Synthesis of precursors en route to the basic skeleton of the anti-tumor drug Taxol

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Seher Yalcin

from Izmir, Turkey

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Germany
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Gutachter: Prof. M. Demuth und Prof. R. Sustmann
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1 Abstract

In this work, a new and efficient synthesis of 9,9-Dimethyl-bicyclo[3.3.1]nonane-2,6-dione, which is a potential precursor of the ABC ring skeleton of the anti-tumor drug taxol (1), has been synthesized by using a photochemical oxa-di-π-methane rearrangement as a key reaction.

Taxol (1):

The synthesis starts with the addition of dilithated propargyl alcohol to 2,2-dimethylcyclohexa-1,6-dione (56). The product 57 was then subjected to a Nazarov-type cyclization in order to obtain the β,γ-unsaturated endione 58. Treatment with CH₃OH/H₂SO₄, HOAc/H₂SO₄ and P₂O₅/CH₃SO₃H resulted in the decomposition of the starting compound. Reaction of 57 with amberlyst 15 gave, however, the expected compound 58.

Oxa-di-π-methane rearrangements, which are analogs of the di-π-methane rearrangement, are widely applied for the synthesis of natural products. Irradiation of 58 in the presence of acetophenone as sensitizer with the 350-nm light (Rayonet reactor) gave the unexpected product 77. Failure of this transformation has been explained by the stabilization of one of the possible intermediate radicals 76. The generated intermediate radical seems to be 1,3-acyl shift product which was stabilized by the neighboring carbonyl groups.
Efforts were then directed to the synthesis of another $\beta,\gamma$-enone so that the oxa-di-$\pi$-methane rearrangement would not have the intermediate like 76. For this reason, 57 was oxidized with Jones reagent and then hydrogenated on 10% Pd/charcoal. When the obtained cyclic lactone 83 was treated with polyphosphoric acid (PPA) the target $\beta,\gamma$-endione 78 was obtained in 60% yield. The oxa-di-$\pi$-methane rearrangement of 78 to 84 was achieved by irradiating at 350-nm light (Rayonet reactor) and acetophenone was used as the sensitizer with a yield of 87%.

The next important step of this work was the cleavage of the central cyclopropane bond of 84. Attempts of cleavage included hydrogenation, $\text{H}_2\text{SO}_4$ in acetone, $\text{HBr}$ in HOAc, HCl in HOAc, BF$_3$Et$_2$O in acetic anhydride treatment. Furthermore, neighboring group participation to facilitate the cleavage by push-pull mechanisms, oxidative opening with Pb(OAc)$_4$ and dissolving metal reduction like Birch and Bouveault-Blanc reductions have also been tried. Although these methods work for other compounds, they were not successful in cleaving the central bond of 84; either the starting material was recovered or
lateral bond cleaved in the cyclopropane occurred. Reasons are, depend on the method applied, either the lack of sufficient orbital interaction between the carbonyls and the cyclopropane bond which is intended to be cleaved or the unfavorable build-up of a carbenium center at the α-position of the carbonyls, i.e. the propellane junction in 84.

In order to still achieve the wanted bond cleavage in 84, potassium-graphite intercalation compound (C₈K) was applied so that conjugation of the carbonyls and lateral bonds were not anymore the predominant factors for the cleavage of the cyclopropane. Similarly, a build-up of cationic intermediates will be avoided by this method which is known to proceed via diradical anions (see below). As a result, the central C-C bond in 84 was cleaved with C₈K and 85 was obtained that is according to our synthetic plan the precursor of the ABC ring skeleton of the anti-tumor drug taxol (1).
For introducing the C ring to the compound 85, one of the carbonyls of 85 was protected and the monoprotected ketone 135 was subsequently transformed to tert-butyldimethylsilyl enol ether 136. Next, ZrCl₄-catalyzed [2+2] cycloadditions with but-2-ynoic acid methylester (133) were studied. Unfortunately, the strong oxophilic character of the catalyst renders the [2+2] reaction of 136 and 133 very difficult to handle and the starting materials were recovered. Further attempts in this direction will be undertaken in the future by handling the reaction under strict oxygen-free conditions (glove box under argon) since analogous transformations in literature sound promising in view of further attempts to carry out this transformation successfully.

It should also be noted that the present approach towards 1 involves – in contrast to most approaches in literature – precursors containing the geminal dimethyl group which is ultimately very important for the biological activity of the target.
2 Introduction

2.1 Short history

Taxol (1, Figure 1) is a natural anticancer product, which is isolated from the bark of the pacific yew tree, *Taxus brevifolia*. The activity of the compound was discovered in a screening process initiated by the National Cancer Institute (NCI) for chemotherapeutic activity. As a result of this screening process *Taxus brevifolia* was found to be cytotoxic to 9KB (human oral epidermoid carcinoma) cells and P1534 leukemia cells by Wani and Wall who gave the name of “taxol” to this antitumor compound. In 1971, they have also cleared the tetracyclic, highly oxygenated diterpene structure of taxol by obtaining the single crystal X-ray structure. Despite its promising activity and novel structure, initial interest in taxol was not great due to its scarcity, poor aqueous solubility and the lack of information about its mechanism of action. The discovery of taxol’s mechanism of action by Horwitz and finding the activity against B16 mouse melanoma cell led to increased interest in taxol. First clinical trials began in 1981 and demonstrated that taxol had significant activity against solid tumors such as ovarian cancer and breast cancer, and stimulated consequence an enormous public interest in the drug. In 1989, *Bristol-Myers Squibb* was selected to commercialise taxol. The Food and Drug Administration (FDA) approved the use of taxol for treatment of ovarian cancer in 1992 and subsequently in 1994 FDA approved taxol for breast cancer chemotherapy. Currently it is used against a variety of tumor types, including lung, head, neck cancers. Also, it has activity against small cell lung cancer, oesophageal, gastricendometrial, bladder, germ cell tumors and AIDS-associated *Kaposi’s sarcoma*.

\[ \text{Figure 1: Structure of taxol (1)} \]
2.2 Mechanism of action of taxol (1)

Taxol was discovered because of its strong cytotoxicity. Because of the supply problem and the poor aqueous solubility, some limited testing was carried out. Taxol’s mechanism of action in promoting polymerization of tubulin was discovered by Horwitz in 1979.

Tubulin is a heterodimeric protein, consisting of two similar but distinct subunits (the α and β tubulins) which are linked to each other. Microtubules are important parts of the cell being essential for the cell division (mitosis) and they are formed by polymerisation of α- and β-tubulins (monomers). The first step of polymerization is the formation of heterodimers which come from the dimerization of one molecule of α-tubulin and one molecule of β-tubulin. For the microtubule polymerization, two molecules of guanosine 5’-triphosphate (GTP) and magnesium ions, which enhance polymerization to microtubules, are needed. Then, a nucleation center is formed by heterodimers for the further polymerization to form protofilaments which subsequently form microtubules. A normal microtubule has a diameter of 24 nm and is formed by 13 protofilaments (Figure 2).

When a cell needs to form microtubules for cell division, the rate of formation of microtubules is greater than the rate of decomposition. The concentration of tubulin decreases until it reaches the critical concentration of tubulin, there exists an equilibrium between tubulin and microtubulin. This process is reversible for a normal cell. The role of taxol is to bind microtubules and stabilize them. Thus, the equilibrium between tubulin-microtubulin is affected, and tubulins are converted into microtubulins irreversibly. Taxol decreases both the critical concentration of tubulin being necessary for polymerization including the induction time for polymerization and taxol does it either in the presence or absence of GTP and magnesium ion. Taxol-induced microtubulins are thinner and much more stable than normal microtubules. At low temperatures and after treatment with calcium, microtubules are depolymerized but these conditions do not affect the taxol-induced microtubules. Hence, taxol blocks cells, making the formation of a normal mitotic apparatus impossible and inhibits cell division or proceeds very slowly to bring about tumor size decrease. Therefore, the best explanation of the cytotoxicity of taxol bases on its ability to disrupt the mitotic spindle.
2.3 Chemistry of taxol (1) and structure-activity relationships (SAR)

Taxol (1) belongs to the class of taxane diterpenoids or taxoids which are natural products. The taxane skeleton consists of a basic pentamethyl[9.3.1.0]tricyclopentadecane skeleton and its unique numbering system is shown in Figure 3. It has mainly two differences as compared to other taxoids which are the N-benzylophenylisoserine ester group at C-13 - known as “side chain” – and an unusual fourth ring in the form of an oxetane attached at the C-4,5 positions.
The structure of taxol (1) is quite unusual, consisting of a bridged tetracyclic skeleton with a β-phenylisoserine side chain and the conformation according to X-ray is called “inverted cup”. Its molecular formula is \( \text{C}_{47}\text{H}_{51}\text{NO}_{14} \) with the molecular weight of 853.92 g mol\(^{-1} \) and the IUPAC systematic name\(^{11c} \) is: \([2\text{aR}-[2\text{aa},4\text{b},4\text{ab},6\text{b},9\text{a}(\text{aR}^*,\text{bS}^*),11\text{a},12\text{a},12\text{aa},12\text{ba}]]-\text{b-}
(Benzoylamino)-\text{a-hydroxybenzenepropanoic acid 6,12b-bis(acetylxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester.\)
Interactions of drugs with their receptors are very specific and the structure-activity relationship (SAR) can give valuable information about the action of a drug. Consequently, new analogs of drugs can be designed in order to get an improved drug activity. By modifying the functional groups of taxol (1), one at a time, it can be learned whether they are necessary for important activity of the drug.

The taxol “side chain” which is essential for the activity, is highly flexible and has different conformations depending on the medium. Studies on structure-activity relationship (SAR) showed that side chains with a free hydroxyl group at the C-2’ position are crucial for the activity. For example, methylated C-2’ is more toxic than taxol itself and has an increased binding affinity to tubulin. Furthermore, replacement of the 3’-phenyl group by small alkyl groups like methyl, decreases the activity significantly. In contrast, larger groups such as isobutyl, improve the activity of taxol (1).

In addition, opening of the “oxetane ring” eliminates the cytotoxicity of the taxol and the tubulin assembly activity. It is concluded that hydrogen bonding properties and rigidification of the taxol ring system by the oxetane ring stabilizes the taxol-tubulin complex. For example, substitution of the oxygen by sulfur decreases the activity while replacement of the oxetane ring by a cyclopropane increases the activity drastically.

Modifications at the C-1, C-2 and C-4 positions which are at the “southern hemisphere” change the activity of taxol importantly. Removal of the acetoxy group from C-4 or the benzoate group from C-2 result in reduced activity as compared with taxol. Interestingly, the difference in activity is modulated by the position of substituents at C-2: While 2-p-azidobenzoyltaxol is inactive, 2-m-azidobenzoyltaxol is more active than taxol.

On the other hand, SAR investigations show that modifications on the northern hemisphere of taxol did not result in remarkable effects concerning the activity. Consequently, the northern hemisphere of taxol does not play an important role in the binding with microtubules. The results of the SAR studies of taxol are summarized in Figure 4.
Obtaining sufficient quantities of the compound from its natural sources was one of the main problems in the development of taxol as an anticancer agent. Taxol only constitutes 0.01% of the dry weight of the inner bark of the Pacific yew tree\(^1\). Since the typical 100 years old yew tree yields about 3 kg of bark and collection of bark kills the tree, the use of taxol from natural sources threatened the species with extinction. Therefore, chemical synthesis or bioproduction through plant tissue became an important aim for the scientists. Fortunately, it was discovered that 10-deacetylbaccatin III (10-DAB) (2) could be extracted from the needles and leaves of the European yew tree,\(^2\) *Taxus baccata* in approximately 0.2% yield with small amount of baccatin III (3) (Figure 3).

**Figure 5:** Components for the semisynthesis of taxol (1)

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**Figure 4:** Some of the structure-activity relationship (SAR)\(^10\) of taxol (1)
The availability of 10-DAB provided an accessible supply for the “semi-synthetic” strategies by synthesizing the side chain\textsuperscript{21}. There are many semi-synthetic approaches to taxol (1) from 10-deacetyl baccatin III (2) and one of these strategies\textsuperscript{22} includes coupling of the protected side chain N-benzoyl-O(1-ethoxyethyl)-3-phenylisoserine (5) and 7-triethylsilyl baccatin III (4) which is the form of modified 10-DAB (2). This semi-synthetic route is applied by \textit{Bristol-Myers Squibb} and is outlined in Scheme 1.

![Scheme 1: Semi-synthetic approach to taxol (1)](image)

2.4 Previous total syntheses of taxol (1)

Although a “semi-synthetic” approach has the advantage of using leaves and needless which are renewable parts of the yew tree, harvesting and extraction of 2 from the tree material, however, represents a time and energy consuming problem. Thus, an intense research is being carried out to produce practical total syntheses of taxol (1) that would alleviate the supply problem. Because of its complex ring system and many chiral centers, six independent syntheses based on very lengthy accesses have been achieved to date by: Nicolaou (1994), Holton (1994), Danishefsky (1995), Wender (1997), Kuwajima (1998) and Mukaiyama (1999).
Nicolaou has chosen a convergent approach\textsuperscript{23} (Scheme 2) in which rings A and C were constructed separately and then brought together to form the 8-membered B ring. Both A and B ring fragments were synthesized via the Diels-Alder reaction. For the regiochemistry of the C ring fragment 12, two reaction partners, i.e. 10 and 11, were temporarily tethered as the boronate and then decomplexed to aldehyde 12.

Scheme 2: Nicolaou approach, synthesis of A and B ring fragments

One of the key steps in Nicolaou’s synthesis is the Shapiro coupling of 9 and 12 that brings A and B ring fragments together. This coupling rendered 13 which is the reactant of another key step, a McMurry cyclization to construct the ABC skeleton 14 (Scheme 3).

Scheme 3: Construction of the ABC rings
After *McMurry* coupling, the oxatane ring was formed. Later in the synthesis, the C-13 oxygen was introduced by chromium-mediated allylic oxidation, followed by stereospecific reduction of the enone. Coupling with the β-lactam side chain gave taxol (1) in a total yield of 0.01% from commercially available materials.

*Holton*’s approach to taxol is linear24 (Scheme 4) which is different from that of *Nicolaou*. The strategy of the total synthesis relies on the ring enlargement of the natural product β-patchouline oxide (15) to construct the AB ring system 17 by using an epoxy to alcohol fragmentation including protection. Then 17 was elaborated to the ABC system 19 through intermediate 18. After the final elaboration of D ring and functional group manipulations, baccatin III (3) was synthesized.

Introduction of the “side chain” was managed by coupling of 3 with β-lactam 20, followed by further desilylation. Taxol (1) was synthesized by this route in a yield of 0.1% from commercially available starting materials.

![Scheme 4: Holton’s synthetic route to taxol (1)](image-url)
Danishefsky’s convergent approach\(^{25}\) is the only one to start with a preformed oxetane ring (Scheme 5). The reason for this success was having a benzyl ether rather than an acetate. For the synthesis of CD ring moiety, Wieland-Miescher ketone (21) was used as starting material.

After fragmentation (21 $\rightarrow$ 22) the A ring fragment 23 was introduced to construct the A-CD part 24. Cyclization to the ABCD skeleton was achieved via intramolecular Heck reaction (23 $\rightarrow$ 24). After manipulating the functional groups, 24 was converted to baccatin III (3) which is a potential precursor of taxol (1). The total synthesis was completed by coupling of the $\beta$-lactam 20, adopting the conditions that have been developed by Ojima before.

Scheme 5: Danishefsky’s strategy
Wender reported the shortest total synthesis of taxol (1) to date (Scheme 6). This synthesis uses verbone (26) as starting material, 26 being an air oxidation by-product of pinene and it supplies 10 of the 20 carbons of the taxol skeleton. Fragmentation of epoxy alcohol 15 resulted in 28 which constitutes a fully functionalised AB system. Formation of the C ring was achieved via aldol condensation of 28 that was elaborated at the C-3 position before. After bromination of C-5, osmylation of C-4 and C-20, the oxetane ring was constructed, followed by acylation of C-4. After synthesis of 10-deacetylbaccatin III, taxol (1) has been reached by employing the β–lactam coupling reactions used before. The overall synthesis has 37 steps from the starting verbone (26).

Scheme 6: Wender’s strategy
Kuwajima has followed a convergent route\textsuperscript{27} to 1 (Scheme 7) like Nicolaou and Danishefsky. By a coupling reaction of the optically pure A ring hydroxy aldehyde 31 with the aromatic C-ring fragment 32 followed by Lewis acid-mediated eight-membered B ring cyclization gave the desired ABC skeleton 34. The former fragment 31 has been synthesized from propargyl alcohol in sixteen steps and the latter fragment 32 is derived from 2-bromo-2-cyclohexenone in eight steps. Before introducing the oxetane moiety, C-8 of 35 was methylated via cyclopropanation and reductive cleavage of cyclopropyl ketone. In order to osmylate the C ring for attachment of the oxetane ring, steric congestion around the A cycle of the taxol skeleton increased by acetylation of C-10. Since these steps - introduction of methyl to C-8 and formation of oxetane ring - needed exchange of the protecting groups, the synthetic route became rather lengthy. Finally, acylation of the C-13 by the β-lactam and removing the protecting groups completed the total synthesis.

Scheme 7: Kuwajima’s strategy
Mukaiyama reported the final synthesis\textsuperscript{28} in 1999 (Scheme 8). Unlike other strategies, a unique pathway starting from an 8-membered ring compound by way of B to BC to ABC to ABCD ring construction achieved the total synthesis of taxol (1). Compound 39 has been converted to the B ring equivalent 40 via aldol cyclization. Although 8-membered ring compounds are not easily available directly from simple linear precursors, this high yielding cyclization proceeds smoothly because the linear precursor having suitable conformations for cyclization. The C ring was introduced via Michael addition and intramolecular aldol cyclization to 40. Construction of the ABC ring system was achieved by way of allylation of C-1 and an intramolecular pinacol coupling reaction of 41. The oxetane ring was finally introduced via allylic bromination, osmylation and ultimately the addition of the side chain has completed the total synthesis.

\textbf{Scheme 8: Mukaiyama’s strategy}
2.5 Biosynthetic studies

In addition to total taxol syntheses, alternative sources for taxol production are vigorously searched for due to the long reaction sequences and low yields of the hitherto synthetic approaches and the required substantial effort for purification of semi-synthesis precursors from plant tissue and separation of the desired intermediates. Improvement of the biosynthetic process based on the understanding of the pathway for taxol formation, i.e. the enzymes an their mechanism of action and the structural gene encoding of these enzymes. To date several investigations have been done for the biosynthetic approach of taxol.

The taxol biosynthetic way consists of approximately 20 enzymatic steps and it has been shown\(^{29}\) that cytochrome P450 enzymes responsible for oxygenation, hydroxylation and acetylation. However, the intermediate steps of the taxol biosynthetic pathway remain undefined and are under investigation. The route to taxol (1) starts with the cyclization of the diterpenoid precursor geranylgeranyldiphosphate (44) to taxa-4(5),11(12)diene (45) by taxadiene synthase (Scheme 9). Then 45 is hydroxylated to taxa-4(20),11(12)-dien-5\(\alpha\)-ol (46) by cyctochrom e P450 taxadiene 5\(\alpha\)-hydroxylase. 46 is subsequently converted to taxa-4(20),11(12)-dien-5\(\alpha\)-yl acetate (47) by taxa-4(20),11(12)-dien-5\(\alpha\)-ol-O-acetyltransferase. Hydroxylation of 47 by cyctochrome P450 taxane 10\(\beta\)-hydroxylase gives 48 that is converted to 49 via yet undefined steps. Taxane-2\(\alpha\)-O-benzoyleftransferase converts 49 into 10-deacetylbaccatin III (2) that is acetylated by 10-deacetylbaccatin III-10-\(O\)-acyetyltransferase to render baccatin III (3).
Scheme 9: Biosynthetic pathways to taxol
2.6 Objectives

The aim of this work was to synthesize precursors en route to a synthesis of the anti-tumor drug taxol (1) skeleton. Primarily structures of types C and D should be approached as an entry to the basic ABC ring skeleton of 1. The envisaged synthetic strategy, which is the result of a retrosynthetic analysis (see Scheme 10, p. 21 and structures below) includes two key steps that are step (a) a photochemical oxa-di-π-methane (ODPM) rearrangement of β,γ-unsaturated cyclic dieneone structures of type A to afford the propellane-type cyclopropyl ketone B. This intermediate should beneficially contain the characteristic geminal dimethyl pattern being seemingly important for the biological activity of 1. A second important step (b) will involve the cleavage of the central cyclopropane bond of the propylene B (→ C) for a proper set-up of the AB ring moiety.

Although the total synthesis of 1 has been achieved six times before, none of these approaches is efficient and the synthetic routes are lengthy. The shortest route consists of 37 steps (synthesis by Wender et al.\textsuperscript{24}). At present, the anti-tumor drug taxol (1) is obtained semi-synthetically by harvesting the leaves of the European yew tree (taxus baccata) and extracting the 10-deacetylbaccarin III (10-DAB) (2) from the leaves. Since the harvesting and extracting consume lots of time and energy, the presently available supply of 1 is problematic. This work is to pioneer a shorter and efficient access of taxol (1) synthetically. Furthermore, the planned reaction scheme should allow to carry out a variety of functional modifications of intermediate precursors to enable broader biological activity testing of the target structures.
3 Results and discussion

3.1 Strategy

The taxane diterpenes, the main representative being taxol (1, Figure 1), stimulated a considerable interest from synthetic chemists because of the broad antitumor activities of this class of compounds and their unique structures which contain an unusual tetracyclic skeleton with an sp² carbon at its bridgehead C-11 and a geminal dimethyl group at the carbon bridge C-15 between the A and B rings. While several approaches to the total and semi synthesis of taxol have been successfully carried out, many attempts have focused on the synthesis of the carbon skeleton of this diterpene. The synthetic approaches are yet very lengthy and especially the achieved total syntheses out of this reason unrealistic for practical applications.

In our studies directed towards the synthesis of the basic taxol skeleton, such as 50 (see Scheme 10, p. 22), we planned a linear route as outlined in a retrosynthetic way. One of the key steps, i.e. 52 ⇒ 53, represents synthetically a photochemical transformation, the so-called oxa-di-π-methane (ODPM) rearrangement, which involves in the present case the reaction of the β,γ-unsaturated enone 53 to 52. The ODPM rearrangement of β,γ-enones was successfully applied to the synthesis of natural products in the presence of other functional groups that are not affected under irradiation. This photochemical key step is thought to be a short entry to achieve a synthetic access to the bicyclic 51 and the tricyclic 50 on the way to 1. To make the photochemical key step possible we should have a short access to the enone 53 which is planned along the retrosynthetic line 53 ⇒ 54 ⇒ 55.

![Figure 7: Structure of taxol (1)](image-url)
3.2 Synthesis of 2,2-dimethylbicyclo[4.3.0]non-1(6)-en-3,9-dione (58)

The retrosynthetic analysis of the diterpene skeleton 50 (Scheme 10) shows how the envisaged ODPM rearrangement strategy (53 → 52) relies on the access to the β,γ-enone 53 or an analog thereof. The first step of the reaction sequence for the synthesis of 58 (Scheme 11), which is a carbonyl analog of 53, starts with dimethylation of the commercially available cyclohexan-1,3-dione (55). Afterwards, dilithated propargyl alcohol was added to 56 at -78 °C to give 57 in 54% yield. For the synthesis of the target β,γ-endione 58, a Nazarov-like cyclization was applied to 57.

Scheme 11: Synthesis of 58 from 55
To accomplish this *Nazarov*-type cyclization, acidic catalysts such as CH$_3$OH/H$_2$SO$_4$, HOAc/H$_2$SO$_4$, and P$_2$O$_5$/CH$_3$SO$_3$H were applied which, however, resulted in decomposition of the starting material. Only the treatment with an acidic ion exchange resin, amberlyst 15 in HOAc, gave 58 from 57, although in a low yield of 13%. The suggested mechanism of this transformation is depicted in Scheme 12.

Scheme 12: The proposed reaction mechanism of the *Nazarov*-like cyclization 57 → 58

Cyclization of divinyl ketones to yield cyclopentenones is called *Nazarov* cyclization. 59 → 58 is a typical *Nazarov* cyclization. 59 is the precursor to form the cyclic cationic intermediate 59b on the way to 58 via the acyclic precursor 59a. In addition, acetylenic diols can be transformed to five-membered cyclic adducts. In case of the cyclization of compound 57, 59 is formed *in situ* by treating 57 with acidic ion exchange resin amberlyst 15 which implies the intermediacy of the vinylic cation 57a and its rearranged isomer 57b on the way to 59 via 57c.

3.3 Oxa-di-$\pi$-methane (ODPM) rearrangements

Photochemical 1,2- and 1,3-acyl sigmatropic shifts of $\beta,\gamma$-enones represent an important class of reactions that are often used to achieve skeletal transformations in total synthesis of natural products. The 1,2-acyl shift is commonly known as the oxa-di-$\pi$-methane (ODPM)
rearrangement since it is structurally and mechanistically analogous to the di-π-methane rearrangement. In principle, β,γ-enones can undergo photoreactions such as, cis-trans isomerization, [2+2] cycloaddition, reduction, decarbonylation, etc. depending on the structure of the enone. However, reactions of the β,γ-unsaturated ketones are dominated by two main transformations, the 1,3-acyl shift and the ODPM rearrangement. In general, direct irradiation of β,γ-unsaturated ketones yield 1,3-shifts, whereas ODPM rearrangements occur with triplet sensitized energy transfer. The former offers the isomerization of the enone (e.g. 60 → 61), the latter results in the formation of cyclopropyl ketones of type 62 (Scheme 13).

Scheme 13: 1,3-acyl shift (→ 61) and ODPM rearrangement (→ 62) from 60

The ODPM rearrangement includes formally a 1,2-acyl migration followed by cyclization. In detail, the biradical intermediate 63a is the primary intermediate of 63 which undergoes ring opening to 63b being a very short-lived 1,3-biradical which recombines to form the final cyclopropyl ketone 64 (Scheme 14). The alternative ring opening of the biradical intermediate 63a that would yield the even shorter-lived oxirane 63c has never been observed.

Scheme 14: General reaction mechanism of the oxa-di-π-methane (ODPM) rearrangement
On the other hand, two competitive routes have been proposed for the 1,3-acyl shift.\textsuperscript{38,44} The first route is a fragmentation-recombination mechanism involving a single intermediate stage corresponding to a free radical pair 66a which forms the final isomerization product 67 (Scheme 15). The second route is called the quasi-concerted process via the two feasible biradical intermediates 66b which can be either a tight intermediate or a loose intermediate radical pair. In the first description of the intermediate, all C-C bonds are formed and in the second one, the radical pair is held together as a loose radical contact pair.

\[ \text{Scheme 15: The reaction mechanism of the 1,3-acyl shift}^{33} \]

The reaction mechanisms of the ODPM rearrangement and the 1,3-acyl shift have been studied and the excited-state reactivity and correlation has been established.\textsuperscript{32,46} Generally, 1,3-acyl shifts can take place from the singlet excited state (S\textsubscript{1}, n\pi\textsuperscript{*}) via direct irradiation, whereas the oxa-di-\pi-methane rearrangement occurs from the lowest triplet excited state (T\textsubscript{1}, \pi\pi\textsuperscript{*}) in the presence of a sensitizer\textsuperscript{47} (Figure 8). During irradiation, the excited state energy of a sensitizer, such as acetophenone, benzophenone or acetone, is transmitted to the \beta,\gamma-enone in the ground state which finally ends up in its lowest triplet state T\textsubscript{1} (\pi-\pi\textsuperscript{*}). It should be pointed out that the sensitizer must have sufficient triplet energy to excite the triplet (T\textsubscript{1}) state of the \beta,\gamma-unsaturated ketone in an exothermic energy transfer process in order to enable the ODPM rearrangement.
Additional investigations provided more detailed information about the excited state-reactivity correlations of β,γ-unsaturated ketones. The intersystem crossing from the singlet to the triplet state populates generally the higher triplet state (T₂, ππ*) and, if the life time allows, 1,3-acyl shifts can also occur from this state. However, this represents a very rare process.\textsuperscript{32,46}

![Jablonsky diagram](image)

**Figure 8:** *Jablonsky* diagram of the oxa-di-π-methane rearrangement vs. the 1,3-acyl shift followed by rearrangement\textsuperscript{46}

ODPM rearrangements give good to excellent yields, especially in case of the semicyclic, bicyclic and bridged β,γ-unsaturated ketones.\textsuperscript{39b,48} The efficiency and the limits strongly depend on the conformational flexibility of the β,γ-enone moiety. For higher chemical yields, rigid structures of reactants are favorable in view of orbital overlap and inhibition of energy decay from the excited state(s) by internal conversion. The bridged, bi- and tricyclic enones exhibit such rigid structures and indeed afford ODPM rearrangements with high yields. For example, photochemical reactions of a variety of bicyclo[2.2.2]octenones have been studied.\textsuperscript{49} Irradiation of 68 in the presence of acetone as the sensitizer gives the ODPM rearrangement products, the tricyclooctanones 70 with excellent yields up to 86% (Scheme 16). Notably, there is no scrambling of substituents observed upon this rearrangement in general. In the absence of a sensitizer the cyclobutanones 69 are obtained.
Scheme 16: 1,3-Acyl shift vs. ODPM rearrangement of the conformationally rigid bicyclic enone 68

In order to provide sufficient rigidity in acyclic enones, the carbon between alkene and the carbonyl group of a $\beta,\gamma$-enone must be fully substituted by alkyl, phenyl or vinyl moieties. Otherwise, other channels of energetic deactivation of the triplet state predominate, such as cis-trans isomerization. This form of energy dissipation is called “free-rotor effect.” One example for this kind of process is shown in Scheme 17. Irradiation of 72 in the presence of a sensitizer results in cis-trans isomerization of 71 and 72, without formation of an ODPM product (e.g. 73).

Scheme 17: Free-rotor effect: cis-trans isomerization of 71

Besides that, additional conjugation of chromophores at either the ketonic or the olefinic part as well as intramolecularly competitive electronic effects have been examined. In general, reactants that have chromophores like A and B (Figure 9) need a sensitizer for the ODPM rearrangement, while reactants having chromophores like C and D undergo ODPM rearrangements upon direct irradiation via intersystem crossing from the singlet state ($S_1$, nπ*) to the triplet excited state ($T_1$, ππ*). Furthermore, ODPM reactions occur exceptionally
from the higher singlet excited state \((S_2, n\pi^* )\) which is exemplified by a \(\beta,\gamma\)-enone that carries a phenyl moiety.

![Diagram of chromophore conjugations]

**Figure 9:** Chromophore conjugations: A and B undergo ODPM rearrangements in the presence of a sensitizer, C and D give low yield ODPM rearrangements without sensitizer.

### 3.4 Photorearrangements of 58 and 78

#### 3.4.1 Attempted ODPM rearrangement of 58

The \(\beta,\gamma\)-endione 58 (for the retrosynthetic route, see chapter 3.2, p. 22) served as the starting compound for the planned photochemical rearrangement.\(^{31}\) Irradiation of 58 (Scheme 18) in the presence of acetophenone as sensitizer with 350-nm light (Rayonet reactor) gave a product showing NMR data not being compatible with the expected 9,9-dimethyl tricyclo[3.3.1.0\(_{1,5}\)]nonan-2,6-dione \((75)\). Finally, the reaction product was assigned as 5-isopropylidiphenyl[3.4]octan-1,6-dione \((77)\) according to \(^1\)H, \(^{13}\)C and the two-dimensional NMR spectra. The unsymmetric signals in the \(^1\)H NMR and the existence of olefinic carbons in the \(^{13}\)C NMR spectra proved the structure of the product 77. Besides 77, starting material 58 was recovered in 16% yield. According to the anticipated ODPM rearrangement mechanism, two possible diradical intermediates (74 and 76a/b) can be formulated. The lack of the expected product 75 via 74 can be explained by the stabilization of the radical intermediate 76a by the neighboring carbonyl group. This stabilization renders this biradical energetically more favorable. Thus, instead of the expected product 75, the spirocyclic
compound 77 was obtained as a result of cyclobutane cleavage in 76a. Alternatively, the rearrangement 58 → 77 could be formulated as a 1,3-acyl shift via 76b.

Scheme 18: The proposed reaction mechanisms of the photoreaction of 58 to 75 (not formed) and 77

3.4.2 Successful ODPM rearrangement of 78

After the failure of the ODPM rearrangement of 58 to 75, the synthetic route was modified and 2,2-dimethylbicyclo[4.3.0]non-1(6)-en-3,7-dione (78) was synthesized (Scheme 19) to probe its photochemistry which is assumed to differ significantly from that of 58. With compound 57 in hand (Scheme 11, p. 22), we have converted it into carboxylic acid 54 via Jones oxidation\(^{51}\) in a yield of 65% along with 56 (18% yield).

Scheme 19: Jones oxidation of 57
On the other hand, the carboxylic acid 54 can be synthesized directly from 2,2-dimethylcyclohexan-1,3-dione (56) by adding dilithated propylate 79 (Scheme 20), adopting the reaction conditions for 56 → 57. However, a longer reaction time is needed in this latter procedure giving 54 in a slightly lower yield (59%).

![Scheme 20](image)

**Scheme 20:** Direct synthesis of 54 from 56 by addition of dilithated propargilic acid (79)

The adduct 54 was then subjected to catalytic hydrogenation\(^{52}\) without further purification to synthesize lactone 83 in an overall yield of 41% from 56. When the hydrogenation reaction time was shortened, spirolactone 83 was obtained besides the unsaturated lactone 82. This means that the reaction proceeds via hydrogenation of the triple bond (→ 80) followed by cyclization to 82 which upon further hydrogenation leads to 83. Two olefinic doublets at 6.11 and 7.40 ppm in the \(^1\)H NMR and –CH signals at 122.27 and 156.08 ppm in the \(^{13}\)C NMR confirm the intermediacy of 82.

![Scheme 21](image)

**Scheme 21:** Hydrogenation of 54
Spirolactones in general undergo rearrangement in the presence of strong acids. For the synthesis of the endione 78 as substrate for the planned alternative ODPM rearrangement, cyclic lactone 83 was treated with concentrated acid which is either polyphosphoric acid (PPA) or Eaton’s reagent (P$_2$O$_5$/MeSO$_3$H). As a result of these treatments, product 78 was obtained in yields of 60% and 40%, respectively. The anticipated reaction mechanism is shown in Scheme 22. Upon opening of the spirolactone 83 carbenium ion 83a is formed prior to elimination to 83b which undergoes cyclization/elimination to afford ultimately the desired mixed endione 78.

Scheme 22: Rearrangement of spirolactone 83 to the mixed endione 78

After the synthesis of 78, its ODPM rearrangement was explored. As mentioned before, β,γ-enones can undergo under certain circumstances ODPM rearrangements without sensitizer. However, such rearrangements under these excitation conditions are real exceptions. Although the compound 78 has a chromophore being further conjugated with the β,γ-enone moiety, the previous studies in our laboratories show that irradiation of 78 without sensitizator gave the expected product 84 (Scheme 23), albeit in 8% yield only. During the attempts to increase the yield in different solvents and in the presence of sensitizaters, 40% yield of ODPM product was achieved when the reaction was run in acetonitrile and acetophenone was added as sensitizer. Moreover, by increasing the reaction time to 30 hours, the product yield increased up to 88%. Irradiation of the reaction mixture was studied by using a Rayonet equipment with $\lambda_{\text{max}}$ = 350 nm. The likely mechanism of the photochemical
transformation of $78 \rightarrow 84$ is depicted in Scheme 23. After energy transfer from acetophenone to the $\alpha,\beta$- and $\beta,\gamma$- unsaturated ketone $78$, biradical $78a$ is generated and it rearranges to the cyclopropyl diketone $84$ via recombination of the radical centers in $78b$. Notably, the spirocyclic product $77$ did not form here.

Scheme 23: ODPM rearrangement of the endione $78$ to $84$ via the biradical intermediates $78a,b$

3.5 Attempts to cleave the central C-C bond of $84$

In the studies directed towards the photochemical construction of the basic carbon skeleton of taxol (1), we have synthesized successfully the key intermediate 9,9-dimethyltricyclo[3.3.1.0$^{1,5}$]nonan-2,6-dione (84) via an ODPM rearrangement from 2,2-bicyclo[4.3.0]non-1(6)-en-3,7-dione $78$ in excellent yield, and expected then to be able to open the central C-1,5 bond of this propellane product so that we can obtain bicyclo[3.3.1]nonan-2,6-dione $85$ as a potential precursor of the AB rings of the taxol skeleton ($\rightarrow 51$).
Scheme 24: Planned route to a precursor (85) of the AB rings of the taxol skeleton 51

Cyclopropane, the smallest cycloalkane, is highly strained and has bond angles of 60°, far away from the 109.5° angle that sp³-hybridized carbons normally adopt. Because of the bond angle compression it is seen that orbitals overlap neither head to head like in σ bonds nor laterally like in π bonds. Thus, bonds are in between σ and π bonding, called “bent bonding”. The result is that the carbon-carbon bonds are weaker than those having normal bond angles and hence cyclopropanes are much more reactive than other cycloalkanes. Controlled cleavage of cyclopropane intermediates provides a useful method and has been successfully employed in the synthesis of multicyclic natural products.

Figure 10: Bent-bonding and the interaction of σ and π orbitals of the cyclopropane

3.5.1 Hydrogenation of 84

Hydrogenation⁵⁶ of cyclopropane is one of the ways to cleave this strained cyclic compound. It has been shown that hydrogenation of cyclopropane derivatives usually results in the preferential cleavage of the least substituted ring bonds.⁵⁷ For the ring opening insertion of the catalyst, such as palladium, is needed, i.e. the steric effect plays a most important role. 9,9-dimethyltricyclo[3.3.1.0¹,⁵]nonan-2,6-dione (84) should be an excellent candidate for such a cleavage with its C₂ symmetry with a fully substituted cyclopropane. However, the
geminal dimethyl group at C-9 and the two five-membered rings seemingly protect this substrate against hydrogenation so efficiently from either side that no hydrogenation of the cyclopropane was found and complete recovery of starting material was the result when hydrogenation was carried out with 10% Pd/C in ethyl acetate.

Scheme 25: Hydrogenation attempt of cyclopropyl diketone 84

3.5.2 Acid-catalyzed treatment of 84

In addition to the catalytic hydrogenation of cyclopropanes, acid-catalyzed reactions are used for opening of cyclopropane rings. For example, H$_2$SO$_4$/acetone was used as the cleaving agent for 86 in our laboratories effectively (Scheme 26). But the same conditions applied to 84 led only to the recovery of the starting material.

Scheme 26: Previous cyclopropyl opening (86 → 87) and application of the same procedure to 84
Furthermore, electrophilic reagents were used for the cleavage of conjugated cyclopropyl ketones. 84 was treated with halogenic acids (HCl or HBr) in acetic acid at reflux temperature and two compounds were obtained. The yield was increased up to 80% by using tetrachloromethane as solvent at room temperature. One of them was identified as 78 (structure, see p. 32) by its NMR analysis, whereas the other one shows NMR and mass spectral data not being compatible with the expected ring opening compounds 88a/88b (Scheme 27). 400 MHz $^1$H, $^{13}$C NMR and IR spectra of these products fit however the structures for the halogenated compounds 89a/89b. Both, the chlorinated and the brominated compound exhibit NMR spectra having doublets of doublets at 3.15 and 3.19 ppm, respectively. In addition, in the $^{13}$C NMR spectrum the existence of two quaternary and one –CH carbons are compatible with the proposed structures 89a/89b. In order to make sure that we have obtained 89a and 89b instead of the expected 88a and 88b, these halogenated products were subjected to dehalogenation by catalytic hydrogenation and Bu$_3$SnH. Unfortunately, the product does not show the NMR data being characteristic for 85, but the existence of a quartet in the $^1$H NMR showing the coupling of two identical methyl groups with –CH together with an unsymmetric $^{13}$C NMR spectrum showing that the unexpected product 90 was obtained. These data were completed with mass spectral information to ensure that 89a/89b were formed as a result of exclusive lateral bond cleavage of the cyclopropane.

![Scheme 27: Treatment of 84 with HCl/HOAc and HBr/HOAc](image-url)
A reasonable mechanism for the acid-catalyzed opening of a cyclopropyl ketone involves initial protonation of the carbonyl group (→ 91), followed by ring opening (→ 92) to yield the halogenated diketones 89a and 89b. In theory, ring cleavage in the tricyclic diketone can yield two different bicyclic skeletons by either cleavage of central (→ 93) or the lateral (→ 92) bonds (Scheme 28). There are some reasons for the failure of the central bond cleavage. It is well known that formation of carbocations are difficult or impossible at bridgehead positions where they cannot be planar, i.e. adapt sp² configuration. Additionally, formation of bridgehead carbocations is possible only with large rings or in adamantane. Furthermore, the formation of a carbocation at α-carbons of carbonyls renders the intermediate energetically unfavorable.

Scheme 28: Anticipated reaction mechanism for the formation of 89a and 89b from 84

Besides the developing carbocationic character, direction of cleavage of the cyclopropyl ketones is controlled by geometrical factors. As mentioned before, cyclopropanes have bent-bonds that have characteristics between σ and π bonds. These bent-bonds have in the present case delocalization with the π orbitals of the carbonyl groups. Owing to the geometry of the
ring system, the central carbon-carbon bond does not overlap largely with the \( \pi \) system of the carbonyl groups, whereas the lateral bond has excellent overlap. Thus, the cyclopropane bond with greatest overlap with the carbonyls cleaves preferentially, i.e. \( 84 \rightarrow 92 \) in Scheme 28 and Figure 11.

![Figure 11: Interaction of orbitals of the carbonyl and the lateral bonds of the cyclopropane in 84](image)

The side product 78 is likely the result of carbocation rearrangement in 92 to form the \( \alpha,\beta;\beta,\gamma \)-endione 78 after proton loss from 94 (Scheme 29). Interestingly, the acid-catalyzed re-formation of 78 from 84 constitutes overall a thermal retrosynthetic process (in cationic intermediate steps) of the photochemical ODPM rearrangement 78 \( \rightarrow \) 84 (Scheme 23).

![Scheme 29: Rearrangement of the carbocation 92 to the \( \alpha,\beta;\beta,\gamma \)-unsaturated endione 78](image)

### 3.5.3 Reaction of 84 with borontrifluoride-etherate

Borontrifluoride-etherate (BF\(_3\)·Et\(_2\)O) was reported\(^6\) to cleavage a cyclopropane being conjugated with a carbonyl group to give an enolacetate. Cyclopropyl diketone 84 was treated with BF\(_3\)·Et\(_2\)O at \(-78 \, ^\circ\text{C}\) under an argon atmosphere (Scheme 30). Unfortunately, the opening proceeded in the same mode of as seen before with acid catalysis to give 96 with a
yield of 62% instead of central bond cleavage. Besides 96, compound 78 was formed again (15%).

Scheme 30: Borontrifluoride-etherate treatment of the cyclopropyl diketone 84

3.5.4 Attempt to cleave the central bond of 98 by the aid of anchimeric assistance

Since the propellane bond in 84 is not sufficiently activated for cleavage as outlined before, we decided to replace one carboxyl by an acetyl function. By this way, the intermediate carbocation is hoped to be stabilized via anchimeric assistance\(^62\) by the acetyl so that cleavage of the central bond might be facilitated. The replacement of a carboxyl with acetyl was achieved in two steps, that are reduction of the carboxyl to the alcohol 97 by NaBH\(_4\) and esterification to 98 (Scheme 31).

Scheme 31: Attempt of the cleavage of the central bond in 98 with the aid of anchimeric assistance by the –OAc group in 99
The ability of oxygen to assist in the intramolecular departure of leaving groups is a classical example of neighboring group participation. The lone pair on oxygen serves as the nucleophile and provides the electrons to form e.g. a Prévost-type intermediate such as 99. We hoped that the reaction would result with nucleophilic opening of the three-membered ring and 100 and/or 101 would form (Scheme 31). Unfortunately, this attempt resulted in four compounds that were isolated and identified. It is seen that ring cleavage of a the lateral bond of the cyclopropyl ketone took again place and 102 formed as the main product in 27% yield indicating that the reaction follows the same path as with 84: Lateral cleavage of the cyclopropane and addition of chloride (→ 102, 105) or rearrangement of the carbocationic intermediate (→ 103, 104).

Scheme 32: Reaction of 98 with HCl in HOAc

3.5.5 Treatment of 84 with the lead tetraacetate

Oxidative cleavage of cyclopropanes by lead tetraacetate (Pb(OAc)₄) yields generally diacetates₆₃ᵃᵇ (107, 108, 111) or mono(un)saturated₆₂ᵃ,₆₄ acetates (109, 113) (Scheme 33). This reaction has been found to be applicable not only for alkyl and aryl cyclopropanes but also for cyclopropyl ketones.₆₅ On the other hand, it has been reported₆₄ that the treatment of carbonyl compounds with lead tetraacetate results in α-acetoxy ketones with the preference of less substituted α-carbons and also it was affirmed that enolization of the ketone is a
required intermediate in the formation of acetoxy ketones (Scheme 33). It might be reasonable to expect the formation of bridgehead-substituted or unsaturated bicyclo[3.3.1]nonan-2,6-dione (85) derivatives when 84 was reacted with lead tetraacetate (Scheme 34).

\[
\begin{align*}
\text{Ph} & \quad \text{Pb(OAc)}_4 \\
& \quad \text{HOAc} \\
& \quad 106 \\
& \quad \text{Ph} \\
& \quad \text{OAc} \\
& \quad \text{OAc} \\
& \quad 107 \\
& \quad \text{Ph} \\
& \quad \text{OAc} \\
& \quad \text{OAc} \\
& \quad 108 \\
& \quad \text{Ph} \\
& \quad \text{OAc} \\
& \quad 109 \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Pb(OAc)}_4 \\
& \quad \text{HOAc} \\
& \quad 110 \\
& \quad \text{O} \\
& \quad \text{AcO} \\
& \quad 111 \\
& \quad \text{O} \\
& \quad \text{AcO} \\
& \quad 112 \\
& \quad \text{AcO} \\
& \quad 113 \\
\end{align*}
\]

Scheme 33: Some examples of opening of cyclopropyl ketones with Pb(OAc)_4

Treatment of 84 with Pb(OAc)_4 in boiling or ice-cold acetic acid/benzene afforded a major (115) and a minor product (116) in yields of 53% and 16%, respectively. When the mol ratio of lead tetraacetate was increased to 5, with respect to 84, 115 was obtained as the major product with a yield of 25% and 116 was the minor product with 8% yield. A plausible mechanism includes displacement of the carbonyl oxygen with acetate ion resulting in the enol intermediate 114 which then rearranges to the products 115 and 116.
In summary, all attempts that included catalytic hydrogenation, acid-catalyzed reactions including, reactions with boron trifluoride-etherate, acid-catalyzed reactions with neighboring group participation by an acetate and reactions with lead tetraacetate in order to cleave the central carbon-carbon bond of compound 84 failed. There are some reasons for the failure. First of all, the fully substituted cyclopropane such as in compound 84 is sterically heavily hindered against reagent additions from any side. The cyclopropane is protected from the upper side by the geminal dimethyl groups and from downside by the five-membered rings. In addition to this and as mentioned before, the propellane bond of the cyclopropane to be cleaved is the one that ought to have sufficient conjugation with the $\pi$ orbitals of carbonyl groups. It must be considered that the lateral bonds fulfill these conditions more satisfactorily than the central bond does.

### 3.5.6 Dissolving metal reduction

After all these unsuccessful attempts to cleave the central bond in 84, it was decided to try dissolving metal reduction which are known from literature to reduce $\alpha,\beta$-enones as well as cyclopropyl ketones efficiently. However, again sufficient orbital interaction is required between the chromophoric parts of the substrate to be reduced.
One of the earliest reduction procedures is the treatment of such chromophores with active metals either in the presence of a proton donor, which is the reaction medium itself, or followed by treatment with a proton donor. Mostly alkali metals, mainly lithium, sodium, potassium and also zinc, calcium, magnesium are utilized. The dissolving metal reductions include electron transfer from the metal surface or from the metal in solution to the substrate.

The generally accepted mechanism for dissolving metal reduction of enones involves reversible addition of an electron to a vacant orbital of the substrate (S), yielding a radical anion (S\(^{-}\)). The latter can be protonated to give a neutral radical which may either dimerize or accept another electron and a proton. Also, stepwise or simultaneous reversible addition of two electrons to S can give a dianion capable of accepting two protons.

\[
\begin{align*}
S & \quad +e^- & S^- & \quad H^+ & HS^- & \quad HS-H \\
& \quad -e^- & & & & \\
& \quad +2e^- & \quad -e^- & \quad +e^- & \quad e^- & \quad +2e^- & \quad -2e^- & \quad +e^- & \quad -e^- \\
S^{2-} & \quad H^+ & HS^- & \quad H^+ & HSH
\end{align*}
\]

Scheme 35: Reaction mechanism of dissolving metal reduction of an \(\alpha,\beta\)-enone as substrate (S)

### 3.5.6.1 Treatment of 84 with zinc

In acetic acid or in ethanol solution of potassium hydroxide, zinc can transfer electrons to the substrate. For example, conjugated 1,4-enedione systems generate a radical dianion which leads to formation of a saturated dione. In addition, treatment of \(\gamma\)-diketones with zinc in acetic acid results in cleavage of the \(\alpha,\beta\)-carbon bond in the four-membered ring. The conversion of 117 to 118 is a good example for such kind of cleavage reactions (Scheme 36). Unfortunately, the reaction of 84 with zinc in acetic acid or with potassium hydroxide in ethanol resulted with complete recovery of the starting material. Moreover, increase of the reaction time and temperature did not change the result.
3.5.6.2 Bir<em>ch</em> and Bouveault-Blanc reduction of 84

Another type of dissolving metal reductions<sup>69</sup> is the Bir<em>ch</em> reduction<sup>70</sup> (Li or Na in liquid ammonia) and Bouveault-Blanc reduction<sup>69</sup> (Li or Na in alcohol). The treatment of 84 with excess lithium in ammonia gave the pinacol 9,9-dimethyltricyclo[3.3.1.2<sup>6</sup>.0<sup>1.5</sup>]non-1,5-diol (123) in 60% yield besides a trace of 85 (Scheme 37) which constituted a first but rather limited success in these efforts. Hence, the compound 85 was generated during the reaction. Bouveault-Blanc reaction of 84 (Na in ethanol or isopropanol/toluene) led exclusively to the pinacol 123. By using a large excess of Na with respect to 84, the reaction yield increased up to 80%. Cleavage of the pinacol 123 was achieved by lead tetraacetate treatment and the target product 85 was synthesized successfully in 55% yield. Bir<em>ch</em> reduction and Bouveault-Blanc reduction, both have the same mechanism to crack the cyclopropane conjugated with the carbonyl groups. As it is seen in Scheme 37, the reaction starts with electron transfer and diketyl forms. After the cleavage of the central bond, the intermediate diradical abstracts protons from the solvent and pinacol 123 is produced. Lead tetraacetate is widely used<sup>71</sup> to cleave pinacols and indeed application of this oxidation process to 123 resulted smoothly in the formation of the expected diketone 85 (yield of the overall process 84 → 85: 44%).
Scheme 37: Reaction mechanism of cleavage of the central bond of 84 by using Birch and Bouveault-Blanc reactions (→ 123)

3.5.6.3 Treatment of 84 with potassium-graphite (C₈K)

A further attempt to transform 84 directly to 85 was finally successful by application of the following method of reduction. Potassium-graphite-intercalated compounds into C₈K is widely used as method to reduce organic compounds. Graphite has a lamellar structure and appears in nature in two forms: hexagonal and rhombohedral. The most stable form is hexagonal having a layer stacking sequence of ABABA-- with an interlayer distance of 3.35 Å and the layers are not superimposable. Rhombohedral graphite has a layer sequence of ABCABC-- stacking where every third layer is superimposable. This form exists rarely and it is not used as a host material for the synthesis of graphite-intercalated compounds.

Electronically, graphite is a semimetal. Bonding between carbon atoms involves sp²-hybridized orbitals. The structure of graphite shows the voids between the planar sp²-hybridized carbon sheets. Intercalation is achieved by the insertion of ions, atoms or molecules into this space without destruction of the host-layered bonding network. Bond
distance and stacking order may be altered but the carbon layers of the graphite remain undistorted after the intercalation that is, the planar hexagonal structure is preserved.

The graphite is called the host and the ingested compound is called intercalant, which is classified as donor or acceptor according to whether it gives electrons to graphite or abstracts electrons from the host.\textsuperscript{72} The known electron donor intercalants are alkali metals including Li, K, Rb, Cs and alkaline earth metals such as Ba, Ca, St as well as transition metals as Eu, Yb. The most widely used electron acceptor intercalants are FeCl\textsubscript{3}, Br\textsubscript{2}, HNO\textsubscript{3}, AsF\textsubscript{5}.

The stage of intercalation is the ratio of host layer (graphite) to guest layers (potassium).\textsuperscript{72} Depending on the conditions of the preparations, the stages may be obtained from 1 to 8. When higher temperature/pressure is applied, higher stages of potassium graphite-intercalation are obtained.\textsuperscript{74} Since the carbon hexagons do not superimpose in two neighboring planes in pure graphite, these planes stack in ABAB configuration. In the first stage (C\textsubscript{8}K), planes stack in A/A/A configuration and it is the most concentrated one because of highly filled interlayer voids. In the second stage (C\textsubscript{24}K), the stacking sequence is AB/BC/CA/AB and the stacking sequence for the third stage (C\textsubscript{36}K) is ABA/ACA/ABA.\textsuperscript{73}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{Sequences of carbon (—) and potassium (●) layers:}
\begin{itemize}
  \item a) C\textsubscript{8}K
  \item b) C\textsubscript{24}K
  \item c) C\textsubscript{36}K
\end{itemize}
\end{figure}
The presence of potassium atoms in the graphite influences the reactivity of 4s electrons and there is a reversible fast electron transfer from the 4s electrons to the $\pi$ system of the graphite.\textsuperscript{75} The substrate is absorbed at the surface of C\textsubscript{8}K and electrons are transferred from the edge of it.\textsuperscript{72} Potassium-graphite was used\textsuperscript{73} for Wurtz reactions, reduction of $\alpha,\beta$-unsaturated carbonyls and alkyl halides, hydrogenation, polymerization and reduction of polycyclic hydrocarbons.

The reducing agent potassium-graphite (C\textsubscript{8}K) was applied to compound 84 for the cleavage of the central bond. C\textsubscript{8}K was synthesized\textsuperscript{76} by adding freshly cut potassium (very important; note that old potassium can lead to explosion and fire under the given reaction conditions) to vigorously stirred graphite at 160 °C under an argon atmosphere. After cooling to room temperature, bronze-colored laminate compound of the intercalation medium C\textsubscript{8}K was formed. Addition of the substrate 84 was completed in dry THF via syringe at room temperature. The reaction takes 5-6 days, in case of a shorter reaction time the yield decreases. In addition, treatment with old potassium also decreases the reaction yield. The reduction of 84 must have the same or at least similar mechanism as the Birch reduction: The anticipated mechanism for this reaction is outlined in Scheme 38. The initial step involves electron transfer from the edge of the potassium-graphite intercalation material to diketone 84 to generate a dianion radical 124. Rearrangement of 124 gives the enolate anions via homolytic cleavage of the central bond (→ 125). By proton abstraction from the solvent, being dry THF, compound 85 is obtained.
3.6 Attempts of ring enlargement in 85

After the cleavage of the central bond of 84, the next target was to synthesize a compound having a structure like bicyclo[5.3.1]undecene (51) which is a potential precursor of the AB-ring part of taxane (Scheme 39).

Scheme 39: AB rings of the skeleton of taxol (1)

The required ring enlargement can be managed by formation of a cyclobutene, followed by fragmentation of this small ring. It has been reported that ZrCl₄-catalyzed [2+2] cycloaddition of ethyl propiolate (127) to tert-butylidimethylsilyl enol ether 126 results in the cyclobutene esters 128 and 129 (Scheme 40). ZrCl₄ was dissolved in the reaction mixture by adding Et₂O to the reaction solvent CH₂Cl₂ in 10:1 ratio. Actually, the catalyst ZrCl₄ is not soluble in apolar solvents. Addition of oxygen-containing solvents, like Et₂O or THF,
provides the solubility of the catalyst by coordination to the ZrCl₄. In addition, it was noted that when acetyl dicarboxylate was used, no cyclobutene was formed.⁷⁷

Scheme 40: ZrCl₄-catalyzed [2+2] reaction of 126 with ethyl propionate 127

Since 85 and 126 have similar structures, 85 was converted to the silylenol ether 132 (Scheme 41). For this reason, one of the carbonyls was protected by using 1,2-ethanediol (130) as the protecting reagent. The monoprotected compound 131 was obtained⁷⁸ with 65% yield in the presence of p-toluenesulfonic acid as catalyst by refluxing in a Dean-Stark apparatus. After that, ketone 131 was transformed into the tert-butyldimethylsilyl enolether 132 in quantitative yield by treatment with tert-butyldimethylsilyltriflate (TBDMSOTf).⁷⁷

Scheme 41: Monoprotection of 84 as tert-butyldimethylsilyl enol ether 132 via 131
The silylenol ether 132 was then treated with ZrCl$_4$ and methyl but-2-ynoate (133) at –78 °C (Scheme 42). Unfortunately, this attempt of ZrCl$_4$-catalyzed [2+2] reaction$^{77}$ of 132 and 133 failed. Compounds 85 and 131 were recovered with 45 and 41% yield, respectively.

![Scheme 42: ZrCl$_4$-catalyzed [2+2] reaction of 132 and methyl but-2-ynoate (133)](image)

The reason of this failure might be the steric hindrance of the 5-membered protecting group towards the reduction medium. For that reason, another protecting group, 2,2-dimethylpropane-1,3-diol (134) which is conformationally more flexible than the previous one, was used$^{77}$ (Scheme 43). This protection yielded 135 in 61%. After treatment of 135 with TBDMSOTf in the presence of NE$_3$, the enolether 136 was obtained in quantitative yield.

![Scheme 43: ZrCl$_4$-catalyzed [2+2] reaction of enolether 136 with 133](image)
Application of the previously applied procedure to the silylenol ether 136 with methyl but-2-ynoate (133) in presence of ZrCl₄ gave unfortunately back 85 and 135. The failure of the ZrCl₄-catalyzed [2+2] cycloaddition of 132 and 136 can be explained by the oxophilic character of the catalyst. Since ZrCl₄ has not any electron at the d orbitals, it is very oxophilic and interacts with any oxygen-containing compound very easily. If there is even a trace amount of air or water in the reaction medium the catalyst turns to ZrOCl₂ and HCl. As a result, the acetal and enolether functions of 132 and 136 reform 85 and the monoprotected diketones 131 and 135, respectively. Due to the oxophilic character of ZrCl₄, the [2+2] cycloaddition of 132 and 136 should be studied in the future under a strictly moisture- and oxygen-free argon atmosphere in a glove box.
The future prospects of this work consist of mainly two parts: The first part involves the cleavage of central bond of 84 and the ring enlargement which starts with the ZrCl₄-catalyzed [2+2] reaction of 136 and but-2-ynoic acid methyl ester (133) in the glove box. As mentioned previously, the oxophilic character of ZrCl₄ makes it very sensitive to even trace amounts of water and oxygen. After the synthesis of the [2+2] adduct 137, the cyclobutene moiety should be rearranged⁷⁷ to give 138 by heating 137 with HBF₄ in EtOH. The C ring of the taxol skeleton is planned to be introduced via Michael addition⁷⁹ (138 → 140) and treatment with HCl (→ 141). The addition of 139 to 138 should preferentially occur from downside (→ 140).
This addition of 139 to 138 is essential for obtaining the correct ring junction geometry in view of the ABC-ring assembly related to the taxane target structure. In order to be able to predict the outcome of this addition, quantum mechanical calculations (geometry optimization) of 138 were performed.

Geometry optimizations were performed employing density functional theory. The pure BP function was used, in combination with SV(P) basis sets. For all calculations, the TURBOMOLE program package was used and the calculations were performed for vacuum conditions. Furthermore, only charge neutral systems were investigated. The structures were plotted employing gopenmol (Figure 14).

Indeed an addition of 139 on the underside of 138 seems to be sterically less hindered as compared to a top side attack. The geminal dimethyl group is seemingly shielding the latter side efficiently enough. As a result, the correct relative configuration of the C-8 methyl should be obtained.

Figure 14: Optimized geometry of 138. Left: South view, Right: North view. Modelling performed in collaboration with Dr. S. Sinnecker (Max Planck Institute for Bioinorganic Chemistry)
A modification of this future approach could involve first the ring enlargement and then the cleavage of the central bond. For the ring enlargement, the known procedure for the ZrCl$_4$-catalyzed [2+2] cycloaddition reaction will be applied (142 → 143). The advantage of this second part is the mild cleavage of the cyclopropane and the introduction of a bridgehead double bond (144 → 145) which will allow further functionalizations. 144 will be treated with Nafion-TMS$^{85}$ for the cyclopropane opening including the elimination step. The C ring of the taxol skeleton will be introduced via Michael addition$^{79}$ (→ 146) and treatment with HCl (→ 147), a reaction sequence which was described before. The stereochemical outcome of this sequences should be analogous to the one described for 138 → 140 → 141.
Another geometry optimization has been performed for the compound 145. As mentioned before, the relative configuration of the methyl at C-8 is important. In order to provide that Michael addition (145 \rightarrow 146) will be achieved on the underside of 145 the geometry optimization, which was studied for 138, was performed also for 145. The result of density functional theory (Figure 15) shows that dienolate 139 again add to 145 on the underside because of more steric interactions to be expected on the top side.

**Figure 15:** Optimized geometry of 145 Left: South view, Right: North view. Modelling performed in collaboration with Dr. S. Sinnecker (Max Planck Institute for Bioinorganic Chemistry)
A last but important point should concern studies regarding the introduction of chirality into our synthetic approach. A likely solution could involve the monoacetalization step on 84 or 85 using a C$_2$-symmetrical reagent like optically active tartrate (148) or butane-2,3-diol (149) to give e.g. 150 as chiral building block.
5 Experimental section

I would like to thank to following co-workers of the Max Planck Institute for Bioinorganic Chemistry and the Max Planck Institute for Coal Research for their most valuable services: Mrs. K. Sand and Mr. J. Bitter (NMR spectra); Mr. W. Schmoeller and Mr. W. Joppek (MS spectra). My appreciation is also extended to all the members of the administration, library staff and technical staff of the Max Planck Institute for Bioinorganic Chemistry, whose assistance has made the completion of this work both possible and enjoyable.

I would like to thank to Dr. Sebastian Sinnecker of our institute especially for the DFT calculations and geometry optimizations.

5.1 Instruments, methods and materials

Melting points (Mp):
Determined on a Reichert or Kofler apparatus and are uncorrected.

Ultraviolet absorption spectra (UV):
Recorded with either a Carry 17 or Bruins Omega-10 spectrometer. \( \lambda_{\text{max}} \) values are given in nm; \( \varepsilon \) values in parantheses.

Infrared spectra (IR):
Recorded with KBr-pressed plates using Brucker IFS 66 (FT-IR-Spectrometer) or a Perkin-Elmer 1600 instrument. Frequency values are given in cm\(^{-1}\). The symbols s (strong), m (medium) and w (weak) characterize the relative band intensities.

Mass spectra (MS):
Recorded on Finnigan MAT 311A or MAT 95 (HRMS) instruments at 70 eV ionization energy. Data are presented in m/z values. When required, molecular ion peaks were ascertained by chemical ionisation (CI) or fast atom bombardment (FAB) techniques.
Nuclear Magnetic Resonance spectra (NMR):
Recorded in Fourier Transform mode on the following Brucker instruments: An ARX-250 (250 MHz for $^1$H, 63 MHz for $^{13}$C), an AM-400 (400 MHz for $^1$H, 100.6 MHz for $^{13}$C) and a DRX-500 (500 MHz for $^1$H, 125.8 MHz for $^{13}$C) with dilute solutions in deuteriochloroform (CDCl$_3$) at 300 K unless stated otherwise. The chemical shift values are given in $\delta$ units (ppm, parts per million) with trimethyl silane as internal standard. All coupling constants, $J$, are reported in Hz. The multiplicity of a signal is designated by one of the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad).

Thin layer chromatography (TLC):
Performed on 0.20 mm (aluminium) silica gel plates (F$_{254}$, Merck). As developing reagent, a solution containing 30 g vanillin, 5 ml conc. H$_2$SO$_4$ and 1000 ml EtOH. The plates were visualized with UV light and then thermally developed.

Column chromatography:
Gravimetric columns or high pressure variants on self-packed Kronlab Sepakron-FPGC glass columns of different sizes on Merck silica gel 60 (0.063-0.20 mm or 0.04-0.063 mm) with pressure pump Buechi 688 or Besta E-100 and pressure 1-10 bar were used; all solvents were distilled before use.

Irradiation:
All samples were stirred and flushed with argon prior to use. Cylindrical Pyrex reaction vessels, equipped with cooling fingers (H$_2$O coolant), were used. Rayonet reactors (RPR-208-System, Southern New England Ultraviolet company) with sixteen 350 nm ($\lambda_{max}$) lamps (24 watt/lamps) were employed for irradiation.

Solvents:
Purchased from Merck, Aldrich or Fluka and used directly or purified by standard procedures. Absolute solvents were purchased from Fluka and kept on molecular sieves.

Reagents: The chemical name, abbreviated molecular formula (with parantheses, if appropriate), quality, purification procedure and company of purchase are listed below.
Acetic acid (HOAc): z.S., Merck
Acetic anhydride: 95%, Merck
Acetophenone: 99%, Fluka
Amberlyst 15: 99%, Fluka
2,2’-Azobisisobutyronitrile (AIBN): 98%, Aldrich
n-Butyl lithium (n-BuLi): 1.6 M in n-hexane, Fluka
Boron trifluoride diethyl etherate (BF$_3$·Et$_2$O): BF$_3$ content of 46.5-49.5%, Fluka
But-2-ynoate: 99%, Acros
Chromium (VI) oxide (CrO$_3$): 99%, Fluka
1,3-Cyclohexadione: 97%, Fluka
1,2-Ethanediol: 99%, Merck
Graphite: 99%, Fluka
Methyl iodide (CH$_3$I): 99%, Fluka
Lead tetraacetate (Pb(OAc)$_4$): 95%, Fluka
Lithium (Li): 99%, Fluka
10% Pd-Charcoal: 99%, Fluka
Polyphosphoric acid: 84%, Fluka
Potassium (K): 99%, Fluka
Potassium carbonate (K$_2$CO$_3$): 99%, Fluka
Propargyl alcohol: 99%, Fluka
Propylic acid: 96%, Across
Pyridine: 99%, Fluka
5% Pt-Charcoal: 99%, Fluka
Sodium (Na): 99%, Fluka
Sodium hydrogencarbonate (NaHCO$_3$): 99%, Merck
Sodium borohydride (NaBH$_4$): 96%, Aldrich
Sulphuric acid (H$_2$SO$_4$): z.S., Merck
tert-Butyldimethylsilyltriflate (TBDMSOTf): 98%, Aldrich
Triethylamine (NEt$_3$): 99%, Merck
Tri-n-butyltin hydride (Bu$_3$SnH): 97%, Aldrich
Toluene-p- sulphonic acid monohydrate (PTSA): 98%, Fluka
Zirconium tetrachloride (ZrCl$_4$): 99%, Aldrich
5.2 Nomenclature and general synthetic and photochemical procedures

Nomenclature: Compounds have been named according to the standard nomenclature rules (IUPAC) by means of the program AUTONOM, with the exception that the numbering system has in some cases been chosen more conveniently with respect to NMR signal assignments.

General synthetic procedures: A cold bath of –78 °C was prepared from a mixture of acetone and dry ice. Oxygen or moisture sensitive reactions were performed under an argon flow in either oven- or heat-gun-dried glassware equipped with rubber septa. Air or moisture sensitive liquids or solutions were transferred through a funnel under a rapid argon flow. “Concentration” involved drying of the combined organic layers over anhydrous Na₂SO₄, filtration and solvent removal by roto-evaporation and high vacuum (10⁻¹-10⁻³ torr). “Chromatography” refers to column separation technique performed on Merck silica gel 60 (0.063-0.20 mm; 100 fold), unless stated otherwise, giving product purities of >97%.

5.3 Reactions

5.3.1 Synthesis of 56

To a stirred solution of 1,3-cyclohexandione (55) (25 g, 0.223 mol) and acetone (200 ml) was added anhydrous K₂CO₃ (90 g, 0.70 mol) at 50 ºC. The reaction mixture was refluxed for 15 hours and then cooled to room temperature. Afterwards the resulting mixture was filtered and the filtrate was concentrated. Chromatography of the crude product on a flash column of silica gel with pentane-ether (1:1) gave 2,2-dimethylcyclohexane-1,3-dione (56) with 55% yield (23.9 g).

2,2-Dimethylcyclohexane-1,3-dione (56):

MS (EI; m/z, rel. int.):
140 (49.37, M⁺, C₈H₁₂O₂), 97 (100), 70 (83), 67 (37), 55 (70), 42 (79), 41 (48).
HRMS (EI; m/z):
calculated for C₈H₁₂O₂: 140.083730; found: 140.083877.

¹H NMR (250 MHz): 2.64 (t, J=6.66 Hz, 4H); 1.9 (m, 2H); 1.26 (s, 6H).

¹³C NMR (63 MHz, BB, DEPT, ¹H, ¹³C-COSY):
210.28 (Cq, C-1,3); 61.55 (Cq, C-2); 37.18 (CH₂, C-4,6); 22.05 (CH₃, C-7,8);
17.86 (CH₂, C-5).

IR (KBr):
2966w, 2941w, 1727m, 1695m, 1383m

5.3.2 Synthesis of 3-Hydroxy-3-(3-hydroxy-prop-1-ynyl)-2,2-dimethyl-cyclohexanone (57)

A solution of propargylalcohol (95%, Fluka, 1.40 g, 25 mmol) in 140 ml dry THF was cooled to –78 °C under stirring and argon atmosphere. To this solution was added dropwise 34.4 ml (55 mmol) of an n-BuLi solution (1.6 M in hexane, Aldrich) during 20 min. The resulting mixture was stirred for further 2 hours, then a solution of 2,2-dimethylcyclohexan-1,3-dione (56, 2.8 g, 20 mmol) in dry THF (20 ml) was added dropwise, before stirring for further 8 hours. 100 ml of water was then added and the mixture slowly warmed to room temperature. The organic phase was separated and the aqueous phase extracted with ether followed by drying of the combined organic layers over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a flash column of silica gel with pentane-ether (1:1) to give product 57 2.04 g (54%) as a white solid.

3-Hydroxy-3-(3-hydroxy-prop-1-ynyl)-
2,2-dimethyl-cyclohexanone (57):

MS (EI; m/z, rel. int.):
196 (8.2, M⁺, C₁₁H₁₆O₃), 178 (6), 163 (28), 150 (9), 135 (18), 122 (13), 111 (36),
98 (100), 93 (16), 86 (41), 83 (19), 70 (21), 65 (31), 55 (37), 41 (38).
HRMS (EI; m/z):
calculated for C_{11}H_{16}O_{3}: 196.109945; found: 196.109824.

$^1$H NMR (400 MHz):
4.15 (s, 2H, H$_2$C-9); 4.1 (br. s, 1H, HOC-9); 3.87 (s, 1H, HOC-3); 2.35-2.23 (br. m, 2H); 2.08-1.71 (br. m, 4H); 1.14 (s, 3H, CH$_3$); 1.08 (s, 3H, CH$_3$).

$^{13}$C NMR (100.6 MHz, BB, DEPT, $^1$H; $^{13}$C-COSY):
214.26 (Cq, C-1); 85.84 (Cq, C-7); 83.86 (Cq, C-8); 75.28 (Cq, C-3); 53.53 (Cq, C-2); 50.12 (CH$_2$, C-9); 36.20 (CH$_2$, C-2); 33.99 (CH$_2$, C-4); 22.17 (CH$_3$); 19.93 (CH$_2$, C-5); 19.07 (CH$_3$).

Mp 42.0-44.0 °C.

IR (KBr):
3588m, 3499w, 3303s (br.), 1698s, 1468w, 1451w, 1426w, 1383w, 1365w, 1349w, 1176w, 1127m, 1018s, 991w, 960m.

5.3.3 Synthesis of 7,7-Dimethyl-3,4,5,7-tetrahydro-2H-indene-1,6-dione (58)

57 (2.02 g, 10.3 mol) was dissolved in 10 ml acetic acid and 1.01 g amberlyst 15 (Acros) added to this solution, then stirred at 95 °C for 20 hours. The amberlyst 15 was filtered off and the filtrate distilled in vacuo to remove acetic acid before the residue was dissolved in ethylacetate, washed with a saturated solution of sodium hydrogen carbonate and the organic phase was thereafter concentrated in vacuo and the residue chromatographed on silica gel with pentan-ether (1:2). The product 58 was obtained as a dark yellow solid in 13.6% yield (0.25 g).

7,7-Dimethyl-3,4,5,7-tetrahydro-2H-indene-1,6-dione (58):
HRMS (EI; m/z):
calculated for C_{11}H_{14}O_{2}: 178.099553; found: 178.099381.

MS (EI; m/z, rel. int.):
178 (95, M^+, C_{11}H_{14}O_{2}), 150 (33), 136 (100), 135 (74), 121 (53), 107 (16), 93 (43), 91 (24), 79 (21), 77 (21).

^1_H NMR (250 MHz):
2.69-2.61 (m, 4H, CH_2); 2.53-2.43 (m, 4H, CH_2); 1.33 (s, 6H, CH_3).

^13_C NMR (63 MHz, BB, DEPT, ^1_H; ^13_C-COSY):
213.56 (Cq, C-6); 207.15 (Cq, C-1); 169.72 (Cq, C-7); 143.92 (Cq, C-9); 44.34 (Cq, C-7); 36.20 (CH_2); 34.61 (CH_2); 28.92 (CH_2); 27.94, (CH_2); 22.86 (CH_3, C-10, 11).

Mp 75-76 °C.

IR (KBr):
3465m (br.), 2956s, 2869w, 1740s, 1720m, 1643s.

5.3.4 Photochemical reaction of 7,7-Dimethyl-3,4,5,7-tetrahydro-2H-indene-1,6-dione (58) (→ 77)

In a cylindrical Pyrex irradiation vessel, equipped with a cooling finger, 58 (88.5 mg, 0.497 mmol) was dissolved in 140 ml acetonitrile and degassed under stirring for 1 hour before irradiation at room temperature for 40 hours. The reaction mixture was irradiated in a photochemical chamber reactor (type Rayonet RPR-208), equipped with 8 lamps (each 24 W, RUL 350 nm, \( \lambda_{\text{max}} = 350 \) nm, emission range 300-400nm). After evaporation of the solvent, the residue was chromatographed on silica gel with pentane-ether (1:2) to give the product 77 (55.1 mg, 62.3%) as a colorless oil besides a second fraction of 14.4 mg (16.3%) of 58.

5-Isopropylidene-spiro[3.4]octane-1,6-dione (77):
MS (EI; m/z, rel. int.):
178 (22, M⁺, C₁₁H₁₄O₂), 150 (96), 136 (100), 135 (82), 121 (95), 107 (24), 93 (83), 91 (39), 80 (32), 79 (49), 77 (33), 39 (23).

HRMS (EI; m/z):
calculated for C₁₁H₁₄O₂: 178.099380; found: 178.099614.

¹H NMR (400 MHz):
3.22-3.08 (m, 2H, CH₂); 2.22 (s, 3H, CH₃); 2.40-2.05 (m, 6H); 1.77 (s, 3H, CH₃).

¹³C NMR (100.6 MHz, BB, DEPT, ¹H; ¹³C-COSY):
212.43 (Cq, C-1); 204.82 (Cq, C-6); 152.51 (Cq, C-9); 133.05 (Cq, C-5); 70.90 (Cq, C-4); 42.97 (CH₂); 37.70 (CH₂); 32.04 (CH₂); 26.52 (CH₂); 25.86 (CH₃); 21.62 (CH₃).

IR (KBr):
3448s (br.), 2961w, 1776s, 1707s, 1619m, 1437w, 1276w, 1194w, 1112w, 1072w.

5.3.5 Synthesis of (1-hydroxy-2,2-dimethyl-3-oxo-cyclohexyl)-propynoic acid (54) from either 57 (a) or directly from 56 (b)

(a) To a solution of 1.91 g (9.73 mmol) of 57 in 16 ml acetone was added dropwise a solution of Jones reagent (mixture of CrO₃ (1.946 g, 19.46 mmol), 10 ml water and 1.56 ml 97-98% H₂SO₄) at 0 °C (ice bath) during 8 hours, then stirred for further 5 hours, extracted with ether and the combined organic layers washed with brine and dried over sodium sulfate. After the evaporation of the solvent, the crude product was chromatographed on silica gel with pentane/ether/acetic acid (1:1:0.1) to give the product 54 in white crystalline form (1.32 g, 64.5%) and 56 (0.25 g, 18.4%).

(b) To a solution of 1.47 g (20 mmol) propylic acid (96%, Across) in 100 ml dry THF were added 16 ml (40 mmol) n-BuLi solution (2.5 M in n-hexane) dropwise under argon and stirring at –78 °C, followed by stirring of the resulting solution at the same temperature for
another 2 hours. Afterwards a solution of 56 (2.8 g, 20 mmol) in 20 ml dry THF was added dropwise and the mixture was stirred still at the same temperature for 7 days (monitoring of the reaction by TLC). 100 ml of water were then added slowly by allowing the reaction mixture to warm to room temperature. The organic phase was separated and the water layer acidified with dilute HCl and extracted with ethyl acetate. After the combined organic layers were dried over anhydrous Na$_2$SO$_4$, and the solvent evaporated at reduced pressure in order to concentrate the crude product which was purified on silica gel with pentane:ether:acetic acid (1:1:0.1) to give 54 in 59% yield (2.47 g).

(1-Hydroxy-2,2-dimethyl-3-oxo-cyclohexyl)-propynoic acid (54):

\[
\begin{align*}
\text{MS} & \quad (\text{EI; m/z, rel. int.}): \\
& \quad 210 \ (21, \ M^+, \ C_{11}H_{14}O_4), \ 192 \ (10), \ 166 \ (13), \ 150 \ (26), \ 149 \ (22), \ 105 \ (16), \ 98 \ (100), \ 91 \ (22), \ 86 \ (20), \ 85 \ (52), \ 70 \ (24), \ 67 \ (58), \ 55 \ (37), \ 53 \ (33), \ 43 \ (39), \ 42 \ (37), \ 41 \ (54), \ 39 \ (31).
\end{align*}
\]

\[
\begin{align*}
\text{HRMS} & \quad (\text{EI; m/z}): \\
& \quad \text{calculated for } C_{11}H_{14}O_4: 210.089208; \ \text{found: } 210.089249.
\end{align*}
\]

\[
\begin{align*}
\text{\textsuperscript{1}H NMR} & \quad (400 \text{ MHz, CD}_3\text{OD}): \\
& \quad 5.19 \ (\text{br.s, 1H, HOC-9}); \ 2.60-1.85 \ (\text{m, 6H}); \ 1.29 \ (\text{s, 3H, CH}_3); \ 1.23 \ (\text{s, 3H, CH}_3).
\end{align*}
\]

\[
\begin{align*}
\text{\textsuperscript{13}C NMR} & \quad (100.6 \text{ MHz, BB, DEPT, \textsuperscript{1}H, \textsuperscript{13}C-COSY, CD}_3\text{OD}): \\
& \quad 213.81 \ (\text{Cq, C-3}); \ 154.78 \ (\text{Cq, C-9}); \ 87.55 \ (\text{Cq, C-7}); \ 74.79 \ (\text{Cq, C-8}); \ 53.02 \ (\text{Cq, C-2}); \ 36.10 \ (\text{CH}_2, \ C-4); \ 33.40 \ (\text{CH}_2, \ C-6); \ 22.35 \ (\text{CH}_2, \ C-5); \ 19.65 \ (\text{CH}_3); \ 18.65 \ (\text{CH}_3).
\end{align*}
\]

\[
\begin{align*}
\text{Mp} & \quad 153-155 \text{ °C.}
\end{align*}
\]

\[
\begin{align*}
\text{IR} & \quad (\text{KBr}): \\
& \quad 3489s, \ 2957s, \ 2605s, \ 2246m, \ 1707s, \ 1678s, \ 1470m, \ 1425m, \ 1368s, \ 1244s.
\end{align*}
\]
5.3.6 Synthesis of 6,6-dimethyl-1-oxa-spiro[4.5]decane-2,7-dione (83)

Carboxylic acid 54 (4.1 g, 0.19 mmol) was dissolved in 50 ml ethyl acetate and 10% Pd-charcoal (0.15 g) was added in a two-necked flask which was connected to water pump and hydrogen-filled balloon. This mixture was evacuated at water pump pressure until evolution of bubbles then the valve of the hydrogen-filled balloon was opened. This process was repeated for several times. Then the reaction was left to react under hydrogen and was monitored by TLC. After completion, the catalyst was filtered off and the filtrate washed with saturated sodium hydrogen carbonate solution and dried over anhydrous sodium sulfate. After evaporation of the solvent at reduced pressure, the crude product was chromatographed on silica gel with pentane-ether (1:1) and spiro lactone 83 (2.65 g, 67.6%) was obtained as a white crystalline material. If the reaction time is shortened, the unsaturated analog 82 is synthesized besides the spiro lactone 83.

6,6-Dimethyl-1-oxa-spiro[4.5]dec-3-ene-2,7-dione (82):

\[
\begin{align*}
\text{MS} & \quad (\text{EI}; \text{m/z, rel. int.}): \\
194 & (41, M^+, C_{11}H_{14}O_3), 179 (18), 138 (14), 123 (19), 110 (100), 96 (35), 85 (160), 82 (14), 70 (17), 67 (65), 55 (27), 54 (19), 53 (16), 43 (21), 42 (28), 41 (55), 39 (33), 27 (22).
\end{align*}
\]

\[
\begin{align*}
\text{HRMS} & \quad (\text{EI; m/z):} \\
\text{calculated for } C_{11}H_{14}O_3: 194.094295; \text{found:194.094013.}
\end{align*}
\]

\[
\begin{align*}
\text{\textbf{1H NMR}} & \quad (400 \text{ MHz}): \\
7.40 & (d, 1H, J=5.8Hz); 6.11 (d, 1H, J=5.8Hz); 2.57-2.53 (2H, m), 2.24, 2.10 (2H, m); 1.95-1.85 (2H, m); 1.17 (s, CH_3); 1.06 (s, CH_3).
\end{align*}
\]

\[
\begin{align*}
\text{\textbf{13C NMR}} & \quad (100.6 \text{ MHz, BB, DEPT, } \text{\textbf{1H; \textbf{13C-COSY}}}): \\
210.59 & (\text{Cq, C-7}); 171.41 (\text{Cq, C-2}); 156.08 (\text{CH, C-4}); 122.27 (\text{CH, C-3}); 94.33 (\text{Cq, C-5}); 51.01 (\text{Cq, C-6}); 36.38 (\text{CH}_2); 31.08 (\text{CH}_2); 22.22 (\text{CH}_3); 20.91 (\text{CH}_2); 18.66 (\text{CH}_3).
\end{align*}
\]
6,6-Dimethyl-1-oxa-spiro[4.5]decan-2,7-dione (83):

**Mp**  85-87 °C.

**IR**  (KBr):
2926m, 1752s, 1712s, 1460m, 1384m, 1149m, 1090w, 964s, 914m, 814s.

**HRMS**  (EI; m/z): calculated for C_{11}H_{16}O_{3}: 196.109945; found: 196.110156

**1H NMR**  (400 MHz):
2.8-2.4 (m, 4H, CH_{2}); 2.25-2.20 (m, 1H, CH_{2}); 2.05-1.76 (m, 5H, CH_{2}); 1.14 (s, CH_{3}); 1.12 (s; CH_{3}).

**13C NMR**  (100.6 MHz, BB, DEPT, {\textsuperscript{1}H; {\textsuperscript{13}C-COSY}):
211.45 (Cq, C-7); 175.77 (Cq, C-2); 91.95 (Cq, C-5); 52.74 (Cq, C-5); 36.37 (CH_{2}, C-8); 33.07 (CH_{2}); 28.55 (CH_{2}); 28.45 (CH_{2}); 21.44 (CH_{3}); 19.69 (CH_{2}); 18.09 (CH_{3}).

**Mp**  97-99 °C.

**IR**  (KBr):
2952m, 1772s, 1706s, 1472m, 1388m, 1273m, 1232m, 1208s, 1179m, 1158s, 956s.
5.3.7 Synthesis of 4,4-Dimethyl-2,3,6,7-tetrahydro-4H-indene-1,5-dione (78)

Compound 83 (673 mg, 3.4 mmol) and polyphosphoric acid (75 ml) were heated at 90 °C under stirring and argon for 50 hours, then the viscous brown mixture was poured on ice, extracted with ethyl acetate and dried over anhydrous sodium sulfate. After evaporation of the solvent at reduced pressure, the residue was chromatographed on a silica gel column with pentane-ether (1:1) to give 78 as dark yellow crystals (359 mg, 58.7%).

4,4-Dimethyl-2,3,6,7-tetrahydro-4H-indene-1,5-dione (78):

\[
\text{MS (EI; m/z, rel. int.):} \\
178 (100, M^+, C_{11}H_{14}O_2), 136 (71), 135 (46), 121 (24), 93 (28), 91 (11), 79 (11).
\]

\[
\text{HRMS (EI; m/z):} \\
\text{calculated for C}_{11}\text{H}_{14}\text{O}_2: 178.099380; \text{found: 178.099348}
\]

\[
\text{^1H NMR (400 MHz):} \\
2.60-2.50 (m, 6H, CH}_2; 2.47-2.45 (m, 2H, CH}_2; 1.29 (s, CH}_3).
\]

\[
\text{^13C NMR (100.6 MHz, BB, DEPT, ^1H, ^13C-COSY):} \\
212.83 (Cq; C-5); 207.35 (Cq, C-1); 177.03 (Cq, C-9); 136.48 (Cq, C-8); 47.25 (Cq, C-4); 34.74 (CH}_2, C-6); 34.72 (CH}_2, C-2); 24.72 (CH}_2, C-7); 23.66 (CH}_3, C-10,11); 19.32 (CH}_2).
\]

\[
\text{Mp 56-58 °C.}
\]

\[
\text{IR (KBr):} \\
3456w, 2970w, 2935w, 1772w, 1735m, 1699s, 1645m, 1447w, 1390w, 1353m, 1231w, 1175m.
\]
5.3.8 Synthesis of 7,7-Dimethyl-tetrahydro-3a,6a-methano-pentalene-1,4-dione (84)

Compound 78 (197 mg, 1.11 mmol) and acetophenone (1.33 g, 11.1 mmol) were dissolved in acetonitrile (180 ml) and placed in a cylindrical Pyrex irradiation vessel, equipped with a cooling finger (water cooling). After degassing of the solution with argon for one hour, the reaction mixture was irradiated in a photochemical chamber reactor (type Rayonet RPR-208), equipped with 8 lamps (each 24 W, RUL 350 nm, $\lambda_{\text{max}}$ = 350 nm, emission range 300-400 nm). After irradiation for 30 hours, the solvent was evaporated in vacuo and the residue was chromatographed on silica gel with pentane-ether (3:1) to afford the product 84 in a yield of 89% (175 mg) as white crystals.

7,7-Dimethyl-tetrahydro-3a,6a-methano-pentalene-1,4-dione (84):

**MS** (EI; m/z, rel. int.):
178 (100, M$^+$, C$_{11}$H$_{14}$O$_2$), 136 (88), 135 (97), 121 (55), 93 (86), 91 (27), 80 (25), 79 (38), 77 (25), 39 (22).

**HRMS** (EI; m/z):
calculated for C$_{11}$H$_{14}$O$_2$: 178.099380; found: 178.099544.

**$^1$H NMR** (400 MHz):
2.65-2.55 (m, 2H, CH$_3$); 2.36-2.26 (m, 4H, CH$_2$); 2.04-1.97 (m, 2H, CH$_2$), 1.29 (s, 6H, CH$_3$).

**$^{13}$C NMR** (100.6 MHz, BB, DEPT, $^1$H; $^{13}$C-COSY):
213.17 (Cq, C-1, 4); 55.58 (Cq, C-8, 9); 43.09 (CH$_2$, C-2, 5); 34.74 (Cq, C-7); 19.22 (CH$_3$, C-8, 9); 19.01 (CH$_2$, C-3, 6).

**Mp** 13-114 °C.

**IR** (KBr):
5.3.9 Treatment of 84 with HCl in HOAc (→ 89a)

162 mg (0.91 mmol) of 84 were dissolved in acetic acid (5 ml) at room temperature and fuming HCl (0.5 ml, 37 %) were added. The mixture was stirred at room temperature for 15 hours, then was washed with sat. sodium hydrogencarbonate solution and dried with anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel using pentane-ether (1:1) as eluting solvent to give white crystalline 89a (159 mg, 81.4 %) as the first fraction; the second fraction was 78 (page 66) (10 mg, 15 %) as a white crystalline material.

3a-(1-Chloro-1-methyl-ethyl)-hexahydro-pentalene-1,4-dione (89a):

\[
\begin{align*}
\text{MS} & \quad (\text{EI}; \text{m/z, rel. int.}): \\
& \quad 214 (14, \text{M}^+, \text{C}_{11}\text{H}_{15}\text{O}_2), 179 (27), 178 (92), 151 (15), 136 (100), 135 (34), 124 (15), 123 (30), 109(17), 95 (16), 93 (22), 81 (18), 79 (23), 77 (17), 67 (25), 55 (46), 53 (17), 41 (30), 39 (19).
\end{align*}
\]

\[
\begin{align*}
\text{HRMS} & \quad (\text{EI}; \text{m/z}): \\
& \text{calculated for C}_{11}\text{H}_{15}\text{ClO}_2: 214.076057; \text{found: 214.076257.}
\end{align*}
\]

\[
\begin{align*}
\text{^1H-NMR} & \quad (400 \text{ MHz}): \\
& \quad 3.15 \text{ (d, } J=9.22, \text{ 1H, CH}); 2.46-2.44 \text{ (m, 2H)}; 2.26-2.09 \text{ (m, 6H)}; 1.69 \text{ (s, 3H, CH}_3); 1.60 \text{ (s, 3H, CH}_3).
\end{align*}
\]

\[
\begin{align*}
\text{^{13}C NMR} & \quad (100.6 \text{ MHz, BB, DEPT, } ^{1}\text{H; } ^{13}\text{C-COSY}): \\
& \quad 219.24 \text{ (Cq, CO); 218.87 (Cq, CO); 73.17 (Cq; C-8); 65.50 (Cq, C-9); 54.33 (CH, C-7); 38.71 (CH}_2, \text{ C-3); 37.94 (CH}_2); 29.54 \text{ (CH}_3); 28.57 \text{ (CH}_3); 27.57 \text{ (CH}_2); 23.32 \text{ (CH}_2).
\end{align*}
\]
5.3.10 Treatment of 84 with HBr in HOAc (→ 89b)

201.5 mg (1.13 mmol) of 84 was dissolved in carbon tetrachloride (10 ml) and 0.23 ml HBr (48 %) was added. The mixture was stirred at room temperature for 17 hours and the mixture was washed with sodium hydrogen carbonate and dried with anhydrous sodium sulfate, after evaporation of solvent, the residue was chromatographed on silica gel using pentane-ether (1:1) as eluting solvent to give white crystal 89b (262 mg, 82.1 %) as the first fraction, the second fraction is 78 (page 66) (82.6 mg, 13 %) as white crystalline material.

3a-(1-Bromo-1-methyl-ethyl)-hexahydro-pentalene-1,4-dione (89b):

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

**MS** (EI; m/z, rel. int.): 258 (5, M⁺, C₁₁H₁₅BrO₂), 179 (100), 151 (27), 123 (22), 55 (46).

**HRMS** (EI; m/z): calculated for C₁₁H₁₅BrO₂: 258.025555; found: 258.025501.

**¹H NMR** (400 MHz): 3.20 (d, J=9.19, 1H, CH); 2.52-2.47 (m, 2H); 2.32-2.07 (m, 6H); 1.91 (s, 3H, CH₃); 1.82 (s, 3H, CH₃).

**¹³C NMR** (100.6 MHz, BB, DEPT, ¹H; ¹³C-COSY): 219.13 (Cq, CO); 218.04 (Cq, CO); 70.87 (Cq, C-8); 66.15 (Cq, C-9); 56.02 (CH, C-7); 39.01 (CH₂); 37.95 (CH₂); 31.37 (CH₃); 30.34(CH₃); 28.73 (CH₂); 23.34 (CH₂).

**Mp** 108-110 °C.
IR (KBr):
3432m, 2899w, 1729s, 1477w, 1457w, 1412w, 1389w, 1371w, 1285wm
1215w, 1179w, 1132w, 1118w, 1102w, 1084w.

5.3.11 Dehalogenation of 89b (→ 90)

(a) 273 mg (1.1 mmol) of 89b and 0.3 ml triethylamine were dissolved in 20 ml ethylacetate, 101 mg 5% Pt-C was added in a two-necked flask which was connected to water pump and hydrogen-filled balloon. This mixture was evacuated at water pump pressure until evolution of bubbles then the valve of the hydrogen-filled balloon was opened. This process was repeated for several times. Then the reaction was left to react under hydrogen and was monitored by TLC. After the catalyst was filtered, the organic phase was washed with diluted HCl (20%, v/v) and washed with brine, before drying over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel with ether/pentane (1:5). The first fraction contained 90 as colorless liquid (91 mg, 48%) and the second fraction consisted of 78 (73.6 mg, 37%) was the second fraction.

(b) 89b (130 mg, 0.5 mmol) was dissolved in 10 ml dry benzene under argon atmosphere. After adding AIBN (6 mg) and Bu₃SnH (0.27 ml, 1 mmol), the reaction mixture was refluxed for four hours and cooled to room temperature. The reaction mixture was concentrated in vacuo and the residue chromatographed on silica gel with pentane/ether (4:1) to give 90 (68 mg, 75%).

3a-Isopropyl-hexahydro-pentalene-1,4-dionedione (90):

MS (EI; m/z, rel. int.):
180 (40, M⁺, C₉₁H₆O₂), 152 (16), 137 (100), 125 (72), 110 (18), 109 (45), 82 (23), 81 (25), 79 (14), 67 (19), 55 (21), 41 (24).

HRMS (EI; m/z):
calculated for C₁₁H₁₆O₂: 180.115030; found: 180.115244.
**1H NMR** (400 MHz):
2.65 (m, 1H); 2.33-2.27 (m, 2H); 2.14-2.04 (m, 5H); 1.97-1.85 (m, 2H); 0.90 (d, \(J=6.91\), 3H, CH\(_3\)); 0.86 (d, \(J=6.81\), 3H, CH\(_3\)).

**13C NMR** (100.6 MHz, BB, DEPT, **1H**, **13C-COSY**):
222.13 (Cq, CO); 220.41 (Cq, CO); 61.06 (Cq, C-7); 52.65 (CH, C-8); 37.91 (CH\(_2\)); 37.70 (CH\(_2\)); 32.97 (CH, C-9); 27.36 (CH\(_2\)); 22.50 (CH\(_2\)); 18.18 (CH\(_3\)); 17.83 (CH\(_2\)).

**IR** (KBr):
3421w, 2964w, 1734s, 1472w, 1408w, 1372w.

### 5.3.12 Reaction of 84 with borontrifluoride-etherate (→ 96)

BF\(_3\)·Et\(_2\)O (*Fluka*, 0.32 ml, 2.5 mmol) was added at –78 °C to a solution of 147 mg (0.827 mmol) of diketone 84 in acetic anhydride (10 ml) under stirring and argon. The mixture was stirred for 6 hours at room temperature, then 15 ml of ice-water were added. The reaction mixture was let to warm slowly to room temperature and was saturated with sodium chloride, then extracted with ether and the organic layer washed with saturated solution of sodium hydrogen carbonate. Before the evaporation of the solvent, the solution was dried over anhydrous sodium sulfate and the residue was chromatographed on silica gel with pentane/ether (1:5) to obtain 96 as a colorless oil (143 mg, 61.6%) and 78 (22 mg, 7%) as crystalline material.

**Acetic acid 3a-(1-acetoxy-1-methyl-ethyl)-4-oxo-2,3,3a,4,5,6-hexahydro-pentalen-1yl ester (96):**

**MS** (EI; m/z, rel. int.):
280 (1, M\(^+\), C\(_{15}\)H\(_{20}\)O\(_3\)), 222 (11), 180 (37), 179 (14), 178 (22), 150 (13), 139 (12), 138 (100), 137 (11), 43 (56).

**HRMS** (EI; m/z):
calculated for C\(_{15}\)H\(_{20}\)O\(_3\): 280.131075; found: 280.131273.
\(^1\)H NMR (400 MHz):
2.95-2.80 (m, 1H); 2.52-2.46 (m, 3H); 2.73-2.05 (m, 2H); 2.12 (s, 3H, CH\(_3\)); 1.99-1.91 (m, 2H); 1.89 (s, 3H, CH\(_3\)); 1.59 (s, 3H, CH\(_3\)); 1.58 (s, 3H, CH\(_3\)).

\(^13\)C NMR (100.6 MHz, BB, DEPT, \(^1\)H; \(^13\)C-COSY):
217.30 (Cq, C-4); 168.96 (Cq, C-9); 167.63 (Cq, C-10); 146.81 (Cq, C-8); 129.62 (Cq, C-1); 88.07 (Cq, C-5); 67.65 (Cq, C-13); 41.65 (CH\(_2\)); 33.85 (CH\(_2\)); 28.62 (CH\(_2\)); 22.45 (CH\(_3\), C-10); 21.73 (CH\(_2\)); 20.60 (CH\(_3\)); 20.38 (CH\(_3\)); 19.88 (CH\(_3\)).

IR (KBr):
3457w, 2944w, 1737s, 1446w, 1386w, 1369m, 1326w, 1251m, 1192s, 1129m, 1052w, 1013w, 935w.

5.3.13 Reduction of 84 with sodium borohydride (→ 97)

84 (350 mg, 1.96 mmol) was dissolved in 15 ml methanol followed by addition of sodium borohydride (22 mg, 0.59 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 8 hours. After addition of 1 ml of water, the solvent was evaporated and the residue chromatographed on silica gel using pentane/ether (3:1) as eluant to give 97 as white crystals (323 mg, 91.5%).

4-Hydroxy-7,7-dimethyl-tetrahydro-3a,6a-methano-pentalen-1-one (97):

MS (EI, m/z, rel. int.):
180 (34, M\(^+\), C\(_{11}\)H\(_{16}\)O\(_2\)), 165 (17), 152 (15), 147 (17), 137 (21), 136 (19), 123 (90), 121 (21), 120 (26), 119 (32), 107 (100), 105 (63), 93 (43), 91 (41), 79 (36), 77 (23), 67 (20), 55 (20), 43 (21), 41 (28), 39 (21).

HRMS (EI; m/z):
calculated for C\(_{11}\)H\(_{16}\)O\(_2\): 180.115030; found: 180.115209.
**1H NMR** (250 MHz): 4.75 (dd, J=5.62, 9.90, 1H, -CH-); 2.62-2.48 (m, 2H); 2.27-2.16 (m, 2H); 2.10-1.95 (m, 2H); 1.87-1.81 (m, 2H); 1.60-1.50 (m, 1H); 1.41 (s, 3H, CH3); 1.22 (s, 3H, CH3).

**13C NMR** (63 MHz, BB, DEPT, 1H; 13C-COSY):
216.47 (Cq, C-1); 82.0 (CH, C-4); 56.96 (Cq, C-8); 53.31 (Cq, C-9); 44.12 (CH2); 42.28 (CH2); 35.25 (Cq, C-7); 25.41 (CH2); 24.10 (CH2); 20.72 (CH3); 20.63 (CH3).

**Mp** 97-98 °C.

**IR** (KBr):
3354s (br.), 2944m, 1713s, 1448w, 1404w, 1327w, 1281w, 1099w, 1059m, 1042m, 1025m, 1009w, 669w.

### 5.3.14 Esterification of 97 (→ 98)

Hydroxyketone 97 (169 mg, 0.95 mmol) was dissolved in 5 ml pyridine at room temperature and heated at 88-90 °C for 2 hours. After distilling off the solvent, the residue was dissolved in 10 ml ethyl acetate and washed with brine. Next, drying over sodium sulfate and evaporation of the solvent in vacuo followed. Chromatography of the residue on silica gel gave 98 as white crystals (174 mg, 83%).

Acetic acid 7,7-dimethyl-4-oxo-tetrahydro-3a,6a-methano-pentalen-1-yl ester (98):

![Acetic acid 7,7-dimethyl-4-oxo-tetrahydro-3a,6a-methano-pentalen-1-yl ester (98)](image)

**MS** (EI; m/z, rel. int.):
222 (5, M+, C13H18O3), 180 (34), 179 (17), 162 (46), 136 (15), 134 (45), 121 (16), 120 (69), 119 (100), 107 (34), 106 (17), 105 (86), 93 (20), 91 (38), 79 (20), 77 (17), 43 (63), 41 (20).
HRMS (EI; m/z):
calculated for C$_{13}$H$_{18}$O$_{3}$: 222.125595; found: 222.125440.

$^1$H NMR (400 MHz):
5.36 (dd, $J$=5.03, 10.21, 1H); 2.75-2.60 (m, 1H); 2.59-2.53 (m, 1H); 2.28-2.20 (m, 2H); 2.15-2.07 (m, 2H); 2.0 (s, 3H, CH$_3$); 1.91-1.84 (m, 1H); 1.79-1.61 (m, 1H); 1.33 (s, 3H, CH$_3$); 1.23 (s, 3H, CH$_3$).

$^{13}$C NMR (100.6 MHz, BB, DEPT, $^1$H, $^{13}$C-COSY):
215.24 (Cq, C-1); 171.06 Cq, C-10); 83.22 (CH, C-4); 56.59 (Cq, C-8); 53.94 (Cq, C-9); 43.22 (CH$_2$); 38.79 (CH$_2$); 34.77 (Cq, C-9); 25.14 (CH$_2$); 23.31 (CH$_2$); 20.99 (CH$_3$, C-11); 20.03 (CH$_3$); 19.73 (CH$_3$).

Mp 82-83 °C.

IR (KBr):
3450m (br), 2950m, 2918m, 1736s, 1707s, 1457w, 1407w, 1377m, 1351w, 1325m, 1280m, 1251s, 1098m, 1050m, 1023s.

5.3.15 Treatment of 98 with HCl in HOAc (→ 102-105)

At room temperature, 98 (410 mg, 1.85 mmol) was dissolved in 10 ml CCl$_4$ under stirring, then 0.2 ml fuming hydrochloric acid (37%) was added. This mixture was stirred for further 12 hours at room temperature before washing it with saturated sodium hydrogen carbonate solution. The concentrated residue was chromatographed on silica gel with pentane/ether (5:1) to give the following 4 products:

Product 102: 127 mg (26.6%), pale yellow oil.

Acetic acid 6a-(1-chloro-1-methyl-ethyl)-4-oxo-octahydro-pentalen-1-yl ester (102):
MS (EI; m/z, rel. int.):
258 (7, M⁺, C₁₃H₁₉ClO₃), 222 (13), 198 (15), 181 (19), 180 (100), 163 (21), 152 (56), 137 (29), 136 (55), 123 (18), 121 (20), 107 (17), 93 (18), 79 (19), 43 (67), 41 (16).

HRMS (EI; m/z):
calculated for C₁₃H₁₉ClO₃: 258.102273; found: 258.102449.

¹H NMR (500 MHz):
5.12-5.10 (m, 1H, CH₃); 2.91-2.88 (m, 1H, CH); 2.56-2.50 (m, 3H); 2.35-2.33 (m, 2H); 2.25-2.05 (m, 1H); 2.04 (s, 3H, CH₃); 1.90-1.80 (m, 2H); 1.79 (s, 3H, CH₃); 1.69 (s, 3H, CH₃).

¹³C NMR (125.8 MHz, BB, DEPT, ¹H; ¹³C-COSY):
221.13 (Cq, C-1); 169.68 (Cq, C-12); 82.95 (CH, C-4); 62.98 (Cq, C-9); 54.33 (Cq, C-8); 41.09 (CH, C-7); 37.80 (CH₂); 32.21 (CH₂); 30.96 (CH₂); 29.38(CH₃); 28.46 (CH₃); 27.82 (CH₂); 21.46 (CH₃).

IR (KBr):
3448w, 2978w, 1737s, 1637w, 1458w, 1391w, 1374w, 1239s, 1144w, 1039w.

Product 103: 59 mg (14.4%), pale yellow oil.

Acetic acid 4,4-dimethyl-1-oxo-2,3,4,5,6,7-hexahydro-1H-inden-5-yl ester (103):

MS (EI; m/z, rel. int.):
222 (48, M⁺, C₁₃H₁₈O₃), 180 (84), 162 (100), 152 (85), 147 (63), 137 (46), 136 (89), 135 (22), 121 (23), 120 (42), 119 (50), 105 (61), 93 (26), 91 (25), 79 (19), 77 (19), 43 (78), 41 (17).
HRMS (EI; m/z):
calculated for C\textsubscript{13}H\textsubscript{18}O\textsubscript{3}: 222.125646; found: 222.125595.

\textsuperscript{1}H NMR (400 MHz):
4.89-4.91 (m, 1H, CH); 2.50-2.51 (m, 2H, CH\textsubscript{2}); 2.40-2.37 (m, 2H, CH\textsubscript{2}); 2.20-2.17 (m, 2H, CH\textsubscript{2}); 2.04 (s, 3H, CH\textsubscript{3}); 1.86-1.84 (m, 2H, CH\textsubscript{2}); 1.15 (s, 3H, CH\textsubscript{3}); 1.13 (s, 3H, CH\textsubscript{3}).

\textsuperscript{13}C NMR (100.6 MHz, BB, DEPT, \textsuperscript{1}H, \textsuperscript{13}C-COSY):
208.67 (Cq, C-1); 176.67 (Cq, C-10); 170.57 (Cq, C-9); 136.52 (Cq, C-8); 76.55 (CH, C-5); 38.40 (Cq, C-4); 34.54 (CH\textsubscript{2}); 25.45 (CH\textsubscript{3}, C-11); 24.87 (CH\textsubscript{2}); 22.97 (CH\textsubscript{2}); 21.60 (CH\textsubscript{3}); 21.07 (CH\textsubscript{3}); 17.30 (CH\textsubscript{2}).

IR (KBr):
3457w, 2968w, 1736s, 1700s, 1641m, 1374w, 1244s, 1046w, 1033w.

Product \textbf{104}: 47.5 mg (14.3%), pale yellow oil.

5-Hydroxy-4,4-dimethyl-2,3,4,5,6,7-hexahydro-inden-1-one (104):

MS (EI; m/z, rel. int.):
180 (100, M\textsuperscript{+}, C\textsubscript{11}H\textsubscript{16}O\textsubscript{2}), 152 (48), 137 (48), 136 (88), 135 (37), 123 (10), 121 (40), 93 (44), 91 (18), 79 (21), 77 (17), 55 (10), 43 (15), 41 (14), 39 (11).

HRMS (EI; m/z):
calculated for C\textsubscript{11}H\textsubscript{16}O\textsubscript{2}: 180.115030; found: 180.115261.

\textsuperscript{1}H NMR (400 MHz):
3.67 (m, 1H); 2.51-2.48 (m, 2H); 2.38-2.36 (m, 2H); 2.24-2.05 (m, 2H); 1.95-1.85 (m, 2H); 1.64 (s, 1H, HOC-3); 1.17 (s, 3H, CH\textsubscript{3}); 1.14 (s, 3H, CH\textsubscript{3}).

\textsuperscript{13}C NMR (100.6 MHz, BB, DEPT, \textsuperscript{1}H, \textsuperscript{13}C-COSY):
209.00 (Cq, C-1); 178.02 (Cq, C-9); 136.26 (Cq, C-8); 75.16 (CH, C-5); 39.58 (Cq, C-4); 34.70 (CH₂); 26.20 (CH₂); 25.17 (CH₃); 25.04 (CH₂); 20.74 (CH₃); 17.67 (CH₂).

**IR** (KBr):
3431s, 2965m, 2934m, 2870m, 1673s, 1628s, 1437w, 1389w, 1231w, 1175s, 1051m.

Product **105**: 37.5 mg (10.2%), pale yellow oil.

6a-(1-Chloro-1-methyl-ethyl)-3,5,6,6a-tetrahydro-2Hpentalen-1-one (105):

**MS** (EI; m/z, rel. int.):
198 (54, M⁺, C₁₁H₁₅ClO), 163 (14), 156 (21), 121 (100), 119 (61), 107 (29), 91 (34).

**HRMS** (EI; m/z):
calculated for C₁₁H₁₅ClO: 198.081143; found: 198.081080.

**¹H NMR** (500 MHz):
5.85 (dd, J=1.58, 1.36); 2.91-2-67 (m, 1H); 2.56-2.52 (m, 2H); 2.44-2.34 (m, 2H); 2.10-2.06 (m, 1H); 1.94-1.89 (m, 1H); 1.71 (s, 3H, CH₃); 1.60 (s, 3H, CH₃).

**¹³C NMR** (125.8 MHz, BB, DEPT):
217.24 (Cq, C-1); 148.53 (Cq, C-8); 129.50 (CH, C-4); 73.01 (Cq, C-9); 70.95 (Cq, C-7); 42.47 (CH₂); 34.75 (CH₂); 33.42 (CH₂); 29.43 (CH₃); 28.62 (CH₃); 24.99 (CH₂).
5.3.16 Oxidation of diketone 84 with lead tetraacetate (→ 115 and 116)

Diketone 84 (179 mg, 1 mmol) was dissolved in 20 ml benzene, then 700 mg (1.5 mmol) lead tetraacetate (95%, Acros) and 5 ml acetic acid were added and the mixture was stirred at room temperature for 6 days. After adding 15 ml of water, the organic phase was separated and the aqueous phase was extracted with ether. The combined organic layers were washed with saturated sodium hydrogencarbonate solution and brine. Before evaporating the solvent, the organic phase was dried over anhydrous sodium sulfate and the organic layer concentrated. The residue was chromatographed on silica gel with pentane/ether (1:3) to give 115 (123 mg, 53%) and 116 (47 mg, 16%) as white crystalline materials.

Acetic acid 7,7-dimethyl-1,4-dioxo-tetrahydro-3a,6a-methano-pentalen-2-yl ester (115):

\[
\begin{align*}
\text{MS} & \quad (\text{EI; m/z, rel. int.}): \\
& \quad 236 (0.3, \text{M}^+), 194 (35), 179 (50), 176 (100), 166 (58), 137 (25), 134 (69), 133 (22), 123 (60), 105 (31), 91 (33), 79 (26), 77 (22), 55 (18), 43 (78), 41 (19).
\end{align*}
\]

\[
\begin{align*}
\text{HRMS} & \quad (\text{EI; m/z}): \\
& \quad \text{calculated for C}_{13}\text{H}_{16}\text{O}_4: 236.104860; \text{found: } 236.104930.
\end{align*}
\]

\[
\begin{align*}
\text{\textsuperscript{1}H NMR} & \quad (400 \text{ MHz}): \\
& \quad 4.51 \text{ (dd, J=4.99, 8.46, 1H); } 2.75-2.69 \text{ (m, 1H); } 2.58-2.17 \text{ (m, 5H); } 2.03 \text{ (s, 3H, CH}_3\text{); } 1.29 \text{ (s, 3H, CH}_3\text{); } 1.23 \text{ (s, 3H, CH}_3\text{).}
\end{align*}
\]
$^{13}$C NMR (100.6 MHz, BB, DEPT, $^1$H; $^{13}$C-COSY):

212.86 (Cq, C-1); 207.70 (Cq, C-4); 170.26 (Cq, C-10); 81.37 (CH, C-2); 54.16 (Cq, C-8); 53.55 (Cq, C-9); 42.30 (CH$_2$); 35.65 (Cq, C-7); 27.99 (CH$_2$); 20.60 (CH$_3$); 20.33 (CH$_3$); 19.70 (CH$_2$); 19.44 (CH$_3$).

Mp 110-111 °C.

IR (KBr):

3442w (br.), 2957w, 1726s, 1383w, 1314w, 1229m, 1195w, 1071w, 1027w.

Acetic acid 5-acetoxy-7,7-dimethyl-1,4-dioxo-tetrahydro-3a,6a-methano-pentalen-2-yl ester (116):

MS (EI; m/z, rel. int.):

294 (4, M$^+$, C$_{15}$H$_{18}$O$_6$), 252 (13), 224 (27), 195 (15), 177 (19), 174 (38), 164 (33), 149 (32), 136 (31), 135 (19), 121 (22), 93 (10), 91 (10), 43 (100).

HRMS (EI; m/z):

calculated for C$_{15}$H$_{18}$O$_6$: 294.110340; found: 294.110090.

$^1$H NMR (400 MHz): 4.84 (dd, J=4.55, 8.50, 2H); 2.58 (dd, J=8.45, 14.80, 2H); 2.30 (dd, J=4.54, 14.83, 2H); 2.07 (s, 6H, CH$_3$); 1.32 (s, 6H, CH$_3$).

$^{13}$C NMR (100.6 MHz, BB, DEPT, $^1$H; $^{13}$C-COSY):

206.14 (Cq, C-1,4); 170.09 (Cq, C-12, 14); 79.17 (CH, C-2,5); 51.74 (Cq, C-8, 9); 36.29 (Cq, C-7); 28.04 (CH$_2$, C-4, 6); 20.88 (CH$_3$); 20.43 (CH$_3$).

Mp 162-163 °C.

IR (KBr):

3456w (br.), 2953w, 1730s, 1448w, 1377w, 1231s, 1167w, 1067w, 1022m.
5.3.17 Birch Reduction of 84 (→ 123)

Liquid ammonia (50 ml) was distilled into a three-necked flask, cooled to –78 °C, followed by addition of 57 mg (8.21 mmol) lithium which resulted in the formation of a deep blue solution. To this solution was added a solution of diketone 84 (92 mg, 0.52 mmol) in 5 ml dry THF, then the reaction was stirred for further 2 hours. After adding 1 g of sodium chloride, the solution was slowly warmed to room temperature. Ammonia was evaporated and 15 ml water were added. The mixture was extracted with ethyl acetate and the organic layers dried over anhydrous sodium sulfate. After evaporation of the solvent at reduced pressure, the residue was chromatographed on silica gel with pentane/ether (1:3) to give 123 (58 mg, 60.2%) as white a crystalline product.

5.3.18 Reduction of 84 with sodium in toluene-isopropanol (→ 123)

Sodium was heated in 7.5 ml toluene to reflux under vigorous stirring and argon to give finely dispersed sodium, then a solution of diketone 84 (92 mg, 0.516 mmol) in 253 ml isopropanol was added, the solution kept under reflux and 3.5 hours later additional 99 mg of sodium and 311 mg isopropanol were added and the stirring was continued for further 2 hours. After cooling the reaction mixture to room temperature, 4 ml ethanol was added to destroy the excess sodium. Next, 20 ml saturated NH₄Cl solution was added, the organic phase was separated after extraction and the water phase was separately extracted with ether. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Chromatography of the residue on silica gel with pentane/ether (1:3) afforded 123 (64 mg, 68%) as a white crystalline product.

5.3.19 Reduction of 84 with sodium in ether saturated by NaHCO₃ (→ 123)

To a solution of diketone 84 (89 mg, 0.5 mmol) in 10 ml diethyl ether was added 1 ml of saturated sodium bicarbonate solution and sodium was carefully added in a small pieces at 0 °C under stirring. After the initial sodium disappeared sodium, further small pieces of sodium were added until the reaction was completed (monitored by TLC). Thereafter water was added ml by ml until no further reaction with sodium was observed; a total of 4.6 mg (198.98 mmol) sodium was consumed. Then, the organic phase was separated and the aqueous phase
was extracted repeatedly with ether and dried over sodium sulfate. After concentration, the residue was purified by chromatography on silica gel using pentane/ether (1:3) as eluent to give 123 (76.1 mg, 83.5%) as a white crystalline product.

7,7-Dimethyl-tetrahydro-1,4-methano-pentalene-3a,6a-diol (123):

MS (EI; m/z, rel. int.):
182 (98, M⁺, C₁₁H₁₈O₂), 167 (44), 164 (47), 149 (44), 122 (23), 121 (28), 111 (83), 109 (37), 107 (47), 106 (21), 99 (22), 98 (20), 96 (96), 93 (28), 84 (21), 83 (74), 79 (28), 70 (20), 69 (100), 67 (24), 55 (55), 43 (54), 41 (64).

HRMS (EI; m/z):
calculated for C₁₁H₁₈O₂: 182.130680; found: 182.130416.

⁻¹H NMR (250 MHz):
1.91-1.87 (m, 2H); 1.58-1.51 (m, 6H); 1.36-1.31 (m, 2H); 0.92 (s, 6H, CH₃).

¹³C NMR (63 MHz, BB, DEPT, ¹H, ¹³C-COSY):
84.90 (Cq, C-1, 4); 49.71 (CH, C-8,9); 31.62 (Cq, C-7); 26.70 (CH₂); 24.99 (CH₃); 21.76 (CH₂).

Mp 149-150 °C.

IR (KBr):
3417s (br.), 2955m, 1636w, 1384m, 1128m, 1062w.
5.3.20 Oxidation of pinacol 123 with lead tetraacetate (→ 85)

To a suspension of 123 (36 mg, 0.2 mmol) in 10 ml absolute benzene was added lead tetraacetate (95%, Fluka, 131 mg, 0.28 mmol) with stirring at room temperature and under argon. After stirring for 6.5 hours, 0.3 ml glycerine was added and the mixture was warmed to 45 °C to destroy the excess of lead tetraacetate. The mixture was filtered by washing the residue with toluene. The combined organic layers were dried over anhydrous sodium sulphate prior to evaporation of the solvents. Chromatography of the residual crude product on silica gel with pentane/ether (1:4) gave the desired 85 with 57% yield (20.6 mg).

9,9-Dimethyl-bicyclo[3.3.1]nonane-2,6-dione (85):

MS (EI; m/z, rel. int.):
180 (27, M⁺, C₁₁H₁₆O₂), 137 (11), 112 (92), 95 (10), 82 (14), 81 (15), 69 (100), 67 (19), 55 (19), 41 (30).

HRMS (EI; m/z):
calculated for C₁₁H₁₆O₂: 180.115030; found: 180.115276.

¹H NMR (400 MHz):
2.56 (dd, 1H, J=7.9Hz, J=18.1Hz); 2.38-2.28 (m, 2H); 2.18-2.12 (m, 1H); 1.88 (dd, 1H, J=9.5Hz, J=14.5Hz); 0.97 (s, 6H, CH₃).

¹³C NMR (100.6 MHz, BB, DEPT, ¹H; ¹³C-COSY):
212.89 (Cq, C-2,6); 54.72 (C-1,5); 37.25 (Cq, C-9); 36.04 (CH₂, C-3,7); 26.25 (CH₃, C-10,11); 22.57 (CH₂, C-4,8).

Mp 140-141 °C.

IR (KBr):
3440w (br), 2965w, 2910m, 1692s, 1458w, 1435w, 1326w, 1235w, 1031w, 744w.
5.3.21 Synthesis of 9,9-Dimethyl-bicyclo[3.3.1]nonane-2,6-dione (85) from 84

Graphite (970 mg, 70.76 mmol) was placed in a two-necked flask and heated under argon atmosphere to degas for 20 min at 160 °C before freshly cut potassium (390 mg, 9.98 mmol) was added under vigorous stirring. Bronze-colored laminate of graphite and potassium (C₈K) was formed. After cooling to room temperature, 20 ml dry THF was added by syringe. To this suspension was added solution of 84 (358 mg, 2.0 mmol) in 20 ml of dry THF at room temperature and stirred for 5 days at the same temperature. After adding 5 ml MeOH, graphite was filtered off and washed extensively with ethyl acetate, the organic phase was concentrated in vacuo and chromatographed on the silica gel with pentane-ether (5:1) to give white crystalline 85 (1.18 mmol, 212 mg, 59%).

9,9-Dimethyl-bicyclo[3.3.1]nonane-2,6-dione (85),
(data see p. 83):

5.3.22 Synthesis of 131

A mixture of 9,9-dimethyl-bicyclo[3.3.1]nonane-2,6-dione (85) (0.678 g, 3.76 mmol), 1,2-ethanediol (130) (0.233 g, 3.76 mmol) and p-TsOH monohydrate (0.071 g, 0.37 mmol) in 200 ml of toluene was vigorously stirred and refluxed for 4.5 hours in a Dean-Stark apparatus. After cooling, reaction mixture was washed with saturated aq. NaHCO₃ (60 ml) and NaCl (2 x 50 ml). After drying over anhydrous Na₂SO₄, the solvent was evaporated in vacuo and the residue chromatographed on silica gel with pentane/ether (1:2) as eluent to give the product 131 (53 mg, 63 % yield) as a crystalline material.

Monoketal 131:

MS (EI; m/z, rel. int.):
224 (10.2, M⁺, C₁₃H₂₀O₃), 100 (99), 86 (54.5), 55 (16.2).
HRMS (EI; m/z):
calculated for C_{13}H_{20}O_{3}: 224.141245; found: 224.141486.

^1H NMR (400 MHz, ^1H-^1H-COSY, CDCl$_3$):
3.97-3.78 (m, 4H); 2.39 (dd, 1H, J=9.2Hz, J=19.2Hz); 2.25 (dd, 1H, J=9.7Hz, J=19.2Hz); 2.17-2.11 (m, 1H); 2.04-1.85 (m, 3H); 1.16 (s, CH$_3$), 0.91 (s, CH$_3$).

^13C NMR (100 MHz, BB, DEPT, ^1H-^13C-COSY, CDCl$_3$):
215.95 (Cq, C-1); 110.87 (Cq, C-6); 64.64 (CH$_2$, C-12); 63.30 (CH$_2$, C-13); 55.70 (CH, C-1); 44.72 (CH, C-5); 36.43 (CH$_3$); 35.66 (Cq, C-9); 30.66 (CH$_2$); 29.22 (CH$_3$); 26.74 (CH$_3$); 22.44 (CH$_2$); 20.59 (CH$_2$).

IR (KBr):
3454 (br.), 3011m, 2960s, 2974s, 1693s, 1455m, 1102s, 909m.

Mp 53 °C.

5.3.23 Synthesis of 132

To a solution of the monoprotected diketone 131 (61 mg, 0.272 mmol) in CH$_2$Cl$_2$ (8 ml), TBDMSOTf (0.057 ml, 86.2 mg, 0.323 mmol), followed by NEt$_3$ (0.094 ml, 0.69 mg, 0.68 mmol), were added dropwise at room temperature. After stirring for 10 min at room temperature, the mixture was hydrolyzed with water (5 ml) and extracted with CH$_2$Cl$_2$ (3x 20 ml). The combined organic layers were dried with NaSO$_4$. After filtration, the solvents were removed under reduced pressure at 25 °C. The crude product was purified by chromatography on a silica gel column with pentane as eluent to give the silylated enol ether 132 (0.09 g, 0.272 mmol, quantitative yield).

Silylenol ether 132:
**MS** (EI; m/z, rel. int.):
338 (54.0, M⁺, C₁₀H₃₄O₃Si₁), 294 (20.1), 293 (85.9), 99 (100.0), 75 (21.8), 73 (47.0), 55 (17.0).

**HRMS** ESIpos: m/z calcd for C₁₀H₃₄NaO₃Si₁ (M+Na):
calculated: 361.217066, found: 361.217493.

**¹H NMR** (400 MHz, ¹H-¹H-COSY, CDCl₃):
4.69 (dd, 1H, J=2.7, 4.6Hz); 3.99-3.81 (m, 4H, CH₂); 2.24 (dd, 1H, J=4.6Hz, J=17.9Hz); 2.11 (ddd, 1H, J=2.7Hz, J=6.3Hz, J=18.0Hz); 1.87 (t, 1H, J=13.1Hz); 1.75 (dt, 1H, J=5.4Hz, J=13.3Hz); 1.62 (s, 1H); 1.56-1.45 (m, 2H); 1.35 (d, 1H, J=5.4Hz); 1.14 (s, CH₃); 0.99 (s, CH₃); 0.89 (s, 9H); 0.12 (s, CH₃); 0.10 (s; CH₃).

**¹³C NMR** (100 MHz, BB, DEPT, ¹H-¹³C-COSY, CDCl₃):
150.56 (Cq, C-2); 112.36 (Cq, C-6); 100.92 (CH, C-3); 64.45 (CH₂); 63.00 (CH₂); 45.56 (CH); 44.44 (CH); 34.52 (Cq); 28.16 (CH₃); 28.13 (CH₂); 26.91 (CH₃); 25.73 (CH₃, C-15,16,17), 24.43 (CH₂); 22.21 (CH₂); 17.95 (Cq, C-14); -4.10 (CH₃), -4.49 (CH₃).

**IR** 3399 (br.) 2910s, 1706s, 1459m, 1435m, 1325m.

**Mp** 44 °C.

### 5.3.24 Attempted ZrCl₄-catalyzed [2+2] reaction of 132 and methyl but-2-ynoate (133)

ZrCl₄ (0.11 mg, 0.49 mmol) was suspended in CH₂Cl₂ (10 ml) and Et₂O (1 ml) and then methyl but-2-ynoate (133) (0.051 ml, 50.5 mg, 0.51 mmol) was added. The resulting mixture was cooled to -78 °C, whereupon a solution of enol ether 132 (83 mg, 0.24 mmol) in CH₂Cl₂ (1 ml) was added dropwise. After stirring for 10 min at -78 °C and for 10 min at room temperature, the mixture was hydrolyzed by the addition of saturated aqueous NaHCO₃ solution (5 ml). After extraction with Et₂O (3 x 30 ml), the combined organic layers were dried with NaSO₄ and the solvents were removed at reduced pressure. The crude product was
chromatographed on silica gel with pentane:ether (10:1). Instead of the expected \([2+2]\) product, 85 and 131 were recovered with 45 and 41% yield, respectively.

9,9-Dimethyl-bicyclo[3.3.1]nonane-2,6-dione (85),
(data see p. 83):

Monoketal 131, (data see p. 84):

5.3.25 Synthesis of 135

Diketone 85 (0.203 g, 1.13 mmol), 2,2-dimethylpropane-1,3-diol (134) (0.12 g, 1.13 mmol), and \(p\)-TsOH (0.023 g, 0.01 mmol) were dissolved in toluene (50 ml). The resulting mixture was refluxed for 17 hours with a Dean-Stark head. It was then cooled to 0 °C, diluted with Et\(_2\)O (10 mL), and then 10% aq. NaOH solution (3 mL) was added. After extraction with Et\(_2\)O (2 × 50 mL), the organic layers were collected, washed with saturated aqueous NaCl solution (100 ml), and dried with Na\(_2\)SO\(_4\). Volatile components were then removed at reduced pressure. The crude material was purified by chromatography on a silica gel column with pentane: ether (10:1) as eluent and 0.27 g 135 was obtained (62% yield).

Monoketal 135:

MS (El; m/z, rel. int.):
226 (10.7, \(M^+\), C\(_{16}\)H\(_{26}\)O\(_3\)), 142 (12.6), 141 (100), 128 (36.5), 69 (35.3), 55 (21.9), 41 (23.7).
HRMS (EI; m/z):
calculated for C_{16}H_{26}O_{3}: 266.188195; found: 226.187915.

^{1}H NMR (400 MHz, ^{1}H-^{1}H-COSY, CDCl_{3}): 3.57 (d, 2H, J=11.4Hz); 3.50 (d, 2H, J=11.3Hz); 2.52 (dd, 1H, J=7.9Hz, J=17.8Hz); 2.36 (dd, 1H, J=9.0Hz, J=20.4Hz); 2.24-1.95 (m, 5H); 1.50-1.37 (m, 1H); 1.14 (s, 6H, CH_{3}); 1.1 (s, CH_{3}); 0.78 (s, CH_{3}).

^{13}C NMR (100 MHz, BB, DEPT, ^{1}H-^{13}C-COSY, CDCl_{3}): 212.85 (Cq, C-2); 99.86 (Cq, C-6); 69.76 (CH_{2}, C-12); 69.56 (CH_{2}, C-13); 56.22 (CH, C-1); 54.64 (CH, C-5); 36.51 (CH_{2}); 31.90 (CH_{2}); 36, 40 (Cq); 30.25 (Cq); 29.83 (CH_{3}); 26.04 (CH_{2}); 23.09 (CH_{3}); 22.34 (CH_{2}).

IR (KBr):
3416 (br.), 2912s, 2854m, 1704m, 1459m, 1261m, 1031m.

Mp 47 °C.

5.3.26 Synthesis of 136

To a solution of the monoketal 135 (0.224 g, 0.84 mmol) in CH_{2}Cl_{2} (40 ml), TBDMSOTf (0.194 ml, 0.223 g, 0.84 mmol) followed by NEt_{3} (0.292 ml, 0.21 g, 2.11 mmol) were added dropwise at room temperature. After stirring for 10 min at room temperature, the mixture was hydrolyzed with water (10 ml) and extracted with CH_{2}Cl_{2} (3 x 25 ml). The combined organic layers were dried with Na_{2}SO_{4}. After filtration, the solvents were removed at reduced pressure and the crude product was purified by chromatography on a silica gel column with pentane:ether (10:1) as eluent to give the silylated enol ether 136 (0.2355 g, quantitative yield).

Silylenol ether 136:
MS 
(EI; m/z, rel. int.): 380 (57.2, M⁺, C₂₂H₄₀O₃Si), 295 (10.7), 294 (32.3), 293 (100), 141 (87.7), 75 (15.9), 73 (34.2), 69 (17.8), 55 (20.9).

¹H NMR 
(250 MHz, ¹H-¹H-COSY, CDCl₃): 4.68 (t, 1H, J=3.5Hz); 3.60 (d, 2H, J=11.4Hz); 3.49 (d, 2H, J=11.1Hz); 2.14-2.07 (m, 3H); 1.96-1.42 (m, 5H); 1.23 (s, 6H, CH₃); 1.13 (s, CH₃), 1.06 (s, CH₃); 0.9 (s, 9H, CH₃); 0.11 (s, CH₃), 0.99 (s, CH₃).

¹³C NMR 
(63 MHz, BB, DEPT, ¹H-¹³C-COSY, CDCl₃): 150.52 (Cq, C-2); 101.12 (Cq, C-6); 100.80 (CH, C-3); 69.57 (CH₂); 69.34 (CH₂); 45.99 (CH); 35.80 (CH); 34.18 (Cq); 30.03 (CH₂); 29.66 (CH₂); 29.62 (Cq); 28.95 (CH₃); 26.08 (CH₃); 25.69 (3C; CH₃); 23.31 (CH₃); 23.16 (CH₂); 22.38 (CH₃); -4.087 (CH₃); -4.57 (CH₃).

IR 
(KBr): 2927s, 2856m, 1666m, 1483m, 1361m, 1206m, 1146m, 1104s, 837m.

5.3.27 Attempted ZrCl₄-catalyzed [2+2] reaction of 136 and methyl but-2-ynoate (133)

ZrCl₄·THF (143 mg, 0.378 mmol) was suspended in CH₂Cl₂ (10 ml) and Et₂O (1 ml) and then methyl but-2-ynoate (133) (0.044 ml, 43 mg, 0.43 mmol) was added. The resulting mixture was cooled to -78 °C, whereupon a solution of enol ether 136 (100 mg, 0.27 mmol) in CH₂Cl₂ (1 ml) was added dropwise. After stirring for 10 min at -78 °C and for 10 min at room temperature, the mixture was hydrolyzed by the addition of saturated aqueous NaHCO₃ solution (5 ml). After extraction with Et₂O (3 x 30 ml), the combined organic layers were dried with NaSO₄ and the solvents were removed at reduced pressure. The crude product was chromatographed on silica gel with pentane:ether (10:1) as eluent. Instead of the expected [2+2] product, 85 and 135 were recovered with 43 and 42 % yield, respectively.

9,9-Dimethyl-bicyclo[3.3.1]nonane-2,6-dione (85), (data see p. 83):
Monoketal 135 (data see p. 87):

5.4 Quantum mechanical calculations

Cartesian coordinates of the optimized molecules are represented. Geometry optimizations were performed for both structures, 138 and 145, employing density functional theory and the TURBOMOLE program package. The structures were plotted employing GOPENMOL. BP is a fast density functional that has proven to give accurate geometrical parameters in many application studies. For the geometry optimization of 138 and 145, the SV(P) basis sets were used. Complete geometry optimization, i.e. no geometrical parameters were fixed. One reasonable conformer was studied. All calculations were performed in vacuum. This is expected to be a good approximation since aprotic solvent THF will be used in the experiment. Furthermore, only charge neutral systems were investigated.

5.4.1 Data for the compound 138
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6 References


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   Wei, C. Q.; Jiang, X. R.; Ding, Y. *Tetrahedron*, **1998**, 54, 12623. i) 


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Curriculum Vitae

Name: Seher Yalcin

25 Nov. 1974: Born in Edirne, Turkey

1980-1985: Yaman Egeli Elementary School, Bandirma, Turkey

1985-1988: Karsiyaka Secondary School, Izmir, Turkey

1988-1991: Gazi High School, Izmir, Turkey

1991-1993: Zootechnics at Department of Agriculture Engineering, Aegean University, Izmir, Turkey

1993-1999: Bachelor of Science (B.Sc.) at Middle East Technical University (METU), Ankara, Turkey. Department of Chemistry, Faculty of Art and Sciences


2001-2005: Ph.D. fellow at the Max Planck Institute for Bioinorganic Chemistry, Mülheim an der Ruhr, Germany, under the supervision of Prof. Dr. Martin Demuth. Ph.D. Thesis: Synthesis of precursors en route to the basic skeleton of the anti-tumor drug taxane