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Intramolecular [2+2] Photocycloadditions as an Approach to the Right-Hand Side of Solanoecelepin A

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Application of the natural hatching agent as a novel method
to control potato cyst nematodes?

Richard Blaauw

Intramolecular [2+2] Photocycloadditions as an Approach Towards the Right-Hand Side of Solanoeclepin A

Application of the natural hatching agent as a novel method
to control potato cyst nematodes?

ACADEMISCH PROEFSCHRIJF

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
Prof. Dr. J. J. M. Franx

een overstaan van een door het college voor promotie ingestelde
commissie in het openbaar te verdedigen in de Aula der Universiteit
op vrijdag 29 juni 2011 te 12.00 uur

Printnaam

Richard Hendrik Blaauw

geboren op 1 oktober 1984

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voor het bijwonen van de
openbare verdediging van
het proefschrift van

Richard Blaauw

op vrijdag 29 juni 2001
om 12:00 uur in de
Oude Lutherse Kerk
Singel 411 (hoek Spui)
te Amsterdam.

Tevens wil ik u uitnodigen voor
de receptie ter plaatse na afloop
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door

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geboren te Eindhoven

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Universiteit van Amsterdam

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Roger J. Lincoln

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LIST OF ABBREVIATIONS

Ac	acetyl	TBDMS	<i>tert</i> -butyldimethylsilyl
Bn	benzyl	TBDPS	<i>tert</i> -butyldiphenylsilyl
br	broad (spectral)	TES	triethylsilyl
^t Bu	<i>tert</i> -butyl	Tf	trifluoromethanesulfonyl
CSA	10-camphorsulfonic acid	THF	tetrahydrofuran
DIBAL-H	diisobutylaluminum hydride	TIPS	triisopropylsilyl
DIPEA	<i>N,N</i> -diisopropylethylamine	TLC	thin layer chromatography
DMAP	4-(dimethylamino)pyridine	TMS	trimethylsilyl
DME	1,2-dimethoxyethane	TPAP	tetrapropylammonium perruthenate
DMF	<i>N,N</i> -dimethylformamide	Tr	trityl
DMSO	dimethylsulfoxide	Ts	<i>para</i> -toluenesulfonyl
EE	1-ethoxyeth-1-yl	UV	ultraviolet
EI	electron impact (in mass spectrometry)		
Et	ethyl		
FAB	fast atom bombardment (in mass spectrometry)		
HMPA	hexamethylphosphoric triamide		
HRMS	high resolution mass spectrum		
IR	infrared		
<i>J</i>	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)		
NIS	<i>N</i> -iodosuccinimide		
NMO	4-methylmorpholine <i>N</i> -oxide		
NMR	nuclear magnetic resonance		
NOE	nuclear Overhauser effect		
PE	petroleum ether (60–80)		
PG	protective group		
Ph	phenyl		
PPTS	pyridinium <i>para</i> -toluenesulfonate		
^t Pr	isopropyl		
<i>p</i> TSA	<i>para</i> -toluenesulfonic acid monohydrate		
<i>R</i> _f	retention factor (in chromatography)		
rt	room temperature		
TBAF	tetrabutylammonium fluoride		

INTRODUCTION

1.1 Solanoecclepin A

Potato cyst nematodes (PCN, figure 1.1), also known as potato root eelworms, are parasitic worms which feed on potato roots causing yield losses or even total crop failure. Two species of the PCN exist: the golden cyst nematode (*Globodera rostochiensis*) and the pale cyst nematode (*Globodera pallida*). Both species were introduced into Europe from Peru (South America) over 100 years ago. Today they are the most important pest of the European potato crop causing annual yield losses of 10% (worth about 470 million € per annum).

Figure 1.1 Potato cyst nematode

Figure 1.2 Cysts on a potato root

While feeding on the potato roots, the bodies of the female nematodes swell to form the cysts (figure 1.2). After having been fertilized by the male eels, the cysts, each containing approximately two hundred next-generation nematodes, end up in the soil. The dormant nematodes inside the cyst can survive in this state for up to thirty years and can withstand drought and frost. The nematodes are triggered to leave the cysts when they come in contact with so-called hatching agents, which are excreted from the roots of young potato plants. The importance of these signal substances was already recognized in the 1920's.¹ Because of their high specificity and biodegradability, the use of hatching factors as a method to control PCN is highly attractive from an environmental point of view. Application of the signal substance to the soil, will trigger the hatching of the nematodes. If this is done in the absence of potato plants, the juvenile PCN will starve within a period of eight weeks. However, the hatching factors are excreted from the plants in minute quantities, which has hampered the isolation and identification of these interesting compounds.

In 1986, an extensive research program, funded by the Dutch government, was initiated in order to isolate and characterize the most active hatching agent for the potato cyst nematodes and to probe its use as a novel method to control them. For this purpose, several expert research teams in the Netherlands worked in close cooperation, *viz.* LUXAN (Elst) as a company specialized in crop protection, 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. From the extracts of approximately one thousand potato plants, 245 μg of the most active ingredient were isolated, which showed hatching activity in concentrations as low as 10^{-9} g/L.² After the material had unexpectedly crystallized during extensive NMR experiments, X-ray crystal structure determination by the group of Schenk (1992, University of Amsterdam) revealed the spectacular architecture of the hatching agent (figure 1.3).^{3,4}

Figure 1.3 Crystal structure of solanoecelepin A (hydrogen atoms omitted for clarity)

This very potent compound was named solanoecelepin A by analogy to glycinocelepin A, the hatching agent for the soybean cyst nematode (see section 1.2). Its highly oxygenated heptacyclic structure ($\text{C}_{27}\text{H}_{30}\text{O}_9$) contains all ring sizes ranging from three to seven and includes nine asymmetric carbon atoms. Actually, solanoecelepin A can be considered as a tetranortriterpene, with the systematic name: *trans*-2-(2,13-dihydroxy-9-methoxy-7,7,16-trimethyl-5,10,20-trioxo-19-oxahexacyclo[9.7.0.1^{3,6}.0^{3,8}.1^{12,15}.0^{12,16}]eicosa-1(11),8-dien-15-yl)-cyclopropanecarboxylic acid.² The most striking structural feature is the densely substituted bicyclo[2.1.1]hexanone unit, a highly strained ring system, which is an unprecedented structural feature in natural products. Other salient features include the cyclopropane-carboxylic acid moiety and the α -diketone moiety in the seven-membered ring, of which one carbonyl group is masked as the methyl enol ether. The limited information available states that the hatching agent is unstable at pH below 2 and above 7 and at temperatures above approximately 35 °C. About the biogenetic origin of solanoecelepin A no information is available. However, it is plausible to assume that the skeleton is derived from cycloartenol (3), a widespread plant sterol, which has also been isolated from potato plants (eq 1.1).⁵ This biosynthetic pathway has been proposed for glycinocelepin A.⁶ Cycloartenol, in turn, is derived from (3*S*)-2,3-epoxysqualene (2), through enzymatic cyclization by *cycloartenol cyclase*.⁷

The extreme scarcity of the natural material, its fascinating structure and its potential role in the search for an environmentally benign method to combat the nematodes, render solanoecelepin a challenging target for total synthesis. Additionally, the synthetic work will provide information on the structure–activity relationship of the hatching agent, which so far is unavailable. This could result in structurally much simpler analogs of solanoecelepin A, with sufficient activity to be used as hatching agents for PCN.

1.2 Glycinocelepin A

The hatching agent for the soybean cyst nematode (*Heterodera glycines*) was isolated by Masamune *et al.* from the dried root of the kidney bean.⁸ This compound was named glycinocelepin A, and the structure was determined as **4**.⁹

This structure shows significant similarities to that of solanoecelepin A. However, although glycinocelepin A shows hatching activity for the soybean cyst nematode at concentrations of 10^{-9} g/L, it provides no stimulus for the potato cyst nematode.¹⁰ This indicates the specificity of the nematodes for a particular host plant. Alongside glycinocelepin A, two closely related structures were isolated from the kidney bean roots, *i.e.* glycinocelepin B (**5**) and C (**6**).¹¹

Even though both compounds are structurally similar to glycinocelepin A, they display no significant hatching activity even at concentrations of 10^{-4} g/L. Removal of the acetyl group from the C-12 hydroxyl group of **5**, increases the activity considerably to 10^{-5} g/L, indicating the importance of this alcohol function. However, compared to glycinocelepin A the activity is still greatly inferior. The interesting characteristics of **4** have resulted in three total syntheses of this compound, by the groups of A. Murai, K. Mori and E. J. Corey.¹² Murai reported the first synthesis, which comprised the convergent assembly of **4** by using building blocks **8** and **10**, derived from dione **7** and carvone (**9**), respectively (scheme 1.1).^{12a}

Scheme 1.1

In this way, glycinoeclepin A was obtained in a total of 28 steps, with a longest linear sequence of 21 steps (overall yield, 0.004% calculated from 9). In 1994, Corey reported an extraordinary semi-synthesis of 12-desoxyglycinoeclepin A (**14**), by an emulation of the assumed biosynthetic route to glycinoeclepin A.⁶ As it was proposed that cycloartenol constitutes one of the key intermediates in the biogenetic pathway, the cycloartenol derivative abietospiran (**11**) was used as a starting material for this unique approach (scheme 1.2).

Scheme 1.2

One of the most noteworthy transformations in this synthesis is the Lewis acid mediated ring expansion of cycloartenol derivative **12** to afford the seven-membered ring of **13**. This reaction provides the basic skeleton of solanoeclepin A and therefore a similar process could well be one of the steps in the biosynthesis of **1**.

1.3 Retrosynthetic Analysis of Solanoeclepin A

To render the synthesis of solanoeclepin A convergent, the complex structure should be divided into two fragments of comparable size. The highly oxygenated seven-membered ring was envisaged to be a good point to connect both fragments. Therefore, the first key disconnection is the bond between the α -diketone moiety (**15** $\rightarrow$ **16**, scheme 1.3).

Scheme 1.3

The seven-membered ring can be formed by way of a ring closing metathesis reaction with divinyl compound **16**. Dihydroxylation of the formed alkene, followed by further oxidation and methylation then leads to **15**. Compound **16** is expected to arise from a chromium mediated coupling¹³ between aldehyde **17** and β -keto ester derived vinyl triflate **18**. The synthesis of aldehyde **17** in enantiomerically pure form and the proof of principle for the formation of the seven-membered ring have been published recently.¹⁴

1.4 Purpose and Outline of the Investigation

This thesis deals with the development of a synthetic pathway to the right-hand side of solanoeclepin A (*i.e.* compound **18**). This delicate part of the natural product contains the highly substituted bicyclo[2.1.1]hexanone moiety as well as the cyclopropanecarboxylic acid function. An efficient route to the right-hand fragment **18** should eventually allow the total synthesis of solanoeclepin A.

In chapter 2 an intramolecular [2+2] photocycloaddition approach towards the tricyclic core of **18** is described. 6-Methyldioxenones tethered to variously substituted alkenes are prepared to investigate the viability of the photochemical approach. Depending on the substitution pattern of the pendent alkenes, the cycloaddition reactions display remarkable unprecedented regiochemistry.

Further chemistry with the 6-methyldioxenone cycloadducts is described in chapter 3. Retro-aldol reactions on the photoproducts, provide a stereoselective pathway to indanes, trifunctionalized spiro[3.5]nonanes or spiro[3.4]octanes as well as to novel substituted cyclobutanes. In addition, chapter 3 deals with the functionalization of the cycloadducts without four-membered ring fragmentation.

In chapter 4 the possible use of a vicinal diol to obtain the required cyclobutanone is explored. Furthermore, chapter 4 describes the attempted use of alternative chromophores, other than the dioxenone, for the [2+2] cycloaddition.

The preparation and cyclization of 6-unsubstituted dioxenones tethered to variously substituted alkenes is described in chapter 5. The cycloadducts obtained from the 6-unsubstituted dioxenones, facilitate the eventual formation of the required cyclobutanone.

Chapter 6 deals with the synthesis of a small right-hand substructure of solanoelepin A, containing both the bicyclo[2.1.1]hexanone unit and the cyclopropane-carboxylic acid moiety of the natural product.

In the final chapter of this thesis a retrospection of the investigations is presented, as well as some future prospects. Parts of this thesis have been published¹⁵ or will be published in the near future.

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Therefore, we sought a method that would allow rapid access to this particular unit of our target molecule. It soon became apparent that the most obvious way to construct cyclobutanes, the thermal intramolecular ketene-alkene [2+2] cycloaddition,¹⁶ in this case could neither be applied, as a cyclopropanation. Sakita observed the instability of the bicyclic [1,1]thiuronone structure under the conditions needed for its formation.² Reaction of ketone **4** did not afford the desired bicyclic, but instead a complex mixture of dimeric products was obtained (eq 2.2). Interestingly, in some of the dimers the oxygen and methylene groups had switched positions in the chain.

The only plausible mechanism is cycloaddition of the ketone **4** to give **5** followed by a retro-reaction to give the isomeric ketone **5** which then reacts with another ketone at acid chloride molecule to give a dimer. The result indicates that formation of bicyclic [1,1]thiuronone is mechanistically feasible, but thermodynamically unfavored. We verified this result with the attempted cycloaddition of ketone precursor **7** (eq 2.3).

CHAPTER 2

[2+2] CYCLOADDITIONS WITH 6-METHYLDIOXENONES

2.1 Introduction

The most delicate part of the right-hand fragment (**3**) of solanoecelepin A (**1**) resides in its highly strained tricyclic core, containing the bicyclo[2.1.1]hexanone (eq 2.1). As far as we know, this is an unprecedented structural feature in natural products.

Therefore, we sought a method that would allow rapid access to this particular unit of our target structure. It soon became apparent that the most obvious way to construct cyclobutanones, the thermal intramolecular ketene-alkene [2+2] cycloaddition,¹ in this case would not be applicable. In a seminal publication, Snider observed the instability of the bicyclo[2.1.1]hexanone structure under the conditions needed for its formation.² Reaction of ketene **4** did not afford the desired bicycle, but instead a complex mixture of dimeric products was obtained (eq 2.2). Interestingly, in some of the dimers the oxygen and methylene groups had switched positions in the chain.

The only plausible mechanism is cycloaddition of the ketene **4** to give **5** followed by cycloreversion to give the isomeric ketene **6** which then reacts with another ketene or acid chloride molecule to give a dimer. The result indicates that formation of bicyclo[2.1.1]hexanones is mechanistically feasible, but thermodynamically unfavored. We verified this result with the attempted cycloaddition of ketene precursor **7** (eq 2.3).

Indeed, a complex mixture of products was obtained, but no desired bicyclo[2.1.1]hexanone **8** could be detected. Therefore, we turned our attention to a photochemical [2+2] cycloaddition approach, to construct the tricyclic core of solanoeclepin A. The retrosynthetic scheme is depicted in eq 2.4.

A formyl acetate derived precursor such as **11** should provide photoadduct **10** with the appropriate handles for elaboration towards **9**. However, it is known that acyclic formyl acetate derived enol ethers are incapable of photoaddition to olefins.³ Therefore, the ester moiety and the enol should be connected through an acetal carbon. In other words, substituents R² and R³ should constitute a ring. The chromophore then obtained is known as a dioxenone.⁴ Indeed, the dioxenone structure has been frequently shown to be a versatile and efficient building block in synthetic photochemistry, especially allowing elegant cyclobutane ring formation via [2+2] cycloaddition.⁵ Moreover, in its intramolecular version, a high degree of stereo- and regiochemical control is usually attainable due to geometric constraints.⁶ For instance, the photocyclization of dioxenone **12** bearing a 3-butenyl side chain at C-5 gives crossed adduct **13** (scheme 2.1), as has been reported by Kaneko and Sato.⁷

Scheme 2.1

The corresponding straight cycloadduct **14** was not observed. This outcome follows the so-called empirical “rule of five”,⁸ which explains the regiochemistry by the supposedly preferential 1,5-closure of intermediate biradical **15**, during the first step of the cyclization process. However, when we started our investigations to the best of our knowledge this was the only example of an intramolecular cycloaddition between a dioxenone and an alkene

connected by a two carbon tether. Therefore we set out to explore the synthetic potential of the [2+2] photocycloaddition for the synthesis of our target fragment.⁹ A remark about the superfluous dioxenone C-6 methyl group should be made here. We were aware that removal of this extra carbon at a later stage of the total synthesis might not be a trivial chore. However, the presence of this methyl group greatly facilitates the synthesis of the required dioxenones. Therefore, we decided at this stage of the research to condone this methyl group and later work towards more appropriately substituted dioxenones.

2.2 Preparation and Cyclization of Monosubstituted 3-Alkenyl Dioxenones

Our first experiments had two objectives, *viz.* (1) to verify the robustness of the photocyclization process of Kaneko and (2) to establish that further transformations of the cycloadducts were possible without destruction of the fragile bicyclo[2.1.1]hexane moiety. Therefore, cyclization precursor **20** was synthesized from *tert*-butyl acetoacetate (**18**) *via* alkylation with 1-bromo-3-butene¹⁰ (**19**) and subsequent dioxenone formation according to a literature procedure¹¹ (eq 2.5).

Cyclization precursor **20** was subjected to irradiation at 300 nm using acetone as a triplet sensitizer. After 4 h, complete conversion of the starting material was observed and the expected crossed cycloadduct **21** was formed (eq 2.6).

This cycloadduct appeared to be unstable, decomposing slowly under the reaction conditions and during the subsequent work-up. This instability was attributed to the fact that dioxanones, when fused to a cyclobutane, can readily undergo a retro-aldol reaction.^{5a} Therefore, we sought a reducing system that would convert the cycloadduct **21** into diol **22**. Reductions with either DIBAL-H or LiAlH₄ at temperatures ranging from -78 to 0 °C gave poor yields and complex product mixtures. We reasoned that a more rapid and exhaustive reduction was necessary to circumvent these problems, which were probably resulting from a competitive retro-aldol process of the intermediate in the reduction process. Gratifyingly, reaction with excess LiAlH₄ at room temperature was successful and gave diol **22** as a crystalline compound in 47% overall yield from **20**. Importantly, the X-ray crystal structure

determination of **22** provided unequivocal proof of the bicyclo[2.1.1]hexane structure (figure 2.1).

Figure 2.1 Crystal structure of **22**

Encouraged by these results we turned our attention to more highly functionalized cyclization precursors, necessary for eventual application in the total synthesis of solanoecepin A. Initially, it was investigated whether similar chemistry could be used with a C-2 oxygen substituent in the 3-alkenyl sidechain. Therefore, allyl dioxenone **24** was synthesized in an analogous way as shown before (eq 2.7).¹²

Oxidative cleavage of olefin **24** by $\text{OsO}_4/\text{NaIO}_4$ allowed formation of aldehyde **25** (eq 2.8), which proved to be a very versatile building block in our subsequent studies (*vide infra*).

Alkylation of **25** with vinylmagnesium bromide gave allylic alcohol **26**, thus allowing the installation of the required secondary alcohol (eq 2.9). Alongside the desired product, a substantial amount of unreacted aldehyde was recovered. This is probably due to partial enolization of **25** under the reaction conditions, rendering it unreactive towards the Grignard reagent. Alcohol **26** was subsequently protected (**27**) with the methoxymethyl group (MOM).

The photocycloaddition of **27** afforded the unstable crossed adduct **28** as a 1:1 mixture of diastereomers (eq 2.10). Immediate reduction as described above led to diol **29** as a 1:1 mixture of isomers in 52% overall yield from **27**.

Now that it was firmly established that the C-2 oxygen substituent in the alkenyl sidechain did not interfere with the synthesis of the cyclization precursors, nor with the photocycloaddition/reduction sequence, the stage was set to investigate more highly substituted pendent alkenes.

2.3 Preparation and Cyclization of Trisubstituted Cycloalkenyl Dioxenones

For the construction of the tricyclic core of solanoeclepin A, a cyclohexene moiety should be tethered to the dioxenone. Since this type of dioxenone cycloaddition with substituted alkenes had no precedent, the five-membered ring analog was prepared as well. In this way the influence of the ring size on the cycloaddition as well as on the stability of the cycloadducts was investigated. The synthesis of these cyclization precursors started with the chromium(II)/nickel(II) mediated coupling¹³ of cyclopentenyl¹⁴ and cyclohexenyl¹⁵ triflate to aldehyde **25** (scheme 2.2).

Scheme 2.2

In its intramolecular form, the [2+2] cycloaddition is generally known to produce the new stereogenic centers of the four-membered ring with a very high degree of stereoselectivity.¹⁶ The stereochemistry of ring fusion between the cyclobutane and other

rings in the photoadducts is nearly always *cis*. Furthermore, substituents in the tether can have a pronounced influence on the overall diastereoselectivity of the process.¹⁷ To investigate the degree of diastereoselection induced by the size of the substituent in our two carbon tether, two protective groups were chosen, differing in size. Allylic alcohols **30** and **31** were protected as MOM ethers, to afford **32** and **33**, respectively (scheme 2.2). In addition, **30** was equipped with the bulky TBDMS group, providing precursor **34**.

To prevent the formation of epimers at the carbon atom bearing the protected alcohol, and in that way aid the characterization of the cycloadducts, the allylic alcohols **30** and **31** were oxidized to the corresponding ketones **35** and **36**, respectively, and subsequently protected according to Noyori's protocol¹⁸ to give dioxolanes **37** and **38** (eq 2.11).

When the precursors were subjected to the irradiation conditions very smooth cyclizations took place. However, we were very surprised to find that all these cycloadditions showed a remarkable complete preference for the undesired straight mode of closure. The results are collected in table 2.1.

Table 2.1

entry	precursor	cycloadduct
1	 37 n=1 38 n=2	 39 n=1, 100% ^a 40 n=2, 95%
2		
3	 32 n=1 33 n=2	 41 n=1, 97% (57:43) 42 n=2, 83% (50:50)
4		
5	 34	 43 97% (75:25)

Notes: (a) yield of unpurified material

The cyclic acetal precursors **37** and **38** (entries 1 and 2) afforded straight cycloadducts **39** and **40** as the exclusive regioisomers, in excellent yields and, as expected, as single diastereomers. This proved that the four stereocenters generated in the [2+2] cycloaddition, are indeed being formed in a completely controlled fashion. A readily noticed and most remarkable property of these bicyclo[2.2.0]hexanes was their greatly enhanced stability compared to crossed adduct **28**, even towards silica gel column chromatography, allowing the isolation and full characterization of these strained molecules. The cyclopentane and cyclohexane adducts appeared to be equally stable, indicating that the size of this ring is of no influence on the stability of the products. Figure 2.2 shows the ^1H -NMR spectrum of **40**.

Figure 2.2 ^1H NMR spectrum (5.0-0.5 ppm) of **40**

MOM protected precursor **32** (entry 3) afforded straight cycloadduct **41** in an excellent yield, as a 57:43 mixture of diastereomers. Analog **33** (entry 4) afforded **42** as a 50:50 mixture of diastereomers. Similarly, TBDMS ether **34** (entry 5) led to adduct **43**, but in this case a 75:25 mixture of diastereomers was obtained. The major isomer was identified as having the protected alcohol *cis* with respect to the cyclopentane ring, whereas the minor isomer bears a *trans* relationship between the two. This small but significant effect on the diastereoselectivity of the cycloaddition can be explained by looking at a model of the transition state (eq 2.12).

In order to arrive at the appropriate geometry for the straight mode of closure, the cyclization precursor **34** has to adopt a boat-like conformation. The orientational preference of the hydroxyl substituent in the transition structure **44** determines the diastereoselectivity. The major diastereomer **43** results from the conformer where the bulky TBDMS ether is in a favorable pseudo-equatorial situation. Obviously, for the less bulky MOM ether this effect is negligible leading to a nearly 50:50 distribution of diastereomers.

2.4 Preparation and Cyclization of Tetrasubstituted Alkenyl Dioxenones

We hypothesized about the origin of the remarkable and unprecedented selectivity for the straight mode of closure, observed with the trisubstituted cycloalkenyl precursors. Our first reasoning was that the first bond formation simply took place at the least hindered side of the pendent alkene, resulting in 1,6-closure. Furthermore, the charge distribution of an excited enone is the opposite of its ground state configuration, and thus the enone β -carbon bears a partial negative charge.¹⁹ If this is also true for dioxenones, this means that the first bond forms at the least electron-rich side of the ground-state alkene, in our systems again resulting in 1,6-closure.²⁰ In order to evaluate the importance of these two factors on the regioselectivity, a new precursor was designed bearing an additional electron-withdrawing ester group on the tethered cycloalkene. The synthesis of such a precursor was easily achieved by coupling of β -keto ester derived vinyl triflate **45**²¹ with aldehyde **25** (scheme 2.3).²² This afforded hydroxy ester **46**, which was subsequently protected with a MOM group (**47**).

Scheme 2.3

However, subjection of precursor **47** to the irradiation conditions again resulted in the exclusive formation of the straight cycloadduct (**48**), as a 60:40 mixture of diastereomers (eq 2.13).

Figure 2.3 ^1H NMR spectrum (5.0-1.0 ppm) of the minor isomer of **48**

The minor epimer of cycloadduct **48** was crystalline (mp 62–64 °C) and appeared suitable for a crystal structure determination (figure 2.4). Thus, from this result we had to conclude that the preference for 1,6-closure was not caused by differences in steric hindrance, nor by the polarization of the tethered alkene.

Figure 2.4 Crystal structure of **48**
 (minor isomer, hydrogen atoms omitted for clarity)

Our next reasoning was that the tether, although only two carbons long, was perhaps too flexible. Because it is known that intramolecular [2+2] cycloadditions are sensitive to geometrical constraints, we hoped that a more rigid precursor could direct the photochemistry towards the desired mode of closure. The appropriate rigidity was found in lactone **50**, which was obtained when aldehyde **25** was coupled with β -keto ester derived vinyl triflate **49**²³ (eq 2.14). While the five-membered ring analog **46** did not lactonize (scheme 2.3), nor could be forced to do so by heating, with the six-membered ring the intermediate allylic alcohol spontaneously lactonized under the coupling conditions.

This precursor again was subjected to the regular cyclization conditions. We were very pleased to find that in this case crossed product **51** was formed with complete regio- and diastereoselectivity, in a very clean cycloaddition (eq 2.15).

As before, this bicyclo[2.1.1]hexane was found to be unstable to silica gel column chromatography. However, crystallization from CH_2Cl_2 /pentane afforded crystals (mp 177–178 °C) suitable for X-ray diffraction and the crystal structure obtained is shown in figure 2.5.

Figure 2.5 Crystal structure of **51**
(hydrogen atoms omitted for clarity)

The complexity of this very compact highly functionalized pentacyclic structure is noteworthy. The four-membered ring of the bicyclo[2.1.1]hexane is exhaustively substituted and consists solely of quaternary carbon atoms.

Figure 2.6 ^1H NMR spectrum (5.0-0.5 ppm) of **51**

2.5 Preparation and Cyclization of Disubstituted Alkenyl Dioxenones

So far, we observed the completely regioselective formation of either crossed or straight cycloadducts, depending on the type of precursor used. Intrigued by the capriciousness of the cycloaddition's regioselectivity, we decided to investigate disubstituted alkenes tethered to the dioxenone. These precursors do not contain the pendent alkene in a ring, but they do have an additional substituent on the double bond. Therefore, they were anticipated to be in-between the unsubstituted alkene **27**, which led to crossed cycloaddition, and cycloalkenyl precursors **32** and **33**, which both led to straight cycloadducts. The synthesis of the precursors was rather straightforward and is depicted in scheme 2.4.

Scheme 2.4

and **27** show ‘normal’ cyclization behavior (“rule of five”). The mechanism of the photocycloaddition reaction of alkenes with cyclic enones has been the subject of a number of investigations.²⁵ The most recent experimental data on inter-²⁶ and intramolecular processes²⁷ suggest that the regiochemistry of the cyclization depends on the partitioning of the 1,4-biradical intermediate in the triplet excited state between cyclobutane ring formation and bond cleavage to give the ground state starting material as was first suggested several years ago by Bauslaugh.²⁸ About dioxenones much less is known. In the intramolecular process the initial bond formation should take place at the C(β) of the formed 1,4-biradical dioxanyl moiety as has been shown by Winkler *et al.*²⁹

Bearing this in mind, modeling studies by molecular mechanics (MM2 force field)³⁰ indicate that in the case of cyclic alkenes **32–34**, **37**, and **38** (see table 2.1) and even with ester **47** (see eq 2.14) initial five-membered ring formation cannot be readily followed by a second CC-coupling due to conformational constraints (the two orbitals containing the radicals are too much parallel). Therefore, the triplet 1,4-biradical intermediate **58** (scheme 2.6, the biradical derived from **47** is taken as an example) would collapse to ground state starting material. However, if biradical structure **59** is formed upon 1,6-closure, both radicals are properly oriented to allow the second CC-bond formation to occur.

Scheme 2.6

On the other hand, in the more rigid lactone intermediate **60** (scheme 2.7) the two radicals are positioned in a favorable orientation (product-like conformation by pyramidalization of the sp^2 -hybridized carbon atom next to the γ -lactone carbonyl), allowing facile crossed adduct formation.

Scheme 2.7

In the case of acyclic alkenes **54** and **55** (see scheme 2.4) the conformational effect is less obvious. Moreover, both low yields and slow reaction rates point towards a difficult process. One could reason that the first attack on the least hindered carbon of **54** could justify the regiochemical outcome leading to the straight adduct. Moreover, the presence of unstable side products in the case of the analog **55**, which we assume to be crossed adducts (see above), suggests that the regioselectivity is less pronounced. However, during the straight adduct formation, the second cyclization step could be favored due to the lack of the methyl group shielding the radical.

2.7 Conclusions

In this chapter the efficient preparation of 6-methyldioxenones tethered to mono- di-, tri- and tetrasubstituted alkenes is described. Monosubstituted olefins cyclized as expected to bicyclo[2.1.1]hexanes, according to the rule of five. Di- en trisubstituted alkenes exhibited a remarkable preference for 1,6-closure, leading without exception to highly substituted bicyclo[2.2.0]hexanes. Ester substituted alkene **47** displayed the same selectivity for the straight mode of closure, indicating that steric hindrance and the electronic nature of the alkene, is not the determining factor for the regiochemical outcome of the cycloaddition.

However, the more rigid lactone precursor **50** afforded the desired bicyclo[2.1.1]hexane skeleton. This allowed the stereoselective synthesis of the highly compact and complex pentacyclic bislactone **51**, which contains the appropriate substitution pattern and stereochemistry for elaboration towards the right-hand side of solanoclepin A. Finally, a mechanistic rationale for the regioselectivity of the [2+2] photocycloadditions, based on molecular modeling results, is presented in this chapter.

2.8 Acknowledgments

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2.9 Experimental Section

General information. All reactions were carried out under an inert atmosphere of dry nitrogen, unless stated otherwise. Standard syringe techniques were applied for transfer of air sensitive reagents and dry solvents. Infrared (IR) spectra were obtained from CHCl₃ solutions, using a Bruker IFS 28 FT-spectrophotometer and wavelengths (ν) are reported in cm⁻¹. ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were determined in CDCl₃ using a Bruker ARX 400 (400 MHz and 100 MHz, respectively) unless indicated otherwise. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. HRMS measurements were carried out using a JEOL JMS-SX/SX 102 A Tandem Mass Spectrometer. Chromatographic purification refers to flash chromatography³¹ using the indicated solvent (mixture) and Acros silica gel (0.030-0.075 mm). *R_f* values were obtained by using thin layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel F₂₅₄) with the aforementioned solvent (mixture) unless noted otherwise. Melting points are uncorrected. Dry THF and Et₂O were distilled from sodium benzophenone ketyl prior to use. Dry DMF, CH₂Cl₂ and MeCN were distilled from CaH₂ and stored over MS 4Å under a dry nitrogen atmosphere. Triethylamine was dried and distilled from KOH pellets. All commercially available reagents were used as received, unless indicated otherwise.

5-But-3-enyl-2,2,6-trimethyl-[1,3]dioxin-4-one (20). To a solution of 2-acetyl-hex-5-enoic acid *tert*-butyl ester¹⁰ (2.38 g, 11.2 mmol) and Ac₂O (3.8 mL, 40 mmol) in acetone (1.8 mL) was added dropwise at -10 °C, concentrated H₂SO₄ (0.7 mL). The solution was allowed to warm to room

temperature over 16 h. The reaction mixture was poured into icewater (150 mL) and subsequently stirred for 1 h. The aqueous phase was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:6) afforded **20** (1.25 g, 57%) as a colorless oil. *R_f* = 0.25. ¹H NMR: 5.80 (ddt, *J* = 17.0, 10.2, 6.8, 1H), 5.06-4.96 (m, 2H), 2.38-2.35 (m, 2H), 2.26-2.20 (m, 2H), 1.98 (s, 3H), 1.64 (s, 6H). IR: 1718, 1644.

General procedure A for the intramolecular [2+2] cycloadditions. The photoreaction was carried out in a Pyrex glass vessel with a Rayonet RPR 3000Å at room temperature. A solution of precursor in acetonitrile/acetone (25mM, 9:1 v/v) 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*.

4,4,6-Trimethyl-3,5-dioxatricyclo[4.3.0.1^{1,7}]decan-2-one (21). According to general procedure A, irradiation of **20** (50 mg, 0.26 mmol) for 3.5 h afforded the unstable cycloadduct **21** (50 mg, 100% crude yield) as a yellow oil. The crude product was used immediately in the next reaction without further purification.

¹H NMR (C₆D₆): 2.56-2.53 (m, 1H), 2.11-2.09 (m, 1H), 1.95-1.89 (m, 1H), 1.46-1.37 (m, 1H), 1.41 (s, 3H), 1.32-1.15 (m, 2H), 1.30 (s, 3H), 1.03 (d, *J* = 6.5 Hz, 1H), 0.88 (s, 3H). ¹³C NMR (C₆D₆): 169.8, 109.8, 83.9, 51.0, 46.2, 42.8, 30.9, 30.7, 25.5, 23.5.

1-Hydroxymethyl-5-methyl-bicyclo[2.1.1]hexan-5-ol (22). To a solution of LiAlH₄ (1M in THF, 0.9 mL, 0.9 mmol) was added dropwise at room temperature a solution of the crude cycloadduct **21** (50 mg) in THF (0.5 mL).

The reaction mixture was stirred for 10 min. Then, the reaction was quenched by addition of EtOAc and saturated aqueous Na₂SO₄ (10 drops) was added. The resulting mixture was stirred for 1 h. After addition of additional solid Na₂SO₄ the mixture was filtered through Celite® and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 3:1) afforded **22** (17 mg, 47% from **20**) as a white powder. X-ray crystal structure determination was allowed after recrystallisation from Et₂O/pentane. Colorless crystals. *R*_f = 0.25. mp 88–89 °C. ¹H NMR: 3.88 (d, *J* = 11.7 Hz, 1H), 3.75 (d, *J* = 11.7 Hz, 1H), 2.67-2.65 (m, 1H), 2.55 (br, 1H), 2.35 (br, 1H), 2.26-2.25 (m, 1H), 1.64-1.60 (m, 2H), 1.45-1.32 (m, 2H), 1.15 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 1H).

Crystallographic data for **22**: orthorhombic, P2₁2₁2₁, *a* = 6.3570(8), *b* = 10.693(1), *c* = 11.866(1) Å, *V* = 806.6(1) Å³, *Z* = 4, *D*_x = 1.317 g cm⁻³, λ(CuKα) = 1.5418 Å, μ(CuKα) = 6.29 cm⁻¹, *F*(000) = 312, 243 K. Final *R* = 0.051 for 745 observed reflections.

Table 2.2 Bond distances of the non-hydrogen atoms (Å) of **22** (standard deviations)

C(1)–C(2)	1.561(6)	C(2)–C(3)	1.532(8)	C(6)–C(8)	1.503(8)
C(1)–C(5)	1.512(7)	C(3)–C(4)	1.522(8)	C(6)–O(2)	1.438(5)
C(1)–C(6)	1.562(6)	C(3)–C(6)	1.536(7)	C(7)–O(1)	1.441(6)
C(1)–C(7)	1.491(6)	C(4)–C(5)	1.565(8)		

Table 2.3 Bond angles of the non-hydrogen atoms (°) of **22** (standard deviations)

C(2)–C(1)–C(5)	100.8(4)	C(2)–C(3)–C(4)	102.1(5)	C(1)–C(6)–O(2)	111.1(4)
C(2)–C(1)–C(6)	85.2(3)	C(2)–C(3)–C(6)	87.1(4)	C(3)–C(6)–C(8)	120.4(5)
C(2)–C(1)–C(7)	121.8(4)	C(4)–C(3)–C(6)	103.1(5)	C(3)–C(6)–O(2)	110.2(4)
C(5)–C(1)–C(6)	102.4(4)	C(3)–C(4)–C(5)	98.1(4)	C(8)–C(6)–O(2)	109.7(5)
C(5)–C(1)–C(7)	118.4(4)	C(1)–C(5)–C(4)	99.8(4)	C(1)–C(7)–O(1)	112.1(4)
C(6)–C(1)–C(7)	121.8(4)	C(1)–C(6)–C(3)	82.3(3)		
C(1)–C(2)–C(3)	82.4(3)	C(1)–C(6)–C(8)	120.6(4)

5-Allyl-2,2,6-trimethyl-[1,3]dioxin-4-one (24). To a solution of 2-acetyl-pent-4-enoic acid *tert*-butyl ester¹² (1.0 g, 5.0 mmol) and Ac₂O (1.7 mL, 18 mmol) in acetone (0.8 mL) was added dropwise at -10 °C, concentrated H₂SO₄ (0.3 mL). The solution was allowed to warm to room temperature over 16 h. The reaction mixture was poured into icewater (50 mL) and subsequently stirred for 1 h. The aqueous phase was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:5) afforded **24** (575 mg, 63%) as a colorless oil. *R*_f = 0.28. ¹H NMR: 5.82 (ddt, *J* = 17.1, 10.1, 6.1 Hz, 1H), 5.07-5.00 (m, 2H), 3.02 (d, *J* = 6.1 Hz, 2H), 1.97 (s, 3H), 1.66 (s, 6H). ¹³C NMR: 164.2, 161.8, 134.9, 114.9, 104.8, 102.8, 28.8, 24.9, 17.2. IR: 1710, 1644.

(2,2,6-Trimethyl-4-oxo-4H-[1,3]dioxin-5-yl)-acetaldehyde (25). To a solution of **24** (10.0 g, 55 mmol) in THF/water (600 mL, 1:1 v/v) were added at 0 °C, osmium tetroxide (10 mL, 1 wt. % solution in water, 0.4 mmol) and NaIO₄ (28 g, 131 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 7 h. Then, most of the THF was evaporated, the remaining mixture was diluted with water (500 mL) and extracted with EtOAc (4 × 300 mL). The combined organic layers were washed with 1N NaHSO₃ (300 mL), water (300 mL), 2N NaHCO₃ (300 mL) and brine (300 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:1) afforded **25** (7.57 g, 75%) as a pale yellow waxy solid. *R*_f = 0.27. ¹H NMR: 9.69 (s, 1H), 3.43 (s, 2H), 1.94 (s, 3H), 1.72 (s, 6H). ¹³C NMR (in C₆D₆): 197.9, 165.72, 161.9, 106.0, 99.2, 40.6, 25.4, 17.7. IR: 1722, 1650. HRMS (FAB) calculated for C₉H₁₃O₄ (MH⁺) 185.0814, found 185.0809.

5-(2-Hydroxy-but-3-enyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (26). To a solution of aldehyde **25** (265 mg, 1.44 mmol) in THF (1 mL) was added at -78 °C vinylmagnesium bromide (1.5 mL, 1.0 M solution in THF, 1.5 mmol) and the resulting solution was stirred at -78 °C for 15 min. Saturated aqueous NH₄Cl (5 mL) was added and the resulting mixture was allowed to warm to room temperature and diluted with EtOAc (1 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄ and concentrated *in vacuo* to yield an inseparable mixture of the desired alcohol **26** and starting material **25** (3:2, 323 mg). The crude product was used in the next reaction without further purification. ¹H NMR: 5.93-5.83 (ddd, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.27 (dt, *J* = 17.1, 1.5 Hz, 1H), 5.12 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.30 (m, 1H), 2.57 (dd, *J* = 14.5, 4.9 Hz, 1H), 2.47 (dd, *J* = 14.5, 7.4 Hz, 1H), 2.38 (br, 1H), 2.01 (s, 3H), 1.66 (s, 3H), 1.65 (s, 3H).

General procedure B for the preparation of the MOM protected products. To a solution of the alcohol in CH₂Cl₂ (0.5M) at 0 °C were added DIPEA (4 equiv.) and MOMCl (2.5 equiv.). The mixture was stirred at 0 °C for 1 h and subsequently at room temperature

for 16 h. Saturated aqueous NH_4Cl was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo*.

5-(2-Methoxymethoxy-but-3-enyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (27).

According to general procedure **B**, the mixture of aldehyde **25** and alcohol **26** (2:3, 323 mg) afforded the MOM protected product **27** (157 mg, 43% from aldehyde **25**) as a colorless oil and recovered aldehyde **25** (58 mg, 22%) after purification ($\text{EtOAc}:\text{PE} = 1:2$). $R_f = 0.34$. $^1\text{H NMR}$: 5.69 (ddd, $J = 17.6, 10.3, 7.6$ Hz, 1H), 5.23-5.15 (m, 2H), 4.62 (d, $J = 6.6$ Hz, 1H), 4.52 (d, $J = 6.6$ Hz, 1H), 4.16 (q, $J = 6.7$ Hz, 1H), 3.31 (s, 3H), 2.51 (d, $J = 6.7$ Hz, 2H), 1.99 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H). $^{13}\text{C NMR}$: 165.0, 162.0, 137.8, 117.5, 104.7, 101.4, 94.0, 76.6, 55.3, 31.3, 25.1, 24.8, 17.8. IR: 1716, 1645. HRMS (EI) calculated for $\text{C}_{13}\text{H}_{20}\text{O}_5$ 256.1311, found 256.1304.

8-Methoxymethoxy-4,4,6-trimethyl-3,5-dioxatricyclo[4.3.0.1^{1,7}]decan-2-one (28).

According to general procedure **A**, irradiation of **27** (157 mg, 0.61 mmol) for 3 h afforded the unstable cycloadduct **28** (159 mg, 100% crude yield) as yellow oil. The crude product was used immediately in the next reaction without further purification. $^1\text{H NMR}$: 4.40 (d, $J = 6.9$ Hz, 1H), 4.37 (d, $J = 6.9$ Hz, 1H), 4.31 (s, 2H), 3.92 (dd, $J = 6.6, 1.6$ Hz, 1H), 3.83-3.81 (m, 1H), 3.07 (s, 3H), 3.04 (s, 3H), 2.68-2.66 (m, 1H), 2.54-2.44 (m, 4H), 2.07 (dd, $J = 12.3, 6.8, 2.9$ Hz, 1H), 1.98 (d, $J = 6.6$ Hz, 1H), 1.93 (ddd, $J = 12.3, 6.8, 2.9$ Hz, 1H), 1.69-1.65 (m, 1H), 1.47 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.26 (s, 3H), 0.87 (d, $J = 6.9$ Hz, 1H), 0.77 (s, 3H).

1-Hydroxymethyl-3-methoxymethoxy-5-methyl-bicyclo[2.1.1]hexan-5-ol (29).

To a solution of LiAlH_4 (1M in THF, 2.5 mL, 2.5 mmol) was added dropwise at room temperature a solution of the crude cycloadduct **21** (159 mg) in THF (1.5 mL). The reaction mixture was stirred for 10 min. Then, the reaction was quenched by addition of EtOAc and saturated aqueous Na_2SO_4 (10 drops) was added. The resulting mixture was stirred for 1 h. After addition of additional solid Na_2SO_4 the mixture was filtered through Celite® and concentrated *in vacuo*. Purification by chromatography (EtOAc) afforded **29** (64 mg, 52% from **27**) as a 1:1 mixture of diastereomers as a colorless oil. $R_f = 0.33$. **29a** (OMOM down): $^1\text{H NMR}$ (C_6D_6): 4.52 (s, 2H), 4.05 (dd, $J = 6.9, 1.6$ Hz, 1H), 3.60 (s, 2H), 3.17 (s, 3H), 2.81-2.75 (m, 1H), 2.49-2.48 (m, 1H), 1.73 (ddd, $J = 11.8, 6.9, 3.0$ Hz, 1H), 1.70 (d, $J = 6.6$ Hz, 1H), 1.32 (dd, $J = 11.8, 2.0$ Hz, 1H), 0.92 (s, 3H). $^{13}\text{C NMR}$ (C_6D_6): 96.2, 84.8, 76.0, 63.1, 55.7, 55.3, 51.9, 37.3, 32.6, 18.8. **29b** (OMOM up): $^1\text{H NMR}$ (C_6D_6): 4.46 (s, 2H), 3.95 (ddd, $J = 8.6, 2.9, 1.7$ Hz, 1H), 3.67 (d, $J = 11.6$ Hz, 1H), 3.53 (d, $J = 11.6$ Hz, 1H), 3.15 (s, 3H), 2.81-2.75 (m, 1H), 2.45 (dd, $J = 3.1, 1.6$ Hz, 1H), 1.63 (dd, $J = 11.8, 8.6$ Hz, 1H), 1.46 (ddd, $J = 11.8, 3.9, 3.1$ Hz, 1H), 1.46 (s, 3H), 0.77 (d, $J = 7.0$ Hz, 1H). $^{13}\text{C NMR}$ (C_6D_6): 97.0, 85.2, 78.1, 63.1, 56.2, 55.8, 52.2, 36.6, 35.6, 34.4, 20.2. HRMS (FAB) calculated for $\text{C}_{10}\text{H}_{19}\text{O}_4$ (MH^+) 203.1283, found 203.1284.

General procedure C for the Cr(II)/Ni(II) mediated coupling reactions. To a solution of aldehyde **25** in DMF (0.4M) at 0 °C were added CrCl₂ (4 equiv.), NiCl₂ (1 mol%) and the vinyl triflate/bromide (2.2 equiv). The mixture was allowed to warm to room temperature and stirred at room temperature for 20 h, unless indicated otherwise. Saturated aqueous NH₄Cl was added and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over MgSO₄ and concentrated *in vacuo*.

5-(2-Cyclopent-1-enyl-2-hydroxy-ethyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (30). According to general procedure C, the reaction of aldehyde **25** (221 mg, 1.2 mmol) with cyclopentenyl triflate¹⁴ afforded **30** (193 mg, 64%) as a colorless oil after purification (EtOAc:PE = 1:4). *R_f* = 0.13. ¹H

NMR: 5.62 (br, 1H), 4.40 (br, 1H), 2.61 (dd, *J* = 14.5, 4.4 Hz, 1H), 2.49 (dd, *J* = 14.5, 8.2 Hz, 1H), 2.34-2.29 (m, 5H), 2.00 (s, 3H), 2.00-1.75 (m, 2H), 1.65 (s, 6H). IR: 3600-3300, 1714, 1644. HRMS (EI) calculated for C₁₄H₂₀O₄ 252.1362, found 252.1362.

5-(2-Cyclohex-1-enyl-2-hydroxy-ethyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (31). According to general procedure C, the reaction of aldehyde **25** (325 mg, 1.76 mmol) with cyclohexenyl triflate¹⁵ afforded **31** (402 mg, 86%) as a colorless oil after purification (EtOAc:PE = 1:2). *R_f* = 0.25. ¹H

NMR: 5.62 (br, 1H), 4.08-4.05 (m, 1H), 2.51 (dd, *J* = 14.4, 5.1 Hz, 1H), 2.43 (dd, *J* = 14.4, 7.7 Hz, 1H), 2.38 (br, 1H), 2.08-1.89 (m, 4H), 1.96 (s, 3H), 1.63-1.44 (m, 4H), 1.61 (s, 6H). ¹³C NMR: 164.5, 163.0, 139.4, 122.5, 104.7, 102.4, 75.4, 31.2, 24.9, 24.7, 24.5, 23.6, 22.3, 17.5. IR: 3600-3300, 1705, 1644. HRMS (FAB) calculated for C₁₅H₂₃O₄ (MH⁺) 267.1596, found 267.1598.

5-(2-Cyclopent-1-enyl-2-methoxymethoxy-ethyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (32). According to general procedure B, alcohol **30** (123 mg, 0.49 mmol) afforded the MOM protected product **32** (102 mg, 70%) as a colorless oil after purification (EtOAc:PE = 1:3). *R_f* = 0.25. ¹H NMR:

5.59 (br, 1H), 4.54 (d, *J* = 6.5 Hz, 1H), 4.46 (d, *J* = 6.5 Hz, 1H), 4.37 (t, *J* = 6.9 Hz, 1H), 3.29 (s, 3H), 2.55 (dd, *J* = 14.2, 7.0 Hz, 1H), 2.49 (dd, *J* = 14.2, 7.0 Hz, 1H), 2.32-2.20 (m, 4H), 1.98 (s, 3H), 1.86-1.79 (m, 2H), 1.61 (s, 3H), 1.59 (s, 3H). ¹³C NMR: 164.7, 161.9, 143.3, 129.0, 104.6, 102.0, 94.0, 74.3, 55.4, 32.0, 30.3, 30.0, 25.1, 24.7, 23.2, 17.7. IR: 1706, 1632. HRMS (EI) calculated for C₁₆H₂₄O₅ 296.1624, found 296.1618.

5-(2-cyclohex-1-enyl-2-methoxymethoxy-ethyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (33). According to general procedure B, alcohol **31** (215 mg, 0.81 mmol) afforded **33** (213 mg, 85%) as a colorless oil after purification (EtOAc:PE = 1:3). *R_f* = 0.27. ¹H NMR: 5.62 (br, 1H), 4.56 (d, *J*

= 6.5 Hz, 1H), 4.45 (d, *J* = 6.5 Hz, 1H), 4.05 (t, *J* = 7.0 Hz, 1H), 3.31 (s, 3H), 2.56 (dd, *J* = 14.2, 6.8 Hz, 1H), 2.49 (dd, *J* = 14.2, 7.2 Hz, 1H), 2.00-1.89 (m, 4H), 2.00 (s, 3H), 1.63-1.45 (m, 4H), 1.63 (s, 3H), 1.61 (s, 3H). ¹³C NMR: 164.5, 161.9, 136.2, 126.4, 104.6,

102.2, 93.6, 79.8, 55.4, 29.6, 25.0, 25.0, 24.8, 22.8, 22.5, 22.4, 17.8. IR: 1710, 1644. HRMS (FAB) calculated for $C_{17}H_{27}O_5$ (MH^+) 311.1858, found 311.1858.

5-(2-*tert*-Butyldimethylsilyloxy-2-cyclopent-1-enyl-ethyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (34). To a solution of alcohol **30** (120 mg, 0.48 mmol) in DMF (2 mL) was added at 0 °C, imidazole (97 mg, 1.4 mmol), TBDMSCl (144 mg, 0.96 mmol) and a catalytic amount of DMAP (5 mg). The reaction mixture was allowed to warm to room temperature and after stirring for 15 h the reaction was quenched by the addition of saturated aqueous NH_4Cl (2 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×4 mL). The combined organic layers were washed with water (2 mL) and brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography ($Et_2O:PE = 1:9$) afforded **34** (150 mg, 86%) as a colorless oil. $R_f = 0.20$. 1H NMR: 5.49 (br, 1H), 4.51 (t, $J = 6.5$ Hz, 1H), 2.47 (dd, $J = 14.0$, 5.6 Hz, 1H), 2.39 (dd, $J = 14.0$, 7.4 Hz, 1H), 2.41-2.34 (m, 1H), 2.29-2.21 (m, 3H), 1.97 (s, 3H), 1.86-1.78 (m, 2H), 1.62 (s, 3H), 1.60 (s, 3H), 0.84 (s, 9H), -0.02 (s, 3H), -0.04 (s, 3H). ^{13}C NMR: 164.7, 162.0, 147.0, 125.7, 104.6, 102.0, 70.9, 32.7, 32.0, 30.5, 25.9, 25.8, 24.2, 23.4, 18.1, 17.9, -5.1, -5.2. IR: 1709, 1644. HRMS (EI) calculated for $C_{20}H_{34}O_4Si$ 366.2226, found 366.2220.

General procedure D for the oxidation of the alcohols. To a solution of oxalyl chloride (1.1 equiv) in CH_2Cl_2 (0.5M) was added dropwise at -60 °C $\rightarrow$ -50 °C, DMSO (2 equiv.), then after 5 min a solution of the alcohol in CH_2Cl_2 (0.5M), and finally, after 30 min triethylamine (5 equiv.). The mixture was stirred for 5 min, allowed to warm to room temperature and stirring was continued for 15 min. Water was added and the resulting mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 . The combined organic layers were washed with saturated aqueous NH_4Cl , saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*.

5-(2-Cyclopent-1-enyl-2-oxo-ethyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (35). According to general procedure D, the oxidation of alcohol **30** (161 mg, 0.64 mmol) afforded ketone **35** (124 mg, 78%) as a colorless oil after purification ($EtOAc:PE = 1:3$). $R_f = 0.30$. 1H NMR: 6.89 (br s, 1H), 3.69 (s, 2H), 2.58-2.24 (m, 4H), 1.94-1.91 (m, 2H), 1.93 (s, 3H), 1.73 (s, 6H). ^{13}C NMR: 194.5, 165.5, 162.1, 144.6, 144.4, 105.2, 99.9, 34.9, 33.9, 30.5, 24.7, 22.5, 17.6. IR: 1718, 1669.

5-(2-cyclohex-1-enyl-2-oxo-ethyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (36). According to general procedure D, the oxidation of alcohol **31** (312 mg, 1.17 mmol) afforded ketone **36** (294 mg, 95%) as a colorless oil after purification ($EtOAc:PE = 1:4$). $R_f = 0.19$. 1H NMR: 7.05 (br s, 1H), 3.63 (s, 2H), 2.36-2.21 (m, 4H), 1.88 (s, 3H), 1.73 (s, 6H), 1.65-1.52 (m, 4H). ^{13}C NMR: 197.0, 165.4, 162.2, 140.8, 138.6, 105.3, 100.3, 33.3, 26.1, 24.9, 23.1, 21.8, 21.4, 17.4. IR: 1709, 1651. HRMS (EI) calculated for $C_{15}H_{20}O_4$ 264.1362, found 264.1357.

General procedure E for the preparation of the acetal protected products. To a solution of ketone in CH_2Cl_2 (0.3M) at -78°C were added dropwise, $(\text{TMSOCH}_3)_2$ (2.5 equiv.) and TMSOTf (0.4 equiv.). The mixture was allowed to warm to 0°C over 1 h and kept at 0°C for 30 h. Saturated aqueous NaHCO_3 was added and the resulting mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 . The combined organic layers were washed with water and brine, dried over MgSO_4 and concentrated *in vacuo*.

5-(2-Cyclopent-1-enyl-[1,3]dioxolan-2-ylmethyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (37). According to general procedure E, ketone **35** (79 mg, 0.32 mmol) afforded acetal **37** (61 mg, 66%) as a colorless oil after purification (EtOAc:PE = 1:6). R_f = 0.13. ^1H NMR: 5.71-5.69 (m, 1H), 3.93-3.90 (m, 2H), 3.87-3.82 (m, 2H), 2.82 (s, 2H), 2.43-2.39 (m, 2H), 2.33-2.27 (m, 2H), 2.01 (s, 3H), 1.93-1.85 (m, 2H), 1.55 (s, 6H). ^{13}C NMR: 165.6, 162.2, 144.0, 127.9, 109.3, 104.2, 100.6, 64.2, 32.2, 31.6, 31.4, 24.7, 23.6, 18.1. IR: 1722, 1644.

5-(2-cyclohex-1-enyl-[1,3]dioxolan-2-ylmethyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (38). According to general procedure E, ketone **36** (165 mg, 0.62 mmol) afforded acetal **38** (127 mg, 66%) as a colorless oil after purification (EtOAc:PE = 1:4). R_f = 0.24. ^1H NMR: 5.77 (br, 1H), 3.84-3.82 (m, 2H), 3.76-3.72 (m, 2H), 2.73 (s, 2H), 2.05-2.03 (m, 2H), 1.98 (s, 3H), 1.96-1.87 (m, 2H), 1.61 (s, 6H), 1.58-1.56 (m, 2H), 1.50-1.47 (m, 2H). ^{13}C NMR: 165.5, 162.2, 136.5, 123.7, 111.0, 104.3, 100.9, 64.0, 31.6, 24.8, 24.7, 23.9, 22.5, 21.8, 18.2. IR: 1721, 1645. HRMS (FAB) calculated for $\text{C}_{17}\text{H}_{25}\text{O}_5$ (MH^+) 309.1702, found 309.1714.

Cycloadduct 39. According to general procedure A, irradiation of **37** (64 mg, 0.22 mmol) for 75 min. afforded **39** (64 mg, 100% crude yield) as a white powder. The crude product was used immediately in the next reaction without further purification. An analytically pure sample was obtained after chromatography (EtOAc:PE = 1:3) to afford **39** as a white powder. R_f = 0.3. mp $126\text{--}127^\circ\text{C}$. ^1H NMR: 4.03-3.82 (m, 4H), 3.13 (d, J = 14.0 Hz, 1H), 2.76 (br d, J = 9.0 Hz, 1H), 2.62 (d, J = 14.0 Hz, 1H), 2.13 (dd, J = 13.4, 5.6 Hz, 1H), 1.92 (dd, J = 14.2, 5.8 Hz, 1H), 1.73-1.64 (m, 3H), 1.60 (s, 3H), 1.53 (s, 3H), 1.48 (s, 3H), 1.42-1.36 (m, 1H). ^{13}C NMR: 169.9, 106.8, 104.0, 74.8, 67.4, 65.0, 64.6, 49.0, 39.0, 37.6, 29.2, 28.6, 27.7, 25.9, 25.6, 25.3. IR: 1729. HRMS (FAB) calculated for $\text{C}_{16}\text{H}_{23}\text{O}_5$ (MH^+) 295.1545, found 295.1555.

Cycloadduct 40. According to general procedure A, irradiation of **38** (127 mg, 0.41 mmol) for 90 min. afforded **40** (121 mg, 95%) as a colorless oil after purification (EtOAc:PE = 1:2). R_f = 0.40. ^1H NMR: 4.04-3.99 (m, 1H), 3.95-3.90 (m, 1H), 3.85-3.80 (m, 1H), 3.77-3.72 (m, 1H), 3.14 (d, J = 14.8 Hz, 1H), 2.70 (dd, J = 9.1, 6.7 Hz, 1H), 2.58 (d, J = 14.1 Hz, 1H), 1.98-1.89 (m, 1H), 1.73-1.39 (m, 5H), 1.58 (s, 3H), 1.55 (s, 3H), 1.51 (s, 3H), 1.26-1.13 (m, 2H). ^{13}C NMR: 169.2, 108.1, 104.5, 77.4,

65.0, 64.4, 58.1, 41.7, 41.1, 36.7, 29.5, 29.2, 24.1, 21.1, 20.9, 20.3, 18.6. IR: 1730. HRMS (FAB) calculated for $C_{17}H_{25}O_5$ (MH^+) 309.1702, found 309.1695.

Cycloadduct 41. According to general procedure A, irradiation of **32** (92 mg, 0.31 mmol) for 30 min. afforded **41** (89 mg, 97%) as an inseparable 1:1.3 mixture of diastereomers as a colorless oil after purification (EtOAc:PE = 1:2). $R_f = 0.27$ and $R_f = 0.22$. 1H NMR: 4.65 (d, $J = 6.8$ Hz, 1H), 4.60 (d, $J = 6.8$ Hz, 1H), 4.59 (d, $J = 6.6$ Hz, 1H), 4.55 (d, $J = 6.6$ Hz, 1H), 4.36 (dd, $J = 5.9, 5.9$ Hz, 1H), 4.31 (dd, $J = 9.9, 5.9$ Hz, 1H), 3.36 (s, 3H), 3.32 (s, 3H), 2.95 (dd, $J = 13.6, 9.9$ Hz, 1H), 2.88 (d, $J = 9.0$ Hz, 1H), 2.80 (dd, $J = 13.6, 5.1$ Hz, 1H), 2.58 (dd, $J = 13.6, 6.3$ Hz, 1H), 2.35 (d, $J = 9.0$ Hz, 1H), 2.25 (dd, $J = 13.6, 5.9$ Hz, 1H), 2.12-2.05 (m, 1H), 2.10 (dd, $J = 13.9, 6.8$ Hz, 1H), 1.94 (dd, $J = 13.8, 5.7$ Hz, 1H), 1.83-1.66 (m, 3H), 1.82-1.36 (m, 4H), 1.60 (s, 3H), 1.55 (s, 3H), 1.52 (s, 3H), 1.51 (s, 3H), 1.50-1.39 (m, 2H), 1.46 (s, 3H), 1.44 (s, 3H). ^{13}C NMR: 170.1, 104.3, 103.9, 96.0, 95.3, 76.0, 74.5, 74.2, 62.2, 61.7, 55.6, 55.4, 54.2, 48.0, 42.6, 41.4, 31.6, 29.3, 29.2, 28.9, 28.6, 27.4, 26.4, 25.8, 25.3, 25.1, 24.9.

Cycloadduct 42. According to general procedure A, irradiation of **33** (145 mg, 0.47 mmol) for 30 min. afforded **42** (120 mg, 83%) as an inseparable 1:1 mixture of diastereomers as colorless oil after purification (EtOAc:PE = 1:2). $R_f = 0.28$. 1H NMR: 4.64 (d, $J = 6.6$ Hz, 1H), 4.59 (d, $J = 6.6$ Hz, 1H), 4.57 (d, $J = 4.4$ Hz, 1H), 4.55 (d, $J = 4.4$ Hz, 1H), 4.15 (t, $J = 6.4$ Hz, 1H), 4.04 (dd, $J = 9.7, 6.6$ Hz, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 3.00 (dd, $J = 13.4, 9.7$ Hz, 1H), 2.79 (dd, $J = 9.7, 4.5$ Hz, 1H), 2.74 (dd, $J = 13.0, 6.5$ Hz, 1H), 2.53 (dd, $J = 13.0, 6.4$ Hz, 1H), 2.16 (t, $J = 7.4$ Hz, 1H), 2.13 (dd, $J = 13.4, 6.6$ Hz, 1H), 2.00-1.00 (m, 8H), 1.59 (s, 6H), 1.56 (s, 3H), 1.52 (s, 6H), 1.45 (s, 3H). ^{13}C NMR: 169.8, 169.1, 104.8, 103.9, 78.6, 77.0, 76.0, 55.5, 52.3, 52.2, 49.8, 43.7, 42.5, 31.2, 29.5, 29.4, 29.1, 29.1, 28.4, 27.9, 24.7, 22.9, 21.6, 21.5, 20.9, 20.9, 20.8, 20.6, 18.4. IR: 1714. HRMS (EI) calculated for $C_{17}H_{26}O_5$ 310.1780, found 310.1776.

Cycloadduct 43. According to general procedure A, irradiation of **34** (150 mg, 0.41 mmol) for 30 min. afforded **43** (146 mg, 97%) as an inseparable 3:1 mixture of diastereomers as a colorless oil after purification (EtOAc:PE = 1:5). $R_f = 0.3$. 1H NMR: 4.43-4.39 (m, 2H), 2.94 (dd, $J = 13.4, 9.5$ Hz, 1H), 2.86 (d, $J = 9.0$ Hz, 1H), 2.71 (dd, $J = 13.2, 5.3$ Hz, 1H), 2.52 (dd, $J = 13.2, 5.3$ Hz, 1H), 2.23 (d, $J = 8.5$ Hz, 1H), 2.11-2.04 (m, 3H), 1.90 (dd, $J = 14.2, 5.5$ Hz, 1H), 1.79-1.17 (m, 9H), 1.57 (s, 3H), 1.53 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.44 (3H), 1.42 (s, 3H), 0.86 (s, 18H), 0.01 (s, 6H), -0.01 (s, 3H), -0.03 (s, 3H). ^{13}C NMR: 170.6, 104.2, 103.6, 76.1, 74.2, 70.4, 65.6, 64.1, 62.6, 54.0, 47.2, 42.2, 41.3, 32.5, 31.9, 31.3, 29.2, 29.1, 28.8, 28.6, 27.1, 26.6, 25.7, 25.6, 25.4, 25.0, 25.0, 24.9, 18.1, 17.9, -4.7, -4.8, -4.9. IR: 1716. HRMS (FAB) calculated for $C_{20}H_{35}O_4Si$ (MH^+) 367.2305, found 367.2301.

2-[1-Hydroxy-2-(2,2,6-trimethyl-4-oxo-4H-[1,3]dioxin-5-yl)-ethyl]-cyclopent-1-enecarboxylic acid methyl ester (46). According to general procedure C, the reaction of aldehyde **25** (133 mg, 0.72 mmol) with vinyl triflate **45**²¹ at 50 °C for 18 h afforded **46** (164 mg, 73%) as a colorless oil after purification (EtOAc:PE = 1:2). R_f = 0.29. ^1H NMR: 4.84-4.77 (br s, 1H), 4.34-4.32 (br s, 1H), 3.74 (s, 3H), 2.80-2.71 (m, 2H), 2.70-2.55 (m, 4H), 2.10 (s, 3H), 1.89-1.81 (m, 2H), 1.67 (s, 3H), 1.66 (s, 3H).

2-[1-Methoxymethoxy-2-(2,2,6-trimethyl-4-oxo-4H-[1,3]dioxin-5-yl)-ethyl]-cyclopent-1-enecarboxylic acid methyl ester (47). According to general procedure B, alcohol **46** (117 mg, 0.38 mmol) afforded the MOM protected product **47** (73 mg, 55%) as a colorless oil after purification (EtOAc:PE = 1:1). R_f = 0.38. ^1H NMR: 5.41 (t, J = 14.2 Hz, 1H), 4.54 (s, 2H), 3.71 (s, 3H), 3.34 (s, 3H), 2.78-2.45 (m, 6H), 2.07 (s, 3H), 1.90-1.73 (m, 2H), 1.63 (s, 3H), 1.60 (s, 3H). ^{13}C NMR: 165.9, 165.3, 161.9, 157.4, 130.9, 104.7, 101.0, 95.4, 72.2, 55.8, 51.2, 34.0, 33.1, 29.4, 25.4, 24.6, 21.6, 17.7. IR: 1712, 1642. HRMS (FAB) calculated for $\text{C}_{18}\text{H}_{27}\text{O}_7$ (MH^+) 355.1757, found 355.1765.

Cycloadduct 48. According to general procedure A, irradiation of **47** (61 mg, 0.17 mmol) for 1 h afforded a 2:3 mixture of diastereomers **48a** and **48b** (48 mg, 78%) as colorless oil after purification (EtOAc:PE = 1:1). Repeated chromatography led to pure isomers. **48a**: X-ray crystal

structure determination was allowed after recrystallisation from CH_2Cl_2 /pentane. Colorless crystals. R_f = 0.41. mp 62–64 °C. ^1H NMR: 4.55 (d, J = 6.6 Hz, 1H), 4.50-4.46 (m, 2H), 3.62 (s, 3H), 3.32 (s, 3H), 2.91 (dd, J = 13.7, 9.9 Hz, 1H), 2.63-2.56 (m, 1H), 2.29 (dd, J = 13.7, 4.5 Hz, 1H), 2.03-2.02 (m, 1H), 1.92 (s, 3H), 1.87-1.76 (m, 3H), 1.66-1.56 (m, 1H), 1.55 (s, 3H), 1.50 (s, 3H). ^{13}C NMR: 174.2, 170.2, 104.3, 95.6, 77.9, 70.6, 65.0, 60.8, 55.4, 51.0, 40.5, 33.9, 32.8, 29.6, 29.1, 28.6, 24.2, 23.4. IR: 1724. **48b**: colorless oil. R_f = 0.34. ^1H NMR: 4.72 (t, J = 6.6 Hz, 1H), 4.68 (d, J = 6.6 Hz, 1H), 4.63 (d, J = 6.6 Hz, 1H), 3.71 (s, 3H), 3.37 (s, 3H), 2.79 (dd, J = 13.2, 6.5 Hz, 1H), 2.58 (dd, J = 13.1, 6.8 Hz, 1H), 2.55-2.52 (m, 1H), 2.11 (dd, J = 12.4, 5.5 Hz, 1H), 1.77-1.44 (m, 4H), 1.60 (s, 3H), 1.55 (s, 3H), 1.44 (s, 3H). ^{13}C NMR: 179.7, 173.1, 104.0, 95.4, 76.3, 70.3, 65.0, 62.5, 55.4, 51.5, 40.2, 32.5, 31.4, 29.3, 28.4, 26.9, 23.2, 22.5.

Crystallographic data for **48a**: triclinic, $P\bar{1}$, a = 7.4493(7), b = 9.6161(8), c = 13.540(2) Å, α = 106.434(10), β = 99.44(1), γ = 95.661(9)°, V = 906.8(2) Å³, Z = 2, D_x = 1.30 g cm⁻³, $\lambda(\text{CuK}\alpha)$ = 1.5418 Å, $\mu(\text{CuK}\alpha)$ = 8.30 cm⁻¹, $F(000)$ = 380, 248 K. Final R = 0.046 for 3197 observed reflections.

Table 2.4 Bond distances of the non-hydrogen atoms (Å) of **48** (standard deviations)

C(1)-C(2)	1.570(3)	C(4)-C(5)	1.482(3)	C(12)-C(13)	1.529(4)
C(1)-C(4)	1.556(2)	C(4)-C(12)	1.548(2)	C(13)-O(4)	1.415(3)
C(1)-C(16)	1.516(3)	C(5)-O(1)	1.348(2)	C(14)-O(4)	1.409(3)
C(1)-O(2)	1.435(2)	C(5)-O(3)	1.205(2)	C(14)-O(5)	1.389(3)
C(2)-C(3)	1.556(2)	C(6)-C(7)	1.506(3)	C(15)-O(5)	1.420(3)
C(2)-C(9)	1.559(2)	C(6)-C(8)	1.517(4)	C(17)-O(6)	1.199(3)
C(2)-C(17)	1.506(3)	C(6)-O(1)	1.466(2)	C(17)-O(7)	1.349(3)
C(3)-C(4)	1.591(3)	C(6)-O(2)	1.403(3)	C(18)-O(7)	1.440(4)
C(3)-C(11)	1.512(3)	C(9)-C(10)	1.526(4)		
C(3)-C(13)	1.547(2)	C(10)-C(11)	1.523(3)		

Table 2.5 Bond angles of the non-hydrogen atoms (°) of **48** (standard deviations)

C(2)-C(1)-C(4)	89.9(1)	C(11)-C(3)-C(13)	123.2(2)	C(9)-C(10)-C(11)	105.2(2)
C(2)-C(1)-C(16)	116.3(2)	C(1)-C(4)-C(3)	89.7(1)	C(3)-C(11)-C(10)	102.9(2)
C(2)-C(1)-O(2)	109.7(1)	C(1)-C(4)-C(5)	118.8(1)	C(4)-C(12)-C(13)	91.2(2)
C(4)-C(1)-C(16)	117.2(1)	C(1)-C(4)-C(12)	116.9(2)	C(3)-C(13)-C(12)	90.9(1)
C(4)-C(1)-O(2)	111.2(1)	C(3)-C(4)-C(5)	119.4(2)	C(3)-C(13)-O(4)	116.4(2)
C(16)-C(1)-O(2)	111.0(2)	C(3)-C(4)-C(12)	88.5(1)	C(12)-C(13)-O(4)	112.7(2)
C(1)-C(2)-C(3)	90.5(1)	C(5)-C(4)-C(12)	116.4(2)	O(4)-C(14)-O(5)	112.3(2)
C(1)-C(2)-C(9)	115.5(1)	C(4)-C(5)-O(1)	118.5(2)	C(2)-C(17)-O(6)	126.5(2)
C(1)-C(2)-C(17)	119.3(2)	C(4)-C(5)-O(3)	123.1(2)	C(2)-C(17)-O(7)	110.3(2)
C(3)-C(2)-C(9)	103.4(2)	O(1)-C(5)-O(3)	118.3(2)	O(6)-C(17)-O(7)	123.0(2)
C(3)-C(2)-C(17)	119.2(1)	C(7)-C(6)-C(8)	112.2(2)	C(5)-O(1)-C(6)	119.5(1)
C(9)-C(2)-C(17)	107.5(2)	C(7)-C(6)-O(1)	105.2(2)	C(1)-O(2)-C(6)	117.7(1)
C(2)-C(3)-C(4)	89.1(1)	C(7)-C(6)-O(2)	106.2(2)	C(13)-O(4)-C(14)	114.2(2)
C(2)-C(3)-C(11)	108.4(1)	C(8)-C(6)-O(1)	107.8(2)	C(14)-O(5)-C(15)	112.6(2)
C(2)-C(3)-C(13)	119.7(1)	C(8)-C(6)-O(2)	115.1(2)	C(17)-O(7)-C(18)	116.1(2)
C(4)-C(3)-C(11)	121.5(2)	O(1)-C(6)-O(2)	110.1(2)		
C(4)-C(3)-C(13)	89.0(1)	C(2)-C(9)-C(10)	106.7(2)

3-(2,2,6-Trimethyl-4-oxo-4H-[1,3]dioxin-5-ylmethyl)-4,5,6,7-tetrahydro-3H-isobenzofuran-1-one (50). According to general procedure **C**, the reaction of aldehyde **25** (300 mg, 1.6 mmol) with vinyl triflate **49**²³ at 50 °C for 7 h afforded **50** (375 mg, 79%) as a white powder after purification (EtOAc:PE = 1:1). R_f = 0.28. ¹H NMR: 4.99 (br, 1H), 2.89 (dd, J = 14.8, 3.8 Hz, 1H), 2.58 (dd, J = 14.8, 6.4 Hz, 1H), 2.58-2.52 (m, 1H), 2.26-2.04 (m, 3H), 2.04 (s, 3H), 1.72-1.64 (m, 4H), 1.66 (s, 3H), 1.57 (s, 3H). ¹³C NMR: 172.9, 167.1, 163.7, 161.7, 126.8, 104.8, 98.6, 81.7, 27.9, 25.7, 23.4, 22.9, 21.2, 19.8, 17.9. IR: 1748, 1706, 1639. HRMS (FAB) calculated for C₁₆H₂₁O₅ (MH⁺) 293.1389, found 293.1395.

Cycloadduct 51. According to general procedure **A**, irradiation of alkene **50** (100 mg, 0.34 mmol) 1 h afforded **51** (95 mg, 95% crude yield), which was used in the next reaction without further purification. X-ray crystal structure determination was allowed after recrystallization from CH₂Cl₂/pentane. Colorless crystals. mp 177–178 °C. ¹H NMR: 4.54 (d, J = 4.2 Hz), 2.39 (dt, J = 13.3, 4.7 Hz, 1H), 2.33 (dd, J = 12.8, 4.2 Hz, 1H), 2.23-2.20 (m, 1H), 1.98 (d, J = 12.8 Hz, 1H), 1.89-1.85 (m, 1H), 1.81-1.61 (m, 2H), 1.73 (s, 3H), 1.64 (s, 3H), 1.56-1.40 (m, 2H), 1.40 (s, 3H), 1.05-0.93 (m, 1H).

^{13}C NMR: 174.7, 164.9, 109.9, 83.2, 79.7, 62.1, 60.4, 51.5, 33.7, 31.1, 29.2, 21.8, 21.7, 21.4, 20.4, 19.4.

Crystallographic data for **51**: monoclinic, $P2_1/c$, $a = 14.219(1)$, $b = 7.3084(7)$, $c = 14.697(2)$ Å, $\beta = 111.05(1)^\circ$, $V = 1425.4(3)$ Å³, $Z = 4$, $D_x = 1.36$ g cm⁻³, $\lambda(\text{CuK}\alpha) = 1.5418$ Å, $\mu(\text{CuK}\alpha) = 8.30$ cm⁻¹, $F(000) = 624$, 248 K. Final $R = 0.056$ for 2510 observed reflections.

Table 2.6 Bond distances of the non-hydrogen atoms (Å) of **51** (standard deviations)

C(1)-C(2)	1.624(3)	C(3)-C(15)	1.559(4)	C(10)-C(11)	1.537(4)
C(1)-C(4)	1.552(4)	C(4)-C(9)	1.526(3)	C(11)-C(12)	1.522(5)
C(1)-C(5)	1.489(3)	C(4)-O(2)	1.432(3)	C(12)-C(13)	1.534(4)
C(1)-C(14)	1.521(4)	C(5)-O(1)	1.342(3)	C(14)-C(15)	1.550(4)
C(2)-C(3)	1.550(3)	C(5)-O(3)	1.199(4)	C(15)-O(4)	1.451(3)
C(2)-C(10)	1.513(4)	C(6)-C(7)	1.500(3)	C(16)-O(4)	1.372(3)
C(2)-C(16)	1.510(4)	C(6)-C(8)	1.511(4)	C(16)-O(5)	1.188(3)
C(3)-C(4)	1.549(3)	C(6)-O(1)	1.488(3)		
C(3)-C(13)	1.507(4)	C(6)-O(2)	1.410(3)		

Table 2.7 Bond angles of the non-hydrogen atoms ($^\circ$) of **51** (standard deviations)

C(2)-C(1)-C(4)	87.9(2)	C(4)-C(3)-C(15)	101.9(2)	O(1)-C(6)-O(2)	111.8(2)
C(2)-C(1)-C(5)	115.2(2)	C(13)-C(3)-C(15)	121.3(2)	C(2)-C(10)-C(11)	108.1(2)
C(2)-C(1)-C(14)	101.9(2)	C(1)-C(4)-C(3)	83.2(2)	C(10)-C(11)-C(12)	113.4(2)
C(4)-C(1)-C(5)	119.4(2)	C(1)-C(4)-C(9)	123.5(2)	C(11)-C(12)-C(13)	112.2(3)
C(4)-C(1)-C(14)	100.9(2)	C(1)-C(4)-O(2)	107.8(2)	C(3)-C(13)-C(12)	110.6(2)
C(5)-C(1)-C(14)	124.5(2)	C(3)-C(4)-C(9)	115.3(2)	C(1)-C(14)-C(15)	95.6(2)
C(1)-C(2)-C(3)	80.9(1)	C(3)-C(4)-O(2)	112.4(2)	C(3)-C(15)-C(14)	102.4(2)
C(1)-C(2)-C(10)	124.5(2)	C(9)-C(4)-O(2)	111.6(2)	C(3)-C(15)-O(4)	104.1(2)
C(1)-C(2)-C(16)	114.0(2)	C(1)-C(5)-O(3)	115.0(2)	C(14)-C(15)-O(4)	104.7(2)
C(3)-C(2)-C(10)	117.4(2)	O(1)-C(5)-O(3)	125.0(2)	C(2)-C(16)-O(4)	107.6(2)
C(3)-C(2)-C(16)	104.6(2)	C(7)-C(6)-C(8)	119.6(2)	C(2)-C(16)-O(5)	130.1(3)
C(10)-C(2)-C(16)	110.7(2)	C(7)-C(6)-O(1)	112.3(2)	O(4)-C(16)-O(5)	122.2(3)
C(2)-C(3)-C(4)	90.7(2)	C(7)-C(6)-O(2)	105.5(2)	C(5)-O(1)-C(6)	122.2(2)
C(2)-C(3)-C(13)	118.2(2)	C(7)-C(6)-O(2)	115.8(2)	C(4)-O(2)-C(6)	115.7(2)
C(2)-C(3)-C(15)	91.5(2)	C(8)-C(6)-O(1)	105.9(2)	C(15)-O(4)-C(16)	104.9(2)
C(4)-C(3)-C(13)	124.9(2)	C(8)-C(6)-O(2)	105.3(2)

5-(2-Hydroxy-3-methyl-but-3-enyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (52). According to general procedure **C**, the reaction of aldehyde **25** (431 mg, 2.3 mmol) with 2-bromopropene afforded **52** (527 mg) as a yellow oil.

The crude product was used in the next reaction without further purification. ^1H NMR: 5.17 (br, 1H), 4.93 (br, 1H), 4.15 (dd, $J = 7.8, 4.4$ Hz, 1H), 2.81-2.79 (br, 1H), 2.54 (dd, $J = 14.6, 4.4$ Hz, 1H), 2.41 (dd, $J = 14.6, 7.7$ Hz, 1H), 1.97 (s, 3H), 1.73 (s, 3H), 1.62 (s, 6H).

5-(2-Hydroxy-(E)-pent-3-enyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (53).

According to general procedure **C**, the reaction of aldehyde **25** (307 mg, 1.7 mmol) with (*E*)-1-bromo-1-propene afforded an inseparable mixture

of starting material **25** and desired alcohol **53** (1:9, 254 mg) as a yellow oil. The crude product was used in the next reaction without further purification. ^1H NMR: 5.63 (dq, $J = 15.0$, 6.4 Hz, 1H), 5.28 (ddq, $J = 15.2$, 5.5, 1.5 Hz, 1H), 4.12–4.07 (m, 1H), 2.53 (dd, $J = 14.4$, 5.2 Hz, 1H), 2.46 (dd, $J = 14.4$, 6.9 Hz, 1H), 2.00 (s, 3H), 1.69 (dd, $J = 6.4$, 1.5 Hz, 3H), 1.65 (s, 3H), 1.63 (s, 3H).

5-(2-Methoxymethoxy-3-methyl-but-3-enyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (54). According to general procedure **B**, alcohol **52** (527 mg, 2.3 mmol) afforded the MOM protected product **54** (437 mg, 69% from aldehyde **25**) as a colorless oil after purification (EtOAc:PE = 1:4). $R_f = 0.20$. ^1H NMR: 4.93 (br, 1H), 4.91 (br, 1H), 4.55 (d, $J = 6.5$ Hz, 1H), 4.48 (d, $J = 6.5$ Hz, 1H), 4.17–4.13 (m, 1H), 3.31 (s, 3H), 2.57 (dd, $J = 14.3$, 6.1 Hz, 1H), 2.49 (dd, $J = 14.3$, 7.1 Hz, 1H), 2.01 (s, 3H), 1.72 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H). ^{13}C NMR: 164.8, 161.9, 143.9, 114.0, 104.6, 101.8, 93.9, 79.1, 55.4, 29.9, 25.1, 24.8, 17.7, 16.8. IR: 1722, 1645. HRMS (FAB) calculated for $\text{C}_{14}\text{H}_{23}\text{O}_5$ (MH^+) 271.1545, found 271.1543.

5-(2-Methoxymethoxy-(E)-pent-3-enyl)-2,2,6-trimethyl-[1,3]dioxin-4-one (55). According to general procedure **B**, the mixture of aldehyde **25** and alcohol **53** (1:9, 254 mg) afforded the MOM protected product **55** (129 mg, 29% from aldehyde **25**) as a colorless oil after purification (EtOAc:PE = 1:4). $R_f = 0.18$. ^1H NMR: 5.65 (ddq, $J = 15.2$, 6.5, 0.5 Hz, 1H),

5.30 (ddq, $J = 15.2$, 8.4, 1.6 Hz, 1H), 4.66 (d, $J = 6.6$ Hz, 1H), 4.50 (d, $J = 6.6$ Hz, 1H), 4.13–4.09 (m, 1H), 3.32 (s, 3H), 2.53 (dd, $J = 14.1$, 7.0 Hz, 1H), 2.48 (dd, $J = 14.1$, 6.9 Hz, 1H), 2.00 (s, 3H), 1.68 (dd, $J = 6.5$, 1.6 Hz, 3H), 1.64 (s, 3H), 1.62 (s, 3H). ^{13}C NMR: 164.7, 161.9, 130.7, 129.5, 104.6, 101.7, 93.4, 76.1, 55.2, 31.4, 25.0, 24.7, 17.7, 17.5. IR: 1722, 1647. HRMS (FAB) calculated for $\text{C}_{14}\text{H}_{23}\text{O}_5$ (MH^+) 271.1545, found 271.1550.

3-Methoxymethoxy-4,6,8-tetramethyl-7,9-dioxatricyclo[4.4.0.0^{1,4}]decan-10-one (56). According to general procedure **A**, irradiation of alkene **54** (277 mg, 1.03 mmol) for 2 h afforded **56** (130 mg, 47%) as a colorless oil after purification (EtOAc:PE = 1:3). $R_f = 0.24$. ^1H NMR: 4.58 (d, $J = 6.6$ Hz,

1H), 4.53 (d, $J = 6.6$ Hz, 1H), 4.06 (dd, $J = 9.8$, 6.7 Hz, 1H), 3.32 (s, 3H), 3.07 (dd, $J = 13.5$, 9.8 Hz, 1H), 2.65 (d, $J = 13.2$ Hz, 1H), 2.11 (dd, $J = 13.6$, 6.8 Hz, 1H), 1.93 (d, $J = 13.2$ Hz, 1H), 1.56 (s, 6H), 1.53 (s, 3H), 1.26 (s, 3H). ^{13}C NMR: 168.9, 104.9, 95.7, 77.1, 74.9, 55.4, 50.1, 42.4, 39.6, 29.8, 29.3, 27.6, 23.0, 21.3. IR: 1729. HRMS (FAB) calculated for $\text{C}_{14}\text{H}_{23}\text{O}_5$ (MH^+) 271.1545, found 271.1539.

3-Methoxymethoxy-5,6,8-tetramethyl-7,9-dioxatricyclo[4.4.0.0^{1,4}]decan-10-one (57). According to general procedure **A**, irradiation of alkene **55** (111 mg, 0.41 mmol) for 6.5 h afforded a mixture of straight adducts (7:2:1) **57** (40 mg, 36%) as a colorless oil after purification (EtOAc:PE =

1:7). $R_f = 0.12$. **Main adduct:** ^1H NMR (C_6D_6): 4.49 (ddd, $J = 9.6$, 6.7, 4.3 Hz, 1H), 4.36 (d, $J = 6.5$ Hz, 1H), 4.34 (d, $J = 6.5$ Hz, 1H), 3.28 (ddd, $J = 13.1$, 9.6, 2.5 Hz, 1H), 3.13 (s, 3H), 2.77 (dq, $J =$

7.2, 4.7 Hz, 1H), 2.62 (ddd, $J = 6.8, 4.7, 2.5$ Hz, 1H), 2.23 (dd, $J = 13.2, 6.9$ Hz, 1H), 1.42 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H), 1.07 (d, $J = 7.2, 3$ Hz). IR: 1731. HRMS (FAB) calculated for $C_{14}H_{23}O_5$ (MH⁺) 271.1545, found 271.1552.

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FURTHER CHEMISTRY WITH 6-METHYLDIOXENONE CYCLOADDUCTS

3.1 Introduction

It has been known for some time that β -dicarbonyl compounds participate in [2+2] photocycloadditions to alkenes. One of the first examples was the addition of 2,4-pentanedione (**1**) to several alkenes to give 1,5-diketones such as **3** (eq 3.1).¹

This reaction is often referred to as the De Mayo reaction and proceeds through a hydrogen bonded enol tautomer of **1** which in the excited state reacts with alkenes in the same way as α,β -unsaturated ketones. The primary photoproduct **2** is not stable and undergoes spontaneous retro-aldol cyclobutane fragmentation to afford the diketone **3**. The intramolecular hydrogen bond in acyclic β -diketones confers sufficient configurational stability to prevent energy consuming *cis-trans* isomerization and thus to allow successful photocycloadditions. Acyclic β -keto esters do not give cyclobutanes on irradiation, probably due to the weak hydrogen bonding capacity compared to the diketones. However, a dioxenone such as **4**, which is in fact a β -keto ester in its covalently restricted enol form, behaves very well in cycloaddition chemistry and leads to cycloadduct **5** in good yield (eq 3.2).²

Although in most cases photoproducts such as **5** are stable and can be isolated, it is well known that a dioxanone fused to a cyclobutane can be readily fragmented *via* a retro-aldol reaction under either acidic or basic conditions.³ This leads to compounds such as **6** providing a useful extension of the classical De Mayo approach to the enols of β -keto esters. This process has found several applications in the synthesis of very complex molecules.⁴ We wanted to apply this protocol to the dioxenone-alkene cycloadducts described in chapter 2, in order to probe the synthetic utility of these interesting bicyclohexanes. Furthermore, it

would provide additional proof of the structure of some of our cycloadducts, which could not always be assigned unequivocally.

3.2 Retro-Aldol Reactions

The bicyclo[2.1.1]hexane **7** was subjected to a retro-aldol reaction under basic conditions followed by methylation with diazomethane (eq 3.3).⁵

Thereby, the crossed adduct **7** allowed formation of the interesting tricycloundecane structure **9** as a single product. This retro-aldol product contains ample functionality for further modification. The pseudo-equatorial position of the ester group was deduced from the nuclear Overhauser effect between the acetyl methyl group and the five-membered ring protons. With these successful retro-aldol conditions in hand, several of the straight cycloadducts were subjected to the fragmentation reaction (table 3.1).

Table 3.1

entry	cycloadduct	product
1		
2		
3		
4		

Notes: (a) main adduct drawn

New functionalized cyclobutane structures **14–17** were obtained in good yields from the straight adducts. The cyclopentane and cyclohexane straight adducts **10** and **11** underwent ring fragmentation to spiro compounds **14** and **15**, respectively, obtained as mixtures of epimers in good yields. Because the retro-aldol reaction proceeds through an ester enolate intermediate, epimerization most probably takes place at this position. Both isomers of **15** could be separated by flash chromatography. The main epimer of **15** was a crystalline solid (mp 86 °C), which was subjected to X-ray analysis. This epimer showed the same stereochemistry as precursor **11**. More importantly, the X-ray structure ultimately proved the mode of photocycloaddition, *i.e.* the structure of **11**.

Figure 3.1 Crystal structure of the main isomer of **15**
(hydrogen atoms omitted for clarity)

The retro-aldol sequence was also applied to the bicyclo[2.2.0]hexanes **12** and **13**. Although the latter was not completely pure, both underwent clean base-induced fragmentation to **16** and **17**, respectively, as 70:30 isomeric mixtures, which were fully characterized as cyclobutanes by extensive NMR experiments. These cyclobutane products can only arise from straight adducts (a crossed adduct would lead to a five-membered ring), so that herewith the 1,6-closure process in the case of acyclic alkenes **12** and **13** was unequivocally proven. Finally, this De Mayo variant provides a synthetic pathway towards trifunctionalized spiro[3.5]nonanes or spiro[3.4]octanes⁶ as well as to novel substituted cyclobutanes.

3.3 Reduction Reactions

As described in chapter 2, we developed reduction conditions to release a diol function from the cycloadducts. In that way, it was possible to prove the structure of cycloadduct **19**, which was not stable towards column chromatography and therefore could not be purified and characterized completely (eq 3.4).

The rather harsh reduction conditions were necessary to prevent a competitive retro-aldol process during the reaction, which would destroy the judiciously constructed cyclobutane ring. Although most of the cycloadducts described in chapter 2 could be purified, either by chromatography or by crystallization and therefore did not need this extra reduction step, we were interested to see whether this sequence could be generally applied to the cycloaddition products, both crossed and straight. Thus, we subjected a number of cycloadducts to the reduction reaction. The results are depicted in table 3.2.

Table 3.2

entry	cycloadduct	product
1	11	23 99%
2	21 R = MOM (57:43) 22 R = TBDMS (75:25)	24 R = MOM, 86% (57:43)
3		25 R = TBDMS, 70% (75:25)
4	7	26 52%

Straight cycloadduct **11** afforded the expected diol **23** in a virtually quantitative yield (entry 1). Analogously, **21** (entry 2) and **22** (entry 3) afforded reduced products **24** and **25**, respectively, in good yields. The somewhat lower yield of **25** is due to the moderate stability of the TBDMS protecting group under the reduction conditions. In addition, crossed cycloadduct **7** was successfully reduced to tetraol **26** (entry 4), albeit in a more moderate yield of 52%. However, this tetraol seemed a good precursor for further model studies towards the right-hand side of solanoelepin A. Apart from the superfluous methyl group on the cyclobutane, which hampers the formation of the required cyclobutanone, **26** contains the appropriate substitution pattern and stereochemistry for further investigations towards the right-hand side of solanoelepin A.

3.4 Model Studies towards the Right-Hand Side of Solanoelepin A

The functionalization of **26** towards our target model system **27**, required the differentiation of all four hydroxyl groups (eq 3.5).⁷

Especially, the distinction between the rather similar primary hydroxyls was deemed to be not a trivial chore. We wanted to utilize the fact that only one of the primary alcohols could form a six-membered ring with the tertiary hydroxyl group upon acetalization (eq 3.6).⁸

However, all efforts under either thermodynamic or kinetic conditions resulted in a complex mixture of acetal isomers. Therefore, a different method was sought that would allow the selective functionalization of one of both primary hydroxy groups. Unfortunately, all attempts to directly mono-protect one of the primary alcohols by means of steric bias met with failure, even when very bulky protective groups such as pivaloyl chloride or TIPSCl were employed. In all cases, no significant distinction between the alcohols was observed. However, it was found that by using a reactive bulky silylating agent such as TBDMSOTf, three out of four hydroxyl functions could be protected (eq 3.7).

This reaction resulted in the formation of tris-silyl ether **29** in good yield. Only the tertiary alcohol was left untouched, allowing selective further functionalization of this group. Again, we wanted to make use of the possible six-membered ring between this tertiary and one of the primary alcohols, but now instead of an acetal linkage, a cyclic carbonate was envisaged.

Therefore, mixed carbonate **30** was prepared from **29** by deprotonation of the tertiary alcohol with KHMDS, followed by acylation with phenyl chloroformate (scheme 3.1).

Scheme 3.1

Formation of the cyclic carbonate, first required the hydrolysis of the primary silyl ethers in the presence of the secondary one. This was effected by treatment of **30** with a catalytic amount of camphorsulfonic acid in a mixture of CH₂Cl₂ and MeOH, to afford diol **31** in 80% yield.⁹ We were very pleased to find that upon deprotonation of the primary alcohols with sodium hydride, the expected primary alcohol cyclized to give cyclic carbonate **32**, leaving only one primary alcohol unprotected and ready for further elaboration. The choice of the phenyl carbonate group proved to be crucial for the success of this strategy. The analogously prepared ethyl carbonate **33** did not engage in the intramolecular cyclization reaction, instead only migration of the carbonate group was observed (eq 3.8).

Apparently, the ethoxy group is a worse leaving group than the tertiary alcoholate, preventing the formation of the cyclic carbonate. The increased acidity of the phenol substituent, however, is sufficient to allow this transformation to occur.

3.5 Conclusions

In this chapter retro-aldol reactions with the 6-methyldioxenone cycloadducts are described. The application of this transformation to the pentacyclic bislactone **7** allowed the stereoselective synthesis of the interesting tricycloundecane **9**. Furthermore, this variant on the classical De Mayo reaction provides a synthetic pathway towards trifunctionalized spiro[3.5]nonanes (**15**) and spiro[3.4]octanes (**14**) as well as to novel substituted cyclobutanes (**16**–**17**). In addition, we have shown that the cycloadducts can be functionalized without four-membered ring fragmentation, by a rapid and exhaustive reduction leading to the release of a diol function from the dioxanone moiety. Application of these conditions on cycloadduct **7** afforded tetraol **26**. This tetraol has been further functionalized by a four-step sequence to cyclic carbonate **32** in which all four hydroxyl groups have been differentiated.

3.6 Acknowledgments

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3.7 Experimental Section

General information. For general experimental details, see Section 2.9.

General procedure A for the Retro-Aldol Reaction. To a solution of the cycloadduct in dioxane (0.05M) at room temperature was added dropwise an aqueous solution of KOH (1M, 10 equiv.). The mixture was stirred for the indicated time. The reaction mixture was cooled to 0 °C, carefully acidified with 2N HCl to pH 2–3 and extracted with CH₂Cl₂. The combined organic layers were washed brine, dried over MgSO₄ and concentrated *in vacuo*. The remaining mixture was dissolved in methanol (0.1M), cooled to 0 °C, treated with an excess of diazomethane and subsequently concentrated *in vacuo*.

6-Acetyl-9-oxo-8-oxa-tricyclo[5.2.2.0^{1,6}]undecane-10-carboxylic acid methyl ester (9**).** According to general procedure **A**, cycloadduct **7** (100 mg, 0.34 mmol) was stirred for 150 min. to afford **9** (71 mg, 78%) as a white powder after purification (EtOAc:PE = 1:1). *R*_f = 0.22. mp 144–146 °C (EtOAc/pentane). ¹H NMR: 4.75 (br s, 1H), 3.69 (s, 3H), 3.29 (dd, *J* = 10.3, 4.5 Hz, 1H), 2.48 (ddd, *J* = 14.4, 4.5, 1.0 Hz, 1H), 2.19–2.15 (m, 2H), 2.15 (s, 3H), 1.96 (ddd, *J* = 6.6, 3.3, 1.3 Hz, 1H), 1.89 (ddd, *J* = 14.4, 10.3, 2.0 Hz, 1H), 1.74–1.57 (m, 3H), 1.45–1.33 (m, 1H), 1.05 (dq, *J* = 13.7, 3.6 Hz, 1H). ¹³C NMR: 205.2, 175.1, 171.8, 78.7, 67.4, 56.8, 52.3, 42.7, 31.6, 25.6, 25.6, 22.3, 21.8, 20.1. IR: 1775, 1732, 1705. Anal. Calcd for C₁₄H₁₈O₅: C, 63.15; H, 6.81. Found: C, 62.98; H, 6.93.

7-Acetyl-1,4-dioxa-dispiro[4.0.4.2]dodecane-11-carboxylic acid methyl ester (14). According to general procedure A, cycloadduct **10** (56 mg, 0.19 mmol) was stirred for 105 min. to afford a 50:50 mixture of diastereomers **14a** and **14b** (40 mg 78%) as a colorless oil after purification (Et₂O:PE = 1:3).

Repeated chromatography led to pure isomers. **14a**: white powder. R_f = 0.21. mp 68–71 °C. ¹H NMR: 3.94–3.70 (m, 4H), 3.58 (s, 3H), 2.89 (dd, J = 9.3, 7.6 Hz, 1H), 2.45 (dd, J = 12.6, 7.6 Hz, 1H), 2.40 (dd, J = 12.6, 9.3 Hz, 1H), 2.29–2.23 (m, 1H), 2.12 (s, 3H), 2.01 (ddd, J = 13.0, 10.2, 7.9 Hz, 1H), 1.83–1.51 (m, 5H), 1.60 (s, 3H). ¹³C NMR: 221.1, 175.3, 109.0, 64.8, 64.4, 62.4, 51.6, 51.4, 37.5, 37.3, 32.2, 29.6, 28.6, 21.7. IR: 1728, 1708. HRMS (FAB) calculated for C₁₄H₂₁O₅ (MH⁺) 269.1389, found 269.1401. **14b**: colorless oil. R_f = 0.13. ¹H NMR: 3.96–3.91 (m, 3H), 3.81–3.76 (m, 1H), 3.66 (s, 3H), 3.27 (dd, J = 7.8, 6.1 Hz, 1H), 3.09 (dd, J = 9.7, 8.8 Hz, 1H), 2.60 (dd, J = 12.3, 9.7 Hz, 1H), 2.24 (s, 3H), 2.21 (dd, J = 12.3, 8.7 Hz, 1H), 2.14–2.08 (m, 1H), 1.86–1.81 (m, 1H), 1.75–1.50 (m, 4H). ¹³C NMR: 210.6, 172.8, 108.6, 64.9, 64.5, 63.1, 53.4, 51.4, 36.3, 36.2, 31.3, 29.7, 28.2, 23.0. IR: 1733, 1702.

7-Acetyl-1,4-dioxa-dispiro[4.0.5.2]tridecane-12-carboxylic acid methyl ester (15). According to general procedure A, cycloadduct **11** (43 mg, 0.14 mmol) was stirred for 105 min. to afford a 30:70 mixture of diastereomers **15a** and **15b** (30 mg 75%) as a colorless oil after purification (EtOAc:PE = 1:5). Repeated chromatography led to pure isomers. **15a**: colorless oil. R_f =

0.17. ¹H NMR: 3.96–3.75 (m, 4H), 3.56 (s, 3H), 2.60 (dd, J = 9.6, 8.0 Hz, 1H), 2.42 (dd, J = 7.9, 12.6 Hz, 1H), 2.33 (dd, J = 9.6, 12.6 Hz, 1H), 2.21–2.12 (m, 1H), 2.10 (s, 3H), 1.94–1.90 (m, 2H), 1.72 (ddt, J = 13.9, 5.8, 3.5 Hz, 1H), 1.60–1.56 (m, 2H), 1.45–1.38 (m, 1H), 1.32 (qt, J = 13.0, 4.0 Hz, 1H), 1.06 (qt, J = 13.2, 3.6 Hz, 1H). ¹³C NMR: 210.5, 174.8, 108.3, 64.6, 64.3, 55.9, 51.3, 47.3, 40.6, 36.7, 29.9, 29.0, 26.1, 23.9, 21.1. IR: 1723 (br). HRMS (FAB) calculated for C₁₅H₂₃O₅ (MH⁺) 283.1545, found 283.1540. **15b**: X-ray crystal structure determination was allowed after recrystallization from EtOAc/PE. Colorless crystals. R_f = 0.08. mp 85–87 °C. ¹H NMR: 3.94–3.68 (m, 4H), 3.67 (s, 3H), 3.54–3.52 (m, 1H), 2.70 (dd, J = 7.2, 4.1 Hz, 1H), 2.58 (dd, J = 12.6, 9.2 Hz, 1H), 2.19 (s, 3H), 2.14 (dd, J = 12.6, 9.0 Hz, 1H), 2.07–2.02 (m, 1H), 1.64–1.50 (m, 5H), 1.27–1.24 (m, 2H). ¹³C NMR: 211.1, 174.0, 109.1, 64.7, 64.3, 56.9, 51.6, 51.4, 36.2, 35.2, 30.4, 27.1, 26.4, 23.9, 21.9. IR: 1731, 1711.

Crystallographic data for **15b**: monoclinic, P2₁/a, a = 10.090(2), b = 9.9196(8), c = 15.0683(10) Å, β = 102.024(7)°, V = 1475.1(3) Å³, Z = 4, D_x = 1.27 g cm⁻³, λ (CuK α) = 1.5418 Å, μ (CuK α) = 7.80 cm⁻¹, $F(000)$ = 608, 293 K. Final R = 0.084 for 2421 observed reflections.

Table 3.3 Bond distances of the non-hydrogen atoms (Å) of **15b** (standard deviations)

C(1)-C(2)	1.523(6)	C(6)-C(12)	1.517(6)	C(11)-O(2)	1.430(7)
C(1)-C(6)	1.539(6)	C(7)-C(8)	1.555(7)	C(12)-C(13)	1.519(7)
C(1)-C(7)	1.566(6)	C(7)-C(14)	1.511(6)	C(12)-O(3)	1.195(6)
C(1)-C(9)	1.593(6)	C(8)-C(9)	1.504(7)	C(14)-O(4)	1.199(7)
C(2)-C(3)	1.532(7)	C(9)-O(1)	1.374(6)	C(14)-O(5)	1.343(6)
C(3)-C(4)	1.517(9)	C(9)-O(2)	1.421(5)	C(15)-O(5)	1.457(9)
C(4)-C(5)	1.514(9)	C(10)-C(11)	1.474(9)		
C(5)-C(6)	1.538(6)	C(10)-O(1)	1.423(7)		

Table 3.4 Bond angles of the non-hydrogen atoms (°) of **15b** (standard deviations)

C(2)-C(1)-C(6)	108.7(4)	C(5)-C(6)-C(12)	109.5(4)	C(10)-C(11)-O(2)	105.8(4)
C(2)-C(1)-C(7)	116.0(3)	C(1)-C(7)-C(8)	89.7(3)	C(6)-C(12)-C(13)	115.8(5)
C(2)-C(1)-C(9)	112.1(4)	C(1)-C(7)-C(14)	117.7(4)	C(6)-C(12)-O(3)	123.6(4)
C(6)-C(1)-C(7)	116.0(4)	C(8)-C(7)-C(14)	112.4(4)	C(13)-C(12)-O(3)	120.3(5)
C(6)-C(1)-C(9)	114.8(3)	C(7)-C(8)-C(9)	91.7(4)	C(7)-C(14)-O(4)	126.4(4)
C(7)-C(1)-C(9)	88.0(3)	C(1)-C(9)-C(8)	90.5(3)	C(7)-C(14)-O(5)	110.0(4)
C(1)-C(2)-C(3)	113.2(4)	C(1)-C(9)-O(1)	116.6(3)	O(4)-C(14)-O(5)	123.6(4)
C(2)-C(3)-C(4)	111.3(4)	C(1)-C(9)-O(2)	112.9(3)	C(9)-O(1)-C(10)	107.5(4)
C(3)-C(4)-C(5)	110.8(5)	C(8)-C(9)-O(1)	115.1(4)	C(9)-O(2)-C(11)	106.9(4)
C(4)-C(5)-C(6)	111.0(5)	C(8)-C(9)-O(2)	114.0(4)	C(14)-O(5)-C(15)	113.3(6)
C(1)-C(6)-C(5)	110.2(3)	O(1)-C(9)-O(2)	107.3(3)		
C(1)-C(6)-C(12)	116.8(4)	C(11)-C(10)-O(1)	102.6(5)

3-Methoxymethoxy-2-methyl-2-(2-oxo-propyl)-cyclobutanecarboxylic acid methyl ester (16). According to general procedure **A**, cycloadduct **12** (81 mg, 0.3 mmol) was stirred for 30 min. to afford a 30:70 mixture of diastereomers **16a** and **16b** (56 mg 77%) as a colorless oil after

purification (Et₂O:PE = 1:4). Repeated chromatography led to pure isomers. **16a**: colorless oil. *R_f* = 0.15. ¹H NMR: 4.55 (d, *J* = 6.6 Hz, 1H), 4.50 (d, *J* = 6.6 Hz, 1H), 3.74 (dd, *J* = 8.7, 7.4 Hz, 1H), 3.63 (s, 3H), 3.34 (s, 3H), 2.80 (d, *J* = 18.0 Hz, 1H), 2.64 (d, *J* = 18.0 Hz, 1H), 2.44 (dd, *J* = 10.8, 7.5 Hz, 1H), 2.34-2.24 (m, 2H), 2.11 (s, 3H), 1.44 (s, 3H). ¹³C NMR: 207.2, 173.3, 96.7, 76.3, 55.3, 51.5, 48.8, 42.5, 40.6, 28.4, 26.1. IR: 1731. HRMS (FAB) calculated for C₁₂H₂₁O₅ (MH⁺) 245.1389, found 245.1382. **16b**: colorless oil. *R_f* = 0.10. ¹H NMR: 4.56 (d, *J* = 6.5 Hz, 1H), 4.53 (d, *J* = 6.5 Hz, 1H), 3.98 (ddd, *J* = 7.0, 5.2, 1.0 Hz, 1H), 3.68 (s, 3H), 3.32 (s, 3H), 3.01 (ddd, *J* = 9.3, 5.9, 1.0 Hz, 1H), 2.80 (d, *J* = 16.8 Hz, 1H), 2.68 (d, *J* = 16.8 Hz, 1H), 2.54 (ddd, *J* = 12.8, 7.1, 5.9 Hz, 1H), 2.15 (s, 3H), 2.01 (ddd, *J* = 12.7, 9.3, 5.2 Hz, 1H), 1.16 (s, 3H). ¹³C NMR: 207.2, 173.9, 95.6, 77.3, 55.4, 51.4, 48.0, 46.0, 42.7, 31.4, 27.3, 20.6. IR: 1733.

3-Methoxymethoxy-2-(1-methyl-2-oxo-propyl)-cyclobutanecarboxylic acid methyl ester (17). According to general procedure **A**, cycloadduct **13** (22 mg, 0.08 mmol) was stirred for 45 min. to afford a 70:30 mixture of diastereomers **17a** and **17b** (15 mg 75%) as a colorless oil after

purification (Et₂O:PE = 1:3). Repeated chromatography led to pure isomers. **17a**: colorless oil. *R_f* = 0.12. ¹H NMR: 4.64 (d, *J* = 6.7 Hz, 1H), 4.56 (d, *J* = 6.7 Hz, 1H), 4.32-4.26 (m, 1H), 3.59 (s, 3H), 3.57 (s, 3H), 3.13-3.06 (m, 1H), 2.99 (ddd, *J* = 8.8, 7.9, 0.9 Hz, 1H), 2.38-2.34 (m, 2H), 2.17-2.14 (m, 1H), 2.15 (s, 3H), 1.13 (d, *J* = 7.0 Hz, 3H). ¹³C NMR: 211.5, 174.3, 94.6, 70.5, 55.5, 51.4,

45.2, 42.9, 35.5, 30.7, 28.3, 16.3. IR: 1714, 1712. HRMS (FAB) calculated for $C_{12}H_{21}O_5$ (MH^+) 245.1389, found 245.1383. **17b**: colorless oil. R_f = 0.08. 1H NMR: 4.66 (d, J = 6.7 Hz, 1H), 4.53 (d, J = 6.7 Hz, 1H), 4.34 (ddt, J = 6.6, 2.3, 0.9 Hz, 1H), 3.67 (s, 3H), 3.37 (s, 1H), 3.03 (ddt, J = 9.1, 8.2, 0.9 Hz, 1H), 2.95 (dq, J = 10.6, 6.8 Hz, 1H), 2.88-2.82 (m, 1H), 2.35 (ddd, J = 12.5, 8.2, 1.0 Hz, 1H), 2.17-2.11 (m, 1H), 2.14 (s, 3H), 1.57 (s, 3H), 1.12 (d, J = 6.8 Hz, 3H). ^{13}C NMR: 211.2, 174.9, 94.5, 71.2, 55.6, 51.6, 46.0, 45.5, 40.0, 30.1, 28.3, 15.1. IR: 1734, 1711.

General procedure B for the reduction reactions. To a solution of $LiAlH_4$ (1M in THF, 5 equiv.) was added dropwise at room temperature, a solution of the cycloadduct in THF (0.5M). The reaction mixture was stirred for 10 min. Then, the reaction was quenched by addition of EtOAc and saturated aqueous Na_2SO_4 (10 drops) was added. The resulting mixture was stirred for 1 h. After addition of additional solid Na_2SO_4 the mixture was filtered through Celite® and concentrated *in vacuo*.

Diol 23. According to general procedure B, cycloadduct **11** (96 mg, 0.31 mmol) afforded diol **23** (78 mg, 99%) as a colorless oil without further purification. 1H NMR: 4.01-3.85 (m, 4H), 3.81-3.75 (m, 2H), 2.62 (dd, J = 8.8, 6.4 Hz, 1H), 2.55 (d, J = 13.9 Hz, 1H), 2.40-2.20 (br s, 2H), 2.20 (d, J = 13.9 Hz, 1H), 1.81-1.73 (m, 2H), 1.70-1.43 (m, 3H), 1.37-1.26 (m, 1H), 1.27 (s, 3H), 1.14-1.06 (m, 1H). ^{13}C NMR: 109.1, 79.4, 64.5, 64.3, 62.7, 51.6, 45.1, 40.7, 40.5, 24.0, 21.5, 20.8, 19.5, 18.3. HRMS (FAB) calculated for $C_{14}H_{23}O_4$ (MH^+) 255.1596, found 255.1592.

4-Hydroxymethyl-2-methoxymethoxy-5-methyl-tricyclo[4.3.0.0^{1,4}]nonan-5-ol (24). According to general procedure B, cycloadduct **21** (41 mg, 0.14 mmol) afforded diol **24** (29 mg, 86%) as an inseparable 57:43 mixture of diastereomers as a colorless oil after purification (EtOAc). R_f = 0.22. 1H NMR: 4.66 (d, J = 6.6 Hz, 1H), 4.59 (d, J = 6.6 Hz, 1H), 4.57 (d, J = 6.6 Hz, 1H), 4.56 (d, J = 6.6 Hz, 1H), 4.17-4.10 (m, 2H), 3.90 (br d, J = 11.2 Hz, 1H), 3.79 (br d, J = 11.7 Hz, 1H), 3.71 (br d, J = 11.2 Hz, 1H), 3.65 (br d, J = 11.7 Hz, 1H), 3.35 (s, 3H), 3.33 (s, 3H), 2.87 (d, J = 8.7 Hz, 1H), 2.59-2.52 (m, 4H), 2.40 (br s, 1H), 2.37 (d, J = 8.8 Hz, 1H), 2.21 (dd, J = 13.3, 9.4 Hz, 1H), 2.15 (dd, J = 13.3, 7.0 Hz, 1H), 2.03-1.81 (m, 6H), 1.80-1.72 (m, 3H), 1.55-1.36 (m, 4H), 1.34 (s, 3H), 1.33 (s, 3H). ^{13}C NMR: 95.4, 95.0, 78.4, 76.3, 75.7, 71.6, 64.2, 63.6, 56.4, 55.4, 55.2, 52.9, 50.3, 47.0, 45.3, 33.9, 33.5, 30.1, 18.1, 27.9, 27.0, 26.1, 26.0, 25.6, 25.0. IR: 3415 (br). HRMS (FAB) calculated for $C_{13}H_{23}O_4$ (MH^+) 243.1596, found 243.1589.

2-(tert-Butyl-dimethyl-silanyloxy)-4-hydroxymethyl-5-methyl-tricyclo[4.3.0.0^{1,4}]nonan-5-ol (25). According to general procedure B, cycloadduct **22** (121 mg, 0.33 mmol) afforded diol **25** (72 mg, 70%) as an inseparable 75:25 mixture of diastereomers as a colorless oil after purification (EtOAc). R_f = 0.40. 1H NMR: 4.21 (dd, J = 9.3, 6.4 Hz, 1H), 4.16 (dd, J = 5.2, 2.2 Hz, 1H), 3.80 (d, J = 11.4 Hz, 1H), 3.77 (d, J = 11.7 Hz, 1H), 3.73 (d, J = 11.4 Hz, 1H), 3.63 (d, J = 11.7 Hz, 1H), 2.87 (d, J = 8.7 Hz, 1H), 2.72 (br s, 4H), 2.55 (dd, J = 13.8, 5.3 Hz, 1H), 2.32 (d, J =

8.2 Hz, 1H), 2.14 (dd, $J = 13.1, 9.3$ Hz, 1H), 2.02 (dd, $J = 13.1, 6.4$ Hz, 1H), 1.96–1.77 (m, 6H), 1.75–1.68 (m, 3H), 1.55–1.23 (m, 4H), 1.32 (s, 3H), 1.30 (s, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.01 (s, 6H), -0.01 (s, 6H). ^{13}C NMR: 78.6, 75.7, 72.2, 66.4, 63.9, 63.4, 57.7, 57.0, 51.9, 50.9, 46.3, 45.2, 36.7, 36.6, 29.8, 28.3, 27.7, 27.4, 25.9, 25.8, 25.8, 24.9, 18.1, 18.0, -4.6, -4.7, -4.9. IR: 3415 (br). HRMS (FAB) calculated for $\text{C}_{17}\text{H}_{33}\text{O}_3\text{Si}$ (MH^+) 313.2199, found 313.2214.

1,7a-Bis-hydroxymethyl-8-methyl-octahydro-1,3a-methano-indene-3,8-diol (26). According to general procedure B, cycloadduct 7 (95 mg, 0.32 mmol) afforded the tetraol **26** (43 mg, 52%) as a white powder after purification (EtOAc:acetone = 1:1). $R_f = 0.31$. ^1H NMR (CD_3OD): 4.38 (dd, $J = 11.4, 2.5$ Hz, 1H), 3.94 (dd, $J = 7.4, 3.1$ Hz, 1H), 3.77 (d, $J = 11.1$ Hz, 1H), 3.38 (d, $J = 11.1$ Hz, 1H), 3.34 (d, $J = 11.4$ Hz, 1H), 3.26 (d, $J = 11.4$ Hz, 1H), 3.03–2.95 (m, 1H), 2.03–1.87 (m, 4H), 1.65–1.61 (m, 1H), 1.55–1.25 (m, 4H), 1.08 (s, 3H). ^{13}C NMR (CD_3OD): 84.5, 73.0, 62.4, 59.1, 58.6, 58.1, 51.9, 37.6, 27.0, 23.0, 22.5, 21.9, 19.3. HRMS calculated for $\text{C}_{13}\text{H}_{22}\text{O}_4\text{Na}$ (MNa^+) 265.1416, found 265.1425.

3-(tert-Butyl-dimethyl-silyloxy)-1,7a-bis-(tert-butyl-dimethyl-silyloxymethyl)-8-methyl-octahydro-1,3a-methano-inden-8-ol (29).

To a solution of **26** (40 mg, 0.17 mmol) in CH_2Cl_2 (1 mL) was added dropwise at 0 °C, TBDMSOTf (195 μL , 0.85 mmol) and 2,6-lutidine (200 μL , 1.7 mmol). The resulting mixture was stirred at 0

°C for 1 h. The reaction was quenched by addition of saturated aqueous NaHCO_3 (1 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×2 mL). The combined organic layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:40) afforded **29** (80 mg, 83%) as a colorless oil. $R_f = 0.19$. ^1H NMR: 4.50 (dd, $J = 10.6, 2.4$ Hz, 1H), 4.04 (d, $J = 10.7$ Hz, 1H), 3.83 (dd, $J = 7.5, 2.5$ Hz, 1H), 3.80 (d, $J = 10.7$ Hz, 1H), 3.25 (d, $J = 10.6$, 1H), 2.88 (s, 1H), 2.86–2.77 (m, 1H), 2.00 (dd, $J = 12.3, 7.5$ Hz, 1H), 2.00–1.87 (m, 2H), 1.64–1.59 (m, 2H), 1.48–1.43 (m, 2H), 1.37–1.18 (m, 2H), 1.13 (s, 3H), 0.88 (s, 27H), 0.04 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H). ^{13}C NMR: 85.0, 73.1, 63.6, 62.7, 57.7, 55.8, 50.6, 37.8, 27.3, 26.0, 25.9, 25.8, 22.0, 21.7, 21.1, 20.8, 18.24, 18.1, 18.0, -4.7, -5.1, -5.3, -5.5, -5.6, -5.7. HRMS (FAB) calculated for $\text{C}_{31}\text{H}_{65}\text{O}_4\text{Si}_3$ (MH^+) 585.4191, found 585.4079.

Carbonic acid 3-(tert-butyl-dimethyl-silyloxy)-1,7a-bis-(tert-butyl-dimethyl-silyloxymethyl)-8-methyl-octahydro-1,3a-methano-inden-8-yl ester phenyl ester (30).

To a solution of **29** (53 mg, 0.091 mmol) in THF (0.5 mL) was added dropwise at -78 °C, KHMDs (0.5M in toluene, 350 μL , 0.18 mmol). The reaction

mixture was stirred at -78 °C for 1 h. To this solution was added at -78 °C, phenyl chloroformate (55 μL , 0.44 mmol). The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×2 mL).

The combined organic layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo* to afford **30** (49 mg, 76%) as a colorless oil, which was used crude in the next reaction. ^1H NMR: 7.40-7.36 (m, 2H), 7.26-7.21 (m, 1H), 7.16 (dd, $J = 8.7, 1.1$ Hz, 2H), 4.49 (dd, $J = 10.7, 2.2$ Hz, 1H), 3.91 (d, $J = 10.8$ Hz, 1H), 3.89-3.87 (m, 1H), 3.80 (d, $J = 10.8$ Hz, 1H), 3.28 (d, $J = 10.7$ Hz, 1H), 2.44-2.37 (m, 2H), 1.99-1.96 (m, 1H), 1.75-1.61 (m, 4H), 1.55 (s, 3H), 1.44-1.26 (m, 3H), 0.89 (s, 27H), 0.08 (s, 3H), 0.04 (s, 6H), 0.04 (s, 3H), 0.01 (s, 6H). ^{13}C NMR: 152.2, 151.3, 129.4, 125.8, 121.4, 93.1, 71.9, 62.7, 59.7, 59.5, 57.9, 50.4, 36.8, 26.0, 25.9, 25.8, 25.7, 21.9, 20.8, 20.6, 18.3, 18.1, 17.9, 17.3, -4.7, -5.1, -5.3, -5.5, -5.6, -5.7.

Carbonic acid 3- (tert-butyl-dimethyl-silanyloxy)-1,7a-bis-hydroxy-methyl-8-methyl-octahydro-1,3a-methano-inden-8-yl ester phenyl ester (31).

To a solution of **30** (49 mg, 0.069 mmol) in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1 mL, 9:1 v/v) was added at 0°C , CSA (2 mg, 0.008 mmol). The mixture was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched by addition of saturated aqueous NaHCO_3 (2 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×2 mL). The combined organic layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo* to afford **31** (26 mg, 80%) as a colorless oil, which was used crude for the next reaction. ^1H NMR: 7.41-7.36 (m, 2H), 7.26-7.22 (m, 1H), 7.16-7.13 (m, 2H), 4.43 (dd, $J = 11.7, 2.3$ Hz, 1H), 3.94 (dd, $J = 6.9, 2.3$ Hz, 1H), 3.74 (d, $J = 12.0$ Hz, 1H), 3.62 (d, $J = 12.0$ Hz, 1H), 3.42 (d, $J = 11.7$ Hz, 1H), 2.25-2.04 (m, 4H), 1.79-1.70 (m, 2H), 1.59-1.36 (m, 4H), 1.44 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR: 152.5, 151.0, 129.5, 126.1, 121.2, 94.1, 71.5, 62.1, 59.7, 59.3, 58.9, 50.6, 37.9, 25.8, 25.6, 21.1, 20.9, 20.6, 18.0, 15.2, -4.8, -5.1.

Cyclic carbonate (32). To a solution of **31** (25 mg, 0.052 mmol) in THF (1 mL) was added at 0°C , NaH (60 wt. % dispersion in mineral oil, 5 mg, 0.13 mmol). The mixture was stirred at 0°C for 15 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×2 mL).

The combined organic layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography ($\text{EtOAc}:\text{PE} = 1:1$) afforded **32** (13 mg, 65%) as a colorless oil. $R_f = 0.23$. ^1H NMR: 4.70 (d, $J = 11.9$ Hz, 1H), 4.48-4.44 (m, 1H), 4.43 (d, $J = 11.9$ Hz, 1H), 3.97 (dd, $J = 7.3, 2.5$ Hz, 1H), 3.45 (d, $J = 11.5$ Hz, 1H), 2.09-1.97 (m, 3H), 1.92 (dd, $J = 12.6, 7.4$ Hz, 1H), 1.77-1.69 (m, 2H), 1.54-1.45 (m, 3H), 1.39-1.22 (m, 2H), 1.22 (s, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR: 148.6, 89.7, 72.8, 70.9, 64.8, 59.2, 50.2, 47.1, 37.3, 28.7, 25.7, 22.0, 21.0, 21.0, 18.0, 16.8, -4.8, -5.1. IR: 1736. HRMS (FAB) calculated for $\text{C}_{20}\text{H}_{35}\text{O}_5\text{Si}$ (MH^+) 383.2254, found 383.2254.

3.8 References

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DIOXENONE DERIVATIVES AND ALTERNATIVE CHROMOPHORES

4.1 Introduction

Compound **4** represents the right-hand fragment of solanoecelepin A (scheme 4.1). As described in chapter 2, we successfully approached the bicyclo[2.1.1]hexane skeleton of **4** by means of a photochemical [2+2] cycloaddition of 6-methyldioxenone **1**. Cycloadduct **2** was then further functionalized to **3** (chapter 3).

Scheme 4.1

However, the implementation of this methodology in the synthesis of **4**, and thus in the total synthesis of solanoecelepin A, is hindered by two major issues. Firstly, **3** lacks the functionality to connect the right-hand side to the left-hand side, *i.e.* the β -keto ester derived vinyl triflate in the cyclohexane ring. Secondly, the methyl group on the cyclobutane, originating from C-6 of the dioxenone, hampers the formation of the necessary cyclobutanone. Therefore, our next experiments had two objectives, *viz.* (1) to construct an analog of **3** with an additional functional handle on the cyclohexane ring, which would allow the connection with the left-hand side and (2) to find a way to equip the C-6 methyl of the dioxenone with a functionality that would allow transformation into a ketone. The combination of the results of the two objectives should then provide a picture of how to synthesize target fragment **4**. For the first objective, only a slightly modified cyclization precursor had to be constructed. The second objective required a more careful evaluation of the photosubstrate. The latter resulted in the design of precursor **7**, which contains an additional oxygen substituent on the dioxenone (eq 4.1). After cycloaddition and

functionalization this would result in vicinal diol **6**, from which the cyclobutanone can be formed by oxidative cleavage.

The oxidative cleavage of a vicinal diol moiety is a known method to prepare cyclobutanones.¹ However, literature precedent for the formation of bicyclohexanones *via* this method is absent. Nonetheless, we were interested to see whether we could employ this strategy in the synthesis of **5**. This would allow us to use the chemistry developed so far, with only a minor modification of the dioxenone.

4.2 The Connection Handle

The synthesis of a cyclization precursor with an appropriate functional handle for connecting the right- and the left-hand side of solanoecepin A, required the use of β -keto ester derived vinyl triflate **10**, containing an additional oxygen substituent on the six-membered ring (eq 4.2).

Vinyl triflate **10** was synthesized from commercially available enone **8**, by carboxylation of the enolate with dimethyl carbonate,² followed by transformation of β -keto ester **9** into the desired triflate **10**.³ Coupling of **10** to aldehyde **11** afforded lactone **12** in good yield (eq 4.3).

Precursor **12** appeared unsuitable for the photochemistry leading to extensive decomposition of the starting material, most likely due to the diene interfering with the cycloaddition. Therefore, enol ether **12** was hydrolyzed to the corresponding ketone **13** (eq 4.4).

However, the photochemistry with **13** was unsuccessful, indicating that a ketone at that position was not tolerated by the cycloaddition as well. Consequently, the strategy was slightly adapted and a protected alcohol was chosen as a masked ketone equivalent. Therefore, ketone **13** was reduced with sodium borohydride, which resulted in alcohol **14** as a 60:40 mixture of diastereomers (eq 4.5).

The hydroxyl group of **14** was subsequently protected with an ethoxyethyl group (EEO), which resulted in the formation of **15** as an inseparable mixture of four diastereomers. The formation of isomeric mixtures is an unavoidable side effect of the use of the ethoxyethyl ether and obviously this group was not our first choice. However, several other protective groups either displayed limited stability towards the subsequent reaction steps, or they proved to be too stable, making cleavage, when necessary, a very problematic process. Thus, the mixture of isomers **15** was subjected to the irradiation conditions, which resulted in the smooth formation of cycloadduct **16** (eq 4.6).

As was observed with the previous bicyclo[2.1.1]hexane adducts (chapter 2), **16** was not stable towards silica gel column chromatography and therefore the crude material was used for the subsequent reaction. Exhaustive reduction of **16** afforded the stable tetraol **17**, which could be purified and completely characterized (eq 4.7).

The successful construction of tetraol **17** now set the stage for the formation of the envisaged ketone from the ethoxyethyl ether. Therefore, all hydroxyl groups of **17** except for the tertiary alcohol were acetylated, to afford triacetate **18** (scheme 4.2).

Scheme 4.2

Subsequently, the ethoxyethyl ether was hydrolyzed under mildly acidic conditions to afford alcohol **19** in quantitative yield. Finally, oxidation of the secondary hydroxyl function furnished ketone **20**. This ketone should eventually allow the connection of the left- and right-hand fragments of solanoeclepin A and thus our first objective was achieved.

4.3 Vicinal Diol Approach to the Cyclobutanone

Our second objective was to investigate the formation of the required cyclobutanone *via* oxidative cleavage of a vicinal diol (*viz.* compound **6**, eq 4.1). To obtain an appropriately substituted precursor for the vicinal diol it was necessary to introduce an additional oxygen substituent on the C-6 methyl of the dioxenone. This was conveniently achieved in two steps. Bromination of the dienolate derived from **21** afforded the allylic bromide **22**, which was subsequently converted into the acetate **23** (eq 4.8).^{4,5}

Subsequently, oxidative cleavage of the terminal olefin of **23** resulted in the formation of aldehyde **24** (eq 4.9).

Making use of the conditions developed for the 6-methyldioxenone precursors, aldehyde **24** was then coupled with cyclohexenyl triflate⁶ (scheme 4.3).

Scheme 4.3

Allylic alcohol **25** was oxidized under Swern conditions to afford ketone **26**, which was acetalized according to Noyori's protocol⁷ to obtain dioxolane **27**. In view of the results obtained with the 6-methyldioxenones (chapter 2), we were aware that the photochemistry with precursor **27** would lead to the undesired straight cycloadduct. However, functionalization of this cycloadduct was anticipated to be more facile than in the case of the appropriate crossed pentacyclic bislactone. Therefore, precursor **27** was used as a model to investigate the formation of the desired cyclobutanone.

Indeed, irradiation of **27** led to the formation of bicyclo[2.2.0]hexane **28** in excellent yield (eq 4.10). Unequivocal structural proof was obtained by X-ray diffraction, providing the crystal structure depicted in figure 4.1.

Figure 4.1 Crystal structure of **28**
(hydrogen atoms omitted for clarity)

Reduction of cycloadduct **28** afforded triol **29**, setting the stage for the oxidative cleavage of the vicinal diol (eq 4.11). Surprisingly, instead of the expected cyclobutanone, keto-acid **30** was isolated in 86% yield.

A possible mechanistic explanation for the formation of **30**, involves the intermediacy of the anticipated cyclobutanone **31** (scheme 4.4). This cyclobutanone undergoes a retro [2+2] cycloaddition, leading to hydroxy-ketene **32**. Intramolecular lactonization followed by β -elimination of the carboxylate leads to α,β -unsaturated acid **33**. Finally, upon acidic workup the dioxolane is hydrolyzed, leading to keto-acid **30**.

Scheme 4.4

This result indicates the instability of the cyclobutanone towards the oxidative cleavage conditions and consequently a different strategy to obtain the target ketone functionality had to be explored.

4.4 Alternative Chromophores

So far, the use of dioxenone derived precursors provided a very efficient entry into the construction of bicyclohexanes, including pentacyclic bislactone **2**, which contains the appropriate substitution pattern and stereochemistry for elaboration towards the right-hand fragment of solanoecelepin A (eq 4.12).⁸ However, the functionalization of cycloadduct **2** proved to be less straightforward than its formation (see section 3.4).

The main reason for the difficult functionalization is the dioxanone carbonyl group, which not only renders the cycloadduct rather unstable, but also makes it very difficult to differentiate this part of the molecule from the 5-membered ring lactone. We realized that the α,β -unsaturated- γ -butenolide moiety of precursor **1** could also be used as the chromophore in the [2+2] cycloaddition, making the dioxenone no longer necessary. Intramolecular photochemical cycloadditions of such lactones with pendent alkenes have been reported,⁹ although seldom with a two atom tether.¹⁰ To investigate the potential of this method in the synthesis of target fragment **5**, we set out to synthesize an appropriate cyclization precursor. The synthesis started with glycerol derived ketone **34**,¹¹ which was subjected to a Horner–

Emmons olefination to afford α,β -unsaturated ester **35** (scheme 4.5). Deconjugation of the double bond by protonation of the dienolate at low temperature¹² afforded β,γ -unsaturated ester **36**.

Scheme 4.5

Reduction of **36** furnished homoallylic alcohol **37**, which was oxidized to aldehyde **38** by means of Dess–Martin periodinane. Unfortunately, the chromium mediated coupling with vinyl triflate **39**¹³ did not afford cyclization precursor **40**, but instead led to complete decomposition of aldehyde **38**. The instability of this aldehyde was attributed to the benzylidene acetal moiety, because rapid cleavage of this group under the reaction conditions was observed. Therefore, we set out to construct an analogous aldehyde containing a dimethyl acetal, which was assumed to be more stable under the coupling conditions. Starting from ketone **41**¹⁴, the same sequence of reactions as before, afforded aldehyde **45** in good overall yield (scheme 4.6).

Scheme 4.6

Aldehyde **45** displayed the expected stability towards the coupling conditions and afforded cyclization precursor **46** in 71% yield. Unfortunately, the photochemistry with butenolide **46** was not successful. Irradiation of **46** only led to decomposition of the starting material, and no cyclization products could be observed after, or even during the reaction. As possible reasons for the failure of the [2+2] cycloadditions, we hypothesized that either the butenolide chromophore was not efficient enough to initiate the cycloaddition, or the pendent alkene was not stable towards the irradiation conditions. To investigate these possibilities enone **48** was prepared by coupling of aldehyde **45** with cyclohexenyl triflate⁶ and subsequent oxidation of allylic alcohol **47** to the corresponding ketone **48** (eq 4.13). Generally, 1,5-dien-3-ones such as **48** are known to participate well in [2+2] cycloadditions,¹⁵ indicating the efficiency of the enone chromophore.

However, irradiation of **48** again resulted in complete decomposition of the photosubstrate, which led to the conclusion that the pendent enol was not stable towards the photochemistry. Therefore, we had to abandon the idea of using this type of cyclization precursors and search for alternative ways to construct the right-hand fragment of solanoeclepin A.

4.5 Conclusions

In this chapter the introduction of a functional handle to connect the left- and the right-hand fragments of solanoeclepin A has been described. The use of β -keto ester derived vinyl triflate **9** enabled the introduction of a masked ketone equivalent into the [2+2] cycloaddition precursor **15**. After elaboration of cycloadduct **16** the original ketone functionality could be restored by TPAP oxidation of alcohol **19**. This handle should eventually allow the connection of the two substructures of the natural product. In addition, we have explored the possible use of a vicinal diol to obtain the required cyclobutanone. Therefore, dioxenone derivative **23** bearing an additional oxygen substituent on the C-6 methyl group was prepared. Unfortunately, this strategy was unsuccessful due to the instability of bicyclohexanone **31** towards the oxidative cleavage conditions. Finally, we have investigated the potential of alternative chromophores, other than the dioxenone, for the [2+2] cycloaddition. To this end, α,β -unsaturated- γ -butenolide **46** and α,β -unsaturated ketone **48** were synthesized. These precursors would greatly facilitate the functionalization of the corresponding cycloadducts. However, in both cases the photochemistry resulted exclusively in decomposition of the substrates, probably due to the instability of the pendent enol ether towards the irradiation conditions.

4.6 Acknowledgments

Angeline van Ginkel is gratefully acknowledged for her contribution to this chapter. Jan Fraanje and Kees Goubitz are kindly acknowledged for the crystal structure determination of cycloadduct **28**.

4.7 Experimental Section

General information. For general experimental details, see Section 2.9.

4-Ethoxy-2-oxo-cyclohex-3-enecarboxylic acid ethyl ester (9). To a solution of diisopropylamine (25 mL, 0.18 mol) in THF (250 mL) was added dropwise at -78°C , *n*-butyllithium (1.6M in hexanes, 112 mL, 0.18 mol). The resulting mixture was stirred at -78°C for 1 h. Then a solution of enone **8** (20 mL, 0.14 mol) in THF (75 mL) was added dropwise at -78°C . The resulting mixture was stirred at -78°C for 30 min. and then transferred by canula to a suspension of NaH (60 wt. % dispersion in mineral oil, 13.6 g, 0.34 mol) in dimethyl carbonate (162 mL, 1.9 mol) at 0°C . The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Then the mixture was cooled to 0°C and MeOH (125 mL) and water (500 mL) were added. The pH was adjusted to 7 with acetic acid (80 mL) and the aqueous phase was extracted with EtOAc (2×500 mL). The combined organic layers were washed with water (500 mL), saturated aqueous NaHCO_3 (500 mL) and brine (500 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 2:3) afforded **9** (14.1 g, 52%) as a white solid. $R_f = 0.42$. ^1H NMR: 5.37 (s, 1H), 3.91 (q, $J = 7.1$ Hz, 2H), 3.74 (s, sH), 3.33 (dd, $J = 8.9, 5.0$ Hz, 1H), 2.60-2.53 (m, 1H), 2.45-2.29 (m, 2H), 2.19-2.12 (m, 1H), 1.36 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR: 193.5, 177.6, 170.6, 101.8, 64.4, 52.1, 52.0, 27.2, 23.9, 13.9.

4-Ethoxy-2-trifluoromethanesulfonyloxy-cyclohexa-1,3-dienecarboxylic acid methyl ester (10). To a suspension of NaH (60 wt. % dispersion of mineral oil, 3.13 g, 78 mmol) in Et_2O (250 mL) was added dropwise at 0°C , a solution of **9** (14.1 g, 71.2 mmol) in Et_2O (100 mL). The reaction mixture was stirred at 0°C for 30 min. Then, triflic anhydride (13.2 mL, 78 mmol) was added dropwise, and the resulting solution was stirred at 0°C for 2 h. The mixture was poured into saturated aqueous NaHCO_3 (350 mL) and the layers were separated. The organic layer was washed with saturated aqueous NaHCO_3 (150 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 3:7) afforded triflate **10** (17.6 g, 75%) as a pale yellow oil. $R_f = 0.62$. ^1H NMR: 4.89 (s, 1H), 3.89 (q, $J = 7.0$ Hz, 2H), 3.78 (s, 3H), 2.72 (t, $J = 9.9$ Hz, 2H), 2.40 (t, $J = 9.9$ Hz, 2H), 1.36 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR: 168.0, 164.8, 151.4, 123.3, 120.0, 116.9, 113.7, 108.5, 91.5, 64.6, 51.7, 27.1, 23.2, 14.0. HRMS (FAB) calculated for $\text{C}_{11}\text{H}_{14}\text{O}_6\text{F}_3\text{S}$ (MH^+) 331.0463, found 331.0475.

3-(2,2-Dimethyl-4-oxo-[1,3]dioxan-5-ylmethyl)-5-ethoxy-6,7-dihydro-3H-isobenzofuran-1-one (12). To a solution of aldehyde **11** (1.0 g, 5.4 mmol) in DMF (30 mL) at 0 °C were added CrCl₂ (2.65 g, 21.6 mmol), NiCl₂ (2 mg, 0.015 mmol) and vinyl triflate **10** (3.6 g, 10.9 mmol). The mixture was warmed to 50 °C stirred at that temperature for 16 h.

Saturated aqueous NH₄Cl (50 mL) was added and the aqueous phase was extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 7:3) afforded **12** (1.35 g, 75%) as a colorless oil. *R*_f = 0.44. ¹H NMR: 5.25 (s, 1H), 5.03-5.01 (m, 1H), 3.97-3.90 (m, 2H), 2.90 (dd, *J* = 14.9, 3.2 Hz, 1H), 2.56-2.41 (m, 5H), 2.04 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.36 (t, *J* = 7.0 Hz, 3H). ¹³C NMR: 172.4, 167.1, 166.9, 162.7, 162.1, 113.4, 105.1, 99.6, 89.0, 79.8, 64.3, 28.9, 28.0, 25.6, 24.3, 18.2, 17.8, 14.2. IR: 1732, 1703, 1648, 1640. HRMS (FAB) calculated for C₁₈H₂₃O₆ (MH⁺) 335.1495, found 335.1477.

3-(2,2,6-Trimethyl-4-oxo-4H-[1,3]dioxin-5-ylmethyl)-6,7-dihydro-3H-isobenzofuran-1,5-dione (13). To a solution of **12** (830 mg, 2.5 mmol) in THF (15 mL) was added, 5% aqueous HCl (15 mL). The reaction mixture was stirred for 2 h, cooled to 0 °C and quenched with saturated aqueous NaHCO₃ (25 mL). The layers were separated and the

aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 7:3) afforded ketone **13** (755 mg, 99%) as a colorless oil. *R*_f = 0.26. ¹H NMR: 5.03 (br s, 1H), 3.55 (br d, *J* = 22.1 Hz, 1H), 3.04 (br d, *J* = 22.1 Hz, 1H), 2.85 (dd, *J* = 14.9, 4.5 Hz, 1H), 2.64 (dd, *J* = 14.9, 5.3 Hz, 1H), 2.60-2.54 (m, 2H), 2.52-2.44 (m, 2H), 2.01 (s, 3H), 1.60 (s, 3H), 1.53 (s, 3H). ¹³C NMR: 205.1, 171.0, 168.0, 162.1, 160.8, 126.7, 105.1, 97.7, 80.3, 37.6, 37.1, 27.7, 25.8, 23.5, 19.6, 18.1. IR: 1761, 1712, 1649, 1634. HRMS (FAB) calculated for C₁₆H₁₉O₆ (MH⁺) 307.1182, found 307.1178.

5-Hydroxy-3-(2,2,6-trimethyl-4-oxo-4H-[1,3]dioxin-5-ylmethyl)-4,5,6,7-tetrahydro-3H-isobenzofuran-1-one (14). To a suspension of NaBH₄ (68 mg, 1.8 mmol) in MeOH (3 mL) was added dropwise at -78 °C, a solution of **13** (495 mg, 1.6 mmol) in MeOH (3 mL). The resulting mixture was stirred at -78 °C for 30 min. and allowed to warm to 0 °C.

The reaction was quenched by the dropwise addition of NaOH (1M in water, 12 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 9:1) afforded alcohol **14** (424 mg, 86%) as a 60:40 mixture of diastereomers as a colorless oil. *R*_f = 0.23. ¹H NMR: 4.90 (br s, 2H), 4.09 (br s, 1H), 4.01 (br s, 1H), 3.40 (br s, 1H), 3.00 (br s, 1H), 2.78-2.73 (m, 3H), 2.59-2.44 (m, 5H), 2.23-1.95 (m, 4H), 1.93 (s, 3H), 1.92 (s, 3H), 1.74-1.59 (m, 4H), 1.52 (s, 6H), 1.43 (s, 6H). ¹³C NMR: 172.4, 167.8, 167.5, 162.5, 161.8, 161.5, 161.1, 126.4, 126.2, 104.9, 104.7, 98.1, 81.4, 81.3, 64.6, 64.3, 31.7, 28.8, 28.4, 27.5, 27.4, 25.8, 25.8, 23.1, 23.0,

17.9, 16.9, 16.6. IR: 3400-3200, 1748, 1701, 1634. HRMS (FAB) calculated for $C_{16}H_{21}O_6$ (MH^+) 309.1338, found 309.1328.

5-(1-Ethoxy-ethoxy)-3-(2,2,6-trimethyl-4-oxo-4H-[1,3]dioxin-5-ylmethyl)-4,5,6,7-tetrahydro-3H-isobenzofuran-1-one (15). To a solution of alcohol **14** (50 mg, 0.16 mmol) in CH_2Cl_2 (1.5 mL) were added ethyl vinyl ether (78 μ L, 0.81 mmol) and a catalytic amount of PPTS. The resulting mixture was stirred for 1.5 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL).

The layers were separated and the aqueous phase was extracted with EtOAc (3 $\times$ 3 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 2:3) afforded **15** (52 mg, 85%) as 60:60:40:40 mixture of diastereomers as a colorless oil. R_f = 0.26. 1H NMR: 4.94-4.93 (m, 4H), 4.79-4.74 (m, 4H), 4.07-3.99 (m, 4H), 3.63-3.54 (m, 4H), 3.49-3.41 (m, 4H), 2.88-2.81 (m, 6H), 2.65-2.21 (m, 18H), 2.01 (s, 3H), 2.00 (s, 3H), 1.99 (s, 6H), 1.84-1.67 (m, 8H), 1.63 (s, 6H), 1.62 (s, 6H), 1.61 (s, 3H), 1.56 (s, 3H), 1.54 (s, 3H), 1.51 (s, 3H), 1.28-1.14 (m, 24H). ^{13}C NMR: 172.3, 167.1, 166.9, 161.9, 161.9, 161.6, 161.5, 161.2, 161.2, 127.0, 126.9, 126.7, 126.5, 105.0, 105.0, 104.9, 104.9, 99.3, 99.0, 98.9, 98.5, 98.3, 98.3, 98.3, 98.2, 81.6, 81.5, 81.5, 81.4, 68.9, 68.7, 68.6, 68.4, 60.6, 60.2, 60.0, 53.7, 29.9, 29.1, 25.7, 25.4, 24.2, 23.7, 20.6, 20.4, 20.3, 18.1, 18.1, 18.0, 15.2, 15.2. IR: 1753, 1716, 1637. HRMS (FAB) calculated for $C_{20}H_{29}O_7$ (MH^+) 381.1913, found 381.1892.

Cycloadduct 16. Irradiation of a solution of **15** (52 mg, 0.14 mmol) in acetonitrile/acetone (15 mL, 9:1 v/v) for 90 min. afforded **16** (52 mg, 100% crude yield), which was used in the next reaction without further purification. 1H NMR (C_6D_6): 4.68-4.35 (m, 4H), 4.09-4.03 (m, 2H), 3.84-3.78 (m, 4H), 3.56-3.20 (m, 12H), 2.61-2.32 (m, 10H), 1.97-1.50 (m, 20H), 1.47-1.02 (m, 48H), 0.69-0.62 (m, 12H). ^{13}C NMR (C_6D_6): 172.4, 172.2, 171.9, 110.0, 110.0, 109.9, 109.8, 99.9, 99.0, 98.6, 83.3, 83.3, 82.5, 82.4, 81.2, 81.1, 79.5, 70.8, 70.4, 70.2, 69.0, 62.3, 60.7, 60.7, 52.3, 52.2, 51.5, 31.4, 31.2, 30.1, 29.6, 29.6, 29.5, 21.7, 21.6, 21.5, 21.4, 21.4, 21.2, 16.3.

5-(1-Ethoxy-ethoxy)-1,7a-bis-hydroxymethyl-8-methyl-octahydro-1,3a-methano-indene-3,8-diol (17). To a solution of $LiAlH_4$ (1M in THF, 0.5 mL, 0.5 mmol) was added dropwise, a solution of the crude cycloadduct **16** (52 mg, 0.14 mmol) in THF (0.5 mL). The

reaction mixture was stirred for 5 min. Then, the reaction was quenched by addition of EtOAc and saturated aqueous Na_2SO_4 (10 drops) was added. The resulting mixture was stirred for 1 h. After addition of additional solid Na_2SO_4 the mixture was filtered through Celite® and concentrated *in vacuo*. Purification by chromatography (EtOAc:acetone = 3:2) afforded tetraol **17** (27 mg, 60%) as a colorless oil. R_f = 0.28. 1H NMR (CD_3OD): 4.89-4.77 (m, 4H), 4.41-4.35 (m, 5H), 4.13-4.07 (m, 1H), 4.03-4.00 (m, 1H), 3.95-3.93 (m, 1H), 3.77-3.63 (m, 8H), 3.57-3.48 (m, 6H), 3.44-3.36 (m, 2H), 3.32-3.30 (m, 2H), 3.27-3.19 (m, 2H), 3.04-2.98 (m, 4H), 2.07-1.44 (m, 24H), 1.34-1.04 (m, 44H). ^{13}C NMR (CD_3OD): 100.7, 100.5, 100.5, 100.3, 83.8,

82.0, 81.9, 74.8, 74.7, 73.0, 72.9, 72.8, 72.7, 72.4, 62.8, 62.1, 62.0, 61.6, 59.3, 59.3, 58.4, 58.3, 58.3, 57.9, 57.9, 51.8, 51.6, 51.6, 51.5, 38.3, 38.2, 37.6, 30.7, 30.4, 30.2, 30.1, 30.0, 27.6, 26.8, 26.4, 23.0, 21.7, 21.7, 21.3, 21.1, 20.9, 20.3, 20.2, 19.3, 19.2, 15.6, 14.5. IR: 3500-3100. HRMS (FAB) calculated for $C_{17}H_{31}O_6$ (MH^+) 331.2121, found 331.2112.

Acetic acid 3-acetoxy-1-acetoxymethyl-5-(1-ethoxyethoxy)-8-hydroxy-8-methyl-hexahydro-1,3a-methano-inden-7a-ylmethyl ester (18). To a solution of **17** (26 mg, 0.08 mmol) in pyridine (0.5 mL) were added, acetic anhydride (75 μ L, 0.8 mmol)

and a catalytic amount of DMAP. The reaction mixture was warmed to 50 $^{\circ}$ C and stirred at that temperature for 16 h. Then the mixture was allowed to cool to room temperature and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:1) afforded **18** (18 mg, 50%) as a colorless oil. R_f = 0.27. 1H NMR: 6.11 (s, 1H), 6.02 (s, 1H), 5.29 (s, 1H), 5.02-5.01 (m, 2H), 4.91-4.88 (m, 2H), 4.84-4.74 (m, 4H), 4.64-4.59 (m, 2H), 4.56-4.49 (m, 4H), 4.34-4.25 (m, 6H), 4.10-4.00 (m, 7H), 3.67-3.56 (m, 4H), 3.50-3.43 (m, 4H), 3.28-3.21 (m, 2H), 3.15-3.06 (m, 2H), 2.54-2.51 (m, 2H), 2.41-2.33 (m, 4H), 2.06-2.02 (m, 36H), 1.97-1.80 (m, 8H), 1.73-1.41 (m, 12H), 1.36-1.11 (m, 36H), 0.98-0.74 (m, 4H). ^{13}C NMR: 172.2, 171.3, 171.1, 171.0, 170.6, 170.6, 170.6, 98.8, 98.7, 98.4, 82.8, 80.5, 80.4, 74.4, 73.3, 71.7, 71.7, 69.9, 69.7, 69.6, 65.1, 65.1, 62.6, 60.3, 60.2, 60.2, 59.4, 59.4, 56.85, 54.8, 54.8, 54.5, 47.9, 34.8, 34.6, 28.9, 28.8, 28.6, 28.5, 21.2, 21.2, 21.1, 21.0, 21.0, 20.9, 20.5, 20.4, 20.3, 15.3, 15.3, 15.2.

Acetic acid 3-acetoxy-1-acetoxymethyl-5,8-dihydroxy-8-methyl-hexahydro-1,3a-methano-inden-7a-ylmethyl ester (19). To a solution of **18** (16 mg, 0.036 mmol) in THF (1.5 mL) was added, acetic acid (5% solution in water, 2.5 mL). The resulting mixture was stirred

for 4 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL). The aqueous phase was extracted with EtOAc (3 $\times$ 3 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc) afforded two pure diastereomers of **19** (60:40, combined yield 14 mg, 99%). **19a**: colorless oil. R_f = 0.30. 1H NMR: 4.95 (dd, J = 7.8, 2.8 Hz, 1H), 4.68-4.41 (m, 4H), 4.11-4.03 (m, 3H), 3.21-3.12 (m, 1H), 2.40 (dd, J = 13.5, 7.8 Hz, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.86 (dd, J = 13.5, 2.8 Hz, 1H), 1.86-1.79 (m, 1H), 1.69-1.54 (m, 4H), 1.14 (s, 3H). ^{13}C NMR: 172.5, 171.1, 170.5, 80.8, 73.8, 64.9, 64.8, 60.9, 56.8, 55.4, 48.7, 36.3, 28.2, 27.7, 22.0, 21.2, 21.1, 21.0, 20.4. **19b**: colorless oil. R_f = 0.25. 1H NMR: 4.91 (dd, J = 7.8, 2.9 Hz, 1H), 4.61 (dd, J = 11.9, 2.5 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.46-4.41 (m, 1H), 4.07-4.02 (m, 2H), 3.14-3.08 (m, 1H), 2.50 (s, 1H), 2.39 (dd, J = 13.5, 7.8 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 1.94-1.84 (m, 3H), 1.76-1.66 (m, 1H), 1.38-1.16 (m, 3H), 1.13 (s, 3H). ^{13}C NMR: 172.3, 171.1, 170.6, 82.8, 73.3, 67.2, 65.1, 61.0, 59.7, 54.8, 48.3, 35.6, 31.4, 30.9, 26.0, 21.2, 21.1, 21.0, 20.5. IR: 3500-3200, 1738. HRMS (FAB) calculated for $C_{19}H_{29}O_8$ (MH^+) 385.1862, found 385.1869.

Acetic acid 3-acetoxy-1-acetoxymethyl-8-hydroxy-8-methyl-5-oxo-hexahydro-1,3a-methano-inden-7a-ylmethyl ester (20). To a solution of **19** (14 mg, 0.036 mmol) in acetone (1 mL) were added NMO (7 mg, 0.06 mmol) and a catalytic amount of TPAP. The resulting mixture was stirred for 75 min. Subsequently the mixture was filtered through a short pad of silica gel and the filter was rinsed with EtOAc. The resulting solution was dried over Na₂SO₄ and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 4:1) afforded ketone **20** (10 mg, 75%) as a colorless oil. *R*_f = 0.36. ¹H NMR: 4.88 (dd, *J* = 7.8, 2.9 Hz, 1H), 4.53 (dd, *J* = 11.7, 1.6 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.13 (d, *J* = 12.0 Hz, 1H), 3.36-3.30 (m, 1H), 2.48-2.23 (m, 6H), 2.08 (s, 6H), 2.05 (s, 3H), 2.04-1.95 (m, 2H), 1.17 (s, 3H). ¹³C NMR: 211.4, 171.6, 171.0, 170.5, 82.2, 72.7, 66.6, 61.4, 60.4, 54.1, 47.0, 37.1, 36.9, 36.0, 29.1, 21.1, 21.0, 20.9, 19.6. IR: 1737. HRMS (FAB) calculated for C₁₉H₂₇O₈ (MH⁺) 383.1706, found 383.1698.

5-Allyl-6-bromomethyl-2,2-dimethyl-[1,3]dioxin-4-one (22). To a solution of lithium bis(trimethylsilyl)amide (28 mL, 1.0M solution in hexanes, 28 mmol) was added at -78 °C, a solution of allyldioxenone **21** (5.0 g, 27 mmol) in THF (25 mL). The resulting mixture was stirred at -78 °C for 30 min. and then allowed to warm to -30 °C. Then, the solution was added by canula to a solution of 1,2-dibromotetrachloroethane (9.23 g, 28.3 mmol) in THF (25 mL) at -78 °C. The resulting mixture was allowed to warm to -50 °C and stirred for 30 min. The reaction was quenched by addition of saturated aqueous NH₄Cl (50 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 × 50 mL). The combined organic layers were washed with brine (25 mL), dried over MgSO₄ and concentrated *in vacuo* to afford **22** (7.15 g, 100%) as a slightly yellow oil. The crude product was used immediately in the next reaction. ¹H NMR: 5.85 (ddt, *J* = 16.3, 10.1, 6.2 Hz, 1H), 5.13-5.04 (m, 2H), 3.93 (s, 2H), 3.07 (dt, *J* = 6.2, 1.5 Hz, 2H), 1.68 (s, 6H).

Acetic acid 5-allyl-2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-ylmethyl ester (23). To a solution of **22** (7.15 g, 27 mmol) in DMF (35 mL) was added at room temperature, sodium acetate (11 g, 81 mmol). After stirring for 16 h, water (30 mL) was added and the resulting mixture was extracted with Et₂O (5 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:4) afforded **23** (6.29 g, 96%) as a colorless oil. *R*_f = 0.19. ¹H NMR: 5.77 (ddt, *J* = 16.2, 10.1, 6.1 Hz, 1H), 5.02-4.95 (m, 2H), 4.62 (s, 2H), 3.04 (dt, *J* = 6.1, 1.6 Hz, 2H), 2.04 (s, 3H), 1.61 (s, 6H). ¹³C NMR: 169.9, 161.3, 159.2, 134.8, 115.5, 106.0, 105.7, 59.4, 28.1, 24.8, 20.3. IR: 1715, 1652.

Acetic acid 2,2-dimethyl-6-oxo-5-(2-oxo-ethyl)-6H-[1,3]dioxin-4-ylmethyl ester (24). To a solution of **23** (6.29 g, 26 mmol) in THF/water (350 mL, 1:1 v/v) were added at 0 °C, osmium tetroxide (5 mL, 1 wt. % solution in water, 0.2 mmol) and NaIO₄ (13 g, 61 mmol). The resulting mixture was

allowed to warm to room temperature and stirred for 6 h. Then, most of the THF was evaporated, the remaining mixture was diluted with water (500 mL) and extracted with EtOAc (5 × 250 mL). The combined organic layers were washed with 1N NaHSO₃ (200 mL), water (200 mL), 2N NaHCO₃ (200 mL) and brine, dried over MgSO₄ and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 2:1) afforded **24** (4.67 g, 74%) as a pale yellow oil. *R*_f = 0.41. ¹H NMR: 9.61 (s, 1H), 4.52 (s, 2H), 3.48 (s, 2H), 1.99 (s, 3H), 1.64 (s, 6H). ¹³C NMR: 197.4, 169.9, 161.4, 161.0, 106.4, 100.6, 59.8, 39.0, 24.6, 20.2. IR: 1726, 1655. HRMS (FAB) calculated for C₁₁H₁₅O₆ (MH⁺) 243.0869, found 243.0874.

Acetic acid 5-(2-cyclohex-1-enyl-2-hydroxy-ethyl)-2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-ylmethyl ester (25). To a solution of aldehyde **24** (200 mg, 0.83 mmol) in DMF (3 mL) at 0 °C were added CrCl₂ (492 mg, 4 mmol), NiCl₂ (1 mg, 0.008 mmol) and cyclohexenyl triflate⁶ (480 mg, 1.7 mmol). The mixture was allowed to warm to room temperature and

stirred at room temperature for 16 h. Saturated aqueous NH₄Cl (2 mL) was added and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:2) afforded **25** (220 mg, 82%) as a colorless oil. *R*_f = 0.17. ¹H NMR: 5.70 (br s, 1H), 4.78 (d, *J* = 13.5 Hz, 1H), 4.73 (d, *J* = 13.5 Hz, 1H), 4.12-4.09 (m, 1H), 2.64 (dd, *J* = 14.5, 4.1 Hz, 1H), 2.53 (dd, *J* = 14.5, 8.5 Hz, 1H), 2.13-1.93 (m, 5H), 2.10 (s, 3H), 1.68 (s, 3H), 1.67 (s, 3H), 1.66-1.50 (m, 4H). ¹³C NMR: 170.3, 162.4, 159.8, 139.4, 122.6, 105.7, 105.6, 74.8, 59.9, 30.7, 24.9, 24.8, 24.7, 23.9, 22.5, 22.4, 20.4. IR: 3550-3300, 1720, 1650. HRMS (EI) calculated for C₁₇H₂₄O₆ 324.1573, found 324.1545.

Acetic acid 5-(2-cyclohex-1-enyl-2-oxo-ethyl)-2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-ylmethyl ester (26). To a solution of oxalyl chloride (132 μL, 1.5 mmol) in CH₂Cl₂ (3 mL) was added dropwise at -60 °C → -50 °C, DMSO (215 μL, 3.0 mmol), then after 5 min a solution of alcohol **25** (445 mg, 1.4 mmol) in CH₂Cl₂ (2 mL), and finally, after 30 min

triethylamine (0.9 mL, 6.5 mmol). The mixture was stirred for 5 min, allowed to warm to room temperature and stirring was continued for 15 min. Water (3 mL) was added and the resulting mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 3 mL). The combined organic layers were washed with saturated aqueous NH₄Cl (2 mL), saturated aqueous NaHCO₃ (2 mL) and brine (2 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:2) afforded ketone **26** (381 mg, 86%) as a colorless oil. *R*_f = 0.27. ¹H NMR (C₆D₆): 6.68-6.67 (m, 1H), 4.45 (s, 2H), 3.69 (s, 2H), 2.22-2.20 (m, 2H), 1.84-1.81 (m, 2H), 1.62 (s, 3H), 1.48 (s, 6H), 1.36-1.22 (m, 4H). ¹³C NMR (C₆D₆): 197.0, 170.2, 162.3, 160.8, 141.1, 139.5, 106.8, 105.3, 60.8, 33.9, 26.7, 25.4, 24.2, 22.8, 22.3, 20.6. IR: 1722, 1665, 1637. HRMS (EI) calculated for C₁₇H₂₂O₆ 322.1416, found 322.1415.

Acetic acid 5-(2-cyclohex-1-enyl-[1,3]dioxolan-2-ylmethyl)-2,2-dimethyl-6-oxo-6H-[1,3]dioxin-4-ylmethyl ester (27). To a solution of ketone **26** (340 mg, 1.06 mmol) in CH_2Cl_2 (3 mL) at -78°C were added dropwise, $(\text{TMSOCH}_2)_2$ (0.65 mL, 2.7 mmol) and TMSOTf (76 μL , 0.41 mmol). The mixture was allowed to warm to 0°C over 1 h and kept at 0°C for 16 h. Saturated aqueous NaHCO_3 (2 mL) was added and the resulting mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were washed with water (2 mL) and brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography ($\text{EtOAc}:\text{PE} = 1:2$) afforded acetal **27** (231 mg, 60%) as a colorless oil. $R_f = 0.27$. ^1H NMR (C_6D_6): 5.86–5.84 (m, 1H), 4.81 (s, 2H), 3.48–3.36 (m, 4H), 3.00 (s, 2H), 2.25–2.21 (m, 2H), 1.91–1.87 (m, 2H), 1.68 (s, 3H), 1.60–1.54 (m, 2H), 1.48–1.38 (m, 2H), 1.40 (s, 6H). ^{13}C NMR (C_6D_6): 170.3, 161.8, 161.0, 138.0, 124.6, 111.6, 105.8, 105.2, 64.8, 61.3, 32.1, 25.8, 25.5, 24.9, 23.6, 23.2, 20.8. IR: 1726, 1651. HRMS (EI) calculated for $\text{C}_{19}\text{H}_{26}\text{O}_7$ 366.1679, found 366.1667.

Cycloadduct (28). Irradiation of a solution of alkene **27** (220 mg, 0.60 mmol) in acetonitrile/acetone (25 mL, 9:1 v/v) for 45 min. afforded **28** (207 mg, 94%), as a crystalline solid after purification by crystallization from CH_2Cl_2 /pentane. Colorless crystals. mp $150\text{--}151^\circ\text{C}$. ^1H NMR (C_6D_6): 4.71 (d, $J = 11.8$ Hz, 1H), 4.47 (d, $J = 11.8$ Hz, 1H), 3.46 (d, $J = 14.1$ Hz, 1H), 3.46–3.41 (m, 1H), 3.37–3.32 (m, 1H), 3.26–3.15 (m, 2H), 3.04 (t, $J = 8.5$ Hz, 1H), 2.45 (d, $J = 14.1$ Hz, 1H), 2.15–1.99 (m, 2H), 1.66 (s, 3H), 1.66–1.54 (m, 3H), 1.41 (s, 3H), 1.39–1.29 (m, 1H), 1.23 (s, 3H), 1.23–1.16 (m, 1H), 1.09–0.99 (m, 1H). ^{13}C NMR (C_6D_6): 170.7, 168.5, 108.9, 104.9, 77.8, 67.8, 65.6, 65.1, 58.8, 41.1, 39.0, 37.9, 29.6, 29.6, 22.4, 22.3, 21.5, 21.1, 21.1. IR: 1733. HRMS (FAB) calculated for $\text{C}_{19}\text{H}_{27}\text{O}_7$ (MH^+) 367.1757, found 367.1785.

Crystallographic data for **28**: monoclinic, $P2_1/n$, $a = 8.896(1)$, $b = 23.700(3)$, $c = 9.383(3)$ Å, $\beta = 112.77(2)^\circ$, $V = 1824.1(7)$ Å³, $Z = 4$, $D_x = 1.33$ g cm⁻³, $\lambda(\text{CuK}\alpha) = 1.5418$ Å, $\mu(\text{CuK}\alpha) = 8.41$ cm⁻¹, $F(000) = 784$, 243 K. Final $R = 0.064$ for 3375 observed reflections.

Table 4.1 Bond distances of the non-hydrogen atoms (Å) of **28** (standard deviations)

C(1)–C(2)	1.560(4)	C(4)–C(13)	1.543(4)	C(13)–C(14)	1.516(4)
C(1)–C(4)	1.549(4)	C(5)–O(2)	1.334(4)	C(14)–O(4)	1.414(3)
C(1)–C(17)	1.526(3)	C(5)–O(3)	1.202(3)	C(14)–O(5)	1.399(4)
C(1)–O(1)	1.423(4)	C(6)–C(7)	1.516(3)	C(15)–C(16)	1.478(7)
C(2)–C(3)	1.555(4)	C(6)–C(8)	1.506(5)	C(15)–O(4)	1.397(6)
C(2)–C(9)	1.541(4)	C(6)–O(1)	1.409(3)	C(16)–O(5)	1.405(7)
C(3)–C(4)	1.595(4)	C(6)–O(2)	1.455(3)	C(17)–O(6)	1.444(3)
C(3)–C(12)	1.513(3)	C(9)–C(10)	1.506(4)	C(18)–C(19)	1.485(6)
C(3)–C(14)	1.580(4)	C(10)–C(11)	1.519(5)	C(18)–O(6)	1.320(4)
C(4)–C(5)	1.500(3)	C(11)–C(12)	1.522(5)	C(8)–O(7)	1.189(4)

Table 4.2 Bond angles of the non-hydrogen atoms (°) of **28** (standard deviations)

C(2)-C(1)-C(4)	91.2(2)	C(3)-C(4)-C(5)	117.1(2)	C(3)-C(14)-O(4)	115.9(2)
C(2)-C(1)-C(17)	112.4(2)	C(3)-C(4)-C(13)	89.9(2)	C(3)-C(14)-O(5)	114.5(2)
C(2)-C(1)-O(1)	112.3(2)	C(5)-C(4)-C(13)	116.9(2)	C(13)-C(14)-O(4)	114.6(2)
C(4)-C(1)-C(17)	117.8(2)	C(4)-C(5)-O(2)	117.8(2)	C(13)-C(14)-O(5)	113.9(2)
C(4)-C(1)-O(1)	112.0(2)	C(4)-C(5)-O(3)	122.5(3)	O(4)-C(14)-O(5)	106.4(3)
C(17)-C(1)-O(1)	110.0(2)	O(2)-C(5)-O(3)	119.5(2)	C(16)-C(15)-O(4)	106.0(4)
C(1)-C(2)-C(3)	89.9(2)	C(7)-C(6)-C(8)	112.7(3)	C(15)-C(16)-O(5)	105.3(6)
C(1)-C(2)-C(9)	116.2(3)	C(7)-C(6)-O(1)	114.5(2)	C(1)-C(17)-O(6)	104.6(2)
C(3)-C(2)-C(9)	116.1(2)	C(7)-C(6)-O(2)	107.4(2)	C(19)-C(18)-O(6)	112.3(3)
C(2)-C(3)-C(4)	89.7(2)	C(8)-C(6)-O(1)	106.4(2)	C(19)-C(18)-O(7)	126.4(3)
C(2)-C(3)-C(12)	119.7(2)	C(8)-C(6)-O(2)	105.4(2)	O(6)-C(18)-O(7)	121.3(3)
C(2)-C(3)-C(14)	114.8(2)	O(1)-C(6)-O(2)	110.0(2)	C(1)-O(1)-C(6)	117.1(2)
C(4)-C(3)-C(12)	124.5(2)	C(2)-C(9)-C(10)	113.5(3)	C(5)-O(2)-C(6)	118.6(2)
C(4)-C(3)-C(14)	86.8(2)	C(9)-C(10)-C(11)	110.0(3)	C(14)-O(4)-C(15)	106.1(3)
C(12)-C(3)-C(14)	115.0(3)	C(10)-C(11)-C(12)	109.9(3)	C(14)-O(5)-C(16)	108.6(3)
C(1)-C(4)-C(3)	88.8(2)	C(3)-C(12)-C(11)	113.2(3)	C(17)-O(6)-C(18)	117.5(2)
C(1)-C(4)-C(5)	118.6(2)	C(4)-C(13)-C(14)	91.0(2)		
C(1)-C(4)-C(13)	117.6(2)	C(3)-C(14)-C(13)	91.5(2)

Triol 29. To a solution of LiAlH_4 (1M in THF, 0.5 mL, 0.5 mmol) was added dropwise, a solution of cycloadduct **28** (52 mg, 0.14 mmol) in THF (0.5 mL). The reaction mixture was stirred for 5 min. Then, the reaction was quenched by addition of EtOAc and saturated aqueous Na_2SO_4 (10 drops) was added.

The resulting mixture was stirred for 1 h. After addition of additional solid Na_2SO_4 the mixture was filtered through Celite® and concentrated *in vacuo*. Purification by chromatography (EtOAc) afforded triol **29** (16 mg, 42%) as a colorless oil. $R_f = 0.14$. ^1H NMR: 4.00-3.77 (m, 6H), 3.52 (d, $J = 10.4$ Hz, 1H), 3.41 (d, $J = 11.3$ Hz, 1H), 2.65 (dd, $J = 8.7, 5.4$ Hz, 1H), 2.59 (d, $J = 14.0$ Hz, 1H), 2.30 (d, $J = 14.0$ Hz, 1H), 1.88-1.73 (m, 2H), 1.61-1.32 (m, 5H), 1.12-1.00 (m, 1H). ^{13}C NMR: 109.1, 80.0, 64.6, 64.3, 60.8, 51.7, 44.7, 40.6, 36.0, 21.7, 20.7, 19.4, 18.8. HRMS (FAB) calculated for $\text{C}_{14}\text{H}_{23}\text{O}_5$ (MH^+) 271.1546, found 271.1549.

4-Cyclohex-1-enyl-2-methylene-4-oxo-butylric acid (30). To a solution of triol **29** (12 mg, 0.044 mmol) in water (0.5 mL) was added at 0 °C, NaIO_4 (21 mg, 0.097 mmol). The resulting mixture was stirred at 0 °C for 4 h.

Then the mixture was basified (pH 10) with 2M NaOH and extracted with Et_2O (3×1 mL). Subsequently, the mixture was acidified (pH 2-3) and extracted with EtOAc (3×1 mL). The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*, to afford ketone **30** (9 mg, 86%) as a colorless oil. R_f (EtOAc) = 0.39. ^1H NMR: 6.96 (br s, 1H), 6.44 (s, 1H), 5.70 (s, 1H), 3.67 (s, 2H), 2.27-2.24 (m, 4H), 1.67-1.58 (m, 4H). ^{13}C NMR: 197.5, 170.9, 140.8, 138.8, 134.5, 130.2, 39.9, 26.1, 23.1, 21.9, 21.5. IR: 3500-2500, 1701, 1668, 1637. HRMS (FAB) calculated for $\text{C}_{11}\text{H}_{15}\text{O}_3$ (MH^+) 195.1021, found 195.1036.

(2-Phenyl-[1,3]dioxan-5-ylidene)-acetic acid ethyl ester (35). To a dispersion of sodium hydride (60 wt. % dispersion in mineral oil, 88 mg, 2.2 mmol) in THF (4 mL) at 0 °C was added dropwise a solution triethyl phosphonoacetate (436

μL , 2.2 mmol). The resulting mixture was stirred for 1 h at 0 °C and a solution of ketone **34** (356 mg, 2.0 mmol) in THF (4 mL) was added dropwise. The solution was stirred for 30 minutes at 0 °C and allowed to warm to room temperature. A saturated aqueous solution of NH_4Cl (10 mL) was added and the resulting mixture was stirred for 15 minutes. The layers were separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic layers were washed with water (5 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography ($\text{EtOAc}:\text{PE} = 1:2$) afforded **35** (402 mg, 81%) as a colorless oil. $R_f = 0.31$. ^1H NMR (C_6D_6): 7.50-7.47 (m, 2H), 7.40-7.35 (m, 3H), 5.75-5.69 (m, 3H), 4.66-4.50 (m, 3H), 4.19 (q, $J = 7.1$ Hz, 2H), 1.29 (t, $J = 7.1$ Hz, 3H).

(2-Phenyl-4H-[1,3]dioxin-5-yl)-acetic acid ethyl ester (36). To a solution of KHMDS (0.5M in toluene, 1.6 mL, 0.8 mmol) was added dropwise at -78 °C, a solution of **35** (173 mg, 0.70 mmol) in THF (0.5 mL). The resulting mixture was stirred at -78 °C for 30 min. The reaction was quenched at -78 °C by the addition of EtOH and allowed to warm to room temperature. Saturated aqueous NH_4Cl (2 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (3×2 mL). The combined organic layers were washed with water (5 mL), dried over MgSO_4 and concentrated *in vacuo*, to afford **36** (168 mg, 97%) as a colorless oil. ^1H NMR: 7.52-7.50 (m, 2H), 7.42-7.38 (m, 3H), 6.63 (s, 1H), 5.78 (s, 1H), 4.61 (d, $J = 15.1$ Hz, 1H), 4.35 (d, $J = 15.1$ Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 2.95 (s, 2H), 1.28 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR: 170.9, 141.5, 136.9, 129.3, 128.4, 126.2, 108.0, 98.1, 66.9, 60.9, 35.1, 14.2.

2-(2-Phenyl-4H-[1,3]dioxin-5-yl)-ethanol (37). To a solution of LiAlH_4 (1M in THF, 1.0 mL, 1.0 mmol) was added dropwise at -78 °C, a solution of the ester **36** (120 mg, 0.48 mmol) in THF (0.5 mL). The reaction mixture was stirred at -78 °C for 30 min. Then, the reaction was quenched by addition of EtOAc and saturated aqueous Na_2SO_4 (15 drops) was added. The resulting mixture was stirred for 1 h. After addition of additional solid Na_2SO_4 the mixture was filtered through Celite® and concentrated *in vacuo*. Purification by chromatography (EtOAc) afforded alcohol **37** (89 mg, 90%) as a colorless oil. $R_f = 0.41$. ^1H NMR: 7.54-7.49 (m, 2H), 7.43-7.38 (m, 3H), 6.24 (s, 1H), 5.66 (s, 1H), 4.18-4.15 (m, 2H), 3.61 (q, $J = 6.2$ Hz, 2H), 2.17 (t, $J = 6.2$ Hz, 2H). ^{13}C NMR: 140.8, 136.3, 129.1, 128.5, 126.3, 109.2, 98.5, 65.3, 61.2, 35.9.

(2-Phenyl-4H-[1,3]dioxin-5-yl)-acetaldehyde (38). To a solution of alcohol **37** (81 mg, 0.39 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C, Dess-Martin periodinane (331 mg, 0.78 mmol). The resulting mixture was stirred at 0 °C for 30 min. The reaction was quenched by addition of saturated aqueous NaHCO_3 (1 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography ($\text{EtOAc}:\text{PE} = 1:1$) afforded aldehyde **38** (68 mg, 86%) as a colorless oil. $R_f = 0.31$. ^1H NMR (C_6D_6): 9.00 (s, 1H), 7.60-7.51 (m, 2H), 7.14-7.03 (m, 3H), 6.17 (s, 1H), 5.52 (s, 1H), 4.09 (d, $J = 15.1$ Hz, 1H), 3.85 (d, $J = 15.1$ Hz, 1H),

2.20-2.08 (m, 2H). ^{13}C NMR: 198.1, 142.9, 138.4, 130.0, 129.1, 127.5, 107.1, 99.1, 67.4, 44.2. HRMS (FAB) calculated for $\text{C}_{12}\text{H}_{13}\text{O}_3$ (MH^+) 205.0865, found 205.0878.

(2,2-Dimethyl-[1,3]dioxan-5-ylidene)-acetic acid ethyl ester (42). To a dispersion of sodium hydride (60 wt. % dispersion in mineral oil, 132 mg, 3.3 mmol) in THF (5 mL) at 0°C was added dropwise a solution triethyl phosphonoacetate (0.65 mL, 3.3 mmol). The resulting mixture was stirred for 1 h at 0°C and a solution of ketone **41** (390 mg, 3.0 mmol) in THF (5 mL) was added dropwise. The solution was stirred for 30 minutes at 0°C and allowed to warm to room temperature. A saturated aqueous solution of NH_4Cl (10 mL) was added and the resulting mixture was stirred for 15 minutes. The layers were separated and the aqueous phase was extracted with Et_2O ($3 \times 10\text{ mL}$). The combined organic layers were washed with water (5 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography ($\text{Et}_2\text{O}:\text{PE} = 2:7$) afforded **42** (529 mg, 88%) as a colorless oil. $R_f = 0.29$. ^1H NMR: 5.61-5.59 (m, 1H), 4.87-4.86 (m, 2H), 4.27-4.26 (m, 2H), 4.16 (q, $J = 7.2$ Hz, 2H), 1.40 (s, 6H), 1.27 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR: 165.7, 157.8, 112.3, 100.1, 62.9, 61.6, 60.1, 23.9, 14.2. IR: 1708, 1647.

(2,2-Dimethyl-4H-[1,3]dioxin-5-yl)-acetic acid ethyl ester (43). To a solution of KHMDS (0.5M in toluene, 4.4 mL, 2.2 mmol) was added dropwise at -78°C , a solution of **42** (400 mg, 2.0 mmol) in THF (2 mL). The resulting mixture was stirred at -78°C for 30 min. The reaction was quenched at -78°C by the addition of EtOH and allowed to warm to room temperature. Saturated aqueous NH_4Cl (4 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O ($3 \times 4\text{ mL}$). The combined organic layers were washed with water (5 mL), dried over MgSO_4 and concentrated *in vacuo*, to afford **43** (388 mg, 97%) as a colorless oil. ^1H NMR: 6.33 (s, 1H), 4.20 (s, 2H), 4.14 (q, $J = 7.1$ Hz, 2H), 2.89 (s, 2H), 1.46 (s, 6H), 1.27 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR: 171.4, 139.9, 108.9, 98.5, 66.4, 60.7, 35.4, 24.1, 14.2.

2-(2,2-Dimethyl-4H-[1,3]dioxin-5-yl)-ethanol (44). To a solution of LiAlH_4 (1M in THF, 3.8 mL, 3.8 mmol) was added dropwise at -78°C , a solution of the ester **43** (364 mg, 1.82 mmol) in THF (2 mL). The reaction mixture was stirred at -78°C for 30 min. Then, the reaction was quenched by addition of EtOAc and saturated aqueous Na_2SO_4 (20 drops) was added. The resulting mixture was stirred for 1 h. After addition of additional solid Na_2SO_4 the mixture was filtered through Celite® and concentrated *in vacuo*. Purification by chromatography (Et_2O) afforded alcohol **44** (248 mg, 86%) as a colorless oil. $R_f = 0.28$. ^1H NMR: 6.29 (s, 1H), 4.15-4.14 (m, 2H), 3.63 (q, $J = 6.1$ Hz, 2H), 2.14 (t, $J = 6.1$ Hz, 2H), 1.44 (s, 6H). ^{13}C NMR: 138.5, 111.7, 98.8, 65.1, 60.8, 36.1, 24.6.

(2,2-Dimethyl-4H-[1,3]dioxin-5-yl)-acetaldehyde (45). To a solution of alcohol **44** (220 mg, 1.39 mmol) in CH_2Cl_2 (4 mL) was added at 0°C , Dess-Martin periodinane (1.18 g, 2.78 mmol). The resulting mixture was stirred at 0°C for 30 min. The reaction was quenched by addition of saturated aqueous NaHCO_3 (4

mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 ($3 \times 4\text{ mL}$). The combined organic layers were washed with brine (3 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:1) afforded aldehyde **45** (200 mg, 92%) as a colorless oil. $R_f = 0.29$. ^1H NMR: 9.00 (s, 1H), 5.98 (s, 1H), 3.87 (s, 2H), 2.11 (s, 2H), 1.36 (s, 6H). ^{13}C NMR: 198.4, 139.6, 107.9, 98.4, 66.2, 44.1, 24.2. HRMS (FAB) calculated for $\text{C}_8\text{H}_{13}\text{O}_3$ (MH^+) 157.0865, found 157.0854.

3-(2,2-Dimethyl-4H-[1,3]dioxin-5-ylmethyl)-4,5,6,7-tetrahydro-3H-isobenzofuran-1-one (46). To a solution of aldehyde **45** (120 mg, 0.77 mmol) in DMF (3 mL) at 0°C were added CrCl_2 (379 mg, 3.1 mmol), NiCl_2 (1 mg, 0.008 mmol) and vinyl triflate **39** (465 mg, 1.5 mmol). The

mixture was warmed to 50°C stirred at that temperature for 16 h. Saturated aqueous NH_4Cl (3 mL) was added and the aqueous phase was extracted with EtOAc ($3 \times 5\text{ mL}$). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:2) afforded **25** (145 mg, 71%) as a colorless oil. $R_f = 0.27$. ^1H NMR: 6.28 (s, 1H), 4.81–4.80 (m, 1H), 4.19–4.07 (m, 2H), 1.26 (dd, $J = 15.1, 3.8\text{ Hz}$, 1H), 2.26–2.20 (m, 4H), 1.06 (dd, $J = 15.1, 6.8\text{ Hz}$, 1H), 1.77–1.67 (m, 4H), 1.42 (s, 3H), 1.39 (s, 3H). ^{13}C NMR: 172.4, 159.8, 139.1, 126.7, 109.4, 98.6, 81.4, 65.9, 29.1, 25.7, 23.5, 23.3, 22.5, 21.1, 20.4. HRMS (FAB) calculated for $\text{C}_{15}\text{H}_{21}\text{O}_4$ (MH^+) 265.1440, found 265.1448.

1-Cyclohex-1-enyl-2-(2,2-dimethyl-4H-[1,3]dioxin-5-yl)-ethanol (47).

To a solution of aldehyde **45** (60 mg, 0.38 mmol) in DMF (2 mL) at 0°C were added CrCl_2 (187 mg, 1.5 mmol), NiCl_2 (1 mg, 0.008 mmol) and cyclohexenyl triflate⁶ (175 mg, 0.76 mmol). The mixture was allowed to warm to room temperature and stirred at room temperature for 16 h. Saturated aqueous NH_4Cl (2 mL) was added and the aqueous phase was extracted with EtOAc ($3 \times 5\text{ mL}$). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:2) afforded **47** (71 mg, 78%) as a colorless oil. $R_f = 0.26$. ^1H NMR: 6.26 (s, 1H), 5.68 (br s, 1H), 4.15 (s, 2H), 3.99–3.96 (m, 1H), 2.14–1.91 (m, 6H), 1.64–1.52 (m, 4H), 1.43 (s, 3H), 1.42 (s, 3H). ^{13}C NMR: 139.4, 137.7, 123.3, 108.0, 98.2, 74.8, 61.6, 35.7, 25.0, 24.4, 23.8, 23.6, 22.5.

1-Cyclohex-1-enyl-2-(2,2-dimethyl-4H-[1,3]dioxin-5-yl)-ethanone (48).

To a solution of oxalyl chloride (26 μL , 0.3 mmol) in CH_2Cl_2 (1 mL) was added dropwise at $-60^\circ\text{C} \rightarrow -50^\circ\text{C}$, DMSO (42 μL , 0.59 mmol), then after 5 min a solution of alcohol **47** (64 mg, 0.27 mmol) in CH_2Cl_2 (1 mL), and finally, after 30 min triethylamine (188 μL , 1.4 mmol). The mixture was stirred for 5 min, allowed to warm to room temperature and stirring was continued for 15 min. Water (1 mL) was added and the resulting mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 ($3 \times 2\text{ mL}$). The combined organic layers were washed with saturated aqueous NH_4Cl (2 mL), saturated aqueous NaHCO_3 (2 mL) and

brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography ($\text{EtOAc:PE} = 1:3$) afforded ketone **48** (59 mg, 92%) as a colorless oil. $R_f = 0.31$. $^1\text{H NMR}$ (C_6D_6): 6.33–6.31 (m, 1H), 6.20 (s, 1H), 4.22 (s, 2H), 2.77 (s, 2H), 2.24–2.19 (m, 2H), 1.79–1.74 (m, 2H), 1.50 (s, 6H), 1.41–1.22 (m, 4H). $^{13}\text{C NMR}$: 198.0, 139.9, 139.7, 139.4, 107.3, 99.4, 62.7, 38.7, 30.9, 26.6, 25.1, 24.2, 22.8, 22.4. HRMS (FAB) calculated for $\text{C}_{14}\text{H}_{21}\text{O}_3$ (MH^+) 237.1491, found 237.1504.

4.8 References

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[2+2] CYCLOADDITIONS WITH 6-UNSUBSTITUTED DIOXENONES

5.1 Introduction

In view of the unsatisfactory results with alternative chromophores (chapter 4), we decided to reinvestigate the application of dioxenones in the synthesis of the bicyclo[2.1.1]hexane subunit of solanoeclepin A. However, instead of using 6-methyldioxenones¹ (chapter 2), we wanted to explore the synthetic potential of 6-unsubstituted dioxenones in [2+2] photocycloaddition chemistry. The retrosynthetic scheme is depicted in eq 5.1.

The secondary oxygen substituent on the four-membered ring, arising from the use of dioxenones of type 3, was envisaged to be a good precursor for the cyclobutanone functionality present in the target structure 1. The 6-unsubstituted dioxenones have already found successful application in intermolecular [2+2] cycloadditions.^{2,4} On the other hand, intramolecular examples are more scarce.³ To the best of our knowledge, the use of 6-unsubstituted dioxenones bearing a pendent alkene at C-5 for intramolecular [2+2] cycloadditions has not been reported to date. Therefore, we set out to investigate the behavior of these substrates in the photochemistry, in order to evaluate their potential in the synthesis of our target fragment 1. Yet, the synthesis of C-5 substituted 6-unsubstituted dioxenones such as 3 is relatively unexplored.^{4,5} Sato *et al.* have reported a straightforward synthesis of unsubstituted dioxenone 6 starting from formyl Meldrum's acid 4 (eq 5.2).⁶

The reaction proceeds *via* a thermal retrocyclization of 4 leading to formyl ketene 5, which in the presence of an excess of cyclohexanone undergoes a hetero Diels-Alder reaction to afford 6. Iododioxenone 8 was then formed in 67% yield over two steps, *viz.* 1) iodoacetoxylation by means of *N*-iodosuccinimide in acetic acid followed by 2) elimination of the β -acetate with Et_3N (eq 5.3).⁵

Vinyl iodide **8** was envisaged to be a good starting point for the synthesis of the desired precursors for the [2+2] photocycloaddition.

5.2 Preparation and Cyclization of a C-5 But-3-enyl Dioxenone

As there was no precedent for the intramolecular [2+2] photocycloaddition with 6-unsubstituted dioxenones, our first goal was to verify whether our strategy was still applicable. Therefore, a dioxenone bearing a simple monosubstituted pendent alkene was chosen as the first cyclization precursor. The synthesis started with the formylation of Meldrum's acid⁷ (**9**), which was achieved by treatment of **9** with trimethyl orthoformate, followed by hydrolysis of enol ether **10** with 1N HCl (eq 5.4).

Compound **4** was then converted to unsubstituted dioxenone **6** by refluxing in xylene in the presence of cyclohexanone, according to a literature procedure (eq 5.5).⁶ However, despite numerous attempts, in our hands this reaction never exceeded the rather disappointing yield of 37%.

Nevertheless, the reaction could be performed on a rather large scale, so that appreciable amounts of **6** could be obtained. In literature, the subsequent introduction of the α -iodo substituent was carried out in a two-step sequence.⁵ In the course of our work, we found that treatment with iodine in pyridine/ CCl_4 directly led to iododioxenone **8** with an improved yield of 95% (eq 5.6).

This type of iododioxenone had already been used in palladium catalyzed CC-bond forming reactions.⁵ Therefore, as the key step in the introduction of the required 3-alkenyl side chain, we applied a Sonogashira reaction of **8** with propargyl alcohol (scheme 5.1).

Scheme 5.1

Cross-coupling product **11** was obtained in a moderate yield of 48%, due to the thermal instability of iododioxenone **8**. This reaction was reported by Kaneko to proceed in a comparable yield.⁵ Subsequently, the acetylene was exhaustively hydrogenated, to afford alcohol **12**. Oxidation to aldehyde **13** followed by Wittig olefination eventually led to cyclization precursor **14** in 81% yield over the last two steps. The use of $KHMDS$ as the base in the Wittig olefination was found to be crucial for the success of this reaction, as the use of lithium bases led to complete decomposition of the aldehyde substrate. Cyclization precursor **14** was subjected to irradiation at 300 nm and after 2 h complete conversion to the expected crossed cycloadduct **15** was reached (eq 5.7).

This mode of closure was also observed with the corresponding 6-methyldioxenone as was described in chapter 2. Cycloadduct **15** was used as a key intermediate in the synthesis of a right-hand substructure of solanoelepin A, as will be described in chapter 6. The successful formation of **15** proved that our cycloaddition strategy could be successfully applied to 6-unsubstituted dioxenones. Encouraged by this result, we set out to construct more appropriately substituted cyclization precursors.

5.3 Preparation and Cyclization of C-5 Alkenyl Dioxenones

For the synthesis of the dioxenones bearing substituted alkenyl side chains, we wanted to employ the methodology developed for the 6-methyldioxenones (chapter 2). Therefore, an allyl group had to be introduced at C-5 of the dioxenone. Kaneko *et al.* reported a photochemical allylation of iododioxenone **8** with allyltrimethylsilane.⁵ Unfortunately, we were unable to reproduce this result. Moreover, because the reaction requires a large excess of the allylsilane (15 equiv.) and highly diluted conditions (0.008M), this method does not allow the formation of sufficient quantities of the allyldioxenone to serve our purpose. Consequently, we sought an alternative way to bring in the allyl side chain. Unfortunately, all attempts to introduce this moiety by means of palladium catalysis failed. Additionally, attempted lithium-iodide exchange with *tert*-butyllithium at -90 °C met with failure. However, Knochel recently reported the conversion of 5-iodouracil derivatives into the corresponding Grignard reagents by magnesium-iodide exchange with *iso*-propylmagnesium bromide.⁸ These polyfunctional organomagnesium compounds could then be reacted with various electrophiles in good yields. We were very pleased to find that the application of this method to iododioxenone **8**, resulted in the quantitative formation of the magnesiated species **16** (eq 5.8).

The *in situ* formed Grignard reagent **16** was then reacted with allyl bromide in the presence of a catalytic amount of copper cyanide to afford allyl dioxenone **17** in 80% yield. Subsequent oxidative cleavage of olefin **17** with OsO₄/NaIO₄ allowed formation of aldehyde **18** (eq 5.9).

Unfortunately, aldehyde **18** proved to be rather unstable in the chromium(II)/nickel(II) mediated coupling⁹ with cyclohexenyl triflate.¹⁰ This resulted, after MOM protection of the intermediate allylic alcohol **19**, in a disappointing 35% yield of the cyclization precursor **20** (scheme 5.2).

Scheme 5.2

As expected from the results with the 6-methyldioxenones, subjection of **20** to the usual irradiation conditions led to the exclusive formation of bicyclo[2.2.0]hexane **21**, as a 55:45 mixture of diastereomers. The cyclization of **20** to **21**, together with the cyclization of **14** to **15**, clearly indicates that the lack of the methyl substituent at C-6 of the dioxenone has no influence on the regioselectivity of the cycloaddition process, nor on the reactivity of the dioxenone itself.

The instability of aldehyde **18** towards the chromium(II)/nickel(II) mediated coupling conditions was even more evident, when the reaction was performed with the less reactive β -keto ester derived vinyl triflate **22**¹¹ (eq 5.10).

Only on one occasion, a trace amount of the desired cyclization precursor **23** could be isolated. All other attempts resulted in rapid and complete decomposition of aldehyde **18**. This prompted us to look for an alternative method to construct **23**.

Baker and Coates had shown the coupling of bromo-amide **24** to aldehydes and ketones *via* the intermediacy of organolithium compound **25**, leading after acidic work-up to tetrahydro-isobenzofuranones **26** (eq 5.11).¹²

We decided to investigate the applicability of this method in our synthesis of cyclization precursor **23**. Therefore, piperidyl-amide **28** was synthesized from known acid **27** (eq 5.12).¹²

Unfortunately, the organolithium species derived from **28** was too reactive to be used in the coupling to sensitive aldehyde **18** and caused complete decomposition of the starting material. The corresponding organozinc intermediate was not reactive enough, even after the addition of accelerating ligands.¹³ However, the Grignard reagent derived from **28**, formed *in situ* from the lithiated species by transmetalation with freshly prepared magnesium bromide, displayed just the right reactivity. In this way, cyclization precursor **23** could be formed, albeit in a modest yield of 36% (eq 5.13).

The main reason for this low yield is enolization of aldehyde **18** during the Grignard addition, rendering it unreactive towards the organometallic reagent and leading to a substantial amount of self-condensation product **29**. However, with **23** in hand the stage was set for the [2+2] photocycloaddition. Pleasingly, subjection of **23** to the usual irradiation conditions led to a very smooth reaction, affording the desired crossed cycloadduct **30** in excellent yield (eq 5.14).

Again, this cyclization product was crystalline (mp 186–187 °C), and the crystals appeared suitable for an X-ray crystal structure determination (figure 5.1).

Figure 5.1 Crystal structure of **30**
(hydrogen atoms omitted for clarity)

Figure 5.2 ^1H NMR spectrum (5.5–0.5 ppm) of **30**

The new preparative method for the cyclization precursors, involving the Grignard addition of a vinyl bromide to aldehyde **18**, enabled the construction of precursors that were inaccessible *via* the previous route. This allowed us to investigate whether the five-membered lactone was crucial for the regiochemical outcome of the cycloaddition, or that connecting the tether and the alkene *via* any other ring would also suffice (for a detailed hypothesis about the effect of conformational constraints on the outcome of the cycloaddition, see section 2.6). Therefore, seven-membered ring acetone **32** was prepared by adding bromo-alcohol **31**¹⁴ to **18**, followed by acetalization of the resulting diol (eq 5.15).

Precursor **32** still holds the tether and the alkene in a cyclic arrangement, however, with a significant reduction of rigidity compared to lactone **23**. This decrease of strain is directly visible in the outcome of the [2+2] photocycloaddition, which afforded exclusively the straight cycloadduct **33** as a single diastereomer in excellent yield (eq 5.16).

Figure 5.3 ¹H NMR spectrum (5.5-0.5 ppm) of **33**

The seven-membered ring clearly offers too much flexibility to direct the cycloaddition towards the crossed mode of closure. Therefore, a new precursor was designed, which closely resembled precursor **23**. Only the five-membered lactone was changed into a five-membered ring lactol. The synthesis started with the addition of bromodiene **34**¹⁵ to aldehyde **18** (scheme 5.3). The terminal alkene of the obtained product **35** was oxidatively cleaved with $\text{OsO}_4/\text{NaIO}_4$, to afford the very sensitive lactol **36**. Subsequent methylation of the hydroxy group at low temperature led to cyclization precursor **37**.

Scheme 5.3

The propensity of lactol **36** to eliminate the hydroxy group became apparent upon attempted silylation, which rapidly led to furan **38** in a virtually quantitative yield (eq 5.17).

The photochemistry with precursor **37** led to a complex mixture of products (eq 5.18). Apparently, **37** offers limited stability towards the irradiation conditions. After exhaustive reduction of the crude product mixture with LiAlH_4 , only a trace amount of diol **39** could be isolated.

Regarding the regioselectivity of the cycloaddition with precursor **37**, no solid conclusions can be drawn from the isolation of **39**, because of the presence of other photoadducts in the ^1H NMR spectrum of the crude cycloaddition mixture.

5.4 Cycloadduct Functionalization

To see whether the retro-aldol reaction could also be performed on the cycloadducts from the 6-unsubstituted dioxenones, **30** was subjected to the hydrolysis conditions as described in chapter 3 (eq 5.19).

This resulted in the very smooth formation of tricyclic aldehyde-acid **40**, as a single diastereomer. This route allows stereocontrolled access to highly substituted *trans*-fused bicyclo[4.3.0]nonanes, with ample functionality for further elaboration.

We now concentrated on the model studies towards solanoeclepin A. Therefore, cycloadduct **30** was exhaustively reduced with LiAlH_4 to afford tetraol **41** (eq 5.20).

Unfortunately, all attempts to directly differentiate the hydroxyl functions by acetalization resulted in a complex mixture of products. However, TIPS protection of the primary alcohols, resulted in the preferential formation of one of both possible mono-silyl ethers (eq 5.21).

The major isomer from this reaction, silyl ether **42**, seemed a good starting point for further functionalization. In order to minimize the amount of protection steps, it was deemed necessary to remove the remaining primary alcohol of **42** as soon as possible. In solanoeclepin A, a methyl group is present at that position. Therefore, we envisaged a reductive removal of the alcohol *via* the corresponding tosylate. Unfortunately, treatment of **42** with tosyl chloride and pyridine resulted in the nearly quantitative formation of tetrahydrofuran **44** (eq 5.22).

A plausible explanation for the formation of **44** is the displacement of the intermediate tosylate by the proximate secondary hydroxy group. Therefore, an alternative strategy towards a suitably functionalized intermediate for our model studies had to be explored. It was found that treatment of tetraol **41** with TBDPSCI resulted in a nearly 50:50 distribution of mono-silyl ethers **45** and **46** (scheme 5.4).

Scheme 5.4

Silyl ether **46** was chosen as the best candidate for further elaboration, and converted to acetone **47** in good yield. This left only one secondary alcohol unprotected, and after treatment of **47** with MOMCl, fully protected intermediate **48** was obtained. Deprotection with TBAF allowed the release of one primary alcohol, leading to **49**.

Unfortunately, conversion of the primary alcohol to the corresponding tosylate did not succeed, instead decomposition of the starting material was observed. Similarly, attempted transformation of the hydroxyl group into the corresponding primary iodide met with failure. Perhaps the proximate MOM ether participates in intramolecular substitution of the formed leaving group (comparable to the facile formation of tetrahydrofuran **44**, eq 5.22), leading to cationic skeletal rearrangements. If this is the case, the use of an electron withdrawing protective group for the secondary alcohol should remedy the problem. However, at this point, lack of material prohibited further investigations towards the removal of the primary alcohol, which proved to be a surprisingly difficult task.

5.5 Conclusions

In this chapter the preparation and cyclization of 6-unsubstituted dioxenones tethered to mono-, tri- and tetrasubstituted alkenes is described. The monosubstituted alkene precursor **14** was made *via* a palladium catalyzed coupling reaction of iododioxenone **8** and propargyl alcohol. The key step in the synthesis of the tri- and tetrasubstituted cyclization precursors comprised a very efficient magnesium–iodide exchange reaction with **8**, which allowed allylation at C-5 of the dioxenone. The 6-unsubstituted dioxenones showed very similar behavior compared to the 6-methyl analogs (chapter 2), with respect to the reactivity and regioselectivity in the [2+2] photocycloaddition reactions. Precursor **32** afforded straight adduct **33** indicating that a seven-membered ring allows too much conformational flexibility in the cycloaddition. The five-membered ring acetal **37** exhibited very poor behavior in the photochemical step, probably due to its limited stability. Crossed cycloadduct **30** was elaborated to alcohol **49**, a useful intermediate in model studies towards solanoelepin A.

5.6 Acknowledgments

Lenny Krap is gratefully acknowledged for her contribution to this chapter. Angeline van Ginkel is kindly acknowledged for the large scale preparation of iododioxenone **8**. Jan Dijkink is kindly acknowledged for the large scale preparation of aldehyde **18**. Jan Fraanje and Kees Goubitz are kindly acknowledged for the crystal structure determination of cycloadduct **30**.

5.7 Experimental Section

General information. For general experimental details, see Section 2.9.

2,2-Dimethyl-4,6-dioxo-[1,3]dioxane-5-carbaldehyde (4**).**⁶ To a suspension of **10** (122.5 g, 0.66 mol) in water (660 mL) was added dropwise at 0 °C, conc. HCl (59 mL, 0.72 mol). The resulting mixture was stirred at 0 °C for 30 min. Then, Et₂O (350 mL) was added and the mixture was stirred for an additional 30 min. The solution was diluted with EtOAc (350 mL) and the layers were separated. The

organic layers was dried over MgSO_4 and concentrated *in vacuo* (bath temperature 30 °C) to afford **4** (105.6 g, 93%) as a pale brown solid. ^1H NMR: 8.54 (s, 1H), 3.77 (s, 1H), 1.75 (s, 6H).

3-Iodo-1,5-dioxaspiro[5.5]undec-3-en-2-one (8).⁵ To a solution of **6** (1.00 g, 6.0 mmol) in CCl_4 /pyridine (20 mL, 1:1 v/v) was added at 0 °C, I_2 (6.09 g, 24 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. An aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (2M, 20 mL) was added and the resulting mixture was stirred for 1 h. The layers were separated and the aqueous phase was extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by crystallization from EtOAc afforded **8** (1.68 g, 95%) as a white solid. mp 104 °C (lit. 97–98 °C, Et_2O /hexane). R_f = 0.35 (EtOAc:PE = 1:4). ^1H NMR: 7.45 (s, 1H), 2.07–1.95 (m, 4H), 1.75–1.44 (m, 6H).

5-Methoxymethylene-2,2-dimethyl-[1,3]dioxane-4,6-dione (10).⁷ Meldrum's acid (100 g, 0.69 mol) was dissolved in trimethyl orthoformate (380 mL). The solution was warmed to 100 °C and stirred for 3 h. The solution was allowed to cool to room temperature and concentrated *in vacuo*, to afford **10** (122.5 g, 95%) as a yellow solid. ^1H NMR: 8.15 (s, 1H), 4.27 (s, 3H), 1.72 (s, 6H). ^{13}C NMR: 172.5, 163.3, 158.8, 104.9, 97.0, 66.5, 27.4.

3-(3-Hydroxy-prop-1-ynyl)-1,5-dioxaspiro[5.5]undec-3-en-2-one (11). To a solution of iododioxenone **8** (600 mg, 2.04 mmol), propargyl alcohol (0.6 mL, 10.3 mmol), triethylamine (0.6 mL, 4.3 mmol) and copper(I) iodide (20 mg, 0.11 mmol) in DMF (15 mL), was added $\text{PdCl}_2(\text{PPh}_3)_2$ (36 mg, 0.05 mmol). The resulting mixture was warmed to 80 °C and stirred for 4 h. Then the solution was allowed to cool to room temperature and water (15 mL) was added. The aqueous phase was extracted with EtOAc (4 $\times$ 15 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:1) afforded **11** (218 mg, 48%) as a colorless oil. R_f = 0.26. ^1H NMR: 7.44 (s, 1H), 4.41 (s, 2H), 2.45 (br s, 1H), 2.05–1.94 (m, 4H), 1.74–1.55 (m, 4H), 1.50–1.43 (m, 2H).

3-(3-Hydroxy-propyl)-1,5-dioxaspiro[5.5]undec-3-en-2-one (12). To a solution of **11** (200 mg, 0.90 mmol) in EtOAc (3 mL), was added PtO_2 (10 mg, 0.05 mmol). The resulting mixture was stirred at room temperature under an atmosphere of H_2 for 4 h. Then the mixture was filtered through Celite® and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 2:1) afforded **12** (195 mg, 96%) as a colorless oil. R_f = 0.27. ^1H NMR: 6.96 (s, 1H), 3.62 (t, J = 6.0 Hz, 2H), 2.27 (t, J = 7.3 Hz, 2H), 2.15 (br s, 1H), 2.03–1.88 (m, 4H), 1.75–1.40 (m, 8H). ^{13}C NMR: 162.2, 153.5, 108.9, 107.3, 61.2, 33.7, 32.0, 24.5, 22.1, 22.0. IR: 1723, 1642. HRMS (FAB) calculated for $\text{C}_{12}\text{H}_{19}\text{O}_4$ (MH^+) 227.1283, found 227.1284.

3-(4-Oxo-1,5-dioxaspiro[5.5]undec-2-en-3-yl)-propionaldehyde (13).

To a solution of **12** (180 mg, 0.80 mmol) in CH_2Cl_2 (2 mL) was added at 0 °C, Dess–Martin periodinane (405 mg, 0.95 mmol). The resulting mixture was stirred at 0 °C for 30 min. The reaction was quenched by addition of saturated aqueous NaHCO_3 (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*, to afford **13** (174 mg, 97% crude yield), which was used crude for the next reaction. ^1H NMR: 9.78 (s, 1H), 7.03 (s, 1H), 2.72 (t, $J = 6.9$ Hz, 2H), 2.47 (t, $J = 6.9$ Hz, 2H), 2.01–1.87 (m, 4H), 1.73–1.41 (m, 6H).

3-But-3-enyl-1,5-dioxaspiro[5.5]undec-3-en-2-one (14).

To a solution of methyltriphenylphosphonium bromide (330 mg, 0.92 mmol) in THF (1 mL) at 0 °C was added dropwise KHMDs (0.5M in toluene, 1.9 mL, 0.95 mmol). The resulting mixture was stirred for 30 minutes at 0 °C and cooled to –78 °C. Then, a solution of aldehyde **13** (174 mg, 0.78 mmol) in toluene (1 mL) was added dropwise. The solution was stirred for 30 minutes at –78 °C, for 30 minutes at 0 °C and allowed to warm to room temperature over 3 hours. The reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL). The layers were separated and the aqueous phase was extracted with Et_2O (4×2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography ($\text{EtOAc}:\text{PE} = 1:6$) afforded **14** (144 mg, 81% from **12**) as a colourless oil. $R_f = 0.27$. ^1H NMR: 6.89 (s, 1H), 5.80–5.73 (m, 1H), 5.05–4.98 (m, 2H), 2.25 (br s, 4H), 2.04–1.89 (m, 4H), 1.73–1.42 (m, 6H). ^{13}C NMR: 161.5, 153.0, 137.5, 115.7, 108.8, 107.0, 34.0, 32.7, 25.5, 25.0, 22.0. IR: 1730, 1639. HRMS (FAB) calculated for $\text{C}_{13}\text{H}_{19}\text{O}_3$ (MH^+) 223.1334, found 223.1333.

Cycloadduct 15.

According to general procedure A, irradiation of alkene **14** (60 mg, 0.27 mmol) for 2 h afforded **15** (60 mg) as a colorless oil. The purity was estimated to be 70% based on the ^1H NMR spectrum of the crude product. ^1H NMR: 3.44 (d, $J = 5.9$ Hz, 1H), 2.68–2.67 (m, 1H), 2.14 (s, 1H), 1.90 (dt, $J = 10.5, 3.9$ Hz, 1H), 1.81–1.77 (m, 2H), 1.56–1.09 (m, 12H). ^{13}C NMR (C_6D_6): 168.8, 109.2, 78.5, 49.1, 42.8, 41.3, 37.9, 35.2, 25.6, 25.4, 23.5, 23.3. IR: 1712.

3-Allyl-1,5-dioxaspiro[5.5]undec-3-en-2-one (17).

To a solution *iso*-propylmagnesium chloride (2M in Et_2O , 2.8 mL, 5.6 mmol) was added *via* syringe pump at –78 °C, a solution of **8** (1.47 g, 5 mmol) in THF (10 mL). After the addition was complete, CuCN (45 mg, 0.5 mmol) and allyl bromide (0.65 mL, 7.5 mmol) were added sequentially. After being stirred for 30 min. at –78 °C the reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography ($\text{EtOAc}:\text{PE} = 1:5$) afforded **17** (833 mg, 80%) as a colorless oil. $R_f = 0.29$. ^1H

NMR: 6.89 (s, 1H), 5.81 (ddt, $J = 16.8, 10.1, 6.6$ Hz, 1H), 5.12-5.04 (m, 2H), 2.91 (dd, $J = 6.6, 1.2$ Hz, 2H), 2.02-1.88 (m, 4H), 1.71-1.39 (m, 6H). ^{13}C NMR: 161.2, 153.4, 134.6, 116.8, 108.0, 107.2, 33.7, 29.8, 24.5, 22.0.

(4-Oxo-1,5-dioxaspiro[5.5]undec-2-en-3-yl)-acetaldehyde (18). To a solution of **17** (890 mg, 4.27 mmol) in THF/water (60 mL, 1:1 v/v) were added at 0 °C, osmium tetroxide (0.4 mL, 1 wt. % solution in water, 0.03 mmol) and NaIO_4 (2.0 g, 9.4 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 7 h. Then, most of the THF was evaporated, the remaining mixture was diluted with water (50 mL) and extracted with EtOAc (4 $\times$ 25 mL). The combined organic layers were washed with 1N NaHSO_3 (25 mL), water (25 mL), 2N NaHCO_3 (25 mL) and brine (25 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:1) afforded **18** (673 mg, 75%) as white waxy solid. $R_f = 0.28$. ^1H NMR: 9.72 (s, 1H), 7.04 (s, 1H), 3.30 (s, 2H), 2.11-1.97 (m, 4H), 1.74-1.43 (m, 6H). ^{13}C NMR: 197.9, 161.1, 155.4, 108.2, 102.1, 40.1, 33.6, 24.5, 22.1. IR: 1725, 1644. HRMS (FAB) calculated for $\text{C}_{11}\text{H}_{15}\text{O}_4$ (MH^+) 211.0970, found 211.0987.

3-(2-Cyclohex-1-enyl-2-methoxymethoxy-ethyl)-1,5-dioxaspiro[5.5]undec-3-en-2-one (20). To a solution of aldehyde **18** (210 mg, 1 mmol) in DMF (3 mL) at 0 °C were added CrCl_2 (492 mg, 4 mmol), NiCl_2 (1 mg, 0.008 mmol) and cyclohexenyl triflate (506 mg, 2.2 mmol). The mixture was allowed to warm to room temperature and stirred at room temperature for 16 h. Saturated aqueous NH_4Cl (2 mL) was added and the aqueous phase was extracted with EtOAc (3 $\times$ 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (2 mL) and treated with DIPEA (0.5 mL, 2.9 mmol) and MOMCl (150 μL , 2 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for 16 h. Saturated aqueous NaHCO_3 (2 mL) was added and the aqueous phase was extracted with EtOAc (3 $\times$ 2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:3) afforded **20** (118 mg, 35%) as a colorless oil. $R_f = 0.29$. ^1H NMR: 6.91 (s, 1H), 5.60 (br s, 1H), 4.55 (d, $J = 6.5$ Hz, 1H), 4.42 (d, $J = 6.5$ Hz, 1H), 4.05 (t, $J = 7.0$ Hz, 1H), 3.29 (s, 3H), 2.42 (dd, $J = 14.2, 7.3$ Hz, 1H), 2.34 (dd, $J = 14.2, 6.9$ Hz, 1H), 2.01-1.84 (m, 8H), 1.65-1.37 (m, 10H). ^{13}C NMR: 161.4, 154.2, 135.7, 127.2, 107.1, 106.4, 93.6, 79.0, 55.6, 33.9, 33.2, 30.1, 25.0, 24.6, 22.7, 22.4, 22.1. IR: 1722, 1640. HRMS (FAB) calculated for $\text{C}_{19}\text{H}_{29}\text{O}_5$ (MH^+) 337.2015, found 337.2019.

General procedure A for the intramolecular [2+2] cycloadditions. The photoreaction was carried out in a pyrex glass vessel with a Rayonet RPR 3000Å at room temperature. A solution of precursor in acetonitrile/acetone (25mM, 9:1 v/v) 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*.

Cycloadduct 21. According to general procedure A, irradiation of **20** (50 mg, 0.15 mmol) for 30 min. afforded **21** (43 mg, 86%) as an inseparable 56:44 mixture of diastereomers as colorless oil after purification (EtOAc:PE = 1:2). R_f = 0.26. ^1H NMR: 4.59–4.51 (m, 5H), 4.33 (d, J = 5.6 Hz, 1H), 4.08 (t, J = 6.4 Hz, 1H), 4.01 (dd, J = 9.6, 6.9 Hz, 1H), 3.30 (s, 6H), 3.14–3.09 (m, 1H), 2.86 (dd, J = 13.0, 9.6 Hz, 1H), 2.59 (dd, J = 12.2, 6.6 Hz, 1H), 2.42–2.38 (m, 2H), 2.04–1.87 (m, 3H), 1.98 (dd, J = 13.0, 6.9 Hz, 1H), 1.81– 0.99 (m, 33H). IR: 1717. HRMS (FAB) calculated for $\text{C}_{19}\text{H}_{29}\text{O}_5$ (MH^+) 337.2015, found 337.2021.

3-(3-Oxo-1,3,4,5,6,7-hexahydro-isobenzofuran-1-ylmethyl)-1,5-dioxo-spiro[5.5]undec-3-en-2-one (23). To a solution of **28** (272 mg, 1.0 mmol) in THF (2 mL) was added dropwise at -78°C , *tert*-butyl lithium (1.7M in pentane, 1.3 mL, 2.2 mmol). The resulting mixture was stirred for 15 min. Then, freshly prepared MgBr_2 (1M in Et_2O /benzene 3:1 v/v, 1.1 mL, 1.1 mmol) was added dropwise at -78°C and the resulting mixture was stirred for 30 min. Next, a solution of **18** (210 mg, 1.0 mmol) in THF (1 mL) was added dropwise at -78°C . After stirring for 1 h at -78°C , the reaction was quenched by addition of a mixture of $\text{AcOH}/\text{H}_2\text{O}/\text{THF}$ (5 mL, 1:4:4 v/v), allowed to warm to room temperature and stirred for 1 h. The layers were separated and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 (5 mL), water (5 mL) and brine (5 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 2:3) afforded **23** (115 mg, 36%) as a colourless oil. ^1H NMR: 7.06 (s, 1H), 4.95 (br s, 1H), 2.77 (dd, J = 14.9, 3.1 Hz, 1H), 2.52–2.46 (m, 1H), 2.48 (dd, J = 14.9, 6.3 Hz, 1H), 2.26–1.84 (m, 7H), 1.72–1.42 (m, 10H). ^{13}C NMR: 173.2, 163.5, 161.4, 156.4, 127.7, 107.7, 102.7, 80.6, 34.3, 32.6, 28.4, 24.5, 23.2, 22.1, 21.5, 20.0. IR: 1745, 1721, 1676, 1635. HRMS (FAB) calculated for $\text{C}_{18}\text{H}_{23}\text{O}_5$ (MH^+) 319.1545, found 319.1548.

(2-Bromo-cyclohex-1-enyl)-piperidin-1-yl-methanone (28). To a suspension of acid **27** (1.08 g, 5.27 mmol) in benzene (10 mL) were added dropwise at 0°C , DMF (100 μL , 1.29 mmol) and thionyl chloride (0.5 mL, 6.85 mmol). The resulting mixture was allowed to warm to rt and stirred for 1 h. Then the solution was cooled to 0°C and piperidine (1.5 mL, 15 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched by the addition of water (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic layers were washed with 2M HCl (10 mL), saturated aqueous NaHCO_3 (10 mL) and brine (10 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 3:2) afforded **28** (1.07 g, 75%) as a white solid. R_f = 0.30. ^1H NMR: 3.57–3.54 (m, 2H), 3.40–3.27 (m, 2H), 2.48–

2.37 (m, 3H), 2.05-2.01 (m, 1H), 1.76-1.46 (m, 10H). ^{13}C NMR: 168.6, 134.5, 119.2, 47.0, 41.8, 35.1, 28.9, 26.4, 25.2, 24.5, 24.0, 21.2. IR: 1614.

Cycloadduct 30. According to general procedure A, irradiation of alkene **23** (120 mg, 0.38 mmol) for 1 h afforded **30** (114 mg, 95%), as a crystalline solid after purification by crystallization from acetone/*n*-hexane. Colorless crystals. mp 186–187 °C. ^1H NMR: 4.67 (d, $J = 3.9$ Hz, 1H), 4.02 (s, 1H), 2.34 (dt, $J = 13.3$, 4.5 Hz, 1H), 2.23 (br d, $J = 13.0$ Hz, 1H), 2.17-2.07 (m, 2H), 1.97-1.90 (m, 3H), 1.81-1.42 (m, 12H), 1.07-0.95 (m, 1H). ^{13}C NMR: 174.5, 165.2, 110.5, 78.4, 78.0, 60.5, 57.8, 46.8, 36.9, 34.8, 34.6, 24.5, 22.2, 22.1, 21.7, 21.6, 21.3, 20.6. IR: 1783, 1740. HRMS (FAB) calculated for $\text{C}_{18}\text{H}_{23}\text{O}_5$ (MH $^+$) 319.1545, found 319.1553.

Crystallographic data for **30**: monoclinic, $\text{P}2_1/\text{c}$, $a = 6.6011(5)$, $b = 16.1185(1)$, $c = 14.513(1)$ Å, $\beta = 91.431(7)^\circ$, $V = 1543.7(2)$ Å 3 , $Z = 4$, $D_x = 1.37$ gcm $^{-3}$, $\lambda(\text{CuK}\alpha) = 1.5418$ Å, $\mu(\text{CuK}\alpha) = 8.2$ cm $^{-1}$, $F(000) = 680$, 243 K. Final $R = 0.050$ for 2586 observed reflections.

Table 5.1 Bond distances of the non-hydrogen atoms (Å) of **30** (standard deviations)

C(1)–C(2)	1.508(4)	C(7)–O(1)	1.351(4)	C(13)–C(14)	1.502(4)
C(1)–C(6)	1.551(3)	C(7)–O(2)	1.205(4)	C(13)–C(18)	1.522(4)
C(1)–C(8)	1.547(4)	C(8)–C(9)	1.552(4)	C(13)–O(3)	1.472(3)
C(1)–C(11)	1.549(3)	C(8)–O(1)	1.464(3)	C(13)–O(4)	1.430(3)
C(2)–C(3)	1.528(4)	C(9)–C(10)	1.519(4)	C(14)–C(15)	1.524(4)
C(3)–C(4)	1.524(5)	C(10)–C(11)	1.535(3)	C(15)–C(16)	1.516(4)
C(4)–C(5)	1.538(4)	C(10)–C(12)	1.489(4)	C(16)–C(17)	1.516(4)
C(5)–C(6)	1.510(4)	C(11)–O(4)	1.418(3)	C(17)–C(18)	1.522(4)
C(6)–C(7)	1.512(4)	C(12)–O(3)	1.340(3)		
C(6)–C(10)	1.617(3)	C(12)–O(5)	1.197(4)		

Table 5.2 Bond angles of the non-hydrogen atoms ($^\circ$) of **30** (standard deviations)

C(2)–C(1)–C(6)	118.0(2)	C(6)–C(7)–O(2)	129.1(3)	O(3)–C(12)–O(5)	119.2(2)
C(2)–C(1)–C(8)	121.5(2)	O(1)–C(7)–O(2)	122.6(3)	C(14)–C(13)–C(18)	112.4(2)
C(2)–C(1)–C(11)	125.1(2)	C(1)–C(8)–C(9)	101.9(2)	C(14)–C(13)–O(3)	105.7(2)
C(6)–C(1)–C(8)	92.3(2)	C(1)–C(8)–O(1)	103.8(2)	C(14)–C(13)–O(4)	106.8(2)
C(6)–C(1)–C(11)	89.6(2)	C(9)–C(8)–O(1)	104.6(2)	C(18)–C(13)–O(3)	107.7(2)
C(8)–C(1)–C(11)	101.7(2)	C(8)–C(9)–C(10)	95.8(2)	C(18)–C(13)–O(4)	112.9(2)
C(1)–C(2)–C(3)	110.4(2)	C(6)–C(10)–C(9)	103.0(2)	O(3)–C(13)–O(4)	111.2(2)
C(2)–C(3)–C(4)	112.3(2)	C(6)–C(10)–C(11)	87.7(2)	C(13)–C(14)–C(15)	111.5(2)
C(3)–C(4)–C(5)	112.5(2)	C(6)–C(10)–C(12)	116.8(2)	C(14)–C(15)–C(16)	110.9(2)
C(4)–C(5)–C(6)	108.6(2)	C(9)–C(10)–C(11)	99.4(2)	C(15)–C(16)–C(17)	111.3(2)
C(1)–C(6)–C(5)	116.9(2)	C(9)–C(10)–C(12)	124.6(2)	C(16)–C(17)–C(18)	111.2(2)
C(1)–C(6)–C(7)	103.9(2)	C(11)–C(10)–C(12)	118.1(2)	C(13)–C(18)–C(17)	110.9(2)
C(1)–C(6)–C(10)	81.0(2)	C(1)–C(11)–C(10)	83.8(2)	C(7)–O(1)–C(8)	105.4(2)
C(5)–C(6)–C(7)	112.6(2)	C(1)–C(11)–O(4)	115.1(2)	C(12)–O(3)–C(13)	123.7(2)
C(5)–C(6)–C(10)	123.7(2)	C(10)–C(11)–O(4)	110.1(2)	C(11)–O(4)–C(13)	111.9(2)
C(7)–C(6)–C(10)	113.3(2)	C(10)–C(12)–O(3)	115.4(2)		
C(6)–C(7)–O(1)	108.3(2)	C(10)–C(12)–O(5)	125.2(2)

3-(7,7-Dimethyl-1,2,3,4,5,9-hexahydro-6,8-dioxabenzocyclohepten-5-ylmethyl)-1,5-dioxaspiro[5.5]undec-3-en-2-one (32). To a solution of **31** (80 mg, 0.42 mmol) in THF (1.0 mL) was added dropwise at -78°C , *tert*-butyl lithium (1.7M in pentane, 0.74 mL, 1.26 mmol). The resulting mixture was stirred for 15 min. Then, a solution of **18** (88 mg, 0.42 mmol) in THF (1.0 mL) was added dropwise at -78°C . After stirring for 1 h at -78°C , the reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude mixture was dissolved in DMF (2 mL) and treated with 2,2-dimethoxypropane (0.25 mL, 2.0 mmol) and a catalytic amount of PPTS. The resulting mixture was stirred for 4 h and quenched by the addition of saturated aqueous NaHCO_3 (2 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×2 mL). The combined organic layers were washed with water (2 mL), brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:5) afforded **32** (67 mg, 44%) as a colorless oil. $R_f = 0.28$. ^1H NMR: 7.02 (s, 1H), 4.62 (br d, $J = 10.0$ Hz, 1H), 4.48 (d, $J = 15.7$ Hz, 1H), 3.61 (d, $J = 15.8$ Hz, 1H), 2.85 (ddd, $J = 14.4, 2.9, 1.1$ Hz, 1H), 2.07 (dd, $J = 14.4, 10.0$ Hz, 1H), 2.04-1.85 (m, 8H), 1.80-1.42 (m, 8H), 1.37 (s, 3H), 1.33-1.27 (m, 2H), 1.30 (s, 3H).

Cycloadduct 33. According to general procedure A, irradiation of alkene **32** (32 mg, 0.088 mmol) for 30 min. afforded **33** (28 mg, 88%), as a colorless oil after purification by chromatography (EtOAc:PE = 1:5). $R_f = 0.24$. ^1H NMR: 4.86 (s, 1H), 4.19 (d, $J = 13.0$ Hz, 1H), 4.10 (dd, $J = 8.7, 1.6$ Hz, 1H), 3.44 (d, $J = 13.0$ Hz, 1H), 2.91 (dd, $J = 12.7, 8.7$ Hz, 1H), 2.20-2.16 (m, 1H), 1.98 (dd, $J = 12.7, 1.6$ Hz, 1H), 1.80-1.35 (m, 16H), 1.39 (s, 3H), 1.37 (s, 3H), 1.21-1.15 (m, 1H). ^{13}C NMR: 171.1, 106.0, 102.3, 78.5, 73.1, 69.9, 54.0, 47.4, 39.6, 36.4, 35.7, 33.4, 30.4, 27.3, 24.8, 24.7, 23.8, 22.8, 22.6, 22.1, 19.5. IR: 1721. HRMS (FAB) calculated for $\text{C}_{21}\text{H}_{31}\text{O}_5$ (MH^+) 363.2171, found 363.2176.

3-[2-Hydroxy-2-(2-vinyl-cyclohex-1-enyl)-ethyl]-1,5-dioxaspiro[5.5]undec-3-en-2-one (35). To a solution of **34** (79 mg, 0.42 mmol) in THF (1.0 mL) was added dropwise at -78°C , *tert*-butyl lithium (1.7M in pentane, 0.50 mL, 0.85 mmol). The resulting mixture was stirred for 15 min. Then, a solution of **18** (88 mg, 0.42 mmol) in THF (1.0 mL) was added dropwise at -78°C . After stirring for 1 h at -78°C , the reaction was quenched by addition of saturated aqueous NH_4Cl (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:2) afforded **35** (63 mg, 47%) as a colorless oil. $R_f = 0.27$. ^1H NMR: 6.94 (s, 1H), 6.85 (dd, $J = 17.1, 11.0$ Hz, 1H), 5.16 (d, $J = 17.1$ Hz, 1H), 5.07 (t, $J = 6.8$ Hz, 1H), 5.01 (d, $J = 11.0$ Hz, 1H), 2.48 (dd, $J = 14.2, 8.0$ Hz, 1H), 2.36-2.31 (m, 1H), 2.33 (dd, $J = 14.2, 5.8$ Hz, 1H), 2.18-2.16 (m, 2H), 2.05-1.87

(m, 6H), 1.70-1.41 (m, 10H). ^{13}C NMR: 162.2, 154.3, 137.4, 133.5, 130.7, 112.6, 107.5, 106.5, 68.5, 34.0, 33.2, 32.3, 25.3, 24.5, 23.5, 22.7, 22.2.

3-(3-Hydroxy-1,3,4,5,6,7-hexahydro-isobenzofuran-1-ylmethyl)-1,5-dioxaspiro[5.5]undec-3-en-2-one (36). To a solution of **35** (40 mg, 0.13 mmol) in THF/water (2 mL, 1:1 v/v) were added at 0 °C, osmium tetroxide (0.1 mL, 1 wt. % solution in water, 0.008 mmol) and NaIO_4 (65 mg, 0.3 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 4 h. Then, most of the THF was evaporated, the remaining mixture was diluted with water (2 mL) and extracted with EtOAc (4 $\times$ 2 mL). The combined organic layers were washed with 1N $\text{Na}_2\text{S}_2\text{O}_3$ (2 mL), water (2 mL), 2N NaHCO_3 (2 mL) and brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*, to afford **36** (30 mg, 72%), which was used without further purification. ^1H NMR: 7.10 (s, 1H), 7.05 (s, 1H), 5.77 (s, 1H), 5.71 (d, J = 2.8 Hz, 1H), 4.88 (br s, 1H), 4.63 (d, J = 3.7 Hz, 1H), 3.00-2.60 (br s, 2H), 2.59 (dd, J = 14.8, 3.1 Hz, 1H), 2.51 (dd, J = 14.8, 3.6 Hz, 1H), 2.42 (dd, J = 14.8, 5.2 Hz, 1H), 2.32 (dd, J = 14.8, 7.2 Hz, 1H), 2.11-1.90 (m, 16H), 1.68-1.41 (m, 20H). ^{13}C NMR: 162.0, 161.6, 155.6, 155.3, 138.8, 138.3, 133.8, 133.4, 107.2, 107.0, 104.9, 104.5, 103.7, 103.6, 84.6, 84.2, 34.6, 34.2, 33.0, 32.2, 30.9, 29.2, 24.6, 24.5, 22.1, 22.1, 22.1, 22.0, 21.6, 21.4, 21.1.

3-(3-Methoxy-1,3,4,5,6,7-hexahydro-isobenzofuran-1-ylmethyl)-1,5-dioxaspiro[5.5]undec-3-en-2-one (37). To a solution of KHMDS (0.5M in toluene, 0.2 mL, 0.1 mmol) was added dropwise at -78 °C, a solution of **36** (30 mg, 0.094 mmol) in THF (1 mL). The resulting mixture was stirred at -78 °C for 30 min. Then, methyl iodide (30 μL , 0.47 mmol) was added dropwise at -78 °C, and the resulting mixture was stirred for 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 $\times$ 2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:4) afforded **37** (25 mg, 81%) as an inseparable 60:40 mixture of diastereomers as a colorless oil. R_f = 0.27. ^1H NMR: 7.07 (s, 1H), 7.02 (s, 1H), 5.47 (d, J = 2.3 Hz, 1H), 5.39 (s, 1H), 4.86 (br s, 1H), 4.68 (s, 1H), 3.39 (s, 3H), 3.30 (s, 3H), 2.62-2.44 (m, 3H), 2.33-2.28 (m, 1H), 2.11-1.82 (m, 16H), 1.76-1.39 (m, 20H). ^{13}C NMR: 162.3, 162.1, 155.8, 155.6, 139.7, 138.7, 131.9, 131.8, 110.2, 109.6, 107.2, 107.0, 105.0, 104.7, 84.9, 84.6, 54.9, 52.9, 34.6, 34.3, 34.2, 33.8, 33.0, 32.2, 30.6, 29.2, 26.2, 24.6, 22.5, 22.1, 21.7, 21.3, 20.9. IR: 1721, 1644. HRMS (FAB) calculated for $\text{C}_{19}\text{H}_{27}\text{O}_5$ (MH^+) 335.1858, found 355.1861.

3-(4,5,6,7-Tetrahydro-isobenzofuran-1-ylmethyl)-1,5-dioxaspiro[5.5]undec-3-en-2-one (38). To a solution of **36** (30 mg, 0.094 mmol) in CH_2Cl_2 (2 mL) were added at 0 °C, triethylamine (65 μL , 0.47 mmol) and TBDMSCl (21 mg, 0.14 mmol). The reaction was stirred for 15 min. at 0 °C and then quenched by the addition of saturated aqueous NaHCO_3 (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 $\times$ 2 mL). The

combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography ($\text{EtOAc}:\text{PE} = 1:5$) afforded **38** (27 mg, 96%) as a colorless oil. $R_f = 0.39$. ^1H NMR: 7.04 (s, 1H), 6.85 (s, 1H), 3.43 (s, 2H), 2.52-2.45 (m, 4H), 2.00-1.92 (m, 4H), 1.68-1.45 (m, 10H). ^{13}C NMR: 161.3, 153.9, 144.7, 135.8, 122.3, 117.6, 107.4, 106.8, 33.8, 24.6, 23.3, 23.2, 22.8, 22.1, 20.2. HRMS (FAB) calculated for $\text{C}_{18}\text{H}_{23}\text{O}_4$ (MH^+) 303.1596, found 303.1601.

6-Formyl-9-oxo-8-oxa-tricyclo[5.2.2.0^{1,6}]undecane-10-carboxylic acid (40). To a solution of cycloadduct **30** (50 mg, 0.16 mmol) in dioxane (4 mL) at room temperature was added dropwise an aqueous solution of KOH (1M, 1.6 mL).

The mixture was stirred for 45 min. The reaction mixture was extracted with Et_2O (3×5 mL). The aqueous phase was acidified carefully with 2N HCl to pH 2-3 and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed brine, dried over MgSO_4 and concentrated *in vacuo* to afford **40** (32 mg, 84%) as a white solid. mp 193-194 °C. ^1H NMR: 9.67 (s, 1H), 4.74 (s, 1H), 4.13 (br s, 1H), 3.22 (dd, $J = 10.2, 4.6$ Hz, 1H), 2.41 (dt, $J = 14.5, 4.6$ Hz, 2H), 2.09-2.01 (m, 2H), 1.94 (dt, $J = 13.4, 4.7$ Hz, 1H), 1.79 (br d, $J = 15.3$ Hz, 1H), 1.72-1.64 (m, 2H), 1.53-1.41 (m, 1H), 1.27-1.12 (m, 1H). ^{13}C NMR: 198.4, 174.2, 171.6, 77.9, 65.4, 56.3, 43.5, 31.7, 24.2, 22.7, 21.7, 20.2. IR: 3250-2700 (br), 1788, 1724. HRMS (FAB) calculated for $\text{C}_{12}\text{H}_{15}\text{O}_5$ (MH^+) 239.0919, found 239.0930.

1,7a-Bis-hydroxymethyl-octahydro-1,3a-methano-indene-3,8-diol (41). To a solution of LiAlH_4 (1M in THF, 2.0 mL, 2.0 mmol) was added in small portions, cycloadduct **30** (120 mg, 0.38 mmol). The reaction mixture was stirred for 5 min. Then, the reaction was quenched by addition of EtOAc and saturated aqueous Na_2SO_4 (10 drops) was added. The resulting mixture was stirred for 1 h.

After addition of additional solid Na_2SO_4 the mixture was filtered through Celite® and concentrated *in vacuo*. Purification by chromatography ($\text{EtOAc}:\text{acetone} = 1:1$) afforded **41** (52 mg, 60%) as a white powder. mp 173 °C. ^1H NMR (CD_3OD): 4.21 (dd, $J = 11.4, 2.2$ Hz, 1H), 3.83 (dd, $J = 7.9, 2.9$ Hz, 1H), 3.76 (d, $J = 11.2$ Hz, 1H), 3.47 (s, 1H), 3.41 (d, $J = 11.2$ Hz, 1H), 3.32 (d, $J = 11.4$ Hz, 1H), 2.77-2.70 (m, 1H), 1.98-1.88 (m, 3H), 1.78 (dd, $J = 12.1, 8.0$ Hz, 1H), 1.65-1.51 (m, 4H), 1.41-1.34 (m, 1H). ^{13}C NMR (CD_3OD): 83.6, 72.8, 61.5, 58.9, 57.5, 57.2, 50.2, 38.0, 25.1, 23.8, 22.7. HRMS (FAB) calculated for $\text{C}_{12}\text{H}_{21}\text{O}_4$ (MH^+) 229.1440, found 229.1437.

7a-Hydroxymethyl-1-triisopropylsilyloxymethyl-octahydro-1,3a-methano-indene-3,8-diol (42). To a solution of **41** (20 mg, 0.088 mmol) in

DMF (1 mL) were added at 0 °C, imidazole (30 mg, 0.44 mmol) and TIPSCl (28 μL , 0.13 mmol). The resulting mixture was allowed to warm to

room temperature and stirred for 16 h. The reaction was quenched by the addition of saturated aqueous NaHCO_3 (1 mL). The aqueous phase was extracted with EtOAc (3×2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography ($\text{EtOAc}:\text{PE} = 2:1$) afforded **42** (24 mg, 72%) as a colorless oil. $R_f = 0.28$. ^1H NMR (CD_3OD): 4.22 (dd, $J = 11.8, 2.2$ Hz, 1H), 3.96 (d, $J =$

10.4 Hz, 1H), 3.83 (dd, $J = 8.0, 2.9$ Hz, 1H), 3.65 (d, $J = 10.4$ Hz, 1H), 3.48 (s, 1H), 3.28 (d, $J = 11.8$ Hz, 1H), 2.77-2.70 (m, 1H), 2.01-1.90 (m, 2H), 1.94 (dd, $J = 12.1, 2.8$ Hz, 1H), 1.79 (dd, $J = 12.1, 8.0$ Hz, 1H), 1.66-1.51 (m, 4H), 1.45-1.34 (m, 1H), 1.19-1.01 (m, 21H).

Tetrahydrofuran 44. To a solution of **42** (24 mg, 0.062 mmol) in pyridine (1 mL) was added, tosyl chloride (24 mg, 0.12 mmol). The resulting mixture was stirred for 1 h and then quenched by the addition of saturated aqueous NaHCO_3 (1 mL). The aqueous phase was extracted with EtOAc (3×2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:3) afforded **44** (23 mg, 97%) as a colorless oil. $R_f = 0.26$. ^1H NMR: 3.99 (d, $J = 4.5$ Hz, 1H), 3.95 (d, $J = 2.2$ Hz, 2H), 3.69 (d, $J = 8.9$ Hz, 1H), 3.55 (d, $J = 8.9$ Hz, 1H), 2.85 (d, $J = 2.3$ Hz, 1H), 2.55 (dt, $J = 14.1, 4.7$ Hz, 1H), 1.92-1.81 (m, 2H), 1.67-1.42 (m, 6H), 1.33-1.19 (m, 1H), 1.17-0.98 (m, 21H). ^{13}C NMR: 82.9, 80.9, 69.0, 61.7, 54.7, 53.1, 52.8, 33.9, 23.6, 22.1, 21.6, 20.7, 18.0, 11.9. HRMS (FAB) calculated for $\text{C}_{21}\text{H}_{39}\text{O}_3\text{Si}(\text{MH}^+)$ 367.2668, found 367.2672.

7a-(tert-Butyl-diphenyl-silanyloxymethyl)-1-hydroxymethyl-octahydro-1,3a-methano-indene-3,8-diol (46). To a solution of **41** (20 mg, 0.088 mmol) in DMF (1 mL) were added at 0°C , imidazole (30 mg, 0.44 mmol) and TBDPSCI (34 μL , 0.13 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched by the addition of saturated aqueous NaHCO_3 (1 mL). The aqueous phase was extracted with EtOAc (3×2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 5:1) afforded **46** (18 mg, 44%) as a white solid. $R_f = 0.25$. ^1H NMR (CD_3OD): 7.68-7.65 (m, 4H), 7.47-7.37 (m, 6H), 4.42 (dd, $J = 11.0, 1.8$ Hz, 1H), 3.93 (d, $J = 11.5$ Hz, 1H), 3.76 (dd, $J = 7.8, 2.8$ Hz, 1H), 3.61 (d, $J = 11.5$ Hz, 1H), 3.48 (s, 1H), 3.38 (d, $J = 11.0$ Hz, 1H), 2.80-2.74 (m, 1H), 2.09-2.05 (m, 1H), 1.97-1.38 (m, 3H), 1.50-1.30 (m, 4H), 1.06 (s, 9H), 0.96-0.90 (m, 1H). ^{13}C NMR (CD_3OD): 137.2, 136.9, 134.7, 134.4, 131.1, 131.0, 129.0, 83.5, 72.8, 63.8, 59.9, 57.6, 50.6, 37.9, 27.7, 24.7, 23.7, 22.8, 22.5, 20.3.

TBDPS acetonide (47). To a solution of **46** (18 mg, 0.039 mmol) in DMF (1 mL) were added, 2,2-dimethoxypropane (24 μL , 0.20 mmol) and a catalytic amount of PPTS. The resulting mixture was stirred for 4 h. The reaction was quenched by the addition of saturated aqueous NaHCO_3 (1 mL). The aqueous phase was extracted with EtOAc (3×2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 2:3) afforded **47** (16 mg, 80%) as a colorless oil. $R_f = 0.33$. ^1H NMR: 7.68-7.64 (m, 4H), 7.44-7.35 (m, 6H), 4.24 (dd, $J = 10.8, 1.7$ Hz, 1H), 4.22 (d, $J = 11.9$ Hz, 1H), 3.96 (d, $J = 11.9$ Hz, 1H), 3.95-3.90 (m, 1H), 3.53 (d, $J = 10.8$ Hz, 1H), 3.43 (s, 1H), 3.25-3.18 (m, 1H), 2.17 (br d, $J = 13.9$ Hz, 1H), 1.90 (d, $J = 4.4$ Hz, 1H), 1.75-1.50 (m, 5H), 1.44 (s, 3H), 1.43-1.36 (m, 1H), 1.36 (s, 3H), 1.25-1.07 (m, 1H), 1.07 (s, 9H). ^{13}C NMR: 135.9, 135.8, 133.9,

133.6, 129.5, 129.5, 127.6, 97.3, 78.9, 73.3, 64.9, 62.5, 56.9, 48.4, 45.1, 36.7, 29.2, 27.1, 26.4, 23.0, 22.3, 22.2, 19.3, 19.0.

MOM TBDPS acetonide (48). To a solution of **47** (16 mg, 0.032 mmol) in CH_2Cl_2 (1 mL) were added at 0 °C, triethylamine (22 μL , 0.16 mmol) and MOMCl (5 μL , 0.064 mmol). The resulting mixture was stirred for 16 h and then quenched by the addition of saturated aqueous NaHCO_3 (1 mL).

The layers were separated and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:3) afforded **48** (14 mg, 78%) as a colorless oil. R_f = 0.40. ^1H NMR: 7.68–7.63 (m, 4H), 7.43–7.32 (m, 6H), 4.35 (d, J = 6.7 Hz, 1H), 4.32 (d, J = 11.9 Hz, 1H), 4.31 (d, J = 6.7 Hz, 1H), 4.14 (dd, J = 10.8, 2.1 Hz, 1H), 3.98 (d, J = 11.9 Hz, 1H), 3.70 (dd, J = 7.5, 3.0 Hz, 1H), 3.49 (d, J = 10.8 Hz, 1H), 3.44 (s, 1H), 3.24–3.17 (m, 1H), 3.10 (s, 3H), 2.33 (br d, J = 14.0 Hz, 1H), 1.74–1.46 (m, 6H), 1.46 (s, 3H), 1.41–1.33 (m, 1H), 1.36 (s, 3H), 1.13–1.06 (m, 1H), 1.06 (s, 9H). ^{13}C NMR: 135.9, 135.8, 134.2, 133.8, 129.4, 127.5, 97.3, 95.5, 78.7, 78.0, 64.0, 62.7, 56.1, 55.1, 48.7, 44.9, 34.9, 29.2, 27.1, 25.7, 23.1, 22.4, 22.0, 19.2, 18.9.

MOM acetonide (49). To a solution of **48** (14 mg, 0.025 mmol) in THF (1 mL) was added at 0 °C, a solution of TBAF (1M in THF, 50 μL , 0.05 mmol). The resulting mixture was stirred at 0 °C for 1 h and then quenched by the addition of saturated aqueous NaHCO_3 (1 mL). The layers were separated

and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 2:1) afforded **49** (8 mg, 93%) as a colorless oil. R_f = 0.28. ^1H NMR: 4.67 (d, J = 6.7 Hz, 1H), 4.60 (d, J = 6.7 Hz, 1H), 4.12 (br d, J = 10.5 Hz, 1H), 4.08 (d, J = 12.3 Hz, 1H), 3.96 (d, J = 12.3 Hz, 1H), 3.87 (dd, J = 7.7, 2.8 Hz, 1H), 3.62 (d, J = 11.6 Hz, 1H), 3.48 (s, 1H), 3.36 (s, 3H), 3.36–3.28 (m, 1H), 1.97–1.88 (m, 2H), 1.81–1.36 (m, 7H), 1.44 (s, 3H), 1.37 (s, 3H). ^{13}C NMR: 97.5, 96.1, 78.5, 78.2, 65.8, 62.5, 56.6, 55.5, 48.3, 45.0, 35.3, 29.1, 27.6, 23.5, 22.4, 22.1, 18.9. HRMS (FAB) calculated for $\text{C}_{17}\text{H}_{29}\text{O}_5$ (MH^+) 313.2015, found 313.2021.

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SYNTHESIS OF THE RIGHT-HAND SUBSTRUCTURE OF SOLANOECLEPIN A

6.1 Introduction

In chapter 5 our successful approach towards the skeleton of the right-hand side of solanoeclepin A has been described. A photochemical [2+2] cycloaddition of 6-unsubstituted dioxenone **1** afforded cycloadduct **2**, which could be elaborated in five steps to the advanced intermediate **3**, containing the appropriate substitution pattern and stereochemistry for the synthesis of the right-hand fragment (eq 6.1).

To secure the chemistry necessary for completion of the right-hand side, we decided to synthesize a smaller model system including the bicyclo[2.1.1]hexanone and the cyclopropane carboxylic acid moiety (**4**), as present in the natural product.¹ The retrosynthetic approach is depicted in eq 6.2.

Compound **4** consists of only ten carbon atoms, but already contains three different ring sizes ranging from three to five, together with four stereogenic centers. The synthesis of this model should allow us to probe both the formation of the strained bicyclo[2.1.1]hexanone unit and the introduction of the cyclopropane ring next to this labile moiety. Cyclization precursor **6** had already been prepared (chapter 5) and was anticipated to provide the bicyclo[2.1.1]hexane skeleton, needed to construct **4**. However, we were not satisfied by the route followed to prepare **6** and therefore an alternative synthesis was necessary. The investigations presented in this chapter deal with the construction of alkenyldioxenone **6**, and the functionalization of diol **5** towards the target compound **4**. The results obtained from these experiments provide useful information about the properties of the right-hand substructure of solanoeclepin A, and could eventually be transferred to the total synthesis of the natural product. Finally, model **4** contains some of the key features of the natural

hatching agent and therefore could be tested for biological activity, to provide insight into the structure–activity relationship of solanoeclepin A.

6.2 Preparation and Functionalization of Bicyclo[2.1.1]hexanediol

For the synthesis of cyclization precursor **6** we attempted the direct introduction of the 3-butenyl side chain at C-5 of the dioxenone. Therefore, iododioxenone **7** (chapter 5) was subjected to an iodide–magnesium exchange reaction² at low temperature, which afforded the intermediate Grignard reagent **8** (eq 6.3).

Unfortunately, **8** appeared to be too unreactive to react with 1-iodo-3-butene. The addition of copper salts did not seem to remedy this problem. Acrolein on the other hand, proved to be an excellent electrophile in this reaction, if the magnesium intermediate was pretreated with copper(I) and HMPA leading to a smooth 1,4-addition to afford aldehyde **9** in high yield (6.4).³

Subsequent Wittig olefination provided butenyldioxenone **6**, setting the stage for the [2+2] photocycloaddition reaction (6.5).

This method to construct cyclization precursor **6** from iododioxenone **7** (64%, 2 steps) proved to be significantly more efficient than the route described in chapter 5 (37%, 4 steps). Alkene **6** was subjected to the standard irradiation conditions, to afford bicyclo[2.1.1]hexane **10** (eq 6.6).

As was observed with previous crossed cycloadducts (chapters 2 and 5), **10** was unstable towards purification by silica gel column chromatography. Therefore, the crude product mixture was exhaustively reduced with excess lithium aluminum hydride to afford the stable diol **5**. The modest yield of this two-step reaction sequence is due to partial polymerization of the terminal alkene precursor during the cycloaddition. Next, the primary alcohol had to be converted into an olefin, to enable the envisaged cyclopropanation. However, the functionalization of the primary hydroxyl group required the differentiation of the two alcohols of **5**. This was efficiently achieved *via* the following two-step sequence. First, both alcohols were converted to the corresponding TES ethers, by treatment with TESCl (eq 6.7).

Subsequently, the primary silyl ether of **11** was selectively oxidized under Swern conditions to afford aldehyde **12**.⁴ This aldehyde proved to be rather unstable and therefore the crude aldehyde was subjected to a Wittig olefination to afford the stable olefin **13** (eq 6.8).

Terminal alkene **13** was envisaged to be a good starting material for the introduction of the cyclopropanecarboxylic acid moiety. Unfortunately, this alkene proved to be very volatile and difficult to handle. Therefore, a new strategy was probed involving allylic alcohol **15** as the cyclopropane precursor. Thus, crude aldehyde **12** was subjected to a Horner-Emmons reaction, affording unsaturated ester **14** as a single double bond isomer (eq 6.9). Subsequent reduction with DIBAL-H led to the desired allylic alcohol **15** in 75% overall yield from silyl ether **11**.

This (*E*)-alkene was expected to be a good precursor for a Simmons–Smith cyclopropanation,⁵ which should lead to the *trans* substituted cyclopropane of the target molecule **4**.

6.3 Cyclopropanation Reactions

When Charette's reagent⁶ was employed on alcohol **15**, smooth three-membered ring formation occurred to give the desired *trans* cyclopropane **16** in 88% yield as an inseparable 60:40 mixture of diastereomers (eq 6.10).

After cleavage of the silyl ether with TBAF, both isomers of diol **17** could be separated by silica gel column chromatography (eq 6.11).

Minor isomer **17b** was a crystalline solid (mp 92–93 °C) and appeared suitable for a crystal structure determination by X-ray diffraction (figure 6.1), thereby providing unequivocal proof of its tricyclic structure. Unfortunately, the crystal structure also revealed that the minor isomer contained the appropriate relative stereochemistry for the synthesis of **4**. Attempts to improve the diastereoselectivity of the cyclopropanation reaction by using enantiomerically pure auxiliaries such as Charette's ligand⁷ or tartaric ester derived additives⁸ failed. In both cases, smooth cyclopropane formation took place but no improved stereoselectivity was observed. It could be that the steric bulk on one side of the alkene prevents the correct approach of the ligand–metal complex.

Figure 6.1 Crystal structure of 17b

Disappointed by the diastereoselectivity of the cyclopropanations with the allylic alcohol, we turned our attention to diazo-ester carbenoid chemistry with alkene **13** (eq 6.12).⁹

However, no reaction was observed in the presence of the bis-oxazoline ligand **18**¹⁰ and the starting material was fully recovered. Assuming that this outcome was due to the bulkiness of our substrate, we paid attention to Haddad's work¹¹ on the formation of enantiomerically enriched cyclopropane rings from sterically hindered alkenes with chiral diazoester derivatives. Following this approach, diazo-amide **20** derived from the Oppolzer's sultam¹² was synthesised, allowing the reaction without the necessity of any external ligands (eq 6.13).

Unfortunately, a complex mixture of products was obtained in which no cyclopropanated product could be detected. Finally, a palladium catalyzed reaction with diazomethane was attempted on the α,β -unsaturated ester **14**. But once again, the starting material was completely consumed and no three-membered ring formation could be

observed in the ^1H NMR spectrum of the crude mixture. These results indicate the instability of bicyclo[2.1.1]hexanes **13** and **14** towards carbenoid species, which probably engage in ring opening reactions under the cyclopropanation conditions.

6.4 Synthesis of the Right-Hand Substructure of Solanoeclepin A

With alcohol **16** in hand, albeit as a 60:40 mixture of diastereoisomers, we decided to probe the follow-up chemistry of our structure and especially to investigate the formation of the bicyclo[2.1.1]hexanone subunit of solanoeclepin A, which was expected to be rather unstable. The carboxylic acid moiety was first introduced *via* oxidation of **16** with $\text{RuCl}_3/\text{NaIO}_4$ to afford **22**, and subsequently transformed into the corresponding benzyl ester **23** (scheme 6.1).

Scheme 6.1

Removal of the TES group with TBAF afforded secondary alcohol **24**, the precursor for the strained cyclobutanone. As far as we know, the only reported oxidations of a bicyclo[2.1.1]hexanol into its cyclobutanone counterpart involve rather harsh chromium(VI) mediated strongly acidic conditions.¹³ So, more subtle conditions which should be compatible with the sensitive substrate during the last stage of the synthesis of our target molecule were sought. We were very pleased to find that a smooth oxidation reaction occurred with TPAP and NMO at 0 °C giving rise to bicyclo[2.1.1]hexanone **25** in a virtually quantitative yield (eq 6.14). Finally, hydrogenolysis of the benzyl ester led to the right-hand substructure of solanoeclepin (**4**).

With these successful oxidation conditions in hand, a shorter pathway towards **4** was investigated. Starting from diol **17**, a one-pot TPAP bis-oxidation afforded keto-aldehyde **26** in good yield (eq 6.15).

A rapid ruthenium oxidation (30 min.) of carboxaldehyde **26** provided target molecule **4**. This compound proved to be sufficiently stable to be isolated and purified. However, slow decomposition of the bicyclo[2.1.1]hexanone was observed by ^1H NMR when **4** was treated with an excess of MeOH in CDCl_3 . It is believed that the instability of the strained cyclobutanone, probably due to the reactivity of the ketone towards nucleophilic attack, could in part be at the origin of the activity and instability of solanoeclepin A. Unfortunately, the isomeric mixture of **4** showed no hatching activity for potato cyst nematodes, indicating that more elaborated structures are necessary for biological activity.

6.5 Conclusions

In this chapter a straightforward synthesis of the right-hand substructure of solanoeclepin A, containing the bicyclo[2.1.1]hexanone unit and the cyclopropanecarboxylic acid moiety, is described. The intramolecular [2+2] photocycloaddition of dioxene **6** followed by exhaustive reduction furnished the bicyclo[2.1.1]hexanol unit **5**. A diastereoselective cyclopropanation using the classical methods failed, due to both the instability and the steric hindrance of this dense bicyclic structure. However, a Simmons-Smith type reaction on the allylic alcohol **15** afforded a diastereoisomeric mixture of *trans* cyclopropanes **16**. Finally, TPAP oxidation allowed the smooth formation of the strained cyclobutanone. This allowed the synthesis of the right-hand substructure **4** of solanoeclepin A. The target molecule **4** unfortunately showed no hatching activity for potato cyst nematodes so that more elaborated structures have to be investigated.

6.6 Acknowledgments

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6.7 Experimental Section

General information. For general experimental details, see Section 2.9.

3-(4-Oxo-1,5-dioxaspiro[5.5]undec-2-en-3-yl)-propionaldehyde (9).

To a solution of isopropylmagnesium chloride (2M in THF, 11 mL, 22 mmol) in THF (16 mL) at -78°C was added dropwise a solution of iododioxenone **7** (5.89 g, 20.0 mmol) in THF (80 mL) over 4 h.

Copper(I) bromide–dimethyl sulfide complex (412 mg, 2.0 mmol) was added in one portion, followed by hexamethylphosphoric triamide (10.4 mL, 57 mmol). Then, a solution of acrolein (2.8 mL, 42 mmol), and trimethylsilyl chloride (7.6 mL, 60 mmol) in 10 mL of THF was added dropwise over 30 min. The mixture was stirred for 5 h at -78°C , allowed to warm to room temperature and stirred for 12 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (40 mL) and most of the THF was evaporated. The aqueous phase was extracted with EtOAc (4×40 mL). The combined organic layers were washed with water (2×15 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:4) afforded **9** (3.99 g, 89%) as a colorless oil. The product showed some degradation after being stored at -20°C for a week. $R_f = 0.21$. ^1H NMR: 9.78 (s, 1H), 7.04 (s, 1H), 2.73 (t, $J = 6.9$ Hz, 2H), 2.47 (t, $J = 6.9$ Hz, 1H), 2.00–1.91 (m, 1H), 1.70–1.57 (m, 3H), 1.48–1.44 (m, 2H). ^{13}C NMR: 201.1, 161.4, 154.3, 107.6, 107.4, 42.6, 33.7, 24.5, 22.1, 18.9. IR: 2710, 1727, 1640, 1187.

3-But-3-enyl-1,5-dioxaspiro[5.5]undec-3-en-2-one (6).

To a solution of methyltriphenylphosphonium bromide (10.4 g, 29 mmol) in THF (18 mL) at 0°C was added dropwise KHMDS (0.5M in toluene, 57 mL, 29 mmol). The resulting mixture was stirred for 30 min. at 0°C and cooled

to -78°C . Then, a solution of aldehyde **9** (5.80 g, 25.9 mmol) in toluene (10 mL) was added dropwise. The solution was stirred for 30 min. at -78°C , 30 min. at 0°C and allowed to warm to room temperature over 3 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (30 mL). The layers were separated and the aqueous phase was extracted with Et_2O (4×20 mL). The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:9) afforded **6** (4.15 g, 72%) as a colorless oil. $R_f = 0.33$. ^1H NMR: 6.90 (s, 1H), 5.83–5.70 (m, 1H), 5.05–4.99 (m, 2H), 2.25 (br s, 4H), 2.01–1.94 (m, 5H), 1.75–1.55 (m, 3H), 1.48–1.45 (m, 2H). ^{13}C NMR: 161.5, 153.0, 137.5, 115.7, 108.8, 107.0, 34.0, 32.7, 25.5, 25.0, 22.0. IR: 1730, 1639, 1186. HRMS (FAB) calculated for $\text{C}_{13}\text{H}_{19}\text{O}_3$ (MH^+) 223.1334, found 223.1333.

Cycloadduct 10. Irradiation of a solution of alkene **6** (351 mg, 1.58 mmol) in acetonitrile/acetone (40 mL, 9:1 v/v) for 2 h afforded adduct **10** (351 mg), which was used in the next reaction without further purification. ^1H NMR: 3.44 (d, $J = 5.9$ Hz, 1H), 2.68–2.67 (m, 1H), 2.14 (s, 1H), 1.90 (dt, $J = 10.5, 3.9$ Hz, 1H), 1.81–1.77

(m, 2H), 1.56-1.09 (m, 12H). ^{13}C NMR (C_6D_6): 168.8, 109.2, 78.5, 49.1, 42.8, 41.3, 37.9, 35.2, 25.6, 25.4, 23.5, 23.3. IR: 1712.

1-Hydroxymethyl-bicyclo[2.1.1]hexan-5-ol (5). To a solution of LiAlH_4 (1M in THF, 28 mL, 28 mmol) was added dropwise at room temperature a solution of crude cycloadduct **10** (1.76 g, 7.9 mmol) in THF (15 mL). The reaction mixture was stirred for 10 min. Then, the reaction was carefully quenched by addition of EtOAc and saturated aqueous Na_2SO_4 (3 mL) was added. The resulting mixture was stirred for 1 h. After addition of additional solid Na_2SO_4 , the mixture was filtered through Celite® and concentrated *in vacuo*. Purification by chromatography (EtOAc) afforded **5** (364 mg, 36% from **6**) as a white powder. R_f = 0.23. mp 66-68 °C. ^1H NMR: 3.91 (d, J = 6.5 Hz, 1H), 3.86 (d, J = 11.6 Hz, 1H), 3.79 (d, J = 11.6 Hz, 1H), 2.80 (br s, 1H), 2.65-2.63 (m, 1H), 2.32-2.30 (m, 1H), 2.14 (br s, 1H), 1.64-1.61 (m, 2H), 1.48-1.45 (m, 2H), 1.22 (dd, J = 6.9-6.7 Hz, 1H). ^{13}C NMR: 82.6, 63.8, 53.6, 42.6, 35.0, 26.4, 24.2. IR: 3334 (br). HRMS (EI) calculated for $\text{C}_7\text{H}_{12}\text{O}_2$ 128.0837, found 128.0822.

5-Triethylsilyloxy-1-triethylsilyloxymethyl-bicyclo[2.1.1]hexane (11). To a solution of alcohol **5** (175 mg, 1.37 mmol) and imidazole (377 mg, 5.5 mmol) in DMF (5 mL) at 0 °C was added TESCl (0.7 mL, 4.1 mmol). The mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was then diluted with water (6 mL) and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic layers were washed with water (2×3 mL) and saturated aqueous NaHCO_3 (5 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:9) afforded **11** (464 mg, 95%) as a colorless oil. R_f = 0.7. ^1H NMR: 3.75 (d, J = 10.5 Hz, 1H), 3.67 (d, J = 6.5 Hz, 1H), 3.55 (d, J = 10.5 Hz, 1H), 2.22-2.19 (m, 2H), 1.55-1.52 (m, 4H), 1.13 (dd, J = 6.4, 6.3 Hz, 1H), 0.95 (t, J = 7.8 Hz, 9H), 0.94 (t, J = 7.8 Hz, 9H), 0.57 (br q, J = 7.8 Hz, 12H). ^{13}C NMR: 80.3, 61.1, 55.2, 43.4, 35.6, 25.9, 24.0, 6.8, 4.9, 4.5. HRMS (FAB) calculated for $\text{C}_{19}\text{H}_{41}\text{O}_2\text{Si}_2$ (MH^+) 357.2645, found 357.2645.

5-Triethylsilyloxy-bicyclo[2.1.1]hexane-1-carbaldehyde (12). To a solution of oxalyl chloride (198 μL , 2.25 mmol) in CH_2Cl_2 (6 mL) was added dropwise at -60 °C DMSO (341 μL , 4.8 mmol), then after 5 min. a solution of silyl ether **11** (381 mg, 1.07 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 40 min. at -40 °C. Finally, triethylamine (2.3 mL, 17 mmol) was added at -78 °C and the solution was allowed to warm to room temperature over 30 min. Water (7.5 mL) was added and the resulting mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with water (2×3 mL), a saturated aqueous solution of NaHCO_3 (3 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude product was used immediately in the next reaction without further purification. An analytically pure sample was obtained after chromatography (EtOAc:PE = 1:9) to afford **12** as a colorless oil. R_f = 0.41. ^1H NMR: 9.75 (s, 1H), 4.08 (d, J = 6.4 Hz, 1H), 2.98-2.96 (m, 1H), 2.31 (br s, 1H), 1.81-1.65 (m, 4H), 1.40 (dd, J = 6.8, 6.7 Hz, 1H), 0.93 (t, J = 7.9 Hz, 9H), 0.57 (q, J

= 7.9 Hz, 6H). ^{13}C NMR: 202.9, 83.9, 62.7, 44.4, 35.2, 24.5, 23.7, 6.6, 4.6. IR: 2800, 2725, 1713.

Triethyl-(1-vinyl-bicyclo[2.1.1]hex-5-yloxy)-silane (13). To a solution of methyltriphenylphosphonium bromide (123 mg, 0.34 mmol) in Et_2O (3 mL) at 0°C was added dropwise *n*-BuLi (1.6M in hexane, 221 μL , 0.35 mmol). The resulting mixture was stirred for 1 h at 0°C . Then, a solution of aldehyde **12** (81 mg, ca. 0.3 mmol) in Et_2O (2 mL) was added dropwise. The solution was stirred for 1 h at 0°C and then allowed to warm to room temperature. The reaction mixture was quenched with acetone (2 mL) and filtered through a short pad of silica gel. The solvent was carefully evaporated to afford the volatile alkene **13** (45 mg, 55% from **11**) as a colorless liquid. ^1H NMR: 5.99 (dd, J = 15.7, 10.7 Hz, 1H), 5.04 (m, 2H), 3.70 (d, 1H), 2.55-2.53 (m, 1H), 2.18 (br s, 1H), 1.61-1.64 (m, 2H), 1.30-1.21 (m, 2H), 0.94 (t, J = 7.9 Hz, 9H), 0.56 (q, J = 7.9 Hz, 6H).

3-(5-Triethylsilanyloxy-bicyclo[2.1.1]hex-1-yl)-acrylic acid ethyl ester (14). To a dispersion of sodium hydride (60% dispersion in mineral oil, 47 mg, 1.2 mmol) in THF (3 mL) at 0°C was added dropwise a solution triethyl phosphonoacetate (244 μL , 1.2 mmol). The resulting mixture was stirred for 1 h at 0°C and a solution of crude aldehyde **12** (260 mg, ca. 1.1 mmol) in THF (3 mL) was added dropwise. The solution was stirred for 30 min. at 0°C and allowed to warm to room temperature. Saturated aqueous NH_4Cl (10 mL) was added and the resulting mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with Et_2O (3×7 mL). The combined organic layers were washed with water (5 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude product was used in the next reaction without further purification. An analytically pure sample was obtained after chromatography ($\text{EtOAc}:\text{PE}$ = 1:9) to afford **14** as a colorless oil. R_f = 0.55. ^1H NMR: 7.05 (d, J = 15.9 Hz, 1H), 5.79 (d, J = 15.9 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.78 (d, J = 6.4 Hz, 1H), 2.64-2.62 (m, 1H), 2.25-2.24 (m, 1H), 1.69-1.59 (m, 4H), 1.31-1.25 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.9 Hz, 9H), 0.56 (q, J = 7.9 Hz, 6H). ^{13}C NMR: 166.8, 147.4, 121.3, 83.7, 60.0, 55.7, 44.0, 37.7, 28.0, 24.1, 14.2, 6.8, 4.7. IR: 1722. HRMS (FAB) calculated for $\text{C}_{17}\text{H}_{31}\text{O}_3\text{Si}$ (MH^+) 311.2042, found 311.2045.

3-(5-Triethylsilanyloxy-bicyclo[2.1.1]hex-1-yl)-prop-2-en-1-ol (15). To a solution of crude ester **14** (340 mg, ca. 1.1 mmol) in CH_2Cl_2 (5 mL) at -78°C was added dropwise a solution of DIBAL-H (1.5M in toluene, 1.7 mL, 2.5 mmol). The resulting mixture was stirred for 1 h at -78°C and allowed to warm to room temperature. Then, the reaction was carefully quenched by addition of EtOAc and a saturated aqueous solution of Na_2SO_4 (10 drops) was added. The resulting mixture was stirred for 1 h. After addition of additional solid Na_2SO_4 the mixture was filtered through Celite® and concentrated *in vacuo*. Purification by chromatography ($\text{EtOAc}:\text{PE}$ = 1:6) afforded **15** (216 mg, 75% from **11**) as a colorless oil. R_f = 0.30. ^1H NMR: 5.85 (d, J = 15.7 Hz, 1H), 5.66 (dt, J = 15.7, 5.9 Hz, 1H), 4.13 (m, 2H), 3.69 (d, J = 6.4 Hz, 1H), 2.54-2.52 (m, 1H), 2.20-2.18 (m, 1H), 1.65-1.52 (m, 4H + OH), 1.23 (dd, J = 6.6, 6.4 Hz, 1H), 0.94 (t, J = 7.9 Hz, 9H), 0.56 (q, J = 7.9 Hz, 6H). ^{13}C NMR: 131.7, 129.5, 83.5, 63.9, 55.1, 43.5, 37.9, 28.1, 24.2, 6.7, 4.7. IR: 3297 (br).

[2-(5-Triethylsilyloxy-bicyclo[2.1.1]hex-1-yl)-cyclopropyl]-methanol

(16). To a solution of DME (150 μ L, 1.4 mmol) and Et_2Zn (1M in hexane, 1.4 mL, 1.4 mmol) in freshly distilled CH_2Cl_2 (3 mL) at -10°C was added dropwise CH_2I_2 (225 μ L, 2.8 mmol). The resulting solution was stirred for 30 min. at -10°C .

To a solution of allylic alcohol **15** (49 mg, 0.18 mmol) in freshly distilled CH_2Cl_2 (2 mL) at 0°C was added dropwise the previously prepared $\text{Zn}(\text{CH}_2\text{I})_2$ -DME reagent (2 mL, 0.3M, 0.6 mmol). The mixture was allowed to warm to room temperature and stirred for 6 h. Saturated aqueous NH_4Cl (4 mL) was added at 0°C and the resulting mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with Et_2O (3×3 mL). The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography ($\text{EtOAc}:\text{PE} = 1:7$) afforded **16** (45 mg, 88%) as a 60:40 mixture of diastereomers as a colorless oil. $R_f = 0.25$. ^1H NMR: 3.67 (d, $J = 6.5$ Hz, 1H), 3.63 (d, $J = 6.5$ Hz, 1H), 3.57 (dd, $J = 10.7, 6.5$ Hz, 1H), 3.45 (dd, $J = 11.0, 7.0$ Hz, 1H), 3.38 (dd, $J = 11.0, 7.3$ Hz, 1H), 3.29 (dd, $J = 10.7, 7.9$ Hz, 1H), 2.23-2.21 (m, 1H), 2.15-2.13 (m, 3H), 1.60-1.58 (m, 4H), 1.54-1.50 (m, 8H), 1.37-1.20 (m, 4H), 1.05 (dd, $J = 6.5, 6.3$ Hz, 2H), 1.01-0.96 (m, 2H), 0.96 (br t, $J = 7.9$ Hz, 18H), 0.89-0.83 (m, 1H), 0.80-0.75 (m, 1H), 0.71-0.61 (m, 3H), 0.42-0.35 (m, 4H), 0.27-0.23 (m, 1H). IR: 3334 (br). HRMS (EI) calculated for $\text{C}_{16}\text{H}_{28}\text{OSi}$ ($\text{M}^+ - \text{H}_2\text{O}$) 264.1909, found 264.1910.

1-(2-Hydroxymethyl-cyclopropyl)-bicyclo[2.1.1]hexan-5-ol (17).

To a solution of alcohol **16** (39 mg, 0.14 mmol) in 4 mL of THF at 0°C was added dropwise TBAF (1M in THF, 280 μ L, 0.28 mmol). The resulting mixture was stirred for 15 min. at 0°C . Saturated aqueous NH_4Cl (5 mL) was added and the resulting mixture was stirred for 15 minutes. The aqueous phase was extracted with Et_2O (3×5 mL). The combined organic layers were washed with water (5 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography (EtOAc) afforded **17** (18 mg, 99%) as a 60:40 mixture of diastereomers as a colorless oil. Both isomers were obtained pure after repeated chromatography. **17a**: colorless oil. $R_f = 0.31$ ^1H NMR: 3.89 (dd, $J = 10.6, 5.4$ Hz, 1H), 3.77 (d, $J = 6.4$ Hz, 1H), 3.07 (dd, $J = 10.6, 9.3$ Hz, 1H), 2.75 (br s, 1H), 2.23 (q, $J = 1.5$ Hz, 1H), 2.14 (br s, 1H), 2.10-2.07 (m, 1H), 1.61-1.38 (m, 4H), 1.25-1.16 (m, 1H), 0.97 (t, $J = 6.6$ Hz, 1H), 0.67-0.63 (m, 1H), 0.35-0.26 (m, 2H). ^{13}C NMR: 82.8, 67.0, 53.7, 41.0, 34.2, 29.0, 24.3, 18.6, 16.9, 3.9. IR: 3300 (br). **17b**: X-ray crystal structure determination was allowed after recrystallization from EtOAc /pentane. Colorless crystals. $R_f = 0.24$. mp $92-93^\circ\text{C}$. ^1H NMR: 3.71 (d, $J = 6.4$ Hz, 1H), 3.66 (dd, $J = 11.0, 6.2$ Hz, 1H), 3.25 (dd, $J = 11.0, 8.0$ Hz, 1H), 2.28 (br s, 1H), 2.22-2.19 (m, 2H), 1.67 (br s, 1H), 1.59-1.53 (m, 2H), 1.41-1.37 (m, 1H), 1.32-1.27 (m, 1H), 1.11 (dd, $J = 6.7, 6.4$ Hz, 1H), 0.93-0.87 (m, 1H), 0.65 (ddd, $J = 8.3, 5.5, 4.6$ Hz, 1H), 0.44 (dt, $J = 9.6, 4.8$ Hz, 1H). ^{13}C NMR: 82.4, 66.1, 53.1, 41.5, 36.2, 29.7, 27.1, 24.2, 16.2, 7.4. IR: 3300 (br).

Crystallographic data for **17b**: monoclinic, $P2_1$, $a = 5.502(2)$, $b = 29.18(2)$, $c = 12.004(4)$ $\text{\AA}$, $\beta = 94.66(3)^\circ$, $V = 1920.9(17)$ $\text{\AA}^3$, $Z = 8$, $D_x = 1.163$ g cm^{-3} , $\lambda(\text{CuK}\alpha) = 1.5418$ $\text{\AA}$, $\mu(\text{CuK}\alpha) = 6.32$ cm^{-1} , $F(000) = 736$, 240 K. Final $R =$

0.062 for 2114 observed reflections.

Table 6.1 Bond distances of the non-hydrogen atoms (Å) of **17b** (standard deviations)

O(1)-C(6)	1.401(9)	C(3)-C(6)	1.5211(2)	C(7)-C(8)	1.506(10)
O(2)-C(10)	1.433(9)	C(3)-C(4)	1.577(10)	C(7)-C(9)	1.514(10)
C(1)-C(2)	1.562(11)	C(4)-C(5)	1.581(11)	C(8)-C(9)	1.516(11)
C(1)-C(5)	1.537(11)	C(5)-C(6)	1.533(10)	C(9)-C(10)	1.463(12)
C(2)-C(3)	1.535(12)	C(5)-C(7)	1.519(12)		

Table 6.2 Bond angles of the non-hydrogen atoms (°) of **17b** (standard deviations)

C(2)-C(1)-C(5)	98.1(5)	C(1)-C(5)-C(7)	120.2(6)	C(8)-C(7)-C(9)	60.3(5)
C(1)-C(2)-C(3)	100.5(5)	C(4)-C(5)-C(6)	85.0(5)	C(5)-C(7)-C(9)	122.0(6)
C(2)-C(3)-C(6)	102.4(6)	C(4)-C(5)-C(7)	119.0(6)	C(7)-C(8)-C(9)	60.1(5)
C(2)-C(3)-C(4)	100.2(6)	C(1)-C(5)-C(6)	102.2(6)	C(7)-C(9)-C(8)	59.6(5)
C(4)-C(3)-C(6)	85.5(6)	O(1)-C(6)-C(3)	113.4(6)	C(7)-C(9)-C(10)	120.0(6)
C(3)-C(4)-C(5)	81.4(5)	C(3)-C(6)-C(5)	84.8(6)	C(8)-C(9)-C(10)	118.8(7)
C(6)-C(5)-C(7)	121.0(7)	O(1)-C(6)-C(5)	115.0(6)	O(2)-C(10)-C(9)	110.0(6)
C(1)-C(5)-C(4)	102.7(7)	C(5)-C(7)-C(8)	120.1(7)

2-(5-Triethylsilyloxy-bicyclo[2.1.1]hex-1-yl)-cyclopropanecarboxylic acid (22).

To a solution of alcohol **16** (21 mg, 0.073 mmol), NaIO₄ (62 mg, 0.29 mmol) and NaHCO₃ (12 mg, 0.15 mmol) in MeCN/CCl₄/H₂O (1.8 mL, 1:1:1.5 v/v) at 0 °C was added a catalytic amount of RuCl₃·xH₂O. The resulting solution was stirred for 3 h at 0 °C and then filtered through Celite®. The filtrate was dried over MgSO₄ and concentrated *in vacuo* (bath temperature: 30 °C) to afford acid **22** (17 mg) as a yellow oil. The crude product was used immediately in the next reaction without further purification. ¹H NMR: 11.52 (br s, 2H), 3.68 (d, *J* = 6.4 Hz, 1H), 3.67 (d, *J* = 6.5 Hz, 1H), 2.24 (br s, 2H), 2.13 (br s, 2H), 1.70-1.66 (m, 1H), 1.61-1.45 (m, 5H), 1.43-1.33 (m, 4H), 1.22-1.19 (m, 2H), 1.08-1.00 (m, 4H), 0.94 (t, *J* = 7.9 Hz, 18H), 0.90-0.85 (m, 2H), 0.58 (q, *J* = 7.9 Hz, 6H), 0.57 (q, *J* = 7.9 Hz, 6H). IR: 2955 (br), 1699.

2-(5-Triethylsilyloxy-bicyclo[2.1.1]hex-1-yl)-cyclopropanecarboxylic acid benzyl ester (23).

To a solution of the crude acid **22** (17 mg, 0.057 mmol) in 2 mL of MeCN at room temperature was added Cs₂CO₃ (20 mg, 0.061 mmol). The solution was stirred for 15 min. and benzyl bromide was added dropwise (8 µL, 0.07 mmol). The resulting mixture was stirred for 16 h at room temperature. Saturated aqueous NH₄Cl (5 mL) was added and the resulting mixture was stirred for 15 min. The aqueous phase was extracted with Et₂O (3 × 4 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by chromatography (EtOAc:PE = 1:7) afforded **23** (18 mg, 64% from **16**) as a 60:40 mixture of diastereomers as a colorless oil. *R*_f = 0.55. ¹H NMR: 7.36-7.31 (m, 10H), 5.14 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 5.06 (d, *J* = 12.4 Hz, 1H), 5.05 (d, *J* = 12.4 Hz, 1H), 3.66 (d, *J* = 6.4 Hz, 2H), 2.29-2.27 (m, 1H), 2.22 (br s, 1H), 2.11 (br s, 2H), 1.78-1.74 (m, 1H), 1.60-1.54 (m, 6H), 1.41-1.33 (m, 4H), 1.20-1.15 (m, 1H), 1.04-0.99 (m, 4H), 0.95-0.89 (m, 1H), 0.93-0.89 (m, 18H), 0.79 (ddd, *J* = 8.2, 6.7, 3.9 Hz, 1H), 0.59-0.51 (m, 12H). ¹³C NMR: 174.7, 174.7, 136.2, 136.2, 128.5, 128.5, 128.2, 128.1, 128.1, 82.5, 82.4, 66.2, 66.1, 53.2, 53.1, 42.6, 42.6, 35.6, 35.6, 27.7, 27.4, 23.9, 23.7, 22.8, 22.6, 17.2, 15.8, 12.8, 11.1, 6.7, 6.7, 4.8, 4.7. IR: 1728.

2-(5-Hydroxy-bicyclo[2.1.1]hex-1-yl)-cyclopropanecarboxylic acid benzyl ester (24). To a solution of ester **23** (18 mg, 0.047 mmol) in THF (2 mL) at 0 °C was added dropwise TBAF (1M in THF, 67 μ L, 0.067 mmol).

The solution was stirred for 1 h at 0 °C. Then, saturated aqueous NH_4Cl (5 mL) was added and the resulting mixture was stirred for 15 min. The aqueous phase was extracted with Et_2O (3 $\times$ 4 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO_4 and concentrated *in vacuo*. Purification by chromatography ($\text{EtOAc}:\text{PE} = 2:5$) afforded **24** (8 mg, 66%) as a 60:40 mixture of diastereomers as a colorless oil. $R_f = 0.21$. ^1H NMR: 7.39-7.30 (m, 10H), 5.14 (d, $J = 12.4$ Hz, 1H), 5.13 (d, $J = 12.4$ Hz, 1H), 5.09 (d, $J = 12.4$ Hz, 1H), 5.08 (d, $J = 12.4$ Hz, 1H), 3.79 (d, $J = 6.4$ Hz, 1H), 3.77 (d, $J = 6.5$ Hz, 1H), 2.22 (br s, 4H), 1.84 (br s, 2H), 1.80-1.76 (m, 2H), 1.59-1.35 (m, 10H), 1.25-1.21 (m, 1H), 1.11-1.02 (m, 4H), 0.79 (ddd, $J = 8.2, 6.7, 4.0$ Hz, 1H). IR: 3444 (br), 1724.

2-(5-Oxo-bicyclo[2.1.1]hex-1-yl)-cyclopropanecarboxylic acid benzyl ester (25). To a solution of alcohol **24** (8 mg, 0.031 mmol) and NMO (11 mg, 0.09 mmol) in acetone (2 mL) at 0 °C was added TPAP (0.5 mg, 0.002

mmol). The resulting solution was stirred for 45 min. at 0 °C, concentrated *in vacuo* to 1 mL (bath temperature: 30 °C) and filtered through a short pad of silica gel. Purification by chromatography ($\text{EtOAc}:\text{PE} = 2:5$) afforded **25** (8 mg, 99%) as a 60:40 mixture of diastereomers as a colorless oil. $R_f = 0.40$. ^1H NMR: 7.37-7.32 (m, 10H), 5.14 (d, $J = 12.4$ Hz, 2H), 5.08 (d, $J = 12.4$ Hz, 2H), 2.79 (br s, 2H), 1.90-1.66 (m, 10H), 1.60-1.56 (m, 2H), 1.44 (d, $J = 7.2$ Hz, 1H), 1.39 (d, $J = 7.2$ Hz, 1H), 1.26-1.20 (m, 4H), 1.13-1.09 (m, 1H), 1.08 (ddd, $J = 8.4, 6.7, 4.3$ Hz, 1H). ^{13}C NMR: 199.7, 199.6, 173.7, 173.7, 138.0, 137.8, 128.5, 128.2, 128.2, 128.1, 128.1, 66.4, 64.5, 66.4, 52.4, 52.2, 31.4, 30.9, 25.4, 25.0, 21.8, 21.7, 19.9, 17.3, 17.1, 12.8, 12.2. IR: 1776, 1725.

2-(5-Oxo-bicyclo[2.1.1]hex-1-yl)-cyclopropanecarboxylic acid (4 from 25).

To a solution of ester **25** (8 mg, 0.031 mmol) in MeOH (2 mL) at room temperature was added a small portion of $\text{Pd}(\text{OH})_2$. The solution was vigorously stirred while hydrogen was bubbled through for 5 min. Finally, the solution was stirred for 30 min. under hydrogen atmosphere. The mixture was filtered through Celite® and concentrated *in vacuo* (bath temperature: 30 °C). Purification by chromatography ($\text{EtOAc}:\text{PE} = 3:4 + 1\%$ acetic acid) afforded **4** (3 mg, 57%) as a 60:40 mixture of diastereomers as a white solid. $R_f \approx 0.21$. ^1H NMR: 11.0 (br s, 2H), 2.81 (br s, 2H), 1.89-1.68 (m, 10H), 1.61-1.57 (m, 2H), 1.45 (d, $J = 7.2$ Hz, 1H), 1.40 (d, $J = 7.2$ Hz, 1H), 1.30-1.23 (m, 4H), 1.18-1.12 (m, 2H). ^{13}C NMR: 199.6, 199.4, 179.7, 64.4, 64.2, 52.4, 52.3, 31.4, 30.9, 25.4, 25.0, 21.8, 21.7, 20.7, 20.7, 17.1, 16.8, 13.3, 12.7. IR: 1776, 1695.

2-(5-Oxo-bicyclo[2.1.1]hex-1-yl)-cyclopropanecarbaldehyde (26). To a solution of diol **17** (17 mg, 0.10 mmol) and NMO (37 mg, 0.31 mmol) in acetone (3 mL) at 0 °C was added TPAP (2 mg, 0.005 mmol). The resulting

solution was stirred for 2 h at 0 °C, concentrated *in vacuo* to 1 mL (bath temperature: 30 °C)

and filtered through a short pad of silica gel. Purification by chromatography (EtOAc:PE = 2:3) afforded **26** (17 mg, 77%) as a 60:40 mixture of diastereomers as a colorless oil. R_f = 0.38. ^1H NMR: 9.15 (d, J = 4.9 Hz, 1H), 9.12 (d, J = 5.0 Hz, 1H), 2.83 (m, 2H), 2.09 (m, 1H), 2.02 (m, 1H), 1.91-1.66 (m, 8H), 1.62-1.56 (m, 2H), 1.47 (d, J = 7.2 Hz, 1H), 1.42 (d, J = 7.2 Hz, 1H), 1.37-1.24 (m, 5H), 0.97-0.85 (m, 1H). ^{13}C NMR: 200.6, 200.5, 199.6, 199.5, 64.4, 64.2, 52.7, 52.6, 31.8, 31.2, 27.0, 26.9, 25.7, 25.2, 22.0, 21.9, 20.2, 19.9, 12.4, 12.0. IR: 1773, 1705.

2-(5-Oxo-bicyclo[2.1.1]hex-1-yl)-cyclopropanecarboxylic acid (4** from **26**).**

To a solution of keto-aldehyde **26** (8 mg, 0.05 mmol) and NaIO_4 (43 mg, 0.20 mmol) in $\text{MeCN}/\text{CCl}_4/\text{H}_2\text{O}$ (1.8 mL, 1:1:1.5 v/v) was added at 0 °C, a catalytic amount of $\text{RuCl}_3 \cdot \text{H}_2\text{O}$. The resulting solution was stirred for 30 min. at 0 °C and then filtered through Celite®. The filtrate was dried over MgSO_4 and concentrated *in vacuo* (bath temperature: 30 °C). Purification by chromatography (EtOAc:PE = 3:4 + 1% acetic acid) afforded **4** (5 mg, 56%) as a 60:40 mixture of diastereomers as a white solid.

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RETROSPECTION AND FUTURE PROSPECTS

7.1 The Right-Hand Side

This thesis deals with the development of a synthetic route towards the delicate right-hand side of solanoecepin **1** (**1**).

Although we have successfully constructed the complex framework of this right-hand fragment (chapters 2, 3 and 5)¹ and secured the chemistry to form the cyclobutanone and the cyclopropanecarboxylic acid moieties (chapter 6),² the actual synthesis of the complete right-hand side remains to be achieved. One of the main difficulties in the synthesis as described in chapter 5, is the formation of the appropriate cyclization precursor **4** (eq 7.1).

This reaction consistently resulted in a rather poor yield and proved especially difficult on larger scale, due to laborious purification. Therefore, this method did not allow the synthesis of sufficient quantities of material, necessary to complete the construction of the right-hand side. However, in the mean time a new procedure for the construction of photosubstrate **4** has been briefly investigated, involving the silver trifluoroacetate mediated coupling of enol ether **5** with allylic iodide **6** (eq 7.2).³

The preliminary results indicate that in this way the cyclization precursor **4** can be obtained in high yield and good purity. The approach *via* the enol ether coupling should also enable the straightforward synthesis of a cyclization precursor containing an appropriate handle for connecting the right-hand side to the left-hand fragment (see section 4.2). This would require the synthesis of enol ether **12**, which probably can be derived from the known triflate **7**⁴ *via* the sequence delineated in scheme 7.1.

Scheme 7.1

Reduction of the ester moiety by means of DIBAL-H, followed by palladium catalyzed carbonylation of vinyl triflate **8**, should furnish furanone **9**.⁵ Subsequent hydrolysis of the dioxolane leads to ketone **10**.⁴ This ketone is then reduced and protected (see section 4.2) to afford **11**. Finally, enol ether formation provides the required coupling substrate **12**. Almost all of these transformations have already been carried out on the system lacking the additional oxygen substituent on the cyclohexane ring and therefore are expected to proceed without difficulties.

Another problematic stage in the synthesis of the right-hand side, proved to be the functionalization of tetraol **14**, derived from cycloadduct **13** (eq 7.3, see section 5.4).

The direct discrimination of the four hydroxyl functions could never be thoroughly investigated, due to the limited amounts of available material. However, because the new method to construct cyclization precursor **4** (*vide supra*) allows the preparation of **4** in larger quantities, a proper re-examination of the tetraol functionalization process should be possible. A careful study of protection strategies in carbohydrate chemistry could perhaps provide some useful information in this case.

7.2 Model Systems

In the course of the investigations, some model systems of solanoecelepin A have been subjected to hatching activity tests, to get insight into the structure–activity relationship of the natural product. Both the tetracycle **15**⁶ and tricycle **16**² proved to be devoid of any activity, although they contain some of the key functionalities of the natural hatching agent.

This triggers the need for more elaborated model systems, resembling the natural product to a greater extent. Therefore, compounds **17**, **18** and **19** are currently under investigation. Especially **19** is of great importance, because it will provide information about the necessity of the cyclobutanone for hatching activity.

If it would prove possible to omit the cyclobutanone and still retain useful biological activity, a whole new range of target structures is opened up. The application of compounds similar to **19** as a method to combat the potato cyst nematodes would become within reach, because efficient synthetic routes towards these structures can be developed. However,

future investigations will have to provide the solutions to the afore mentioned problems, which to a great extent are associated with the four-membered ring, in order to achieve a successful total synthesis of solanoeclepin A.

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SUMMARY

INTRAMOLECULAR [2+2] PHOTOCYCLOADDITIONS AS AN APPROACH TOWARDS THE RIGHT-HAND SIDE OF SOLANOECELEPIN A

Solanoecelepin A (**1**) is the most active natural hatching agent for the potato cyst nematode. This compound is excreted in minute quantities from the roots of young potato plants, which serves as a signal for the nematodes to leave the cysts. Subsequently, they migrate to the roots of the plant and feed on them, with disastrous consequences for the host. An extensive research program from 1985 until 1992, involving several research groups in the Netherlands, has resulted in the isolation and characterization of this interesting natural product.

Its heptacyclic structure contains all ring sizes ranging from three to seven and encloses nine stereogenic carbon atoms. The most striking structural feature is the densely substituted bicyclo[2.1.1]hexanone unit, a highly strained ring system, which is an unprecedented structural feature in natural products. The structure of **1** to a certain extent resembles that of glycinocelepin A (**2**), the hatching agent of the soybean cyst nematode, from which the name of solanoecelepin A has been derived. The extreme scarcity of the natural material, its fascinating architecture and the potential role it has in the search for an environmentally benign method to combat the nematodes, make **1** a challenging target for total synthesis.

In chapter 1 some general information about solanoecelepin A and glycinocelepin A, is presented, as well as a retrosynthetic analysis of the target natural product.

Chapter 2 deals with the preparation and intramolecular photochemical cycloaddition of 6-methyldioxenones with mono-, di-, tri- and tetrasubstituted alkenes, connected at C-5 of the dioxenone *via* a two atom tether. Depending on the substitution pattern of the alkene and the rigidity of the tether, the photocycloaddition exhibited remarkable regiochemistry, switching with complete selectivity from crossed to straight and *vice versa*. Monosubstituted alkene **1** afforded exclusively the crossed cycloadduct **2** (eq 1).

Di-, tri- and tetrasubstituted alkenes, on the other hand, afforded exclusively the straight products (e.g. the conversion of **3** to **4**, eq 2).

The more rigid lactone precursor **5** showed the opposite regioselectivity again, leading to the desired bicyclo[2.1.1]hexane skeleton (eq 3).

This allowed the stereoselective synthesis of the highly compact and complex pentacyclic bislactone **6**, which contains the appropriate substitution pattern and stereochemistry for elaboration towards the right-hand side of solanoeclepin A. Finally, a mechanistic rationale for the regioselectivity of the [2+2] photocycloadditions, based on molecular modeling results, is presented in chapter 2.

In chapter 3 further chemistry with the 6-methyldioxenone cycloadducts is described. Retro-aldol reactions on the photoproducts provide stereoselective pathways to indanes, trifunctionalized spiro[3.5]nonanes and spiro[3.4]octanes as well as to novel substituted cyclobutanes (e.g. the formation of **8** from **7**, eq 4).

In addition, chapter 3 deals with the functionalization of the cycloadducts without four-membered ring fragmentation, by a rapid and exhaustive reduction leading to the release of a diol function from the dioxanone moiety. Application of these conditions to cycloadduct **6** afforded tetraol **9** (eq 5).

This tetraol has been further functionalized by a four-step sequence to cyclic carbonate **10** in which all four hydroxyl groups have been differentiated.

In chapter 4 the possible use of a vicinal diol to obtain the required cyclobutanone is explored. Therefore, dioxenone derivative **11** bearing an additional oxygen substituent on the C-6 methyl group was prepared (eq 6). Unfortunately, this strategy was unsuccessful, due to the instability of the intermediate bicyclohexanone towards the oxidative cleavage conditions.

Furthermore, chapter 4 describes the attempted use of alternative chromophores, other than the dioxenone, for the [2+2] cycloaddition. To this end, α,β -unsaturated- γ -butenolide **14** and α,β -unsaturated ketone **15** have been synthesized.

These precursors would greatly facilitate the functionalization of the corresponding cycloadducts. However, in both cases the photochemistry resulted exclusively in decomposition of the substrates, probably due to the instability of the pendent enol ether towards the irradiation conditions.

In chapter 5 the preparation and cyclization of 6-unsubstituted dioxenones tethered to mono-, tri- and tetrasubstituted alkenes is described. The key-step in the synthesis of the tri- and tetrasubstituted cyclization precursors comprised a very efficient magnesium-iodide exchange reaction with **16**, which allowed allylation at C-5 of the dioxenone (eq 7).

The 6-unsubstituted dioxenones showed very similar behavior compared to the 6-methyl analogs (chapter 2), with respect to the reactivity and regioselectivity in the [2+2]

photocycloaddition reactions. Thus, photocycloaddition of precursor **19** afforded the bicyclo[2.1.1]hexane **20** in excellent yield (eq 8).

Crossed cycloadduct **20** was elaborated to alcohol **21**, a useful intermediate in model studies towards solanoecepin A. In order to investigate whether the five-membered lactone was crucial for the regiochemical outcome of the cycloaddition, or that connecting the tether and the alkene *via* any other ring would also suffice, seven-membered ring acetonide **22** was prepared (eq 9). However, **22** afforded straight cycloadduct **23** indicating that a seven-membered ring allows too much conformational flexibility in the cycloaddition.

In chapter 6 the synthesis of a small right-hand substructure of solanoecepin containing both the bicyclo[2.1.1]hexanone and the cyclopropanecarboxylic acid moieties of the natural product, is described (scheme 1). The key steps involve the [2+2] photocycloaddition of dioxenone **25** to afford **26**, and the cyclopropanation of allylic alcohol **28**, which afforded a 60:40 mixture of *trans* cyclopropanes. Attempts to improve the diastereoselectivity of the latter reaction, remained unsuccessful.

Scheme 1

Compound **29** (60:40 mixture of *trans* cyclopropanes, minor isomer drawn) has been subjected to hatching activity tests, but unfortunately proved to be devoid of any activity.

SAMENVATTING

INTRAMOLECULAIRE [2+2] FOTOCYCLOADDITIES IN DE SYNTHESE VAN DE RECHTERHELT VAN SOLANOECELEPINE A

Solanoecelepine A (**1**) is de meest actieve natuurlijke wekstof voor het aardappelpycysteaaltje. De wekstof wordt in minieme hoeveelheden uitgescheiden door de wortels van jonge aardappelplanten, wat als signaal voor de aaltjes werkt om uit de cystes te komen. Hierna bewegen zij zich naar de wortels van de plant en voeden zich eraan, met desastreuze gevolgen voor de gastheer. Een uitgebreid onderzoeksproject van 1985 tot 1992, waarin meerdere Nederlandse instellingen nauw hebben samengewerkt, heeft geleid tot de isolatie en karakterisering van deze interessante natuurstof.

De heptacyclische structuur van solanoecelepine A omvat alle ringgroottes van drie tot zeven en herbergt negen asymmetrische koolstofatomen. Het meest opvallende structurelement is het sterk gesubstitueerde bicyclo[2.1.1]hexanonfragment, een zeer gespannen ringsysteem dat nog niet eerder in natuurstoffen is aangetroffen. De structuur van **1** lijkt in enige opzichten op die van glycinocelepine A (**2**), de wekstof van het sojapycysteaaltje, aan welke solanoecelepine A zijn naam ontleent. De extreme schaarste van het natuurlijke materiaal, zijn fascinerende architectuur en de rol die het zou kunnen spelen in de milieuvriendelijke bestrijding van het aardappelpycysteaaltje, maken solanoecelepine A tot een uitdagend doel voor totaalsynthese.

In hoofdstuk 1 wordt algemene informatie over solanoecelepine A en glycinocelepine gegeven, alsmede een retrosynthetische analyse van solanoecelepine A.

Hoofdstuk 2 behandelt de synthese en intramoleculaire fotocycloadditie van 6-methyldioxenonen met mono-, di-, tri- en tetraesubstitueerde alkenen, gebonden aan C-5 van het dioxenon door middel van een twee atomige keten. De cycloadditie vertoonde zeer opmerkelijke regiochemie, wisselend met complete selectiviteit van "crossed" naar "straight" en *vice versa*, afhankelijk van het substitutiepatroon van het alkeen en de rigiditeit van de keten. Monogesubstitueerd alkeen **1** leverde uitsluitend het "crossed" product **2** (vgl 1).

Di-, tri- en tetra-substitueerde alkenen daarentegen, leiden uitsluitend tot de "straight" producten (bijvoorbeeld de omzetting van **3** naar **4**, vgl 2).

Het meer starre lacton **5**, vertoonde wederom de omgekeerde regioselectiviteit, wat resulteerde in de vorming van het gewenste bicyclo[2.1.1]hexaanskelet (vgl 3).

Op deze wijze kon het zeer compacte en complexe pentacyclische bislacton **6** worden gesynthetiseerd, dat het juiste substitutiepatroon en de juiste stereochemie bevat voor verdere functionalisering tot de rechterhelft van solanoelepine A. Tenslotte wordt in hoofdstuk 2 een mechanistische verklaring gegeven voor de opmerkelijke regiochemie van de [2+2] fotocycloaddities, gebaseerd op molecular modeling resultaten.

In hoofdstuk 3 wordt de vervolgscheimie met de 6-methyldioxenonycycloadducten beschreven. Door middel van retro-alldol reacties met de fotoproducten, worden indanen, trifunctionaliseerde spiro[3.5]nonanen of spiro[3.4]octanen en nieuwe gesubstitueerde cyclobutanen stereoselectief verkregen (bijvoorbeeld, de vorming van **8** uit **7**, vgl 4).

Verder wordt in hoofdstuk 3 de functionalisering van de cycloadducten zonder fragmentatie van de vier-ring behandeld. Een snelle, volledige reductie van de fotoproducten, maakt een diolfunctie vrij uit het dioxenon. Het toepassen van deze condities op cycloadduct **6**, leidde tot de vorming van tetraol **9** (vgl 5).

Tetraol **9** is vervolgens gefunctionaliseerd tot cyclisch carbonaat **10** door middel van een vierstapssequentie, waarbij alle hydroxylgroepen zijn gedifferentieerd.

In hoofdstuk 4 wordt het mogelijke gebruik van een vicinaal diol om het benodigde cyclobutanon te verkrijgen behandeld. Derhalve werd dioxenonderivaat **11** gesynthetiseerd, waarin een extra zuurstofsubstituent is opgenomen (vgl 6). Helaas bleek deze strategie niet succesvol, wat te wijten is aan de instabiliteit van het intermediaire cyclobutanon onder de omstandigheden die nodig zijn voor de oxidatieve splitsing van het diol.

Voorts worden in hoofdstuk 4 de pogingen beschreven tot het gebruik van alternatieve chromoforen, anders dan het dioxenon, voor de [2+2] cycloadditie. Derhalve werden α,β -onverzadigd γ -butenolide **14** and α,β -onverzadigd keton **15** gesynthetiseerd.

Deze precursors zouden het functionaliseren van de cycloadducten aanzienlijk vereenvoudigen. Echter, in beide gevallen leidde de fotochemie uitsluitend tot ontleding van de substraten, wat mogelijk veroorzaakt wordt door de instabiliteit van de enolether onder de reactieomstandigheden.

In hoofdstuk 5 wordt de synthese en cyclisatie van 6-ongesubstitueerde dioxenonen verbonden met mono-, tri- en tetra-substitueerde alkenen beschreven. De belangrijkste stap in de synthese van de tri- en tetra-substitueerde cyclisatieprecursors omvat een magnesium-jodide uitwisselingsreactie met **16**, wat allylering op C-5 van het dioxenon mogelijk maakte (vgl 7).

De 6-ongesubstitueerde dioxenonen bleken zeer vergelijkbaar te zijn met de 6-methyl analoga (hoofdstuk 2), in termen van reactiviteit en regioselectiviteit in de fotochemie. Dit

bleek onder andere uit de cycloadditie van precursor **19**, waarbij bicyclo[2.1.1]hexaan **20** in zeer goede opbrengst werd verkregen (vgl 8).

Cycloadduct **20** werd vervolgens verder gefunctionaliseerd tot alcohol **21**, een nuttig intermediair in model studies naar de rechterhelft van solanoelepin A. Om te onderzoeken of het vijf-ring lacton van **19** cruciaal was voor de regiochemie van de cycloadditie, of dat een andere ring die de keten met het alkeen verbindt zou volstaan, werd zeven-ring acetonide **22** gesynthetiseerd (vgl 9). Echter, **22** leverde "straight" adduct **23**, wat aangeeft dat een zeven-ring te flexibel is om de regioselectiviteit van de cycloadditie te dicteren.

In hoofdstuk 6 wordt de synthese behandeld van een kleine substructuur van solanoelepine A, waarin zowel de bicyclo[2.1.1]hexanoneenheid als de cyclopropan-carbonzuurgroep van de natuurstof vertegenwoordigd zijn (schema 1). De belangrijkste stappen zijn de fotochemische omzetting van dioxenon **25** tot **26** en de cyclopropanering van de allylische alcohol **28**, wat leidde tot een 60:40 mengsel van *trans* cyclopropanen. Pogingen om de diastereoselectiviteit van deze laatste reactie te verbeteren, bleven zonder resultaat.

Schema 1

Verbinding **29** (60:40 mengsel van *trans* cyclopropanen, de minst voorkomende isomeer is getekend) is getest als wekstof, maar bleek helaas geen activiteit te bezitten.