J = 6.5 Hz, 1 H), 4.47 (d, J = 12 Hz, 1 H), 4.39 – 4.35 (m, 2 H), 4.27 (d, J = 11 Hz, 1 H), 4.13 – 4.09 (m, 3 H), 3.93 – 3.85 (m, 2 H), 3.63 (d, J = 10.5 Hz, 1 H), 3.59 (d, J = 10.5 Hz, 1 H), 3.47 (d, J = 11 Hz, 1 H), 3.36 (s, 3 H), 2.43 (dd, J = 7 Hz, J = 11.5 Hz, 1 H), 2.09 (d, J = 10 Hz, 1 H), 1.83 – 1.70 (m, 3 H), 1.64 – 1.58 (m, 3 H), 1.28 (s, 3 H), 1.27 (s, 3 H), 0.85 (s, 9 H), 0.00 (s, 6 H). $^{13}$C NMR: 138.6, 127.9, 127.8, 126.9, 109.7, 104.7, 96.5, 88.5, 78.9, 73.1, 68.7, 65.5, 64.5, 63.5, 60.9, 60.2, 57.0, 55.2, 45.3, 36.1, 30.5, 30.2, 26.3, 25.7, 21.4, 18.0, -5.5, -5.8. IR (neat): 2928, 1062.

**Synthesis of alcohol 11**

To a stirred solution of silyl ether (50 mg, 0.08 mmol) in THF (2 mL) at rt was added TBAF (0.16 mL, 2 equiv) (1 M solution in THF). The reaction mixture was warmed up to 50 °C and stirred for 1 h and quenched by saturated aqueous NaHCO$_3$ (5 mL) at rt. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO$_4$ and concentrated in vacuo to afford the desired alcohol 11 (35.9 mg, 92%) as a colorless oil after purification (PE:EtOAc=1:1). R$_f$ = 0.2. $^1$H NMR: 7.36 – 7.25 (m, 5 H), 5.05 (d, J = 9 Hz, 1 H), 4.66 (d, J = 6 Hz, 1 H), 4.64 – 4.52 (m, 3 H), 4.22 (d, J = 12 Hz, 1 H), 4.05 (dd, J = 2 Hz, J = 7 Hz, 1 H), 3.98 – 3.87 (m, 5 H), 3.56 (d, J = 9 Hz, 1 H), 3.36 (s, 3 H), 3.38 – 3.32 (m, 1 H), 3.22 (d, J = 11 Hz, 1 H), 2.26 – 2.13 (m, 3 H), 1.85 (d, J = 15 Hz, 1 H), 1.82 – 1.65 (m, 3 H), 1.71 (d, J = 15 Hz, 1 H), 1.38 (t, J = 12 Hz, 1 H), 1.25 (s, 6 H). $^{13}$C NMR: 136.8, 128.3, 127.8, 127.6, 109.5, 104.8, 96.2, 87.4, 78.2, 73.5, 65.8, 65.1, 64.5, 63.6, 60.7, 60.0, 56.4, 55.3, 45.8, 35.9, 30.6, 30.3, 25.9, 25.7, 20.5. IR (neat): 3457, 1059.

**Synthesis of tosylate 12**

To a stirred solution of alcohol 11 (25 mg, 0.05 mmol) in pyridine (2 mL) at rt was added TsCl (19.4 mg, 2 equiv) and the reaction mixture was stirred overnight. The reaction was quenched by ice-5% aqueous solution of citric acid and the layers were separated. The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO$_4$ and concentrated in vacuo to afford the desired tosylate 12 (15 mg, 69% yield, 68% conversion) as a slightly yellow oil after purification (PE:EtOAc=2:1). R$_f$ = 0.26. $^1$H NMR: 7.72 (d, J = 8 Hz, 2 H), 7.36 – 7.25 (m, 7 H), 5.09 (d, J =
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9 Hz, 1 H), 4.83 (dd, J = 2 Hz, J = 11 Hz, 1 H), 4.53 (d, J = 7 Hz, 1 H), 4.49 (d, J = 7 Hz, 1 H), 4.42 (s, 2 H), 4.41 (d, J = 9 Hz, 1 H), 4.01 – 3.83 (m, 6 H), 3.55 (d, J = 11 Hz, 1 H), 3.51 (d, J = 11 Hz, 1 H), 3.26 (s, 3 H), 2.41 (s, 3 H), 2.28 (dd, J = 7 Hz, J = 12 Hz, 1 H), 1.87 (d, J = 12 Hz, 1 H), 1.78 – 1.27 (m, 6 H), 1.26 (s, 3 H), 1.24 (s, 3 H).

Reduction product 13

To a stirred solution of tosylate 12 (88 mg, 0.137 mmol) in THF (2 mL) at 0 °C was added Super-Hydride (1.0 M solution in THF, 1.5 mL, 10 equiv). The reaction mixture was refluxed for 1 h and carefully quenched by water at 0 °C. The layers were separated and the aqueous layer was extracted with ether (3 × 5 mL). The combined organic layers were washed with 3 N aqueous NaOH (10 mL) and 30% aqueous H2O2 (10 mL), water (20 mL), brine (20 mL), dried over MgSO4 and concentrated in vacuo to afford the desired product as a colorless oil after purification (PE:EtOAc = 2:1). Rf = 0.24. 1H NMR: 7.34 – 7.24 (m, 5 H), 5.09 (d, J = 9 Hz, 1 H), 4.66 (d, J = 6.5 Hz, 1 H), 4.57 (d, J = 6.5 Hz, 1 H), 4.45 (s, 2 H), 4.30 (d, J = 9 Hz, 1 H), 4.06 (dd, J = 2.2 Hz, J = 7 Hz, 1 H), 4.01 – 3.86 (m, 4 H), 3.54 (d, J = 10.5 Hz, 1 H), 3.48 (d, J = 10.5 Hz, 1 H), 3.36 (s, 3 H), 2.25 (d, J = 7.4 Hz, J = 11.4 Hz, 1 H), 1.92 (d, J = 15 Hz, 1 H), 1.86 – 1.62 (m, 5 H), 1.43 – 1.30 (m, 1 H), 1.27 (s, 3 H), 1.26 (s, 3 H), 1.18 (s, 3 H).

IR (neat): 2930, 1103, 1036.

Synthesis of silyl ether

To a solution of alcohol 10 (311 mg, 0.555 mmol) in THF (20 mL) at rt was added benzylbromide (0.2 mL, 1.68 mmol), and sodium hydride (60 wt.% dispersion in mineral oil) (90 mg, 2.25 mmol). The resulting mixture was stirred at rt for 30 min and n-Bu4NI(cat) was added and stirred overnight. The reaction was quenched with ice-water. The layers were separated and the aqueous phase was extracted with ether (3 × 20 mL). The combined organic layers were washed with brine (60 mL), dried over MgSO4 and concentrated in vacuo to afford the desired product (276 mg, 91% yield, 91% conversion) as a colorless oil after column chromatography purification (PE:EtOAc = 4:1). Rf = 0.28. 1H NMR: 7.34 – 7.19 (m, 10 H), 5.20 (d, J = 9 Hz, 1 H), 4.66 (d, J = 12 Hz, 1 H), 4.48 (d, J = 12 Hz, 1 H), 4.44 (d, J = 12 Hz, 1 H), 4.40 – 4.35 (m, 3 H), 4.02 – 3.85 (m, 5 H), 3.65 (d, J = 10.5 Hz, 1 H), 3.59 (d, J = 10.5 Hz, 1 H), 3.48 (d, J = 11 Hz, 1 H), 2.38 (dd, J = 7 Hz, J = 11 Hz, 1 H), 2.12 (d, J = 12 Hz, 1 H), 1.94 (d, J = 15 Hz, 1 H), 1.80 (d, J = 15 Hz, 1 H), 1.76 (d, J = 16 Hz, 1 H), 1.66 – 1.56 (m, 3 H), 1.31 (s, 3 H), 1.29 (s, 3 H), 0.84 (s, 9 H), - 0.02 (s, 6 H). 13C NMR: 138.85, 138.81, 138.79, 127.99, 127.94, 127.1, 126.99, 126.92, 109.8, 104.7, 88.7, 80.0, 73.1, 71.3, 68.6, 65.5, 64.5, 63.5, 60.9, 60.5, 57.0, 45.2, 35.0, 30.6, 30.5, 30.1, 26.4, 25.7, 21.2, 18.0, - 5.5, - 5.8. HRMS (FAB) calcd for C38H55O7Si (MH+) 651.3712, found 651.3705. IR (neat): 2928, 1064.

Synthesis of alcohol 15

To a stirred solution of silyl ether (263 mg, 0.404 mmol) in THF (10 mL) at 0 °C was added TBAF (1.2 mL, 3 equiv) (1 M solution in THF). The reaction mixture was warmed up to 50 °C and stirred for 2 h and quenched by saturated aqueous NaHCO3 (10 mL) at rt. The layers were separated and the aqueous
layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄ and concentrated in vacuo to afford the desired alcohol 15 (164 mg, 76%) as a colorless oil after purification (PE:EtOAc=2:1). R_f=0.15. ¹H NMR: 7.36 – 7.23 (m, 10 H), 5.13 (d, J = 9 Hz, 1 H), 4.59 (d, J = 12 Hz, 1 H), 4.53 (s, 2 H), 4.41 (d, J = 12 Hz, 1 H), 4.27 (d, J = 13 Hz, 1 H), 4.03 – 3.87 (m, 6 H), 3.57 (d, J = 9 Hz, 1 H), 3.38 (d, J = 9 Hz, 1 H), 3.40 – 3.35 (m, 1 H), 3.18 (d, J = 10.6 Hz, 1 H), 2.24 – 2.13 (m, 3 H), 1.98 (d, J = 15 Hz, 1 H), 1.76 – 1.56 (m, 3 H), 1.43 – 1.29 (m, 1 H), 1.26 (s, 3 H), 1.25 (s, 3 H). ¹³C NMR: 138.5, 136.9, 128.3, 128.0, 127.7, 127.5, 127.0, 126.9, 109.6, 104.7, 87.6, 79.8, 73.5, 71.3, 66.0, 65.2, 64.4, 63.5, 61.0, 60.3, 56.4, 45.7, 35.0, 30.7, 30.3, 25.9, 25.7, 20.7.

**Byproduct cyclic ether 14**

¹H NMR: 7.34 – 7.27 (m, 5 H), 4.81 (d, J = 7.6 Hz, 1 H), 4.52 (d, J = 9.6 Hz, 1 H), 4.47 (d, J = 9.6 Hz, 1 H), 4.32 (d, J = 7.6 Hz, 1 H), 4.21 (d, J = 8.4 Hz, 1 H), 3.64 (d, J = 8.4 Hz, 1 H), 3.57 (d, J = 8.4 Hz, 1 H), 2.20 (dd, J = 7.6 Hz, J = 9 Hz, 1 H), 1.96 (d, J = 12 Hz, 1 H), 1.89 – 1.84 (m, 1 H), 1.80 (d, J = 12 Hz, 1 H), 1.67 – 1.63 (m, 4 H), 1.32 (s, 3 H), 1.29 (s, 3 H). ¹³C NMR: 138.5, 128.2, 127.4, 127.2, 109.3, 105.4, 87.5, 84.5, 73.3, 67.7, 67.4, 65.0, 64.6, 63.8, 57.8, 57.3, 48.5, 32.7, 29.8, 29.6, 26.5, 26.1, 20.1. IR (neat): 2984, 1100, 1056.

**Synthesis of diol 18**

To a stirred solution of LiAlH₄ (1 M in THF) (0.6 mL, 4 equiv) in THF (2 mL) at 0 °C was added a solution of lactone 7 (53 mg, 0.144 mmol) in THF (2 mL). The reaction mixture was warmed to rt, stirred for 1 h and carefully quenched with EtOAc. Saturated aqueous Na₂SO₄ (0.5 mL) was added and the resulting mixture was stirred for 1 h. After adding solid Na₂SO₄, the mixture was filtered through Celite® and the filtrate was concentrated in vacuo. Purification by column chromatography (EtOAc) afforded the desired product (44 mg, 83%) as a colorless oil (R_f = 0.33). ¹H NMR: 7.36 – 7.25 (m, 5 H), 4.60 (s, 1 H), 4.55 (s, 2 H), 4.40 (s, 1 H), 4.22 (d, J = 12 Hz, 1 H), 3.99 – 3.87 (m, 5 H), 3.55 (d, J = 9.6 Hz, 1 H), 3.51 – 3.46 (m, 1 H), 3.47 (d, J = 9.6 Hz, 1 H), 3.21 (br, 1 H), 2.23 (dd, J = 2.5 Hz, J = 12 Hz, 1 H), 2.14 – 2.02 (m, 3 H), 1.80 (s, 2 H), 1.71 – 1.62 (m, 3 H). ¹³C NMR: 155.4, 137.0, 128.3, 127.7, 127.6, 109.9, 94.5, 73.4, 72.4, 65.9, 64.3, 63.7, 62.6, 58.2, 57.8, 47.5, 39.2, 30.6, 30.5, 22.4. IR (neat): 3399, 2945, 2874, 1028.

**Synthesis of monosilyl ether**

To a solution of diol 18 (329 mg, 0.884 mmol) in DMF (20 mL) at rt was added TBSCl (200 mg, 1.5 equiv) and imidazole (420 mg, 7 equiv). The reaction mixture was stirred overnight and quenched by saturated aqueous NaHCO₃ (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (60 mL), dried over MgSO₄ and concentrated in vacuo to afford the desired silyl ether (300 mg, 70%) as a colorless oil (R_f = 0.2). ¹H NMR: 7.35 – 7.24 (m, 5 H), 4.62 (s, 1 H), 4.50 (d, J = 12 Hz, 1 H), 4.44 (d, J = 12 Hz, 1 H), 3.97 – 3.85 (m, 7 H), 3.57 (d, J = 10 Hz, 1 H), 3.51 (d, J = 10 Hz, 1 H), 3.59 – 3.50 (m, 1 H), 2.22 (dd, J = 7.6 Hz, J = 12 Hz, 1 H), 2.06 – 1.58 (m, 7 H), 0.89 (s, 9 H), 0.075 (s, 3 H), 0.071 (s, 3 H).
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$^1$H NMR: 156.6, 138.4, 128.0, 127.2, 127.1, 110.0, 94.2, 73.1, 72.5, 67.3, 64.5, 64.2, 63.7, 62.9, 58.4, 46.1, 40.0, 31.1, 30.7, 27.7, 25.6, 17.8, -5.7, -6.0. IR (neat): 3447, 2951, 2856, 1101, 1070. HRMS (FAB) calcd for C$_{28}$H$_{43}$O$_5$Si (MH$^+$) 487.2874, found 487.2881.

**Synthesis of benzyl ether**

To a solution of alcohol (286 mg, 0.588 mmol) in THF (10 mL) at rt was added benzylbromide (0.14 mL, 2 equiv), and sodium hydride (60 wt. % dispersion in mineral oil) (118 mg, 5 equiv). The resulting mixture was stirred at rt for 30 min and n-Bu$_4$NI(cat) was added. The reaction mixture was stirred overnight and quenched with ice-water. The layers were separated and the aqueous phase was extracted with ether (3×10 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO$_4$ and concentrated in vacuo to afford the desired product (289 mg, 85%) as a colorless oil after column chromatography purification (PE:EtOAc=5:1). $R_f=0.35$. $^1$H NMR: 7.41 – 7.20 (m, 10 H), 4.79 (s, 1 H), 4.66 (d, J = 12 Hz, 1 H), 4.56 (d, J = 12 Hz, 1 H), 4.51 (d, J = 12 Hz, 1 H), 4.42 (d, J = 12 Hz, 1 H), 4.26 (d, J = 11 Hz, 1 H), 3.98 – 3.85 (m, 4 H), 3.69 – 3.67 (m, 1 H), 3.68 (d, J = 10 Hz, 1 H), 3.60 – 3.56 (m, 1 H), 3.59 (d, J = 10 Hz, 1 H), 2.30 (dd, J = 7 Hz, J = 11.6 Hz, 1 H), 2.02 (dt, J = 3 Hz, J = 14 Hz, 1 H), 1.93 - 1.80 (m, 2 H), 1.90 (d, J = 14 Hz, 1 H), 1.83 (d, J = 14 Hz, 1 H), 1.63 - 1.44 (m, 2 H), 0.84 (s, 9 H), -0.01 (s, 3 H), -0.02 (s, 3 H). $^{13}$C NMR: 156.7, 138.6, 138.5, 128.0, 127.2, 127.1, 127.0, 110.1, 95.0, 79.2, 73.2, 70.8, 68.5, 64.3, 63.6, 61.4, 59.0, 58.1, 47.4, 35.9, 30.8, 30.5, 25.7, 22.7, 17.9, -5.6, -5.8. IR (neat): 2945, 2870, 1095, 1055.

**Synthesis of alcohol 19**

To a stirred solution of silyl ether (129.6 mg, 0.225 mmol) in THF (5 mL) at 0 °C was added TBAF (1.1 mL, 5 equiv) (1 M solution in THF). The reaction mixture was warmed up to 50 °C and stirred for 2 h and quenched by saturated aqueous solution of NaHCO$_3$ (5 mL) at rt. The layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO$_4$ and concentrated in vacuo to afford the desired alcohol (91 mg, 88%) as a colorless oil after column chromatography purification (PE:EtOAc=2:1). $R_f=0.22$. $^1$H NMR: 7.37 – 7.24 (m, 10 H), 4.62 (s, 1 H), 4.57 (d, J = 12 Hz, 1 H), 4.55 (s, 2 H), 4.41 (d, J = 12 Hz, 1 H), 4.40 (s, 1 H), 3.96 – 3.87 (m, 4 H), 3.70 (dd, J = 2.5 Hz, J = 7 Hz, 1 H), 3.56 (d, J = 9.5 Hz, 1 H), 3.48 (d, J = 9.5 Hz, 1 H), 3.38 – 3.45 (m, 1 H), 3.15 (d, J = 10 Hz, 1 H), 2.31 (dd, J = 2.5 Hz, J = 12 Hz, 1 H), 2.14 (d, J = 10 Hz, 1 H), 1.93 (d, J = 14 Hz, 1 H), 1.92 (d, J = 11.6 Hz, 1 H), 1.81 (d, J = 14.5 Hz, 1 H), 1.73 – 1.62 (m, 4 H). $^{13}$C NMR: 156.7, 138.6, 138.5, 128.0, 127.2, 127.1, 127.0, 110.1, 95.0, 79.2, 73.2, 70.8, 68.5, 64.3, 63.6, 61.4, 59.0, 58.1, 47.4, 35.9, 30.8, 30.5, 25.7, 22.7, 17.9, -5.6, -5.8. IR (neat): 3460, 2945, 2870, 1095, 1055. HRMS (FAB) calcd for C$_{29}$H$_{35}$O$_5$ (MH$^+$) 463.2479, found 463.2488.

**Synthesis of tosylate 20**

To a stirred solution of alcohol 19 (742 mg, 1.61 mmol) in pyridine (30 mL) at rt was added TsCl (957 mg, 3 equiv) and the reaction mixture was stirred overnight. The reaction was quenched by ice-5% aqueous solution of citric acid and the layers were separated. The aqueous layer was extracted with EtOAc
(3×20 mL). The combined organic layers were washed with 3% aqueous solution of citric acid (60 mL), water (60 mL), brine (60 mL), dried over MgSO₄, and concentrated in vacuo to afford the desired tosylate 20 (614 mg, 95% yield, 65% conversion) as a colorless oil after purification (PE:EtOAc=2:1). Rᵢ=0.34. ¹H NMR: 7.65 (d, J = 8 Hz, 2 H), 7.37 – 7.26 (m, 10 H), 7.17 (d, J = 8 Hz, 2 H), 4.76 (s, 1 H), 4.72 (d, J = 11 Hz, 1 H), 4.67 (s, 1 H), 4.51 (d, J = 7 Hz, 1 H), 4.48 (d, J = 7 Hz, 1 H), 4.40 (d, J = 12 Hz, 1 H), 4.10 (d, J = 12 Hz, 1 H), 3.95 (d, J = 11 Hz, 1 H), 3.95 – 3.84 (m, 4 H), 3.63 – 3.58 (m, 1 H), 3.59 (s, 2 H), 2.40 (s, 3 H), 2.15 (dd, J = 7 Hz, J = 12 Hz, 1 H), 2.04 – 1.77 (m, 4 H), 1.65 (dd, J = 2 Hz, J = 12 Hz, 1 H), 1.54 (d, J = 13 Hz, 1 H), 1.44 (dd, J = 5 Hz, J = 13 Hz, 1 H).

By product cyclic ether

¹H NMR: 7.35 – 7.25 (m, 5 H), 4.66 (s, 1 H), 4.62 (s, 1 H), 4.50 (d, J = 12 Hz, 1 H), 4.46 (d, J = 12 Hz, 1 H), 4.17 (d, J = 4.4 Hz, 1 H), 3.97 – 3.83 (m, 4 H), 3.85 (d, J = 9 Hz, 1 H), 3.73 (d, J = 9 Hz, 1 H), 3.62 (d, J = 10 Hz, 1 H), 3.56 (d, J = 10 Hz, 1 H), 2.01 (d, J = 14 Hz, 1 H), 1.97 (d, J = 11.5 Hz, 1 H), 1.95 – 1.87 (m, 1 H), 1.75 (d, J = 14 Hz, 1 H), 1.74 (d, J = 11.5 Hz, 1 H), 1.61 – 1.56 (m, 3 H). ¹³C NMR: 154.6, 138.5, 128.3, 127.49, 127.46, 109.7, 95.2, 82.4, 73.3, 66.8, 66.4, 64.5, 63.8, 61.0, 56.7, 53.4, 36.1, 29.8, 29.6, 19.1. IR (neat): 2871, 1105.

Reduction product 21

To a stirred solution of tosylate 20 (667 mg, 1.08 mmol) in THF (40 mL) at 0 °C was added Super-Hydride (1.0 M solution in THF, 3.25 mL, 3 equiv). The reaction mixture was refluxed for 6 h and carefully quenched by water at 0 °C. The layers were separated and the aqueous layer was extracted with ether (3×20 mL). The combined organic layers were washed with 3 N aqueous NaOH (60 mL) and 30% aqueous H₂O₂ (60 mL), water (60 mL), brine (60 mL), dried over MgSO₄ and concentrated in vacuo to afford the desired product 21 (274.5 mg, 57%) as a colorless oil after purification (PE:EtOAc=4:1). Rᵢ=0.33. ¹H NMR: 7.37 – 7.25 (m, 10 H), 4.63 (s, 1 H), 4.59 (d, J = 12 Hz, 1 H), 4.56 (s, 2 H), 4.51 (s, 1 H), 4.43 (d, J = 12 Hz, 1 H), 3.98 – 3.86 (m, 4 H), 3.70 (dd, J = 3 Hz, J = 7 Hz, 1 H), 3.58 (s, 2 H), 2.15 – 1.99 (m, 3 H), 2.01 (d, J = 14 Hz, 1 H), 1.85 (dd, J = 2 Hz, J = 14 Hz, 1 H), 1.70 (td, J = 3.5 Hz, J = 14 Hz, 1 H), 1.63 – 1.59 (m, 1 H), 1.41 (dt, J = 3 Hz, J = 13 Hz, 1 H), 1.25 (s, 3 H). ¹³C NMR: 157.4, 138.7, 138.5, 128.1, 128.0, 127.19, 127.11, 127.0, 126.9, 110.4, 94.2, 79.3, 73.1, 70.8, 67.2, 64.2, 63.6, 61.6, 58.0, 42.5, 36.7, 30.8, 30.4, 29.7, 14.9. HRMS (FAB) calcd for C₂₉H₃₅O₄ (MH⁺) 447.2530, found 447.2538. IR (neat): 2923, 2852, 1105, 1062.

Synthesis of epoxide 26

To a stirred solution of 21 (31 mg, 0.069 mmol) and Na₂HPO₄ (30 mg, 3 equiv) in CH₂Cl₂ (2 mL) at 0 °C was added MCPBA (18 mg, 1.5 equiv). The reaction mixture was warmed to rt and stirred for 2 h. Water was added (5 mL) and the aqueous layer was extracted with CH₂Cl₂ (3×5 mL). The combined organic layers were washed with saturated Na₂SO₃ (10 mL), saturated NaHCO₃ (10 mL), brine (10 mL), dried over MgSO₄ and concentrated in vacuo to afford epoxide 26 (27 mg, 85%) as a colorless oil after purification (PE:EtOAc=3:1). Rᵢ=0.3. ¹H NMR: 7.36 – 7.24 (m, 10 H), 4.60 (d, J = 12 Hz, 1 H), 4.44 (d, J = 14 Hz, 1 H), 4.43 (s, 2 H), 3.93 – 3.85 (m, 5 H), 3.61 (d, J = 4.7 Hz, 1 H), 3.44 (d, J = 10 Hz, 1 H), 3.35 (d, J
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= 10 Hz, 1 H), 3.02 (d, J = 4.7 Hz, 1 H), 2.20 – 2.13 (m, 2 H), 2.02 (dd, J = 2.5 Hz, J = 11.5 Hz, 1 H), 1.96 (d, J = 14.6 Hz, 1 H), 1.74 (td, J = 3.4 Hz, J = 14 Hz, 1 H), 1.64 – 1.63 (m, 1 H), 1.58 (dd, J = 1.7 Hz, J = 16.5 Hz, 1 H), 1.47 (dt, J = 3.4 Hz, J = 14 Hz, 1 H), 1.25 (s, 3 H). 13C NMR: 138.7, 138.3, 128.1, 128.0, 127.2, 127.0, 126.9, 79.0, 73.0, 71.3, 71.0, 66.1, 64.1, 63.7, 57.4, 53.2, 51.2, 41.0, 35.1, 30.7, 29.7, 28.7, 15.6. IR (neat): 2928, 1100.

Synthesis of ketone 30

To a stirred solution of 21 (12 mg, 0.026 mmol) in acetone (2 mL) at rt was added pTsOH monohydrate (30 mol%). The reaction mixture was warmed to 50 °C and stirred for 1 h. Saturated aqueous NaHCO3 (2 mL) was added at rt. The layers were separated and the aqueous layer was extracted with ether (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO4 and concentrated in vacuo to afford 30 (8 mg, 74%) as a colorless oil after purification (PE:EtOAc=4:1). Rf=0.33. 1H NMR: 7.34 – 7.12 (m, 10 H), 4.61 (d, J = 12 Hz, 1 H), 4.52 (d, J = 12.3 Hz, 1 H), 4.47 (d, J = 12.5 Hz, 1 H), 4.46 (s, 1 H), 4.44 (d, J = 12 Hz, 1 H), 4.40 (s, 1 H), 3.71 (dd, J = 2.6 Hz, J = 6 Hz, 1 H), 3.56 (s, 2 H), 2.68 (d, J = 16 Hz, 1 H), 2.45 – 2.28 (m, 1 H), 2.37 (d, J = 16 Hz, 1 H), 2.24 – 2.08 (m, 4 H), 1.66 – 1.53 (m, 1 H), 1.41 (s, 3 H). IR (neat): 2930, 2858, 1714, 1101.

Synthesis of diol 32

A solution of 21 (69 mg, 0.15 mmol) in THF (1 mL) was added to liquid ammonia at –78 °C. To this solution was added sodium (3 equiv) in small portions. The blue solution was stirred at –78 °C for 30 min and t-BuOH (1 mL) was added and the resulting mixture was stirred for an additional 30 min. The reaction was carefully quenched by solid NH4Cl at –78 °C until disappearance of the blue color was observed. The reaction mixture was allowed to warm up slowly to rt until all ammonia was evaporated. EtOAc (5 mL) was added and the organic phase was washed with brine (5 mL), dried over MgSO4 and concentrated in vacuo to afford 32 (37 mg, 93%) as a colorless oil after purification (EtOAc). Rf=0.3. 1H NMR: 4.66 (s, 1 H), 4.57 (s, 1 H), 4.14 – 3.88 (m, 5 H), 3.83 (d, J = 9 Hz, 1 H), 3.79 (d, J = 9 Hz, 1 H), 2.18 – 2.09 (m, 2 H), 1.98 (dd, J = 2 Hz, J = 9 Hz, 1 H), 1.87 (d, J = 11.6 Hz, 1 H), 1.84 (d, J = 11.6 Hz, 1 H), 1.71 – 1.62 (m, 2 H), 1.49 (d, J = 11 Hz, 1 H), 1.24 (s, 3 H). 13C NMR: 157.3, 110.4, 94.6, 72.9, 64.4, 63.8, 61.9, 60.3, 59.5, 42.4, 38.6, 30.9, 30.3, 30.0, 15.0. IR (neat): 3407, 2928, 1106. HRMS (FAB) calcd for C15H23O4 (MH+) 267.1591, found 267.1603.

Synthesis of ketone 33

To a stirred solution of 32 (37 mg, 0.14 mmol) in acetone (2 mL) at rt was added pTsOH monohydrate (30 mol%). The reaction mixture was warmed to 50 °C and stirred for 1 h. Saturated aqueous solution of NaHCO3 (2 mL) was added at rt. The layers were separated and the aqueous layer was extracted with ether (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO4 and concentrated in vacuo to afford 33 (27 mg, 87%) as a colorless oil after purification (EtOAc). Rf=0.31. 1H NMR: 4.50 (s, 1 H), 4.43 (s, 1 H), 4.15 (dd, J = 3 Hz, J = 8 Hz, 1 H), 3.81 (d, J = 11 Hz, 1 H), 3.75 (d, J = 11
Hz, 1 H), 2.62 (d, J = 16 Hz, 1 H), 2.44 – 2.20 (m, 5 H), 2.08 (dd, J = 3 Hz, J = 12 Hz, 1 H), 2.00- 1.75 (br, 2 H), 1.75 – 1.66 (m, 1 H), 1.41 (s, 3 H).

**Synthesis of silyl ether 34**
To a stirred solution of diol 33 (10 mg, 0.044 mmol) in DMF (1 mL) at rt was added TBSCl (10 mg, 1.5 equiv) and imidazole (21 mg, 7 equiv). The reaction mixture was stirred overnight and quenched by saturated aqueous solution of NaHCO₃ (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄ and concentrated in vacuo to afford the desired silyl ether 34 (12 mg, 81%) as a colorless oil after purification (PE:EtOAc=2:1). Rₛ=0.23. ¹H NMR: 4.48 (s, 1 H), 4.40 (s, 1 H), 4.02 – 3.99 (m, 1 H), 3.72 (d, J = 11 Hz, 1 H), 3.67 (d, J = 11 Hz, 1 H), 2.60 (d, J = 16 Hz, 1 H), 2.44 (dd, J = 5 Hz, J = 14 Hz, 1 H), 2.35 (d, J = 16 Hz, 1 H), 2.34 – 2.15 (m, 1 H), 2.13 (d, J = 7.6 Hz, 1 H), 2.07 (dd, J = 3 Hz, J = 12 Hz, 1 H), 1.81 (d, J = 5 Hz, 1 H), 1.70 – 1.65 (m, 1 H), 1.40 (s, 3 H), 0.87 (s, 9 H), 0.03 (s, 6 H). ¹³C NMR: 211.9, 156.5, 93.4, 72.3, 63.5, 60.0, 59.5, 41.9, 38.8, 37.2, 36.6, 32.0, 25.5, 17.9, 14.9, -5.8. IR (neat): 3540, 2928, 1707.

**Synthesis of ketone 40**
To a stirred solution of 39 (17 mg, 0.039 mmol) in acetone (2 mL) at rt was added pTsOH monohydrate (30 mol%). The reaction mixture was warmed to 50 °C and stirred for 1 h. Saturated aqueous NaHCO₃ (2 mL) was added at rt. The layers were separated and the aqueous layer was extracted with ether (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄ and concentrated in vacuo to afford 40 (11 mg, 72%) as a colorless oil after purification (PE:EtOAc=4:1). Rₛ=0.28. ¹H NMR: 4.80 (d, J = 4 Hz, 1 H), 4.75 (s, 1 H), 4.66 (s, 1 H), 3.95 (d, J = 11 Hz, 1 H), 3.90 (d, J = 11 Hz, 1 H), 2.66 (d, J = 12 Hz, 1 H), 2.59 (d, J = 12 Hz, 1 H), 2.45 (dt, J = 3 Hz, J = 13 Hz, 1 H), 2.29 – 2.33 (m, 3 H), 2.12 – 2.10 (m, 1 H), 1.96 (d, J = 13 Hz, 1 H), 1.12 - 1.00 (m, 21 H). IR (neat): 2943, 2865, 1779, 1718.

**Synthesis of TMS-enol ether 41**
To a stirred solution of ketone 40 (11 mg, 0.028 mmol) in THF (2 mL) at -78 °C was added LHMDS (1 M in THF, 0.15 mL, 5 equiv). The resulting mixture was stirred at -78 °C for 30 min and then MeOCOCN (22 µL, 10 equiv) was added. The reaction mixture was warmed to rt and stirred for an additional 30 min before adding water (5 mL). The aqueous layer was extracted with ether (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄ and concentrated in vacuo to afford 41 (12 mg, 85%) as a colorless oil after purification. ¹H NMR: 4.91 (d, J = 1.6 Hz, 1 H), 4.74 (d, J = 4 Hz, 1 H), 4.62 (s, 1 H), 4.57 (s, 1 H), 3.93 (d, J = 11 Hz, 1 H), 3.89 (d, J = 11 Hz, 1 H), 2.25 – 2.12 (m, 3 H), 1.95 – 1.84 (m, 2 H), 1.92 (d, J = 12 Hz, 1 H), 1.09 – 1.00 (m, 21 H), 0.18 (s, 9 H). ¹³C NMR: 175.2, 157.2, 156.5, 95.9, 95.0, 80.4, 65.7, 59.5, 58.2, 54.3, 39.7, 27.1, 17.9, 17.1, 11.8, 0.15. IR (neat): 2943, 2866, 1779, 1642.
Further Chemistry towards the Right-Hand Substructure of Solanoeclepin A

Synthesis of lactol 43

To a stirred solution of 7 (529 mg, 1.44 mmol) in CH₂Cl₂ (18 mL) at -78 °C was added DIBAL-H (1.5 M in toluene, 1.44 mL, 1.5 equiv). The resulting mixture was stirred at -78 °C for 30 min and carefully quenched by water at 0 °C. Saturated aqueous Na₂SO₄ (1 mL) was added and the resulting mixture was stirred for 1 h. After adding solid Na₂SO₄, the mixture was filtered through Celite® and the filtrate was concentrated in vacuo. Purification by chromatography (PE:EtOAc=1:1) afforded the desired product 43 (367 mg, 69%) as a colorless oil (Rf=0.28). ¹H NMR: 7.37 – 7.25 (m, 5 H), 5.44 (d, J = 10 Hz, 1 H), 4.91 (d, J = 10 Hz, 1 H), 4.66 (s, 1 H), 4.62 (d, J = 12 Hz, 1 H), 4.56 (d, J = 12 Hz, 1 H), 4.52 (s, 1 H), 4.24 (d, J = 4.5 Hz, 1 H), 3.96 – 3.85 (m, 4 H), 3.58 (d, J = 9 Hz, 1 H), 3.54 (d, J = 9 Hz, 1 H), 2.32 (d, J = 11 Hz, 1 H), 1.98 (d, J = 14 Hz, 1 H), 1.87 (d, J = 14 Hz, 1 H), 1.79 – 1.64 (m, 3 H), 1.62 – 1.53 (m, 2 H). ¹³C NMR: 151.7, 136.7, 128.3, 127.8, 127.5, 108.8, 98.5, 95.4, 81.3, 73.3, 64.6, 64.3, 64.0, 63.6, 57.1, 56.7, 38.0, 29.8, 29.2, 17.7. IR (neat): 3422, 2941.

Synthesis of methyl acetal 44

To a stirred solution of lactol 43 (176 mg, 0.475 mmol) in CH₂Cl₂ (10 mL) at rt was added CH(OMe)₃ (0.52 mL, 10 equiv) and PPTS (36 mg, 0.3 equiv). The resulting mixture was stirred at rt overnight, quenched with saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with water (30 mL), brine (30 mL), dried over MgSO₄ and concentrated in vacuo to afford a (3:1) mixture of 44 (166 mg, 91%) as a colorless oil after purification (PE:EtOAc=4:1). ¹H NMR (major, Rf=0.17): 7.33 – 7.25 (m, 5 H), 5.07 (s, 1 H), 4.84 (s, 1 H), 4.68 (s, 1 H), 4.55 (d, J = 12 Hz, 1 H), 4.49 (d, J = 12 Hz, 1 H), 4.20 (d, J = 4.5 Hz, 1 H), 3.98 – 3.90 (m, 4 H), 3.68 (s, 2 H), 3.39 (s, 3 H), 2.11 (d, J = 11 Hz, 1 H), 2.01 (m, 2 H), 1.89 (dd, J = 11 Hz, J = 4.6 Hz, 1 H), 1.82 (d, J = 14 Hz, 1 H), 1.75 (dt, J = 14 Hz, J = 3 Hz, 1 H), 1.62 – 1.58 (m, 1 H), 1.53 (dd, J = 14 Hz, J = 4 Hz, 1 H). ¹³C NMR (major): 153.8, 138.6, 128.0, 127.16, 127.12, 109.1, 106.5, 95.3, 82.1, 73.1, 68.3, 64.6, 64.4, 63.7, 56.9, 56.3, 55.8, 37.7, 30.0, 29.3, 18.7. IR (neat): 2941, 2879, 1100. ¹H NMR (minor, Rf=0.25): 7.36 – 7.25 (m, 5 H), 4.87 (s, 1 H), 4.67 (s, 1 H), 4.58 (s, 1 H), 4.51 (d, J = 12 Hz, 1 H), 4.47 (d, J = 12 Hz, 1 H), 4.29 (d, J = 4.3 Hz, 1 H), 3.97 – 3.82 (m, 4 H), 3.63 (d, J = 10 Hz, 1 H), 3.54 (d, J = 10 Hz, 1 H), 3.39 (s, 3 H), 2.13 – 2.05 (m, 1 H), 2.02 (dd, J = 14 Hz, J = 1.5 Hz, 1 H), 1.89 (d, J = 11 Hz, 1 H), 1.82 (d, J = 14 Hz, 1 H), 1.79 – 1.75 (m 2 H), 1.72 (dd, J = 11 Hz, J = 4.4 Hz, 1 H), 1.58 – 0.88 (m, 1 H). ¹³C NMR (minor): 154.8, 138.3, 128.1, 127.3, 127.0, 109.8, 105.0, 95.1, 80.3, 73.1, 66.3, 64.3, 63.5, 59.3, 56.4, 55.4, 53.6, 37.5, 31.6, 29.5, 18.8. HRMS (FAB) calcd for C₂₃H₂₉O₅ (MH⁺) 385.2010, found 385.2018.

Synthesis of ketone 45 and 46

(See the synthesis of ketone 40). Starting from 44 (3:1 mixture) (150 mg, 0.39 mmol) gave 45 (56 mg, 42%) and 46 (26 mg, 20%) as colorless oils after purification. ¹H NMR (major 45, Rf=0.19): 7.36 – 7.25 (m, 5 H), 5.29 (s, 1 H), 4.75 (s, 1 H), 4.53 (s, 1 H), 4.51 (s, 2 H), 4.30 (d, J = 4.6 Hz, 1 H), 3.69 (s, 2 H), 3.46 (s, 3 H), 2.60 (s, 2 H), 2.27 (d, J = 10 Hz, 1 H), 2.26 – 2.19 (m, 2 H), 2.16 (d, J = 11 Hz, 1 H), 2.04 (d, J = 9.2 Hz, 1 H), 1.92 (dd, J = 11
Hz, J = 4.6 Hz, 1 H). $^{13}$C NMR: 209.8, 152.8, 138.3, 128.1, 127.2, 127.0, 106.3, 94.7, 81.2, 73.1, 68.2, 67.2, 57.7, 56.5, 55.8, 37.5, 36.5, 36.1, 20.9. HRMS (FAB) calcd for C$_{21}$H$_{25}$O$_4$ (MH$^+$) 341.1747, found 341.1756.

By product 47

$^1$H NMR: 7.38 – 7.18 (m, 5 H), 5.66 (d, J = 10 Hz, 1 H), 5.00 (d, J = 10 Hz, 1 H), 4.62 (d, J = 12 Hz, 1 H), 4.58 (d, J = 12 Hz, 1 H), 4.50 (s, 1 H), 4.47 (s, 1 H), 4.34 (d, J = 4.5 Hz, 1 H), 3.57 (d, J = 9.5 Hz, 1 H), 3.54 (d, J = 9.5 Hz, 1 H), 3.54 (s, 1 H), 2.85 – 2.76 (m, 1 H), 2.17 (dd, J = 6.8 Hz, J = 19 Hz, 1 H), 2.00 (d, J = 11 Hz, 1 H), 1.96 – 1.79 (m, 3 H). IR (neat): 2951, 1650, 1603, 1446, 1067.

TMS-enol ether 52 (R$_f$=0.43): $^1$H NMR: 7.37 – 7.25 (m, 5 H), 5.02 (s, 1 H), 4.90 (s, 1 H), 4.52 (d, J = 12 Hz, 1 H), 4.48 (d, J = 12 Hz, 1 H), 4.44 (d, J = 4 Hz, 1 H), 4.41 (s, 1 H), 4.37 (s, 1 H), 3.62 (d, J = 10 Hz, 1 H), 3.55 (d, J = 10 Hz, 1 H), 3.57 (s, 3 H), 3.40 (s, 3 H), 2.85 – 2.76 (m, 1 H), 2.17 (dd, J = 6.8 Hz, J = 19 Hz, 1 H), 2.00 (d, J = 11 Hz, 1 H), 1.96 – 1.79 (m, 3 H). IR (neat): 2956, 1650, 1196.

Synthesis of enol ester 51

To a stirred solution of 46 (141 mg, 0.432 mmol) in THF (15 mL) at -78 °C was added LHMDS (1 M in hexane, 0.86 mL, 2 equiv). The reaction mixture was stirred at -78 °C for 30 min and MeOCOCN (171 µL, 5 equiv) was added. The mixture was stirred at -78 °C for 1 h and quenched with water (5 mL). The mixture was acidified with 3 M aqueous CH$_3$COOH (0.5 mL) and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with water (30 mL), brine (30 mL), dried over MgSO$_4$ and concentrated in vacuo to afford enol ester 51 (74 mg, 48%) along with TMS-enol ether 52 (22 mg, 14%) as colorless oils after purification (PE:EtOAc=4:1). $^1$H NMR (51, R$_f$=0.28): 12.48 (s, 1 H), 7.37 – 7.25 (m, 5 H), 4.94 (s, 1 H), 4.83 (d, J = 4 Hz, 1 H), 4.53 (d, J = 12 Hz, 1 H), 4.48 (d, J = 12 Hz, 1 H), 4.41 (s, 1 H), 4.37 (s, 1 H), 3.76 (s, 3 H), 3.64 (d, J = 10 Hz, 1 H), 3.57 (d, J = 10 Hz, 1 H), 3.40 (s, 3 H), 2.85 – 2.76 (m, 1 H), 2.17 (dd, J = 6.8 Hz, J = 19 Hz, 1 H), 2.00 (d, J = 11 Hz, 1 H), 1.96 – 1.79 (m, 3 H). IR (neat): 2951, 1650, 1603, 1446, 1067.

Synthesis of enol ester 48

(See the synthesis of 51). Starting from 45 (142 mg, 0.417 mmol) gave a (5:1) mixture of 48 and 49 (131 mg, 79%) as a colorless oil after purification (PE:EtOAc=6:1) (R$_f$=0.23) along with TMS-enol ether 50 (28 mg, 16%). $^1$H NMR (48): 12.39 (s, 1 H), 7.37 – 7.28 (m, 5 H), 5.03 (s, 1 H), 4.69 (s, 1 H), 4.64 (d, J = 4.5 Hz, 1 H), 4.54 (s,
2 H), 4.46 (s, 1 H), 3.79 (s, 3 H), 3.77 (s, 2 H), 3.43 (s, 3 H), 2.46 – 2.35 (m, 2 H), 2.21 – 2.10 (m, 2 H), 2.09 – 1.86 (m, 2 H). 13C NMR: 175.0, 172.3, 157.6, 138.7, 128.2, 127.38, 127.33, 106.4, 93.99, 93.91, 80.4, 73.3, 68.5, 63.5, 56.8, 56.5, 56.2, 51.5, 38.5, 26.4, 17.4. IR (neat): 2950, 1651, 1604, 1224.

**Synthesis of vinyl triflate 53**

To a stirred solution of (5:1 mixture) of 48 and 49 (14 mg, 0.035 mmol) in CH2Cl2 (1 mL) at -78 °C was added DIPEA (31 µL, 5 equiv) and Tf2O (30 µL, 5 equiv). The reaction mixture was slowly warmed to rt and stirred overnight. Saturated aqueous NaHCO3 (2 mL) was added and the aqueous layer was extracted with ether (3×2 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over MgSO4 and concentrated in vacuo to afford 53 (16 mg, 86%) as a colorless oil after purification (PE:EtOAc=6:1, Rf =0.23). 1H NMR: 7.36 – 7.25 (m, 5 H), 4.97 (s, 1 H), 4.74 (s, 1 H), 4.65 (d, J = 4.5 Hz, 1 H), 4.60 (s, 1 H), 4.51 (s, 2 H), 3.82 (s, 3 H), 3.72 (s, 2 H), 3.41 (s, 3 H), 2.69 – 2.60 (m, 1 H), 2.42 (dd, J = 6 Hz, J = 19 Hz, 1 H), 2.28 – 2.22 (m, 1 H), 2.15 (d, J = 11 Hz, 1 H), 2.12 – 1.96 (m, 2 H).

**The coupling product 63**

To a stirred solution of 53 (32 mg, 0.06 mmol) in DMF (1 mL) at rt was added CrCl2 (37 mg, 5 equiv) and NiCl2 (cat) followed by cyclohexanecarboxaldehyde (7 µL). The reaction mixture was stirred at 50 °C overnight and cooled to rt. Saturated aqueous NH4Cl (2 mL) was added and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over MgSO4 and concentrated in vacuo to afford 63 (8 mg, 30%) as a colorless oil after purification. 1H NMR: 7.38 – 7.27 (m, 5 H), 7.18 (dd, J = 2 Hz, J = 4 Hz, 1 H), 4.98 (d, J = 3.6 Hz, 1 H), 4.85 (d, J = 3.6 Hz, 1 H), 4.75 (s, 1 H), 4.69 (s, 1 H), 4.54 (s, 2 H), 4.46 (s, 1 H), 3.76 (s, 2 H), 3.42 (s, 3 H), 2.37 – 2.31 (m, 2 H), 2.21 (d, J = 9 Hz, 1 H), 2.10 – 2.07 (m, 2 H), 2.01 (dd, J = 3.6 Hz, J = 9 Hz, 1 H), 1.85 – 1.69 (m, 5 H), 1.27 – 1.07 (m, 6 H). 13C NMR: 172.0, 166.4, 155.8, 138.6, 128.2, 127.4, 127.3, 123.2, 106.5, 95.0, 86.9, 77.9, 73.4, 68.4, 60.9, 57.5, 56.6, 39.9, 38.3, 30.0, 26.4, 25.9, 25.8, 24.0, 21.1, 18.3.

**Reduction product 61**

1H NMR: 7.38 – 7.27 (m, 5 H), 7.18 (dd, J = 2 Hz, J = 4 Hz, 1 H), 4.98 (d, J = 3.6 Hz, 1 H), 4.95 (s, 1 H), 4.56 (d, J = 9.6 Hz, 1 H), 4.52 (d, J = 9.6 Hz, 1 H), 4.41 (s, 1 H), 4.35 (s, 1 H), 3.76 (s, 3 H), 3.69 (d, J = 8.4 Hz, 1 H), 3.61 (d, J = 8.4 Hz, 1 H), 3.39 (s, 3 H), 2.65 – 2.61 (m, 1 H), 2.28 – 2.23 (m, 1 H), 2.02 (d, J = 9 Hz, 1 H), 1.91 (dd, J = 3.6 Hz, J = 9 Hz, 1 H), 1.81 – 1.12 (m, 2 H). 13C NMR: 166.5, 158.9, 146.1, 138.4, 128.3, 127.5, 127.2, 124.7, 105.0, 93.0, 80.8, 73.3, 66.3, 57.4, 57.0, 55.9, 55.3, 51.4, 37.8, 26.0, 16.9. IR (neat): 2947, 1711, 1259, 1061.
6.8 References

Summary

Studies towards the Total Synthesis of Solanoeclepin A

Potato cyst nematodes (PCN) are parasites feeding solely on roots of the potato plant and causing the disease known as potato sickness. This is a serious menace to agriculture in several parts of the world. The hatching of the encysted worms is controlled by the so-called hatching agents, excreted in minute quantity by the roots of the growing potato plant. Among various natural factors found, solanoeclepin A (1) is the most active hatching agent for PCN, showing hatching activity in concentration as low as 10^{-9} g/L. The compound could play a role in the development of an environmentally friendly way to combat PCN. The structure of solanoeclepin A was eventually elucidated in 1992 after an extensive research program involving several research groups in the Netherlands. The natural product indicates a close structural relationship with the previously reported hatching factor of the soybean cyst nematode glycinoelepin A (2), although the latter shows no hatching activity towards PCN.

Solanoeclepin A (C_{27}H_{30}O_{9}) contains all ring sizes ranging from three to seven and includes nine asymmetric carbon atoms. The most distinctive structural feature of this fascinating compound is the tricyclic core containing the bicyclo[2.1.1]cyclohexanone skeleton which unprecedented in natural products.

The unavailability of the natural product in useful amounts from natural sources and its unique structural characteristics render solanoeclepin A a challenging synthetic target. Our retrosynthetic analysis of solanoeclepin A (1) reveals two synthetic fragments, namely bicyclic aldehyde 2 and the more complex tetracyclic ester 3 (eq 1).
The synthesis of aldehyde 2 in enantiopure form and the proof of principle for the formation of the seven-membered ring have been published recently by our research group. This thesis is devoted to the development of a strategy for the synthesis of the right-hand substructure 3.

Chapter 1 presents general information about solanoeclepin A and the retrosynthetic analysis of the ultimate target natural product.

In chapter 2, the first generation approach towards the right-hand substructure 3 is described. Based on an intramolecular [2+2] photocycloaddition of dioxenone 4 (Scheme 1) the desired bicyclo[2.1.1]hexane skeleton of 5 was obtained in good yield. Exhaustive reduction of the cycloadduct 5 followed by selective protection gave 6. Alcohol 6 was subsequently converted into xanthate 7 which underwent elimination to afford olefin 8 in good yield. A six-step sequence eventually transformed 8 into cyclopropane 9 in a chemoselective but not stereoselective way. Moreover, this synthetic strategy was quite lengthy so that a more direct approach was deemed necessary.

![Scheme 1](image)

The second generation approach towards the right-hand fragment 3 of solanoeclepin A is presented in chapter 3. By using allene butenolide 13 as the photosubstrate (eq 2), the tricyclic core containing the bicyclo[2.1.1]hexane skeleton of 14 was efficiently constructed. This unprecedented photocycloaddition successfully assembled the three quaternary centers in a highly compact setting in a single step.

![Scheme 2](image)

Furthermore, several cyclic \(\alpha,\beta\)-unsaturated carbonyl compounds bearing an allene-containing substituent were prepared and irradiated in order to acquire knowledge on the regioselectivity of the intramolecular photocycloaddition of allenes.
In all cases, the outcome of the reaction was in agreement with the "rule of five". Depending on the position of the allene substituents, however, either the crossed or the straight adduct were formed. Allenes 15 and 17 gave predominantly the crossed adducts (eq 3), while the straight adducts were the main products in the case of allene 19 and 22 (Scheme 2). In the latter case, interesting routes to fused pyroles and furans were discovered.

Scheme 2

Chapter 4 describes the chemistry developed for the model cycloadduct 14 to introduce the required structural features of solanoeclepin A. Reductive opening of the lactone moiety of 14 followed by a three-step protection-deprotection sequence gave alcohol 25 in good yield (Scheme 3).

Scheme 3

Activation of the hydroxyl moiety of 25 via sulfonylation followed by hydride reduction produced the desired angular methyl group of 26. The cyclobutanone function was successfully put in
place through a three-step transformation. In the course of this sequence, the double bond was first
dihydroxylated to form diol 27 followed by hydrogenolysis of the benzyl ether and finally, oxidative
cleavage of the vicinal diol to afford 29. Compound 29 contains the most intricate tricyclic
substructure of solanoeclepin A containing the bicyclo[2.1.1]cyclohexanone moiety with the correct
substitution pattern of the natural product.

In chapter 5, the preparation and photocycloaddition of the highly substituted butenolide 33 is
presented (Scheme 4). Starting from the commercially available ylide 30, the required butenolide 33
was efficiently prepared through a seven-step sequence. Photocycloaddition of 33 took place smoothly
to provide the desired crossed adduct 34 in good yield as the sole product. Cycloadduct 34 contains
the required substituents for further functionalization towards the right-hand substructure 3 of
solanoeclepin A.

Scheme 4

Further functional group transformations on cycloadduct 34 are described in chapter 6. The
previously developed chemistry of the model 14 was successfully applied to 34 leading to the
bridgehead methyl group of 35 (eq 4). Attempts to achieve the dihydroxylation of the double bond of
35, however, met with failure, most likely due to steric and strain effects of the tricyclic core of 35.
Alternatively, epoxidation of the double bond took place smoothly to give the epoxide 36 in good
yield. However, efforts to convert the epoxide 36 into a vicinal diol were unsuccessful. These results
indicate that steric and strain effects indeed play an important role in the chemistry of the compact
skeleton of the carbotricyclic structures.
Investigations towards the installation of a vinyl triflate moiety in the cyclohexane ring are also presented in chapter 6. This critical transformation appears to be possible only if the lactone ring or the protected lactol remains intact.

Scheme 5

The desired regioselective carbomethoxylation of ketone 38 was achieved by treatment of 38 with LHMDS at -78 °C followed by Mander's reagent to give 39 (Scheme 5). The high regioselectivity probably results from the higher acidity of the C-2 hydrogens adjacent to the cyclobutane ring. Finally, the hydroxyl moiety was converted into its vinyl triflate in good yield using triflic anhydride and DIPEA. The required vinyl triflate 40 was efficiently prepared through a thirteen-step sequence starting from the commercially available ylide 30.

Vinyl triflate 40 was then coupled with the left-hand fragment (2) in the presence of CrCl₂/NiCl₂ (Scheme 6). However, only the reduced product 41 was formed, most likely due to steric hindrance of aldehyde (2) and vinyl triflate 40. In order to verify this speculation, compound 40 was allowed to couple with cyclohexanecarboxaldehyde (42) under the same conditions. This led to the formation of the desired coupling product 43 in moderate yield. Further investigation is therefore, required in order to bring about the coupling reaction between the left- and the right-hand substructures of solanoeclepin A.
Samenvatting
Onderzoek naar de Totaalsynthese van Solanoëclepine A

Aardappelcystenaaltjes (ACA) zijn parasieten die zich voeden aan de wortel van de aardappelplant. Zij veroorzaken hiermee een ziekte die bekend staat als aardappelmoeheid, een serieuze bedreiging voor de aardappelteelt in verschillende delen van de wereld. De jonge aaltjes worden uit hun cyste gelokt door een wekstof die in zeer kleine hoeveelheden door de groeiende wortel van de aardappelplant wordt uitgescheiden. De meest actieve wekstof voor ACA is solanoëclepine A (1). Deze stof vertoont nog wekstofactiviteit bij een concentratie van $10^{-9}$ g/L. De stof zou een rol kunnen spelen in de ontwikkeling van een milieuvriendelijke bestrijding van ACA. Een uitgebreid onderzoek, waaraan verschillende Nederlandse onderzoeksgroepen hebben meegewerkt, heeft geleid tot de structuuropheldering van solanoëclepine A in 1992. De structuur van de natuurstof (1) vertoont gelijkenis met de eerder beschreven wekstof voor het sojacystenaaltje, glycinoëclepine A (2). Deze laatste stof vertoont echter geen wekstofactiviteit voor ACA.

Solanoëclepine A ($C_{27}H_{30}O_9$) bevat alle ringgroottes van drie tot zeven en heeft negen asymmetrische koolstofatomen. Het meest opvallende structuurelement is het sterk gesubstitueerde bicyclo[2.1.1]cyclohexanonskelet, dat nog niet eerder in een natuurstof is aangetroffen. De schaarste van de natuurstof en haar unieke structuur maken de verbinding tot een uitdagend doel voor totaalsynthese. Onze retrosynthetische analyse is gebaseerd op het splitsen van solanoëclepine A in twee fragmenten, namelijk het bicyclische aldehyde 2 en de complexere tetracyclische ester 3 (vgl. 1).

[^1]: PG = protective group
De synthese van aldehyde 2 in enantiomeerzuivere vorm en de bereiding van een modelsysteem voor de zevenring zijn recentelijk gepubliceerd door onze onderzoeksgroep. Dit proefschrift is gewijd aan de ontwikkeling van een strategie voor de synthese van verbinding 3.

In hoofdstuk 1 wordt algemene informatie over solanoëclepine A gegeven, alsmede een retrosynthetische analyse van de natuurstof.


Schema 1

In hoofdstuk 3 wordt de tweede synthetische benadering van het rechter fragment 3 van solanoëclepine A beschreven. Door butenolide 13 met een alleensubstituent als fotosubstraat te gebruiken (vgl. 2), kon het bicyclo[2.1.1]hexaan 14 in goede opbrengst gesynthetiseerd worden. Met behulp van deze nog niet eerder beschreven fotocycloadditie werden de drie quaternaire centra in het centrale deel van de natuurstof in één stap geïntroduceerd.

Dit succes leidde ons er toe verschillende cyclische α,β-onverzadigde carbonylverbindingen met een alleengroep in de zijketen te bereiden en vervolgens te bestralen om zo meer kennis te vergaren over de regioselectiviteit van de intramoleculaire fotocycloadditie van allenen.
In alle gevallen verliep de reactie volgens de zogenaamde "rule of five". Afhankelijk van de positie van de alleensubstituent werd het rechte (straight) of het gekruiste (crossed) adduct gevormd. Allenen 15 en 17 gaven voornamelijk het "crossed" adduct (vgl. 3), in tegenstelling tot allenen 19 and 22 (Schema 2) waar het "straight" adduct het hoofdproduct vormde. In het laatste geval werd een interessante route naar bicyclische pyrrolen en furanen ontdekt.


Activering van de hydroxylgroep van 25 door middel van tosylering, gevolgd door een hydridehydrogenatie, leidde tot 26 met de methylgroep in de juiste oriëntatie. De cyclobutanonfunctie kon
met succes worden geïntroduceerd in drie stappen. In de eerste stap werd de dubbele binding gedihydroxyleerd tot het diol 27 waarna hydrogenering van de benzylether en oxidatieve splitsing van het vicinale diol cyclobutanon 29 opleverde. Deze verbinding bevat het compacte gespannen bicyclo[2.1.1]hexanonskelet met het juiste substitutiepatroon van de natuurstof.

In hoofdstuk 5 wordt de synthese en fotocycloadditie van het gesubstitueerde butenolide 33 beschreven (Schema 4). Uitgaande van het commercieel verkrijgbare ylide 30 werd butenolide 33 gesynthetiseerd in zeven stappen. Fotocycloadditie van 33 gaf het gewenste gekruiste adduct 34 in een goede opbrengst. Cycloadduct 34 bevat de benodigde substituenten voor verdere functionalisering naar het rechter fragment 3 van solanovéclopine A.

**Scheme 4**

De omzetting van de functionele groepen van cycloadduct 34 zijn beschreven in hoofdstuk 6. De eerder ontwikkelde chemie voor model 14 kon met succes worden toegepast op 34 voor de introductie van methylgroep op het bruggenhoofd van 35 (vgl. 4). Pogingen om de dubbele binding van 35 te dihydroxyleren waren helaas niet succesvol. De dubbele binding kon echter wel eenvoudig geëpoxideerd worden en epoxide 36 kon in goede opbrengst worden geïsoleerd. Omzetting van het epoxide naar het diol bleek helaas niet mogelijk. Deze resultaten geven aan dat sterische factoren en ringspanningseffecten een belangrijke rol spelen in de chemie van deze compacte tricyclische structuur.

Tevens staat in hoofdstuk 6 het onderzoek beschreven naar het introduceren van het vinyltriflaat in de cyclohexaanring. Deze belangrijke stap bleek alleen mogelijk wanneer de lactonring of het afgeleide methylacetaal in de structuur aanwezig zijn.
Regioselectieve carbomethoxylering van keton 38 kon uitstekend worden gerealiseerd door 38 bij -78 °C te behandelen met LHMDS gevolgd door methylcyanaformiaat. (Schema 5). De hoge regioselectiviteit komt vermoedelijk doordat de C-2 protonen door stereoelectronische effecten van de kleine cyclobutaanring zuurder zijn dan de C-4 protonen. Uiteindelijk kon de hydroxylgroep eenvoudig worden omgezet in een vinyltriflaat met behulp van het anhydride van trifluormethaansulfonzuur en DIPEA. Zo kon uiteindelijk vinyltriflaat 40 in dertien stappen worden gesynthetiseerd uit het commercieel verkrijgbare ylide 30.

Vinyltriflaat 40 werd vervolgens in reactie gebracht met het linker fragment 2 onder invloed van CrCl$_2$/NiCl$_2$ (Schema 6). Helaas werd alleen het gereduceerd product 41 gevormd, waarschijnlijk door ongunstige sterische interacties tussen het aldehyde 2 en het vinyltriflaat 40. Om dit vermoeden te bevestigen werd de koppeling ook uitgevoerd met 40 en cyclohexancarboxaldehyde (42) onder dezelfde reactiecondities. Dit gaf het verwachte koppelingsproduct 43 in lage opbrengst. Verder onderzoek is daarom nodig om de juiste reactiecondities te vinden voor de koppeling tussen de beide fragmenten om uiteindelijk te komen tot een synthesesroute naar solanoëclepine A.