Natural Product-like Compound Libraries from D-(-) Ribose

Inauguraldissertation
der Philosophisch-naturwissenschaftlichen Fakultät
der Universität Bern

vorgelegt von

Roland Messer
von Etzelkofen

Leiter der Arbeit:
Prof. Dr. R. Häner
Departement Für Chemie und Biochemie
der Universität Bern

Von der Philosophisch-naturwissenschaftlichen Fakultät angenommen.

Bern , 17. Juni 2005

Der Dekan:
Prof. Dr. P. Messerli

Für Isabelle,
meine Eltern und meine Schwester Sandra

Table of Content

Summary

The need for new bioactive entities has been always present with the desire to cure disease. With the use of small molecules as tools for biomedical research this demand has even increased. Small molecules can exert powerful effects on the functions of macromolecules that comprise living systems. Diversity-oriented synthesis is an intriguing approach for creating structurally diverse compounds that cover the pharmaceutically relevant chemical space in an optimal way. On the other hand, an over-proportionally large number of drugs or lead structures originate from compounds isolated from natural sources. Thus, not surprisingly, an increasing number of combinatorial libraries are based on motifs resembling natural products. During our work aimed at the synthesis of natural product-like scaffolds, we became attracted to a group of compounds belonging to the *iridoid* family. These tricyclic compounds possess a variety of interesting biological activities.

In this work the construction of natural product-like, tricyclic compounds is reported. Starting from D-(-)-ribose-derived dihydrofurane esters of different acylacrylic acids, the tricyclic scaffolds were prepared via an *intramolecular* hetero-*Diels-Alder* reaction. The reaction proceeds with very high diastereoselectivity through an *E-endo or Z-exo* transition state, as established on the basis of X-ray structural analysis of the products. Further modification and derivatisation of the obtained products is described. An alternative route to the construction of the same scaffold has been found involving the use of 1,2 diketones. This method proved to have advantages over the one using acylacrylic acids, leading to the stereoselective synthesis of bicyclic dihydropyrane derivatives.

Furthermore tricyclic scaffolds amenable to solid support chemistry have been developed. On the basis of these scaffolds, a multi-dimensional library has been generated by solid phase synthesis. The library products could be isolated and were fully characterized.

Characteristics of the hetero *Diels-Alder* reaction involved, in particular the influence of the substituents on the reaction rate, could be put into context with theory. The use of the D-(-)-ribose-derived dihydrofurane as a dienophile for Diels-Alder reactions involving carbodienes has been studied on several examples. Rate acceleration of the hetero *Diels-Alder* reaction was found in some examples by the use of lithium perchlorate. This helped to lower reaction temperatures and thus to avoid side reaction by *syn*-elimination in the dihydrofurane acylacrylate esters.

Compounds originating from this diversity oriented synthesis (DOS) approach are being tested for their inhibitory activity in cellular proliferation assays.

1 Introduction

Life is based on a set of molecules, in which the principal element is carbon. These carbon frameworks are called organic compounds and include fats, sugars, proteins and nucleic acids just to name a few. Since the dawn of humanity the number of organic compounds has been expanded by invention of various synthetic materials like soaps, dyes, fuels, polymers and drugs. Drugs are natural products or synthetic chemicals that can alter the way the body works, or which are used to prevent or treat disease. Drugs include pharmaceuticals, biologically-derived products such as vaccines, serums, and blood derived products; tissues and organs; disinfectants, and radiopharmaceuticals.

1.1 Drug Discovery

The need to make appropriate medicine available has probably been present longer than humanity can trace its roots. Since antiquity people have tried to cure diseases by eating, drinking, smoking or applying substances, which are often herbal extracts. There is even evidence that animals eat certain plants to help digestion or cure indisposition.
Originally, the attempts to discover new drugs were based on intuition and empirical observation, while successful findings were often mere chance. Only in the last century, the search for new medicines has changed dramatically. Advances in the understanding of human biology, technological innovations and synthetic access to organic compounds have altered the way drugs are being discovered. Today pharmaceutical companies are seeking to optimise their drug discovery processes by combining a multitude of different strategies and techniques.

1.1.1 A Brief History of Drug Discovery

Deliverances of early sophisticated civilisations like the Egyptians, Greek and the Arabs include already evidence for compounding and dosage requirements for various diseases.
1800-1900: The beginning of the 19th century scientists started to classify illnesses systematically by symptoms and began to search for means to “attack” these symptoms. The

methods of these days were often very unpleasant and cruel. In the second half of the 19th century, things changed remarkably as the industrial revolution brought technological progress and inspired the development of medical technology. Almost by accident, a few authentic drugs were discovered: quinine, digitalis, and cocaine. The century ended with the development of the first of two synthesized drugs. The discovery of antipyrine in 1883 and aspirin® in 1897 set the stage for the next 10 decades of what we can look back as the Pharmaceutical Century[1].

1901- 1930: In 1910 Paul Ehrlich's arsenic compound 606, marketed by Hoechst as salvarsan®, became the first effective treatment for syphilis. It was the birth of chemotherapy. Other milestones in these three decades were the discovery of vitamins and vaccines. Among them one of the most important ones penicillin was found by Alexander Fleming in 1928.

1940s[2]: Wars throughout the world pushed the development of penicillin production and demanded for a treatment of malaria. In 1944, William E. Doering and Robert B. Woodward synthesized quinine - a natural product - from coal tar. Woodward's achievements in the art of organic synthesis earned him the 1965 Nobel Prize in Chemistry. In 1948, Benjamin M. Duggar, a professor at the University of Wisconsin, isolated chlortetracycline from *Streptomyces aureofaciens.* Chlortetracycline, also called aureomycin, was the first tetracycline antibiotic and the first broad-spectrum antibiotic.

1950s[3]: In the 50s a large number of new drugs were discovered, among them cortisone and oral contraceptives. In 1953 James Watson and Francis Crick published the structure of DNA in *Nature*. By the end of the 1950s, all of pharmaceutical science had been transformed by a concatenation of new instruments and new technologies - from GCs to X-ray diffraction, from computers to tissue culture - coupled, perhaps most importantly, to a new understanding of the way things (meaning cells, meaning bodies) worked. The understanding of DNA's structure and function - how proteins are designed and how they can cause disease.

1960s: People became aware that pills could not only influence their health but also their lives. Pharmaceuticals like contraceptives had brought about changes in society which culminated in an era remembered as a social revolution. The technology of drug discovery, analysis, and manufacture also proliferated. New forms of chromatography became available, including HPLC, capillary GC, GC/MS, and the rapid expansion of thin-layer chromatography techniques. Proton NMR was developed to analyze complex biomolecules.

1970s: The war on cancer had begun. In 1978 the cancer suppressor gene P53 was first observed and by the end of the decade bone marrow transplants together with

chemotherapeutics had become available. The implementation of computers in life science put the instrumentation in place for the rational drug design of the next decades.

1980s: Instead of an empirical “try and see” method, pharmaceutical designers began to look for the cause of the illness on the protein level. The term “target” for a protein causing medical disorder became popular. With computer assisted techniques chemists started to design ligands to fit to these “targets”. Finally with the development of combinatorial chemistry thousands of organic compounds became available for screening for biological activity.

1990s: Miniaturisation of robotics and computers allowed manipulation of thousands of samples and processing the information gained thereof in short time. High-throughput processes became state of the art. Especially the screening processes saw an enormous progress not only in instrumentation but also in techniques like fluorescence labelling and micro array scanning. The knowledge on disease underlying causes started to grow exponentially with initiatives like the Human Genome Project and studies of the proteome. Bioinformatic tools were put into place to process the vast amount of information and to recognise patterns within the data.

At the same time traditional antibiotics began to lose their power due to resistances in bacteria and the ongoing battle against AIDS had proven the failure of technology to master some of its problems.

The growing cost of cutting-edge research and a new economic climate lead to mergers and a consolidation in pharmaceutical industry.

1.1.2 Medicinal Chemistry

The term “medicinal chemistry” is used in a very broad sense. It means the application of chemical research techniques to the design and synthesis of pharmaceutical compounds. It also includes the study of existing drugs, their biological properties, and their structure-activity relationships. It is a scientific discipline at the intersection of chemistry and pharmacy. The focus on development of new drug compounds has resulted in the incorporation of many other disciplines, such as biochemistry, computational chemistry, molecular biology, statistics, and physical chemistry. Medicinal chemistry comprises three principals: The first step of drug discovery involves the identification of new active compounds, often called 'hits'. These 'hits' can come from non-natural or natural sources, and

are typically found by screening many compounds for the desired biological properties. The second step of drug discovery involves the synthetic modification of the 'hits' in order to improve the biological properties of the compounds. The structure-activity relationships of the pharmacophore play an important part in finding 'lead compounds', which exhibit the optimum in potency, most selectivity, and least toxicity. The final step involves the rendering the 'lead compounds' suitable for use in clinical trials. This involves the optimization of the synthetic route for bulk production, and the preparation of a suitable drug formulation.

With Structure-Activity Relationship (SAR) the biological activity is correlated with synthetic modifications of the structure of interest. Through this comparison of biological assay results with structure an iterative process of structure optimisation is set off. To predict which modification in the molecule might improve its mode of action; rules like the *Lipinski's Rule of Five*[4] as well as computer based models are being used.

Lipinski's Rule of Five:

-not more than 5 hydrogen bond donors

-no more the 10 hydrogen bond acceptors (notably N and O)

-molecular weight under 500

-LogP under 5

1.1.3 Combinatorial Chemistry

The pharmaceutical industry depends on the generation of new drugs. Leading companies state that the average 0.5 drug registrations per year and pharmaceutical company will not be enough to sustain the economical growth of these firms[5]. But the drug discovery process is also devoted to the identification of compounds that cure or help to treat diseases. Welfare is one of the main goals of public authorities, which are the investors for academic research. One way or the other there is pressure to increase productivity. The past decade has seen tremendous progress in many of the different aspects of the drug-discovery process. These aspects include the development of combinatorial chemistry technologies, the implementation of high-throughput screens and bioinformatics tools, the sequencing of the human and other genomes, as well as the integration of functional genomics platforms[6]. Combinatorial Chemistry is a set of techniques for creating a multiplicity of compounds and analyse them for activity. The idea is to form large "libraries" (a number or collection of compounds) instead

of synthesizing compounds one by one, as has been done traditionally—and to identify the most promising “lead” (compound with biological activity) by high throughput screening. Combinatorial chemistry can also be described as the industrialization of chemistry; the chemistry has not changed, just the way in which it is carried out, which is principally by exploiting instrumentation and robotics coupled to the extensive use of computers to efficiently control the process and analyse the vast amounts of resulting data. Combinatorial chemistry was first conceived about 20 years ago. Initially, the field focused on the synthesis of peptide and oligonucleotide libraries on solid phase. Even though the first examples of polymer supported organic synthesis came out in the early 70s, it wasn’t until the 90s that people started to use this technique for synthesis of small molecule libraries. Prior to this small (up to 500 units) molecule libraries were made in solution, which meant a strong limitation in library size.

In solid-phase synthesis, the compounds being made are attached (through a linker) to an insoluble, functionalized, polymeric material (usually beads), allowing them to be readily separated, (by filtration or centrifugation) from excess reagents, soluble reaction by-products or solvents.

There are two approaches of producing high numbers of compounds. One is parallel synthesis, where after each step in the synthesis the product is portioned and submitted to the next step. The other way producing even higher numbers of library members, is the split-and-mix method. The solid support is divided into portions, each of which is subjected to reaction with a single reaction partner. In contrast to the first method, these portions are recombined which results in a single batch of solid support bearing a mixture of components. Repetition of the divide/react/recombine processes results in a library, in which each discrete particle of solid support carries a single library member. To identify members of a combinatorial bead-based library, an encoding strategy is necessary. An analyte is associated with each member of the combinatorial library. This is often achieved by the use of tags attached to the beads on which the library members are assembled, which allows the reaction history of each bead to be determined. The last decades have afforded various encoding strategies[7]. There is spatial- and graphical encoding, chemical-, spectrometric- and electronic encoding just to name a few.

Initially the focus in library production was set on numbers of compounds and not on qualitative aspects of the products. The idea was that first a hit, say a compound with some activity, had to be found. Further target oriented synthesis would yield leads. Although rendering many new potential biological target molecules, this route of industrialising the

drug-discovery process failed, however, to deliver the number of lead compounds required to maintain the necessary productivity of pharmaceutical R&D[5,8]. The efforts aimed at increasing the output of lead compounds relied too strongly on a quantitative increase of compounds to enter the screening process, while qualitative aspects were neglected[9,10,11].

1.1.4 Natural Product-like Compounds

Natural products play an eminent role in the discovery and development of new drugs[12,13,14,15]. Over half of the nearly 1000 small-molecule drugs introduced on the market over the past two decades are either natural products or in some way related to natural products[16].

Nature provides us with a vast pool of highly potent compounds. According to evolutionary theory, each species is optimally adapted to life in its environment, leading to a highly diverse system. Only the best organisms can survive and, eventually, the ones functioning better will supersede them. Yet, the basis of all biological function resides in the molecules that organisms are built of. The ever ongoing selection of the best adapted species can be viewed, in the given context, as the largest possible effort on this earth towards the synthesis of new molecular entities followed by their screening for biological usefulness, ultimately resulting in a pool of highly potent and diverse compounds. It is not surprising that humans have tapped into this pool of compounds in their quest for cures, from the times of ancient cultures to modern medicine[13]. On the other hand, one of the recurrent drawbacks associated with natural products is a limited access to the material. Isolation of sufficient quantities from natural resources is often not possible, and chemical synthesis is usually a lengthy and low-yielding process. The benefit of high chance for success is often made up for by high costs.

Even though every natural product should be considered a potential lead compound, it’s not certain that a target in another biological system is found. Genes are conserved throughout nature and so are the resulting protein structures. The chances of a natural product binding exactly to a human or bacterial target are therefore intact. The chance for “a close fit” – a molecule with poor binding properties - is even higher. Due to posttranslational modifications of proteins even a conserved gene results in two different but similar proteins in two different species. It’s an obvious idea to alter the natural product in a combinatorial manner to regain the uniqueness lost by modifications between species.

In light of all this, the synthesis of large numbers of compounds that are based on a naturally occurring structural motif with demonstrated biological activity is an appealing idea. This

provides the process of lead identification with a starting point that has a likelihood of producing compounds with natural product-like activities, and all compounds with interesting activity are definitely accessible through chemical synthesis.

1.1.5 Natural Products in Chemical Genomics

Natural products have evolved to interact with biomolecules, which is why so many can be found in pharmacopoeias. However, the cellular targets and modes of action of these fascinating compounds are seldom known, hindering the drug development process. The need for tools identifying cellular receptors, thereby generating protein / ligand pairs is obvious. By this way new drug targets can be validated and new biologically active small molecule scaffolds will be found in an iterative process.

Chemical genomics is a set of tools for the industrial scale analysis of many proteins and their interactions, over time, ultimately tying this into physiological processes and biological pathways and networks. Chemical genomics involves exposing cells to libraries of small molecules selecting a molecule that induces a phenotypic change of interest. If possible the protein involved in this phenotypic change is then identified. In reverse chemical genomics a protein of interest is screened against a library of compounds searching for the best binding partner. The ligand found is then added to cells to observe the predicted phenotypic change. This approach is analogous to reverse genetics, in which a gene is deliberately mutated or knocked out in order to study the resulting phenotype. Chemical proteomics aims at directly finding a binding protein using visualization by a tagged small molecule. The tag can either consist of a radioactive label, to allow visualisation of bound proteins on an electrophoresis gel, or a solid phase bead, to allow affinity purification of proteins.
Chemical genomics have proven to be a very powerful tool in identifying new cellular targets and modes of drug action. These techniques can be used to identify a drug's receptor and its corresponding gene, thereby completing the gene-protein-ligand trinity. The successfulness of such screening methods depends strongly on the qualities of the small molecule compounds used. Natural products and natural-product analogs have proven especially successful in this setup.[11]

1.1.6 Diversity Oriented Synthesis with Natural-Products

A further recent development is the concept of diversity-oriented libraries. Diversity-oriented synthesis (DOS) is a skilful approach towards generating a large number of different molecules and, at the same time, introducing a maximal degree of structural diversity into the library[17,18,19]. DOS aims to create a broad distribution of compounds in chemistry space, where each dimension in space is defined by a value of a descriptor. Descriptors can be of a biological or chemical nature and are either computed or measured. If a natural product is used as a starting point for combinatorial chemistry, not a maximal degree of structural diversity is achieved but rather focused libraries are made. Such an approach could be described as population of chemical space in close proximity to a given natural product. The degree of structural diversity is not as high as in DOS but the quality of the structures can be higher.

In view of the difficulties encountered on the way to lead compounds, diversity-oriented, natural-product-like libraries appear to be an ideal approach for the generation of high-quality structures. By combining positive features from several different areas, such libraries are expected to add value to the lead identification process (Figure 1.1).

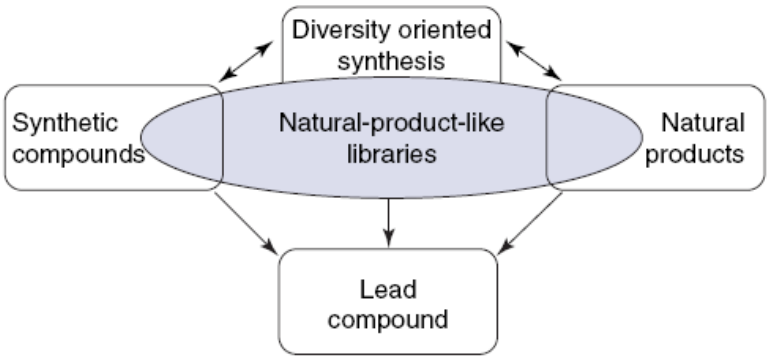


Figure 1.1

Natural-product-like libraries bring value to the drug-discovery process by combining positive aspects from several different areas.

Because of the attractiveness of the concept, a significant effort has been devoted to the chemical synthesis of natural-product-like scaffolds and libraries over the past few years. A large number of chemical libraries based on motifs of natural compounds with proven biological and pharmaceutical activity (so-called privileged structures) have been reported. Similarity to natural products is ensured by synthesizing structurally diverse derivatives of privileged substructures[14,20,21,22] or hybrid structures[23,24], rather than arbitrarily chosen

scaffolds. The number of reports is rapidly increasing, and several reviews have addressed the topic of natural-product-like libraries[9,10,25,26,27,28,29,30,31].

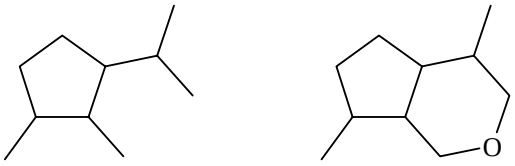
Non-aromatic polycyclic compounds hold the promise of a high structural, and hence functional, specialisation. The rigidity often invoked by the fusion of several rings leads to geometrically well-defined structures. A certain degree of flexibility required for receptor fitting is, on the other hand, ensured by the individual substituents attached to the rigid scaffold via rotatable bonds. Furthermore, such scaffolds usually imply the presence of several stereogenic elements, which are a fundamental parameter of DOS. Only in the past two years several examples of natural-product-like libraries that are based on fused polycyclic structural motifs have demonstrated the timeliness of this approach[32]

1.2 Natural Product Leads for this Work

Natural products have had a large impact on drug discovery. Many natural products, or derivatives thereof, are used in modern medicine. Furthermore, the large structural diversity of natural compounds has always served medicinal scientists as a source of inspiration in the search for new molecular entities with pharmacological activity.[33] The synthesis of natural product analogues, therefore, represents a key challenge for medicinal chemists. [23,24,34] In addition, combinatorial methods are increasingly applied for the generation of derivatives of natural products and natural product-like scaffolds. [9,25,26] During our work aimed at the synthesis of natural product-like scaffolds, we became attracted to a group of compounds belonging to the *iridoid* family (see Scheme 1.1). These tricyclic compounds, which have a common perhydrofuropyrane core, [35,36] possess a variety of interesting biological activities.

1.2.1 Iridoids[33]

The monoterpene subclass of the *iridoids* (Scheme 1.1) contains the iridane skeleton with a cyclopentane ring which is usually fused to a second six-membered oxygen heterocycle. The name derives from *Iridomyrmex*, a genus of ants that produces these compounds as a defensive secretion.



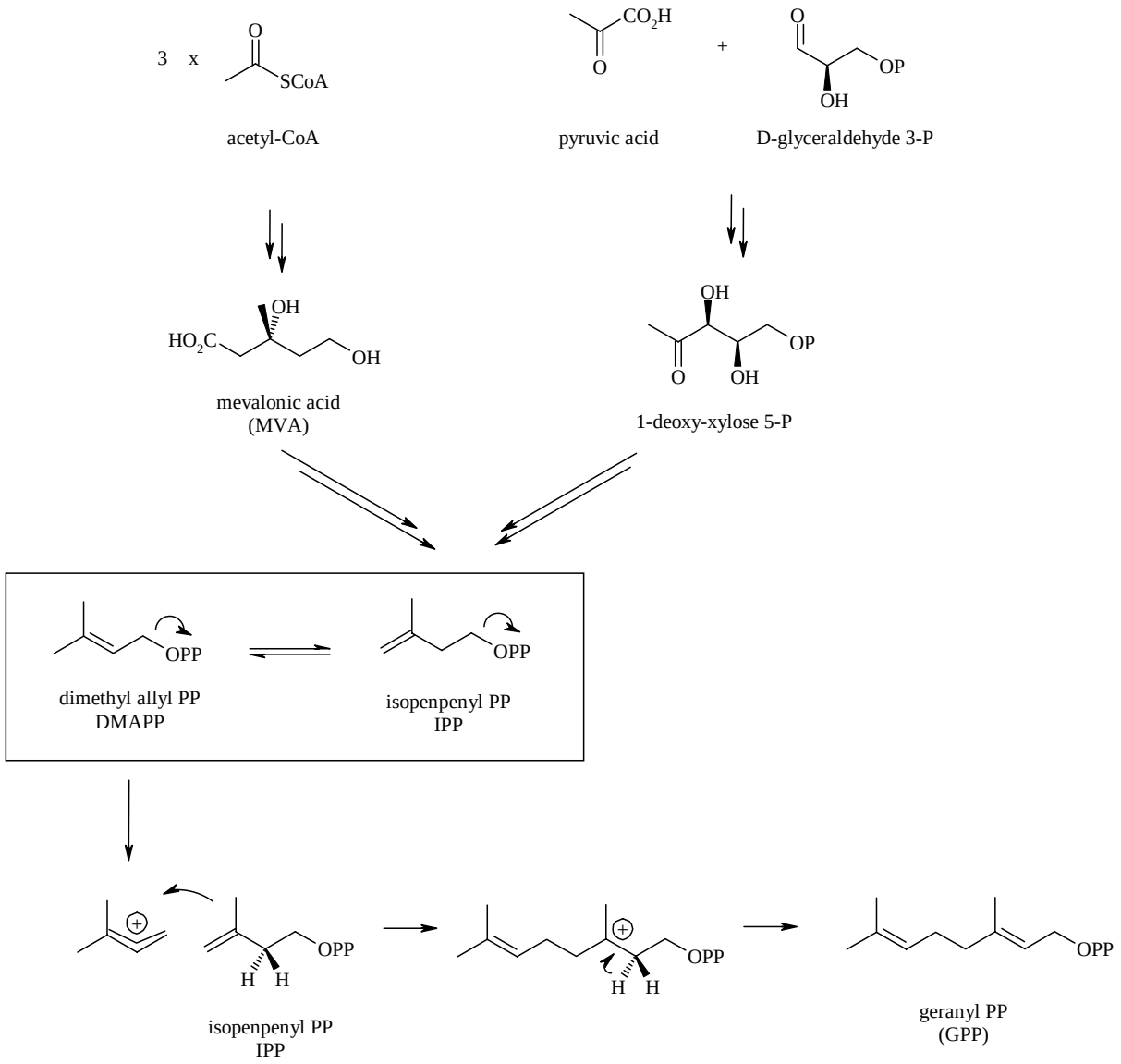
iridane iridoid

Scheme 1.1

Iridioids represent a subclass of monoterpenes containing a cyclopentane ring.

Monoterpenes are metabolic products of the mevalonate and deoxyxylulose pathways (Scheme 1.2). Mevalonic acid itself is a product of the acetate metabolism and is produced from three molecules acetyl-coenzyme A. 1-Deoxy-D-xylulose 5-phosphate is formed from pyruvic acid and glyceraldehyd 3-phosphate. Both intermediates are transformed in a convergent biosynthesis into isopentenyl PP (IPP). This is further isomerised into dimethylallyl PP (DMAPP), which represents together with IPP the key intermediate in

terpene biogenesis. The subsequent linkage of the two subunits IPP and DMAPP by the enzyme prenyl transferase leads to higher terpenes that are classified according to the number of C atoms they bear. Starting from hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpens (C_{15}) and diterpenes (C_{20}) on to stereoids (C_{18}-C_{30}) and carotenoids (C_{40}). The monoterpene precursor geranyl PP (GPP) is presumably synthesised from IPP and DMAPP by electrophilic addition. GPP is then further isomerized, oxidized or reduced to the alcohol geraniol.

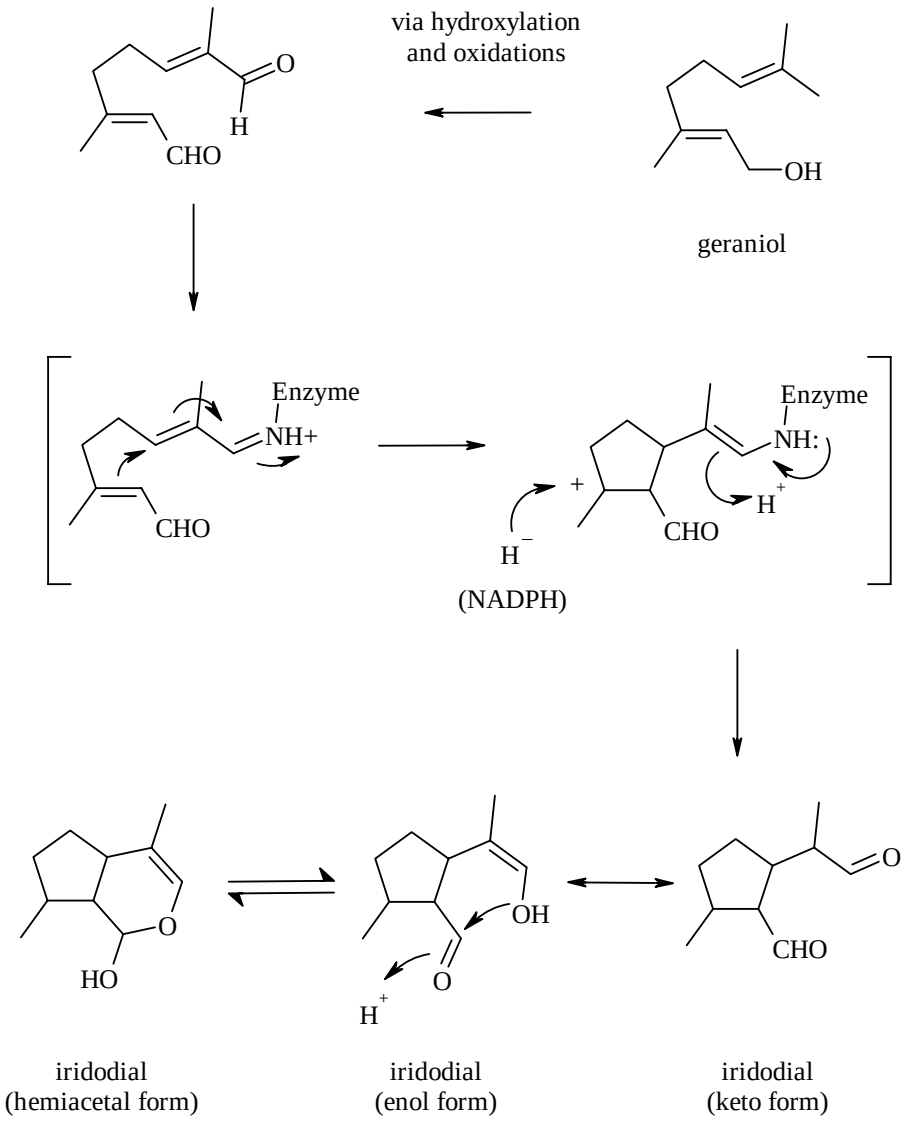


Scheme 1.2

Biosynthesis of geranyl PP from mevalonic acid or 1-deoxy-xylulose 5P over dimethyl allyl PP

The iridoid system arises from geraniol by a cyclisation to iridodial (Scheme 1.3), which was produced by a series of hydroxylation and oxidation reactions on geraniol. The cyclisation is

most likely enzyme assisted and goes through a Schiff base-intermediate. The thus formed iridodial is in equilibrium with its bicyclic hemiacetal form.



Scheme 1.3

Assumed endogenous synthesis of *iridoids*

Iridoids are sometimes further modified into secologanins or terpenoid indole alkaloids and find use in herbal drugs such as the Gentian root and the Valerian root.

1.2.2 Euplotin and ent-Udoteatrial-hydrate

The sesquiterpene euplotin and the diterpene udoteatrial hydrate are both of marine origin (Scheme 1.4). Euplotin is a secondary metabolite from the ciliate *Euplotes crassus* (Table 1.1) and was shown to inhibit the cell division of or kill the related marine ciliates *E. vannus* and *E. minuta via* cell-to-cell encounter. The species gains though this a competitive advantage over its close relatives[37]. Udoteatrial hydrate has been isolated from the green algae *Udotea flabellum* (Table1.1) and has moderate antimicrobial activity against *Staphylococcus aureu*s and *Candida albicans.*[38]

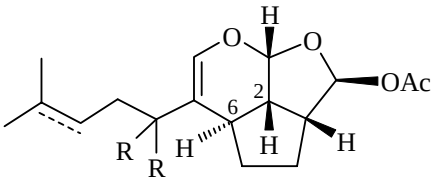
Euplotes crassus

Udotea flabellum

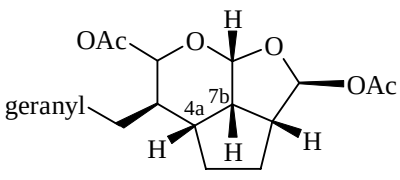
Table 1.1

Marine species known to produce biologial active compounds

The absolute configuration of udoteatrial has been determined by Isoe et al.[39] These more recent studies[40,41] revealed significant *in vitro* cytotoxicity against human carcinoma KB and A-549 by synthetic antipodes of udoteatrial.



euplotin A and B: R,R =O
euplotin C: R,R = H,H



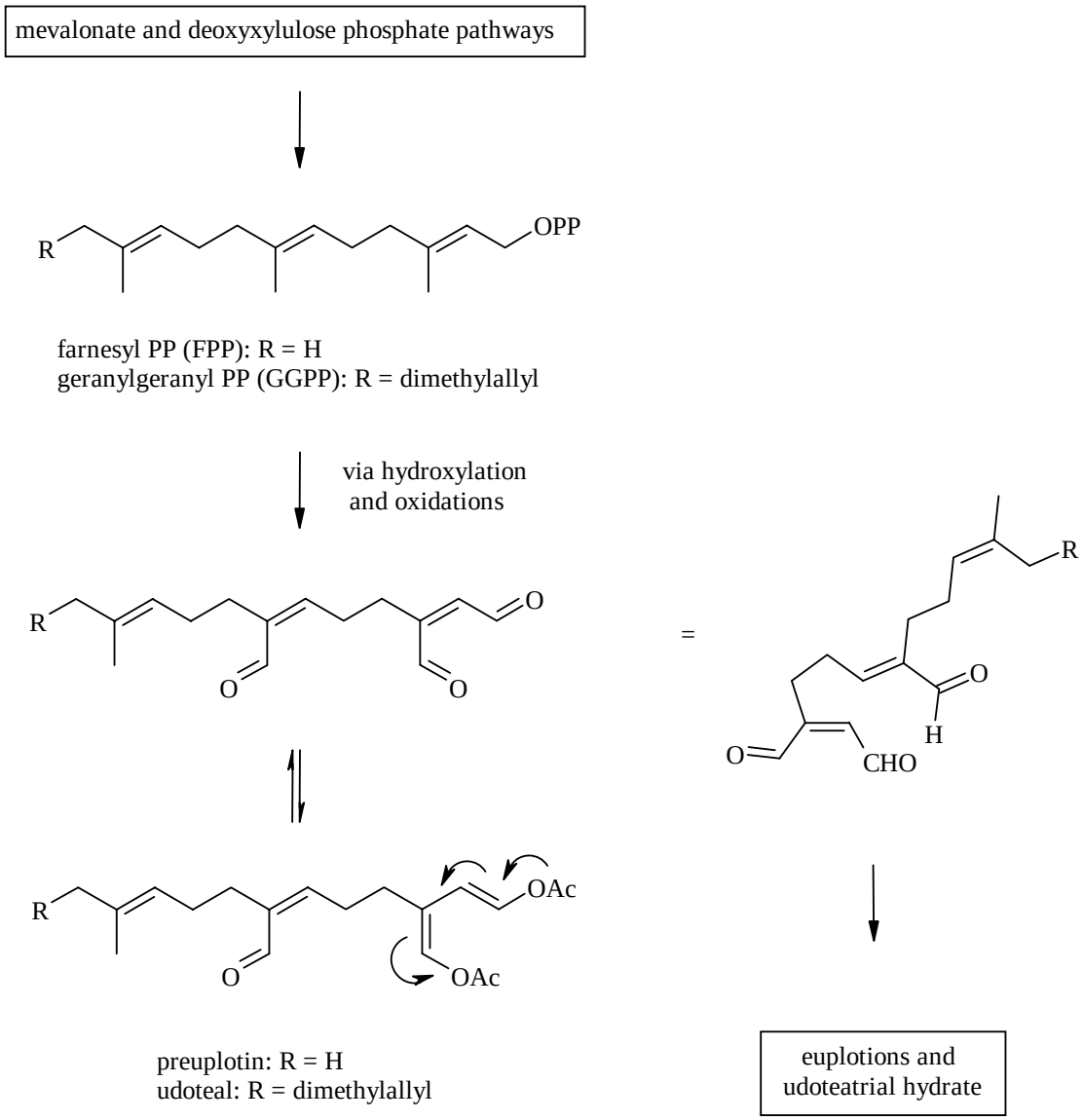
ent-udoteatrial
α- and β-acetates

Scheme 1.4

Euplotin and ent-udoteatrial acetates

Furthermore, the activity of these *ent*-udoteatrial acetates was discovered to depend on the structure of the geranyl side chain.

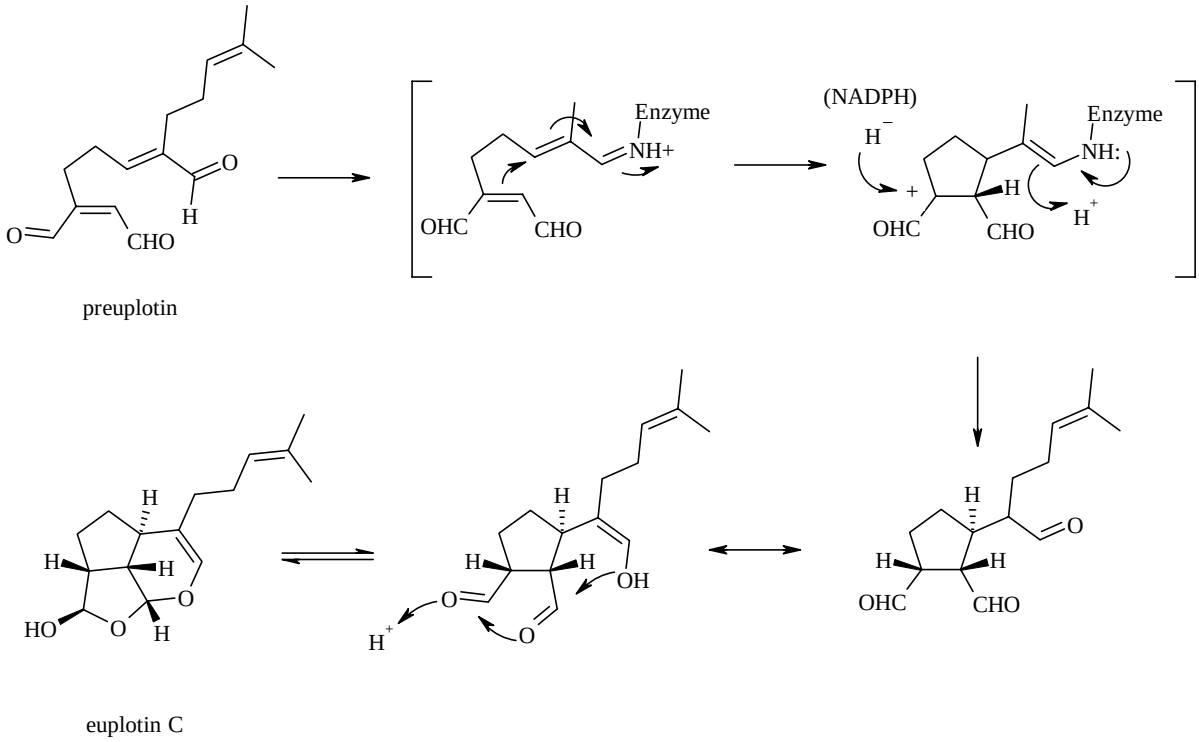
In the case of euplotin and the natural udoteatrial-hydrate similar putative terpenoid precursors were found. [37,38] preuplotin as well as udoteal are very likely to be intermediates in the biogenic synthesis of these natural triacetates and show the typical farnesyl- and geranygeranyl motif of sesquiterpens and diterpenes respectively (Scheme 1.5). They are most likely products of the mevalonate and deoxyxylulose pathways described earlier. Hydroxylation- and oxidation steps similar to those in the *iridioid* biosynthesis followed by acetylation of the resulting trials would explain the occurrence of such metabolites.



Scheme 1.5

Farnesyl and geranylgeranyl precursors of euplotin and udoteatrial hydrate respectively

This leads to the assumtion that preuplotin and udoteal go through the same enzymatic cyclisation as the proposed hydroxylation- and oxidation-product of geraniol (see above). Evidence for this assumption is the natural occurrence of udoteatrial.[38] Based on biosynthetic hypotesis by Pietra et al[37c] and an assumed analogy to the process involved in Iridodial hemiacetal formation the endogenous synthesis shown in Scheme 1.6 could be proposed.



Scheme 1.6

Assumed endogenous synthesis of euplotin

The fact that in the euplotins the centers 2 and 6 are *trans*-configured (see Scheme 1.4) is very remarkable. The ring system is therefore very constrained and an intermolecular acetalisation in the laboratory by the same pathway should be difficult. In the case of udoteatrial hydrate the configuration on the centres 4a and 7b is *cis*, so if the cyclisation goes through the same Schiff base intermediate it is not catalysed by the same enzyme activity.

1.2.3 Plumericin and Allamandin

Plumericin was first isolated in 1951 by Little and Johnstone[42] from the roots of *Plumeria multiflora,* a plant found in Kongo but also known in central America by the name *Flor de*

Mayo. Along with its assumed precursor plumeride, the isomer isoplumericin and other structurally close related compounds plumericin was subsequently also found in the roots or the bark of many other species of *Plumeria* like in *Pl. acutifolia, Pl. rubra* or *Pl. alba*. *Plumeria* belonging to the plant family *Apocynaceae* can be found in tropical habitats all around the world (Table 1.2).

Allamandin, allamandicin and allamdin are very close structural relatives of plumericin and were first found by Kupchan et al[43] in *Allamanda cathartica* also belonging to the family of *Apocynaceae.* Always together with plumericin other *Allamanda* species like *Al. neriifolia*, *Al. acutifolia* or *Al. schottii* contain allamandin, allamandicin and closely related iridoids, too (Table 1.2).

Plumeria rubra

Plumeria alba

Plumeria acutifolia

Allamanda cathartica

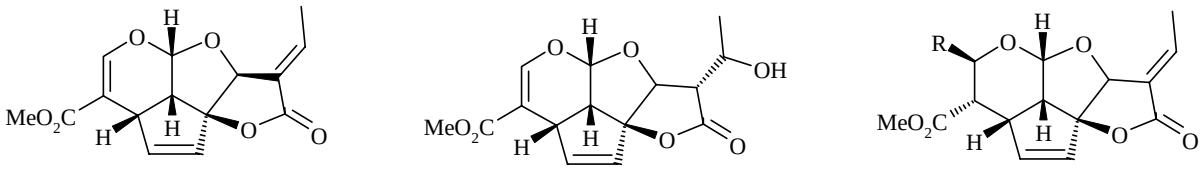
Allamanda schottii

Allamanda neriifolia

Table 1.2

The roots or the bark of various species of plumeria and allamanda contain biologically active ingredients.

Plumericin, allamandin, allamadicin and allamcin have been reported to possess bioactivity towards KB Tissue culture[43]; *brine shrimps*, 9KB cells and 3PS cells[44]; P388 and KB cancer cells[45]; monoamine oxidase B (MAO-B)[46]; RS321 *yeast* strain cells[47] in numerous studies.



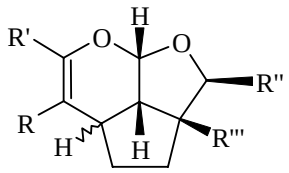
plumericin | allamandicin | allamandin: R = H
acetylallamandin: R = Ac

Scheme 1.7

Structures of plumericin, allamandicin and allamandin

Plumericin, allamandin and allamandicin are all registered compounds undergoing clinical trials (NSC-112152, NCS-251690 and NSC-251691 respectively) at the National Cancer Institute.

Further bi- and tricyclic *iridoidal* structures like (+)-genipin[48], duroin[49] or aucubigenin[50] all show interesting biological activities, too. All of these examples indicate not only the wide abundance and usefulness of this type of structural motives in nature but suggest the existence of an optimal adoption towards interaction with biological systems.
The natural compounds described show a remarkable structural resemblance. They all consist of a tricyclic dioxa-cyclopenta[c,d]indene scaffold (Scheme 1.8) containing a acetal or triacetal function. Except for euplotin the three rings in the scaffold have the exact same stereochemical configuration.



Scheme 1.8

Common structural features in natural product leads

1.2.4 Synthetic Approaches to the Natural Product Leads

Several examples of total- or partial syntheses of the natural products described have been realised over the years.

Euplotin A: Funk and Aungst[51] showed the construction of euplotin A by an intramolecular hetero-*Diels Alder* reaction of a dihydrofuran moiety with a (*Z*)-2-acyl-2-enal through an *exo*

transition state. The thus achieved connection of the ring system is, as noted earlier, remarkable for the system is very constrained. Nevertheless in their work the cyclisation is *exo*-selective.

Udoteatrial: Starting from a bicyclical ketone with given stereochemistry Whitesell et al.[52] use a ozonolysis step to obtain a trial which forms the desired cyclic mixed acetal system. Isoe et al[39] reported the synthesis for *ent*-udoteatrial starting from (+)-genipin.

Plumericin and Allamandin: In a biomimetic approach, Trost B. et al[53] started from the same ketone as Whitesell et al.[52] in their udoteatrial synthesis; but they use a periodate oxidation followed by basic treatment to get the tricyclic ring system. Starting from plumericin the same authors found a way to further modification of allamandin.

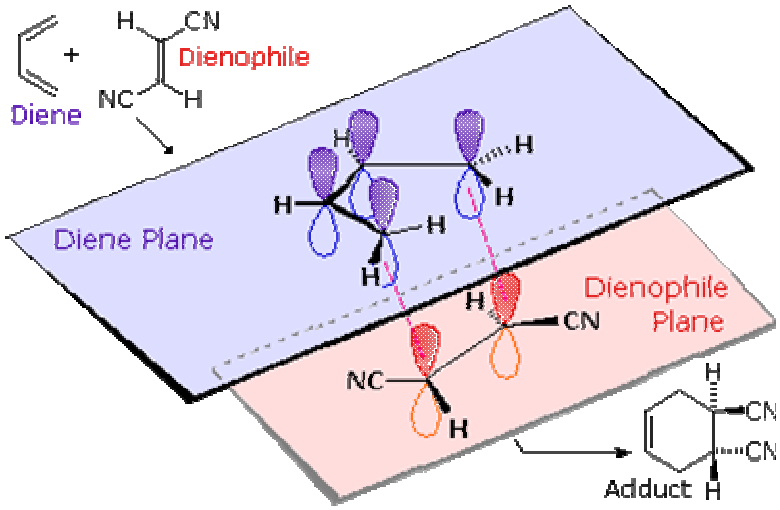
Due to the complexity of these natural products, the total syntheses are rather long and tedious.

1.3 Synthetic & Technical Aspects

1.3.1 *Diels Alder* Reactions

As demonstrated in the work of Funk and Aungst[51] ring bearing compounds like the natural products mentioned are accessible through *Diels-Alder* reactions. The *Diels-Alder* (DA) reaction, discovered by Otto Diels and Karl Alder[54] in 1928, has been a cornerstone in organic chemistry. The various types of DA reactions have continued to further develop and their spectrum of applications is enormous.

The DA reaction is a concerted addition reaction of a conjugated diene to an alkene (the dienophile) to produce a cyclohexene. This reaction belongs to the class of pericyclic reactions and is known as [2+ 4] cycloaddition, which is characterized by the formation of a ring by bond formation (orbital overlap) of two π-electrons of one reactant and four π-electrons of the other. Such reactions tend to be electronically favoured because the transition state involves six circularly delocalized π - electrons, much like in benzene. It has, therefore, aromatic character and is particularly stabilised. [2 + 2] and [4 + 4] cycloadditions in comparison tend to be much slower. The DA reaction is a concerted process (Scheme 1.9). In concerted reactions, bond making and bond breaking occurs simultaneously. Due to that reaction mechanism, no intermediates are observed.



Scheme 1.9

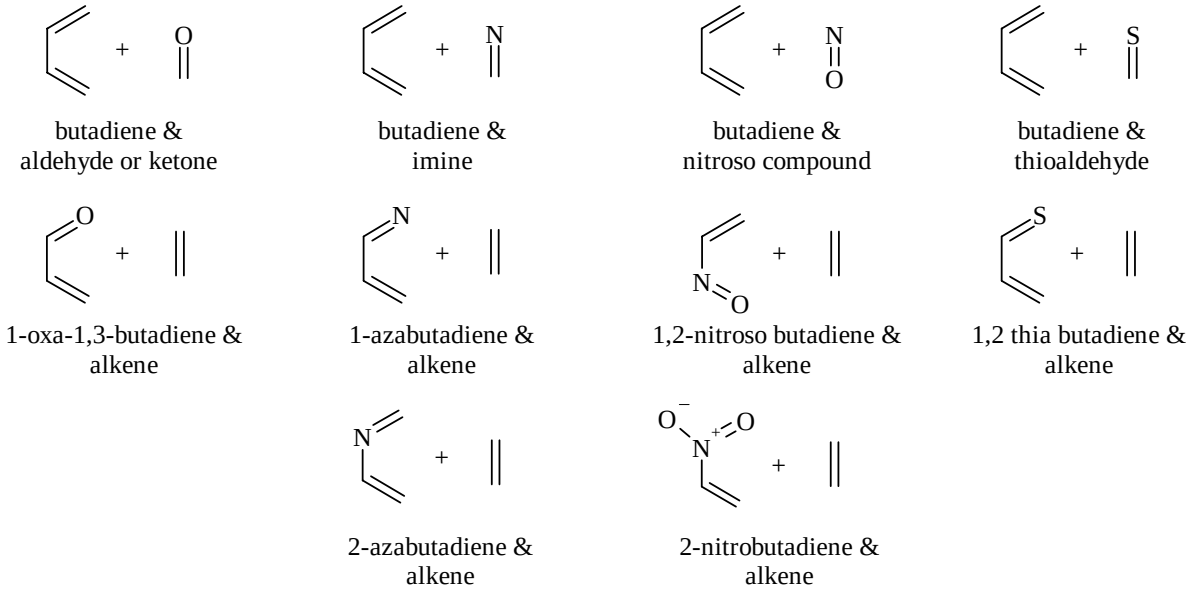
Representation of the 2+4 cycloaddition mechanism

As in most pericyclic reactions coulombic forces (like solvent polarity) have little effect on the reaction rate. The major factor influencing reactivity is the size of frontier orbital interaction.[55]

The high degree of regio- and stereoselectivity makes the *Diels-Alder* reaction a very powerful reaction. If the DA reaction involves asymmetrically substituted Ene-Diene Pairs **regioselectivity** is observed in a lot of examples. Both regioselectivity as well as the rate of these reactions can be explained by frontier orbital theory.[55] Each reaction partner possesses a set of molecular orbitals. The one molecular orbital still filled with electrons which is highest in energy is called the highest occupied molecular orbital (HOMO). The orbital with the next higher energy, being unoccupied, is called the lowest unoccupied molecular orbital (LUMO). As in ionic, radical and photochemical reactions, one reaction partner provides the HOMO, the other the LUMO. The smaller the energy gap between these two orbitals, the larger the overlap (gain of stabilisation in the product) and thus the faster the reaction. If in a DA reaction the diene provides the HOMO and the dienophile provides the LUMO the reaction is called a DA reaction with **normal electron demand**. The opposite is called a DA reaction with **inverse electron demand**. Due to secondary electronic effects, the DA reaction is often very selective in its stereochemical outcome. The bonding or antibonding overlap of two or more orbitals not involved in bond formation can lead to a lower or higher transition state. Depending on the situation, ***endo***- or ***exo***- conformation of the diene to the dienophile is preferred.

1.3.2 Hetero-*Diels Alder* Reactions

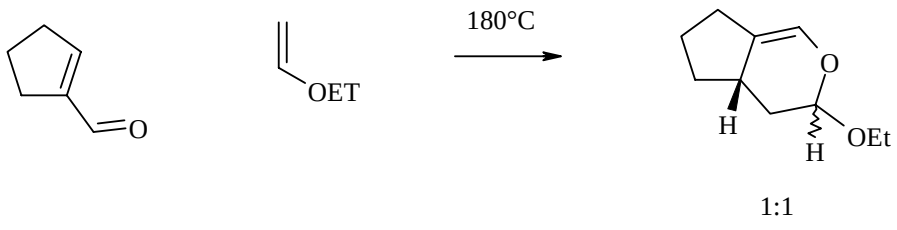
DA reactions are not limited to all carbon ene-diene pairs. A large number of so called **hetero-*Diels-Alder* (HDA)** reactions are known. The hetero-*Diels-Alder* reaction is one of the most important reactions for the construction of heterocyclic six-membered rings.[56,57,58,59,60] Its concerted character allows the selective formation of up to three stereogenic centers in a single reaction step. Some examples of *Diels-Alder* reactions involving a heteroatom are given below (Scheme 1.10).



Scheme 1.10

Some examples of HDA reaction partners

HDA reactions involving an oxygen bearing diene or a dienophile are called oxa *Diels-Alder* reactions. The oxygen atom among the reaction partners is either present in an aldehyde / ketone or in a oxa-1,3-butadiene. In the later case the oxa-1,3-butadiene provides the LUMO and therefore the reaction is a HDA reaction with inverse electron demand. The reaction between α,β-unsaturated aldehydes and ketones with electron rich (high HOMO) species like enol ethers, thioenol ethers, ketene acetals, enamines, alkynylethers, ketene aminals, yneamines, as well as selected simple alkenes gives an excellent access to substituted 3,4-dihydro-2H-pyrans[61]. Cycloaddition of ethyl vinyl ether and cyclopentene carbaldehyde for instance gives a 1:1 mixture of 3-ethoxy-hexahydro-cyclopenta[*c*]pyrans[62] (scheme 1.11) which was used for the synthesis of *iridoids.*

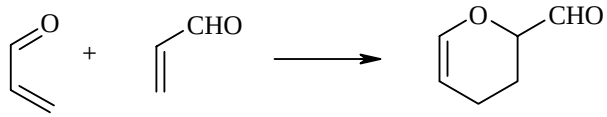


Scheme 1.11

Example of a 3,4-dihydro-2H-pyran synthesis

The DA reactions with oxabutadienes usually show a high **regioselectivity**, which can be further enhanced by the presence of Lewis acids. The reason for this lies in the coefficients of

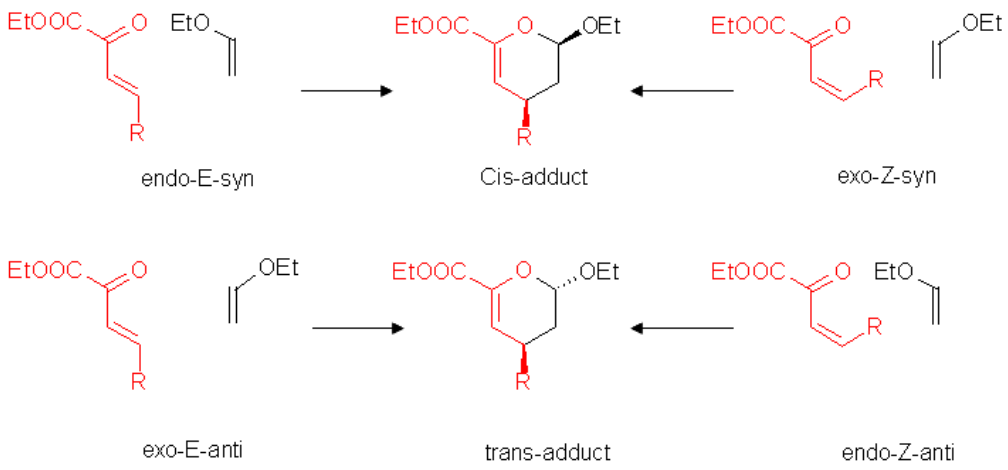
the atomic orbitals making up the whole molecular orbital. In summary the explanation for regioselectivity is that the coefficients of the atomic orbital of unsymmetrical diene - dienophil pairs are not equal at each end as they are in symmetrical cases. Therefore the frontier orbitals are polarised. Again, as outlined above, maximum stabilisation and gain in energy upon bond formation is achieved, if the difference in energy of the orbitals overlapping is smallest. That means orbitals with similar coefficients will undergo bond formation more likely. This explains why in the dimerisation reaction of acrolein only one regioisomer is formed (Scheme 1.12). Lewis acids can change coefficient distribution in the molecular orbital by coordinating to a lone pair of the oxygen and by this way may increase or change regioselectivity.



Scheme 1.12

Regioselectivity in acrolein dimer synthesis

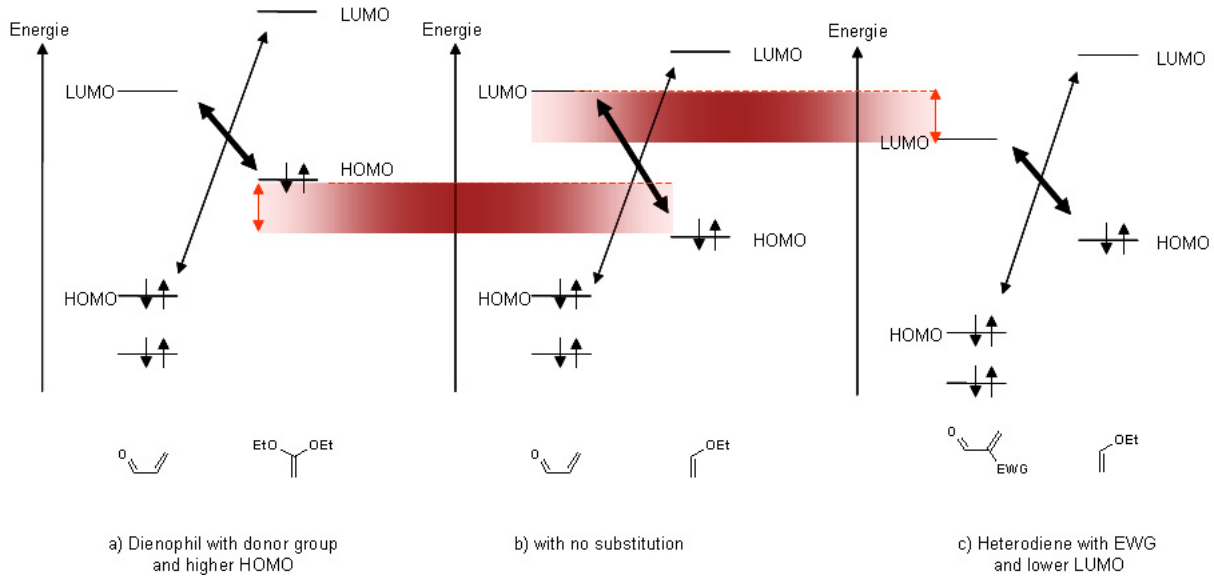
Because of this regioselectivity, the number of possible stereoisomers in HDA reactions is four. Depending on the configuration in the transition state, the *cis*- or the *trans*-adduct is formed. Scheme 1.13 containing only two of the four possible adducts shows that always two different possible transition states lead to the same conformation in the product. Of all possible transition states, one is often clearly favoured by secondary interactions as outlined above.



Scheme 1.13

Stereoselective outcome of oxa-HDA reactions

DA reactions can be very different from each other in activation energy. Some have high rates at room temperature already while other examples require high temperatures or even pressure to proceed. The rate depends mostly on the energy difference in HOMO-LUMO partners in the reactive species. The substitutions of the diene or dienophile have a major influence on these energies. In oxa-hetero-*Diels-Alder* reactions, electron withdrawing groups at the oxa-1,3-butadiene greatly enhance their reactivity by lowering the energy of the LUMO. The same thoughts count for the dienophile as well: electron donating groups raise the energy of the HOMO and increase reactivity. The effect of substituents on the relative energy distribution of HOMO and LUMO is graphically shown in the simplified scheme below (Scheme 1.14). Again Lewis acids can enhance these effects even further.[60]



Scheme 1.14

Influence of EWG (electron withdrawing groups) and donor groups on the frontier orbitals of oxa-HDA reactions with inverse electron demand

Because of the atomic orbital coefficients, the position of the substitution matters. Thus, in an intermolecular cycloaddition with benzylidenepyrazolone, ethyl vinyl ether reacts about 50 times faster than (*Z*)-1,2-dimethoxyethene and 1,1-diethoxyethene about 2000 times faster 1,1,2,2-tetramethoxyethene, 3000 times faster than (*E*)-1,2-diethoxyethene and 5000 times faster than (*Z*)-diethoxyethene.[63]

1.3.3 Solid Support Chemistry

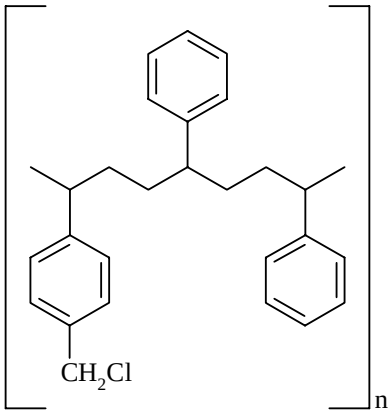
A solid support is a polymeric material decorated with functional groups for immobilisation of a molecule of interest. This immobilisation facilitates chemical operations and purification steps. The idea to use solid supports for chemistry was introduced by Merrifield[64] in 1966. While it was first used for peptide synthesis, the adaptation to nucleic acid synthesis and organic chemistry in general followed soon. To carry out a synthesis on solid support means a lot of advantages over classical methods:

- Reaction procedures are simplified. Time consuming purification and isolation steps are avoided. Reagents can be used in excess and the support bound product is filtered off and washed.
-Higher yields can be obtained by using excess of reagents. However, too large excesses can lead to side reactions.
-Possibility of automation.

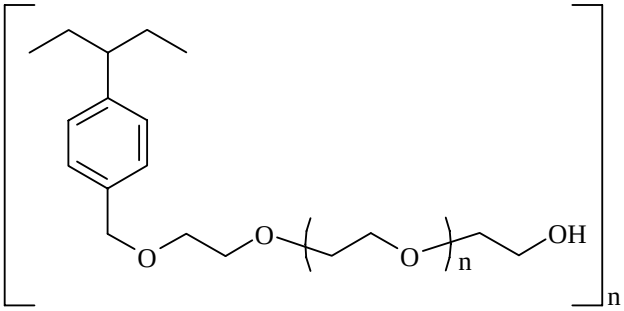
Especially the last point leads to the breakthrough of solid support chemistry. Today synthesizers for proteins, nucleic acids and small molecule libraries exist, saving time in otherwise repetitious work.

Over the years, a large number of different types of solid supports have been developed. They differ from each other by the polymer material the bead is made of and the linker type they carry. The most commonly used resin supports for solid phase synthesis (SPS) include spherical beads of low cross linked gel type polystyrene (1–2% divinylbenzene) and poly(styrene-oxyethylene) graft copolymers. A prominent characteristic of lightly cross linked **gel type polystyrene (GPS)** beads (Scheme 1.15) is their ability to absorb large relative volumes of certain organic solvents (swelling). This swelling causes a phase change of the bead from a solid to a solvent-swollen gel and therefore, the reactive sites are accessed by diffusion of reactants through a solvent-swollen gel network. In solvents, which swell the polymer well, the gel network consists of mostly solvent with only a small fraction of the total mass being polymer backbone. This allows relatively rapid access of reagents by diffusion to reactive sites within the swollen bead. In solvents, which do not swell the polymer, the cross-linked network does not expand and the diffusion of reagents into the interior of the bead is impeded. GPS has good swelling characteristics in solvents of low to medium polarity ranging from aliphatic hydrocarbons to dichloromethane. Polar, protic solvents, such as alcohols and water, do not swell GPS resins, and accessibility to all reaction sites may be compromised. Hence GPS supports are most suitable for chemistry performed in solvents of

low to medium polarity. **Poly(styrene-oxyethylene) graft copolymers (PEG)** also called TantaGel® resins (Scheme 1.15) consists of polyethylene glycol attached to cross-linked polystyrene through an ether linker. They combine the benefits of the soluble polyethylene glycol support with the insolubility and handling characteristics of the polystyrene bead. A disadvantage of PEG resins is the lower stability and lower functional group loading compared with GPS.



Cross-linked gel type polystyrene

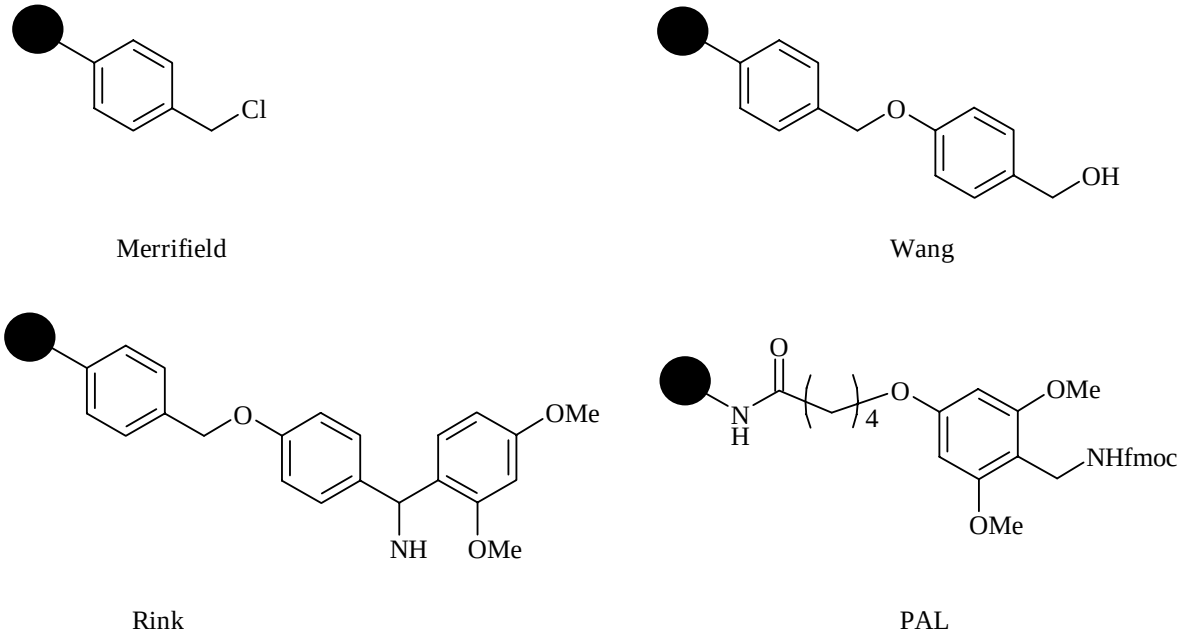


TantaGel resin onto a cross-linked polystyrene

Scheme 1.15

Typical solid phase synthesis polymers

The aspect of the linker (or anchor) is crucial. The linker determines what functional groups can be linked to the solid support and how the product will be cleaved at the end of the synthesis. The linker is a specialized protecting group and normally names the solid support (Scheme 1.16). The oldest linker principle is the **Merrifield**[64] based linker. It's simply a chloromethylated polystyrene. Another simple modification thereof is the **Wang**[65] resin, which consists of an activated benzyl alcohol. Both can be cleaved under acidic conditions. Two typical linkers for amino acid synthesis together with fmoc protection strategy are the **Rink**[66] and the Peptide Amide Linker (**PAL)**[67] resins. In both cases the electron donating methoxy groups on the benzylamine moiety allow for mild cleavage with TFA.



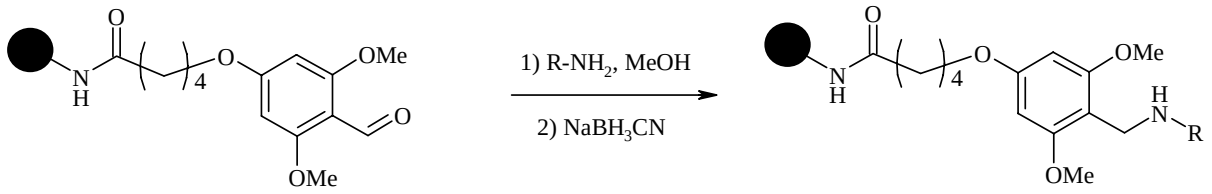
Merrifield Wang

Rink PAL

Scheme 1.16

Typical linkers used in solid phase synthesis

***N*-Substituted Pal** resins (Scheme 1.17) have also been prepared by reductive amination of the Backbone Amide Linker (BAL) resin using borohydride reagent like $NaBH_3CN$[68]. After cleavage from the support the N-substituting group stays on the product molecule.



BAL N-substituted PAL resin

Scheme 1.17

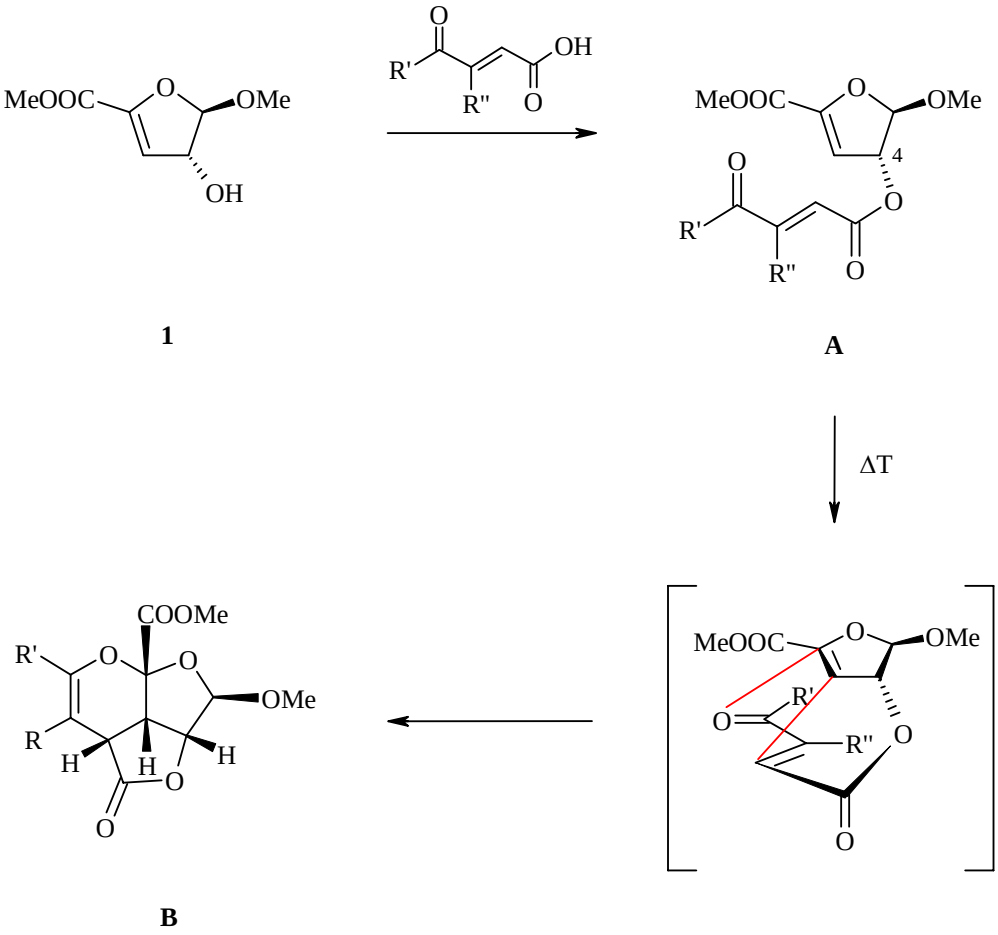
N-Protected PAL resin

All of the above examples of linkers except for the last are so called **traceless linkers**. The final compound reveals no trace of the point of linkage to the solid phase. Depending on the synthetic goal one or the other kind of linker is preferable.

The concept of a UV light cleavable linker[69] is highly attractive too, as UV light is only occasionally used in synthetic transformations, and there is consequently less chance of the library chemistry prematurely cleaved products from the solid support.

1.3.4 Construction of a Tricyclic, Natural Product-like Scaffold from D-(-) Ribose

The natural products (leads) described in chapter 1.2 are structurally very similar and share a common tricyclic core structure (see Scheme 1.8). A very closely related scaffold, in turn, should be accessible through an *intramolecular* hetero-*Diels-Alder* reaction of a simple, D-(-)-ribose-derived precursor **1** (Scheme 1.18). Linkage of an (*E*)-acylacrylic acid to **1** leads to an ester with predefined stereochemistry at C(4). Cyclisation of **A** would lead to only two possible stereoisomers if both *endo*- and *exo*-transition state occurred. Earlier work had shown the cyclisation to be completely *endo*-selective.[70]



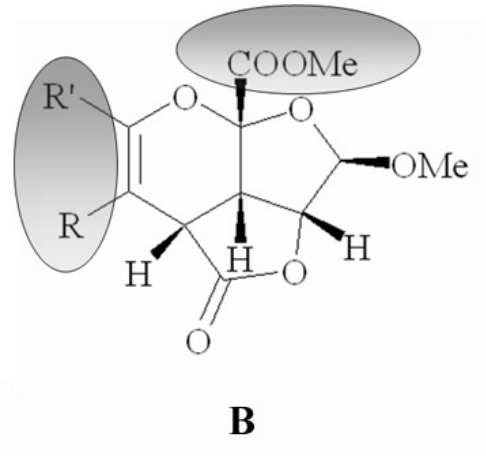
Scheme 1.18

Synthetic approach to a natural-product like scaffold

The analogies to the natural product leads are remarkable. With the exception of the C(6) position in euplotin all the stereocenters in the synthetic structure **B** are configured alike. **B** just differs from natural structures by the lacton and the methoxycarbonyl group. In some of the natural leads the enol ether double bond is found reduced. A feature that can be easily

addressed. In most of the lead structures substitution of the enol ether seems to be crucial. Especially the β-position seems to be very important. Ge et al[40] state that their synthetic *ent*-udoteatrial acetate without geranyl rest is much less cytotoxic to human KB cells relative to the true *ent*-structure. Also, a recent study by Pandey and coworkers[71] indicates the importance of substitution on the β-position of the enol ether in Plumeride.

In order to use this synthetic scaffold in a combinatorial or parallel synthetic manner, it is necessary to have a chemical point of immobilisation in hand, which allows for the use of solid support chemistry. The methoxy carbonyl group on **B** is an ideal onset to attach a linker for a solid support (Scheme 1.19).



B

Scheme 1.19

Potential regions of modification in scaffold B for the use in a combinatorial manner

1.4 Aim of the Work

The elaboration of a scaffold for combinatorial chemistry is the main topic of this work. It can be roughly divided into two issues:

Synthesis of a scaffold suitable for derivatisation in a combinatorial fashion

The scaffold should be accessible through an easy, selective and high yielding synthesis. Therefore, for each step in the synthesis the optimal conditions ought to be found. Especially the potential of the hetero *Diels-Alder* reaction or other cycloadditions to the chiral furanoside **1** should be investigated. The scaffold has to bare as many orthogonal points of diversity as possible allowing for a subsequent discrete derivatisation. The combinatorial modifications should be attached to the scaffold in positions indicating potential for activity relation. Therefore, the focus will be set on introducing functional groups to the pyran ring of the scaffold.

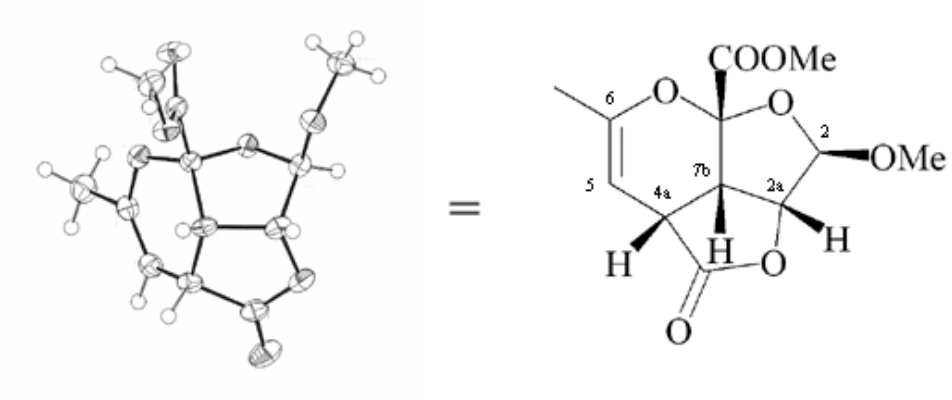
Development of a solid phase synthesis for the generation of natural-product like libraries

In order to be applicable in a solid phase synthesis the scaffold needs a point of attachment. In the case of N-protected PAL (Peptide Amide Linker) resins a carboxylic acid group is most promising. It should be in some distance to the scaffold otherwise sterical hindrance during the coupling step could occur. The scaffold is required to survive all the chemical conditions during the solid phase synthesis. In particular the stability of the acetal groups towards acidic conditions has to be sufficient. Reagents and conditions for the sequence of derivatisations on solid support have to be found. Finally one or several small test libraries shall be synthesized, purified and characterized.

2 Results and Discussions

2.1 Synthesis of Functionalized Scaffolds

The first synthesis of a molecular framework (shown in Scheme 1.18) was accomplished *via* intramolecular hetero *Diels-Alder* reaction as described in a preceding diploma thesis.[70] The scaffold introduced there, consists of a rigid tricyclic structure with definite stereochemistry, containing a double ketal/acetal structure, a γ-lactone and a methyl ester (Scheme 2.1). The first compound of this kind synthesized had a methyl group at C(6) position. This original derivative will be simply called "scaffold" in the ongoing text because it doesn't contain many functional features with potential to extend the structure at the same time conserving its tricyclic character, except for the relative unreactive methoxy carbonyl group and the enol ether.



Scheme 2.1

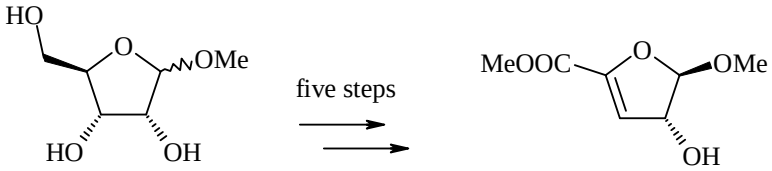
Natural-product like scaffold. Crystal structure of **4a** and schematic representation.

The positions C(5) and C(6) are, as stated earlier, the region of primary interest for further substitution. Substituents containing further functional groups should be introduced. Once functional groups were in place diversity oriented synthesis could then be carried out leading to a variety of C(5) and C(6) –substituted derivatives. Following the approach outlined in Scheme 1.18, one simple way to introduce further functionalisation into the scaffold is by using substituted acylacrylic acids in a later step, opening of the lacton by solvolysis or reactions involving the acetal centers of the tricycle could be envisaged, which would lead to

disintegration of the structure yielding new bi- or monocyclic structures. Such structures might also be of interest (see chapter 2.2).

2.1.1 Synthesis of 6-Alkyl or -Aryl Substituted Scaffolds

The precursors for the hetero-*Diels-Alder* reaction were readily prepared according to literature procedures. Following the method by Schmidt et al.[72], the dihydrofuranoside **1** was obtained in five steps from D-(-) ribose with an overall yield of 35% (Scheme 2.2). The synthesis can be easily carried out on the mol-scale.

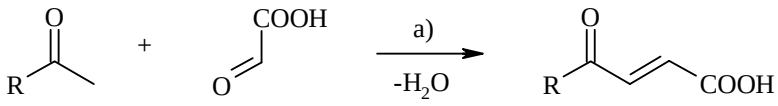


D-(-)ribose **1**

Scheme 2.2

D-(-) ribose derived furanoside **1**

The acylacrylic acids **2a-e** were either commercially available or prepared according to literature procedures.[73,74] Acids **2a-e** were exclusively obtained with *E*-configured double bonds.



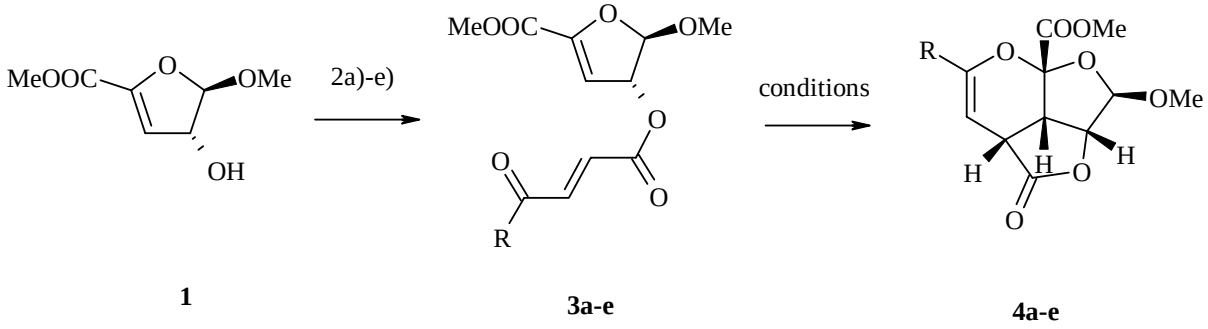
2a-e

Scheme 2.3

5-Subsituted acylacrylic acids. Reagents and conditions: a) either morpholine·HCl or AcOH, reflux, 4.5 h – 3 days.

The esterification of alcohol **1** (Scheme 2.4 and Table 2.1) with the different acids was best carried out *via* the mixed anhydrides obtained using pivaloyl chloride. Isolated yields of the esters **3a-g** varied between 60 and 80%. These esters were subsequently treated in high boiling aromatic hydrocarbons. Table 2.1 shows the tricyclic derivatives **4a-e** formed in the

cyclisation reaction. Yields were in the range of 50-70%. The two compounds **4d** and **4e** were not purified but directly used for further modifications. The stereochemical outcome of the hetero-*Diels-Alder* reaction was, of course, of particular interest. Based on the ^{1}H-NMR spectra of the crude materials, only a single diastereomer was formed in all reactions. Structural analysis (^{1}H-NMR *nuclear Overhauser* experiments) as well as x-ray structures of compounds **4a** and **b** revealed that the hetero-*Diels-Alder* reaction follows the same pathway as shown previously for the parent compound (see Scheme 1.18). Only if the substituents R of the (*E*)-acylacrylic ester are arranged *endo* to the sugar, the respective diastereomers are formed. The reaction proceeds, thus, with *endo*-*E*-selectivity as commonly observed in inverse electron-demand hetero-*Diels-Alder* reactions.[75,76]



1 **3a-e** **4a-e**

Scheme 2.4

6-Substituted scaffolds

	R	**3a-e** yield (%)[a]	**4a-e** yield (%)	conditions
a	methyl	61	53	o-xylene, reflux, 16h
b	phenyl	69	73	o-xylene, reflux, 5h
c	4-bromo-phenyl	67	45	o-xylene, reflux, 18h
d	3-nitro-phenyl	63	(96)[b]	toluene, reflux, 20h
e	4-nitro-phenyl	78	(99)[b]	o-xylene, reflux, 3h

Table 2.1

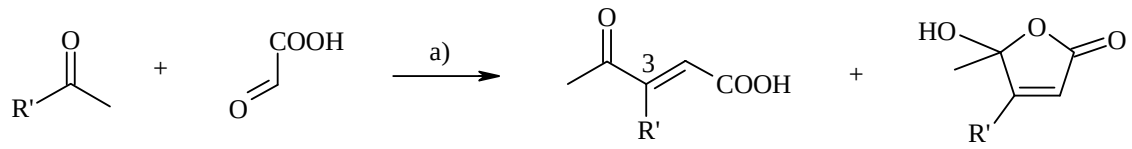
Hetero-Diels-Alder reactions of D-(-)-ribose derived acylacrylate ester. Reagents and conditions:[a] Et_3N, pivaloyl chloride, DMAP, 2h, 0°C. [b]Crude material was directly used in the next step.

In a recent report, Aungst and Funk[51] reported on the total synthesis of (±)-euplotin A using a hetero-*Diels-Alder* reaction as a key step in the synthesis. The stereochemical outcome, however, was different from the one observed here. The difference is most likely a result of the altered substitution pattern of the dihydrofurane, leading to changed steric and electronic parameters in the transition state. On the other hand, Kim and coworkers described an

analogous stereochemical course in an *intermolecular Diels-Alder* reaction between cyclopentadiene and a cyclic, sugar-derived dienophile.[77] Furthermore, we observed the same course in the intramolecular hetero-*Diels-Alder* reaction of acyclic allylic alcohols of acylacrylates.[78]

2.1.2 Synthesis of 5-Alkyl or –Aryl Substituted Scaffolds

To obtain scaffolds with substitutions at the C(5) position, access to the corresponding acylacrylates first had to be found. Aldol reaction under strongly acidic conditions led to the condensation products **2f-h** as shown in Scheme 2.5. Due to the harsh reaction conditions a ring-chain tautomerism[79] was observed. Unfortunately this method[80] gives only access to 3-alkyl- and aryl substituted acids. Efforts to apply the same conditions to the synthesis of 3-(2-butanone) or 3-ethyl-acetate substituted acylacrylic acids failed. Furthermore mixtures of (*E*)- and (*Z*)- configured acids were obtained in these cases. (*E*)- configuration was predominant, however.

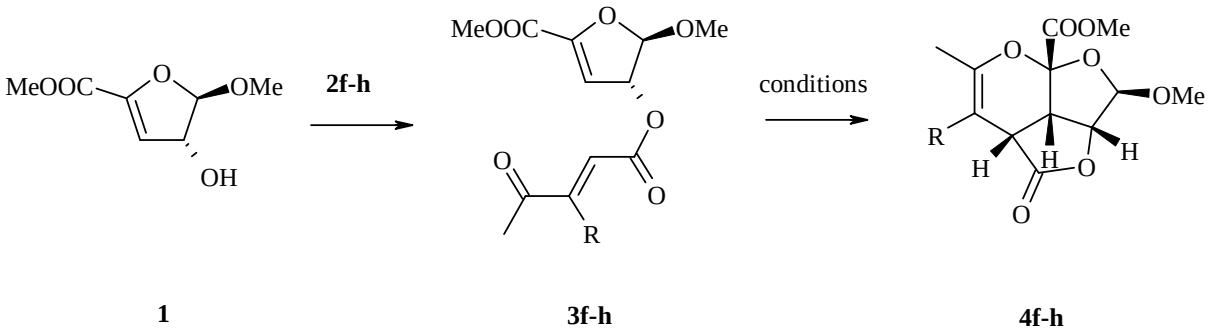


2f-h

Scheme 2.5

5-Substituted acylacrylic acids. Reagents and conditions: a) neat, H_3PO_4, 4 h 80-90°C, 18 – 24 h, rt.

The esterification of alcohol **1** with the acids **2f-h** (Table 2.2) was again carried out via the mixed anhydride obtained with pivaloyl chloride. The yields of the esters **3f-h** varied between 60% and 75% which is very similar with the reactions described previously (Table 2.1). These esters were subsequently treated in toluene or in a sealed steel autoclave at 170 °C. Table 2.2 shows the tricyclic derivatives **4f-h** formed in the cyclisation reaction. Yields varied between 25 and 40% and were; thus, lower than in the cases of **4a-e** (Table 2.1). This is due to a partial decomposition at 170 °C. The higher reaction temperatures are well in agreement with the σ-donor effect of the alkyl substituent on the dienes in the case of **3g** and **h.** Ester **3f,** on the other hand, reacts at considerable lower temperature due to conjugation of the diene with the phenyl group, which is lowering the HOMO.



1 **3f-h** **4f-h**

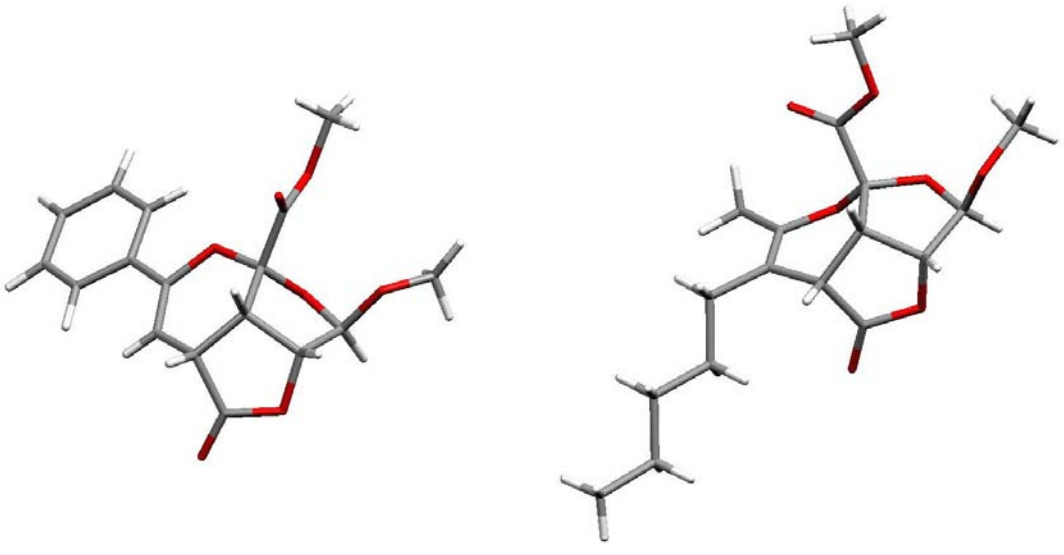
Scheme 2.6

5-Substituted scaffolds

	R	**3f-h** yield (%)[a]	**4f-h** yield (%)	conditions
f	phenyl	69	39	toluene, 100°C, 21h
g	benzyl	75	24	toluene, 170°C[b], 3h
h	pentyl	60	30	toluene, 170°C[b], 5h

Table 2.2

Hetero-Diels-Alder reactions of D-(-) ribose derived acylacrylate ester. Reagents and conditions: a) Et_3N, pivaloyl chloride, DMAP, 2h, 0°C. b) The reaction was carried out in a sealed, Teflon®-coated steel autoclave.



Crystal structure of **4b** Crystal structure of **4h**

Scheme 2.7: Crystal structures of **4b** and **4h** represented with software Mercury v1.3. For the crystal structure of **4a** see Scheme 2.1.

The stereochemical outcome of the hetero-*Diels-Alder* reaction was the same as in **4a-e**, which was confirmed by structural analysis (1H NMR Nuclear *Overhauser* Experiments) of the products. Eventually we were successful in obtaining crystals of products 4a,b and h from methanol, which allowed us to verify the stereochemistry of the products by x-ray structure determination.[81]

The structures suggest a high tension within the ring system. They all show more or less the same overall geometry (see Scheme 2.1). Only in structure **4h** the pyran ring shows a boat-like conformation whereas in the other two structures all three rings are nearly flat.

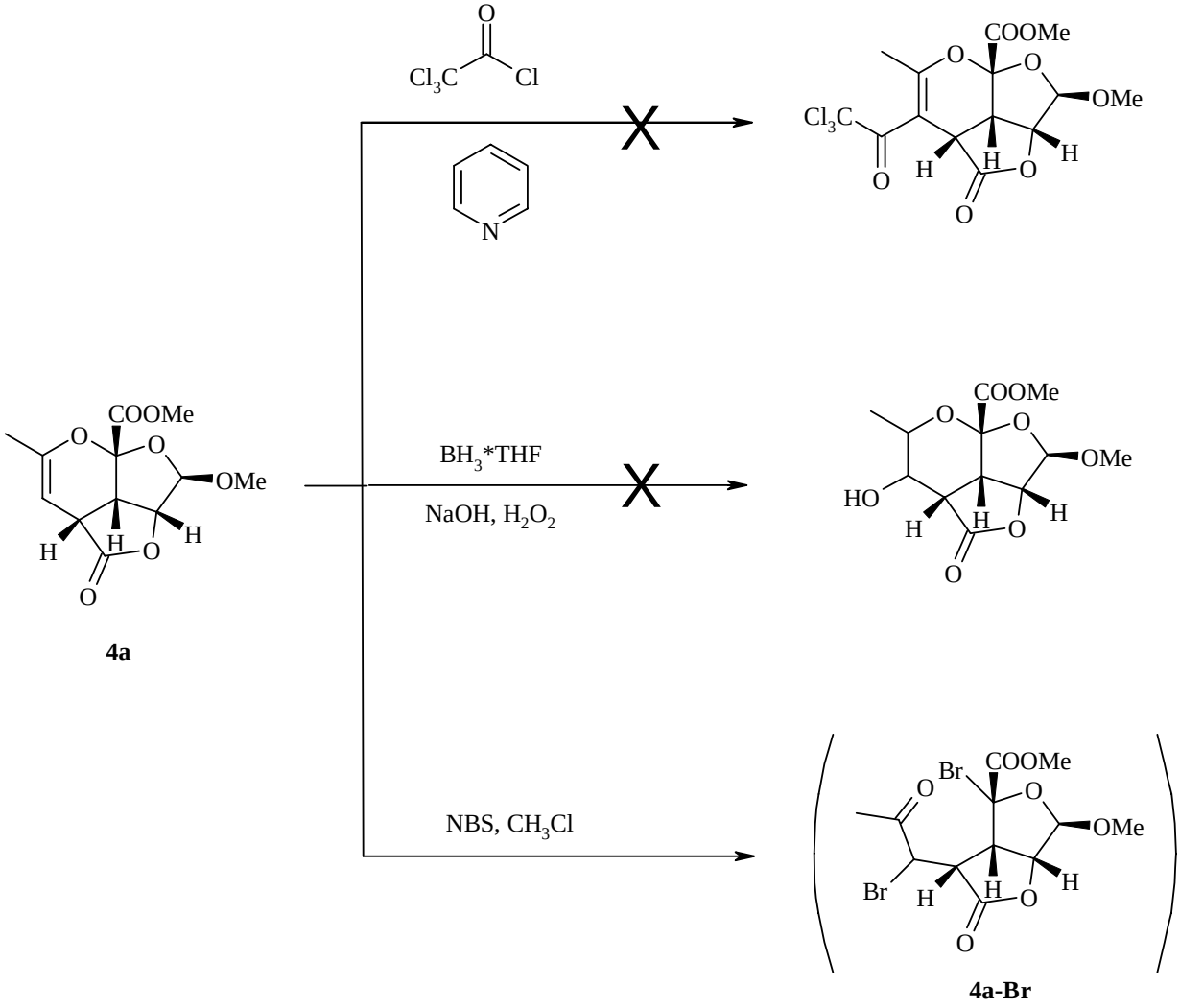
2.1.3 Reactivity of the Enol Ether

A straightforward way of adding a functional group to the pyran ring to the basic scaffold **4a** would reside in the reaction the enol ether itself. As a matter of fact the biomimetic approach to plumericine by Trost B. et al[53] made use of this. Acylation of the enol ether leads to the trichloro ketone which can be further hydrolysed to the corresponding carboxylic acid. The same acylation of an enol ether was also shown by Effenberger[82] and Takagawa[83]. However in our case the same procedure did not work. Under various conditions (heating, excess reagent) no reaction was observed. In each attempt the starting material was retrieved (Scheme 2.8).

In a next effort a hydroboration of the enol ether was believed to be more successful. Very similar operations had been carried out by Clark and Kettle[84] in their construction of subunits of brevetoxin B. Several 3,4-dihydro-2H-pyrans were treated with borane tetrahydrofuran complex, sodium hydroxide and hydrogen peroxide at 0°C. In our case only decomposition of the starting material was found.

Another promising approach to functionalised alkenes is a simple halogenation. The treatment of **4a** with N-bromo-succinimide in chloroform yielded cleanly one product. From the results obtained by Obrecht[85] who used NBS on 2,3-dihydro-4H-pyran-4-ones we expected bromination only at C(5). However closer analysis of our product revealed that another reaction than the desired one had taken place. Apparently a first bromination of the enol ether double bond had been followed by ketal-opening and further bromination at C(7a). From ^{13}C and ^{1}H NMR analysis of the isolated product, the structure **4a-Br** can be tentatively assigned. Mass spectrometry of the compound however gives the mass of a compound 80 au lighter

than the one suggested. This could account for an elimination of HBr during ionisation. Efforts to eliminate HBr from **4a-Br** in a controlled manner were not successful.



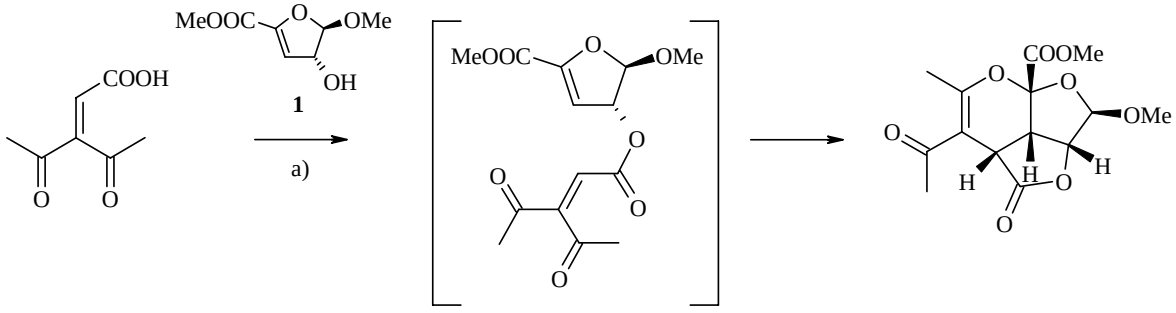
Scheme 2.8

Attempted enol derivatisations of **4a**.

2.1.4 Scaffold with a Carbonyl Group at Position C(5)

After scaffolds containing functionalized aryl groups at C(6) on the pyran ring had been made and derivatised.[86] The synthesis of such a scaffold with the option to build up side chains at C(5) position of the scaffold was still sought. This would substantially increase the number of potential derivatives and offer the option of additional diversity points. As stated earlier, the synthesis of 3-substituted acylacrylic acids directly from glyoxylic acid is somewhat limited. A very elegant way to obtain a single product in a condensation reaction, however, is the use

of acetylacetone. Acylacrylic acid **2i** is obtained by reaction in hot acetic acid in very good yield (92%). From this acid the corresponding ester was made again using the mixed anhydride method. Ester **3i** behaved exceptionally in this reaction. Isolation of this compound was not possible, since cyclisation took place under the conditions of the ester formation, i.e., at room temperature in 1,2-dichloroethane (Scheme 2.9). This observation of a faster reaction is in good agreement with the expected influence of an electron-withdrawing substituent at the diene moiety in this inverse electron-demand hetero-Diels-Alder reaction. The yield over two steps was with 51% within the expectations based on the individual yields of earlier reactions (examples **4a – h)**.



2i **3i** **4i**

Scheme 2.9

Cyclisation to 5-ketone scaffold proceeds at ambient temperature. Reagents and conditions: a) Et_3N, pivaloyl chloride, DMAP, 20h, 0°C → RT, 51%.

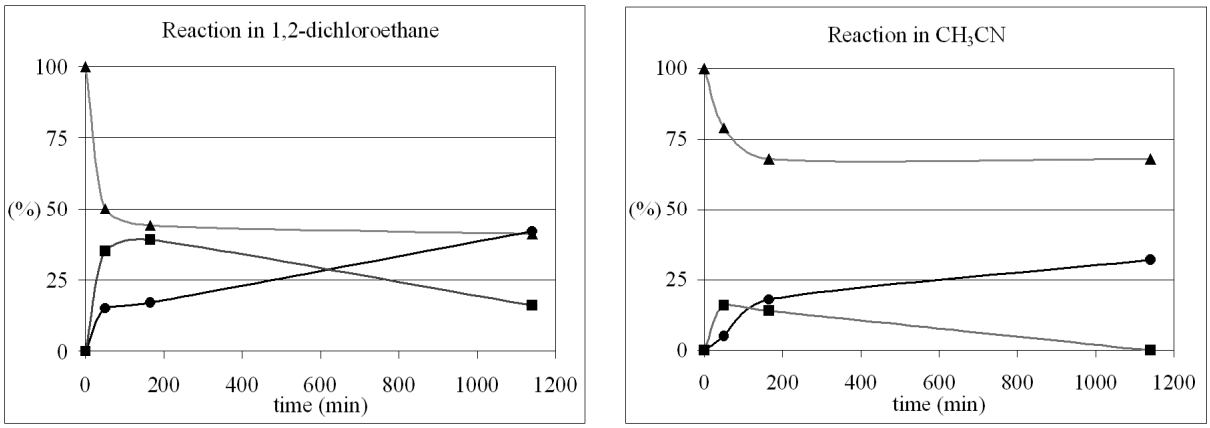
Initial yields for this reaction, were however much below expectations. First attempts involved the use of different coupling reagents like DCC in combination with HOBT or conversion of **2i** into an acid chloride prior to esterification. Yields were never higher than 20-30%. In the course of optimizing the conditions for the reaction, we found that the temperature and duration of the esterification had a big influence on the yields. In an equimolar solution of **2i** and **1,** together with triethylamine in 1,2-dichloroethane, the disappearance of **2i** could be monitored. When measuring an aliquote of the reaction after 24h at rt using ^{1}H-NMR, 50% loss of **2i** compared to **1,** which served as internal standard, was observed. A further negative influence of 4-N,N-dimethylamino-pyridine at temperatures above 25°C after prolonged reaction times was also observed. After many unsuccessful attempts to improve the yield of the esterification reaction, the best conditions were finally very close to the original mixed anhydride method with the exception that the reaction was performed between 0°C and 20°C.

Another interesting aspect of this unexpected tandem reaction is the influence of the solvent. A simple look at the kinetics of this reaction by ^{1}H-NMR shows that formation of the ester intermediate in 1,2 dichloroethane goes further towards completion than in AcCN (Table 2.3, Figs. 2.1 and 2.2). Under the assumption that in the course of the reaction all of **1** is either transformed into product or found unreacted in the end the following interpretation can be made: In CH_3CN the decomposition of **2i** is faster than in 1,2-dichloroethane (and therefore less ester is formed). The more ester intermediate was formed in the first 2 hours of the reaction, the higher was the final yield of **4i**. Therefore the conclusion can be drawn, that the acylacrylate ester opposed to the acylacrylate acid is stable towards basic conditions or decomposes much slower. The yields for **4i** as well as for **1** isolated after column chromatographie corresponded well with the percentages of composition found in the NMR experiments after 1140 minutes (19 hours).

	Alcohol **1** (%)		Ester intermediate **3i** (%)		Product **4i** (%)	
Time (min)	AcCN	$ClCH_2CH_2Cl$	AcCN	$ClCH_2CH_2Cl$	AcCN	$ClCH_2CH_2Cl$
0	100	100	0	0	0	0
50	79	50	16	35	5	15
165	68	44	14	39	18	17
1140	68	41	0	16	32	42

Table 2.3

Composition of reaction participants (in percent of starting quantity based on integrals of the NMR signals; samples were taken after the specified time).



Figures 2.1 and 2.2:

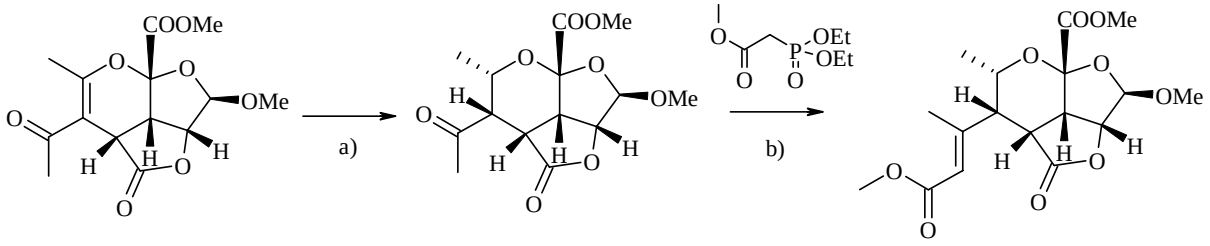
Influence of two different solvents on the formation of intermediate **3i** and product **4i**. (Percentage values of Table 2.3 against time) ▲= alcohol **1**, ■ = ester **3i**, ● = product **4i**

With **4i** we expected to have everything in hand to prepare 5-substituted derivatives of our basic scaffold. Unfortunately the ketone moiety of **4i** proved to be stable towards enolate formation and unreactive towards *grignard* reagents or *Wadsworth-Emmons* phosphonate ylides. Enolisation with lithium diisopropyl amine (LDA) and subsequent treatment with methyl iodide gave a product of the expected mass but not with the expected structure. After treatment of the supposed enolate with benzaldehyde starting material was retrieved. Further studies revealed that the enolate doesn't seem to form upon treatment with LDA, since quenching of the reaction mixture with D_2O didn't lead to the absence of a proton in the ^{1}H-NMR spectra. A second equivalent of butyllithium after LDA deprotonation gave the same result. Lihium hexamethyldisilazide didn't afford deprotonation of the ketone either.

Alkylation with butyl lithium or *Grignard* reaction with CH_3MgBr was not successful. In the case of the alkylation with butyl lithium some decompositon and reaction with the methylester occurred. A *Horner-Wadsworth- Emmons* olefination with triethylphosphonoacetate only afforded the starting material even when an excess of the reagents was used.

The ketone **4i** therefore behaves as α,β - unsaturated carbonyl, which can not be enolized. The additional deactivating effect of the conjugated oxygen of the pyran ring would explain the weak electrophilic behaviour in the addition reactions, which were attempted. As a consequence hydrogenation of the enol ether double bond should render the ketone more reactive.

Hydrogenation of **4i** worked best in tetrahydrofurane using standard conditions involving palladium on charcoal catalysts. The reaction worked in a good yield and absolute stereoselectivity. The configuration of **5** (Scheme 2.10) was confirmed by N*O*E-experiments.



4i **5** **6**

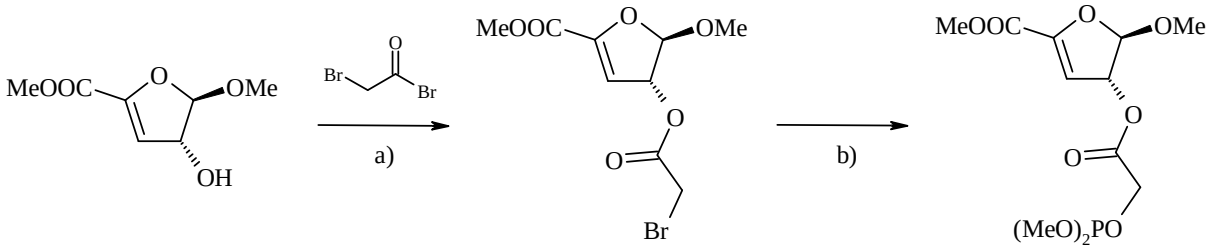
Scheme 2.10

Hydrogenation and *Horner-Wadsworth-Emmons* olefination of **4i**. Reagents and conditions: a) Pd/C 10%, H_2, THF, 2h, RT, 78%. b) LiHMDS, THF, 2h, 0°C → rt, 10%.

The obtained ketone **5** was submitted to a *Horner-Wadsworth-Emmons* (HWE) olefination using lithium hexamethyldisilazide as a base. Even though the reaction seems *E*-selective, the exact configuration of the formed double bond in **6** has not been inspected any further in this case. Yields of this step are very low. Since no starting material or side product was found after reaction, decomposition of the material has to be assumed. At this point, attempts aimed at this kind of derivatisation were discontinued.

2.1.5 An Alternative Route for the Construction of the Scaffold Involving 1,2 Diketones

A quite different approach to a scaffold is to build the acylacrylic acid ester from a phosphonate ester instead of preparing the precursor for the cyclisation step by an esterification. This would involve use of the phosphonate **7**, which can be prepared in two steps by acylation of **1** to ester **8** followed by an *Arbuzow* reaction. Both steps are straightforward and proceed with very good yields (Scheme 2.11)

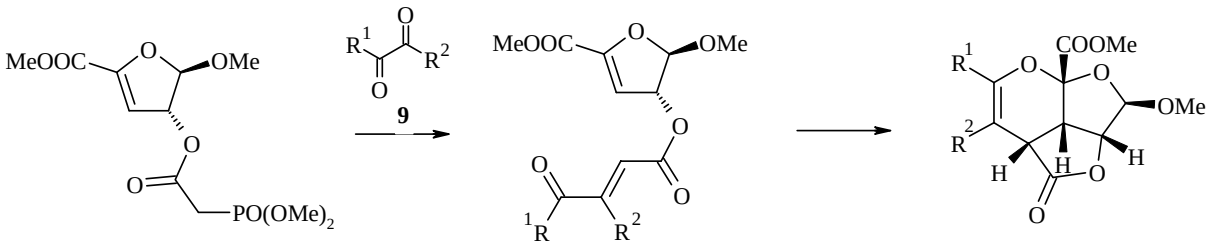


1 **8** **7**

Scheme 2.11

Arbuzow reaction on furanoside **1**. Reagents and conditions: a) TBME, pyridine, 4.5 h, 0°C, 89%. b) $P(OMe)_3$, THF, 4-5 days, 80°C, 94%.

Treatment of **7** with an asymmetric 1,2-diketone **9** can possibly yield two regioisomers of ester **10** which should be separable. Depending on the substituents of **9,** a high regioselectivity might be obtained in the *Horner-Wadsworth- Emmons* olefination to **10**, either by electronic or by steric effects.

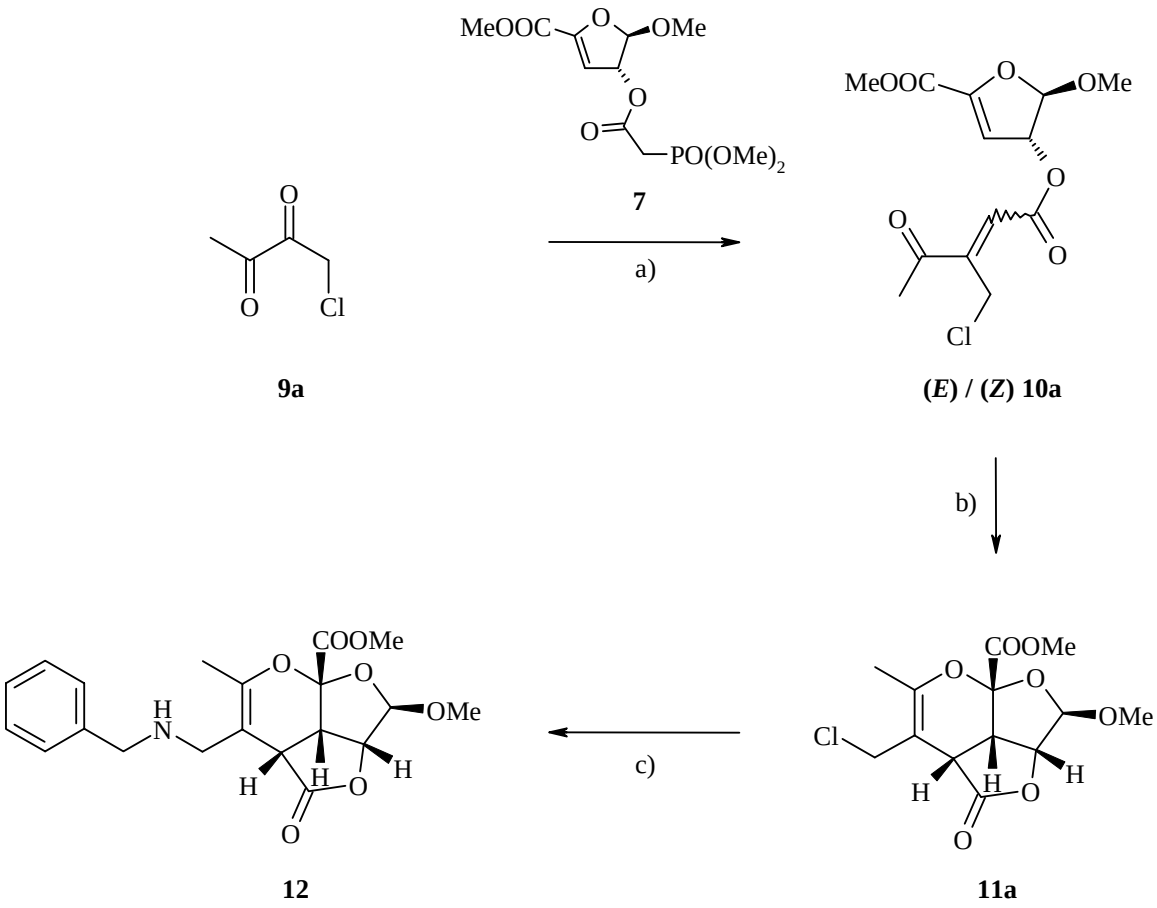


7 **10 (*E*+*Z*)** **11**

Scheme 2.12

Approach to a 5,6-disubstituted scaffold through a *Horner-Wadsworth- Emmons* olefination involving a 1,2-diketone

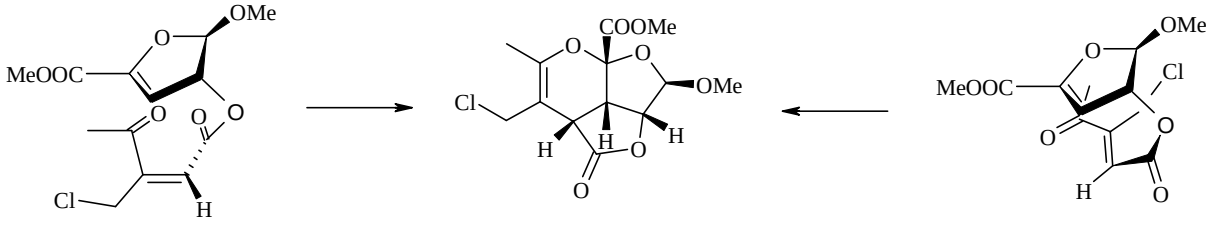
A first example of this approach (outlined in Scheme 2.12) could be realised involving 1-chorobutane-2,3,-dione (**9a**), which was made from 2,3-butanedione by chlorination.[87] The use of one equivalent of sulfuryl chloride and temperature control of the reaction affords a maximum of 39% of mono-chlorinated 2,3-butanedione after distillation of the product. Dione **9a** reacts very regioselectively with phosphonate **7** (Scheme 2.13). No other regioisomers than the one originating from olefination the 2-carbonyl group could be found. The isomer **10a** is obtained as isomeric mixture (*E/Z* ratio approximately 1/2) with a yield of 55%. Since the separation of the isomers was not possible the mixture was used in the following cyclisation step. Ester **10a** can be cyclised at 90-100°C within 6 hours to afford **11a** as a single product. The structures of the regioisomers of **10a** and **11a** have been confirmed by N*O*E-experiments**.** The cyclisation to **11a** turned out to be absolutely selective and a single diastereomer was formed. Like in the cases of **4a-i** the *syn*-product was found. Most importantly, the formation of the product does not depend on the geometry of the diene moiety as assumed in the beginning of this work. The same isomer is formed from either the (*E*)- or the (*Z*)-precursor.



Scheme2.13

Functionalisation of the 5 position by synthesis from 1-chloro-butane 2,3-dione and phosphonate **7**. Reagents and conditions: a) LiHMDS, THF, 1h 20min, -70°C, 55%. b) toluene, 3h 30min 90°C and 2h 30min 100°C, 10% isolated. c) AcCN, $BnNH_2$ (1eq.), RT, 19h, 60%

Based on the structural information, the stereochemical course of the hetero-Diels–Alder reaction of the two stereoisomeric intermediates (*E*)- and (*Z*)-**10a** must proceed as illustrated in Scheme 2.14.



(*E*)-**10a**
exo-Z-syn
favored

11a

(*Z*)-**10a**
endo-E-syn

Scheme 2.14

Stereochemical course of intramolecular hetero-*Diels–Alder* reaction of (*E*)- and (*Z*)-**10a** leading to **11a**

Since both geometrical isomers afford the same product, the (*E*)-isomer reacts via the *endo-syn* and the (*Z*)-isomer via the *exo-syn* transition state.[78,88,89]

This is in good agreement with our findings in the stereoselective synthesis of bicyclic dihydropyrane derivatives from α,β-unsaturated ketones via *intramolecular* hetero-*Diels–Alder* reaction.[78] In addition to that, the *exo-syn* transition state seems to be favored. At 90°C faster conversion of **(*Z*)-10a** can be observed as monitored by proton NMR (Table 2.4 and Fig. 2.3)

Time (min)	(*E*)-**10a** (%)	(*Z*)-**10a** (%)	**11a** (%)
0	37	63	0
35	34	38	27
65	30	25	44
95	27	17	55
125	25	13	62
210	22	4	74

Table 2.4

Composition of reaction participants in percent derived from integrals in the NMR samples of the specified components at the time indicated. Percent of **(*E*)-10a, (*Z*)-10a** and **11a**.

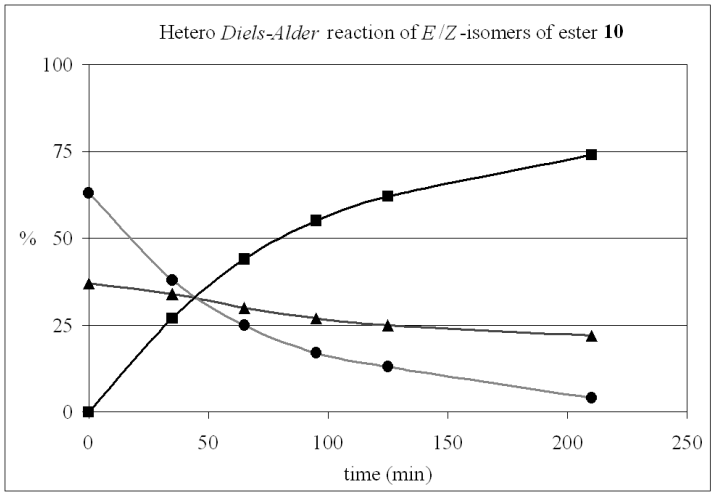


Figure 2.3

Percentage values of table 2.4 against corresponding times. ▲= *E*-isomer, ● = *Z*-isomer, **4i** ■ = product.

Although product **11a** was obtained in very good yield, it proved to be a rather unstable compound. While the crude **11a** after cyclisation is quite pure containing only little decomposition product, column chromatography yielded only little product even when eluents

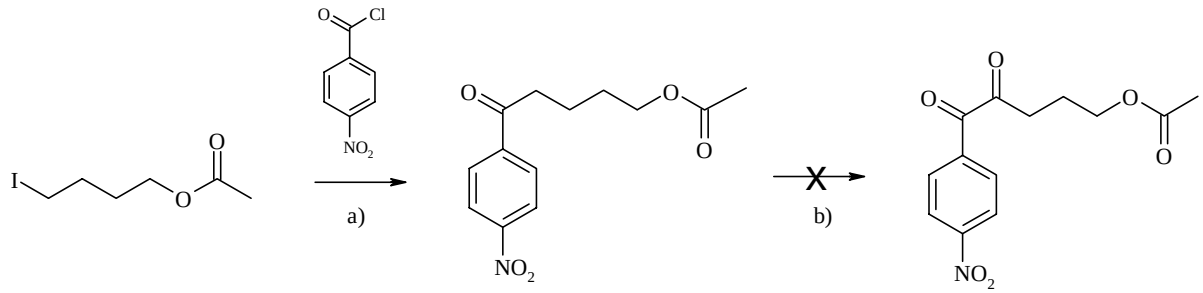
containing triethylamine were used. Since the analogous des-chloro compound **4g** is very stable the chloromethyl group must be the reason for this instability. The relatively easy replacement of the halogen atom is not unexpected because of its allylic character. Similar findings have been made by Miethchen and coworkers[90] on 2-chlorodifluoromethyl-substituted monosaccharides. Nucleophilic replacement of the chlorine in **11a** was therefore possible in acetonitrile using benzylamine affording amine **12a** as a single example. The yield was however low due to decomposition and undesired side reactions of **11a** (Scheme 2.13).

2.1.6 Asymmetric 1,2 Diketones for the Synthesis of Disubstituted Oxadienes *via Wittig* Olefination

1,2 Diketones are versatile intermediates on the way to α,β-unsaturated carbonyl compounds. In the work mentioned so far we used only symmetrical 1,2 - diketones. Symmetrical 1,2 - diketones are either commercially available or easily accessible by reported methods. They can be prepared by the addition of vinyl ethers to oxalyl chloride.[91] Alternatively, *Grignard* addition is possible to N,N-dimethoxy-N,N-dimethylethanediamide[92]. Quite common are also methods involving the oxidation of methyl- or methylene ketones in the α - position. Typical procedures use selenium dioxide as an oxidant[93]. A related approach involves the benzoin condensation[94] followed by oxidation of the resulting α–hydroxyl ketone.

In Scheme 2.12, the approach to scaffolds with different functionalisations at C(5) and C(6) position of the scaffold was shown. For the purpose of a diversity oriented synthesis, *asymmetrical* 1,2 –diketones would be very welcome. Most of the existing methods for the preparation of 1,2 –diones, however are suitable only for obtaining symmetrical diketones; furthermore, they are limited with regard to the presence of further functional groups. Initial experiments intending the selective substitution on commercially available 1,4-bromo-2,3-dione or the addition to 3-bromopyruvic acid chloride were not successful.

A further attempt consisted of the oxidation of ketone **14** prepared from iodobutyl acetate **13** and p-nitro-benzoylchloride (Scheme 2.15). While ketone **14** was obtained by a zinc-cuprate mediated *Knochel*-type reaction, the oxidation to dione **15** was achieved only with partial conversion. Since the oxidation step could not be reproduced and yielded in some cases the hydrolysis product of acetate **14,** no further efforts were made involving this strategy.

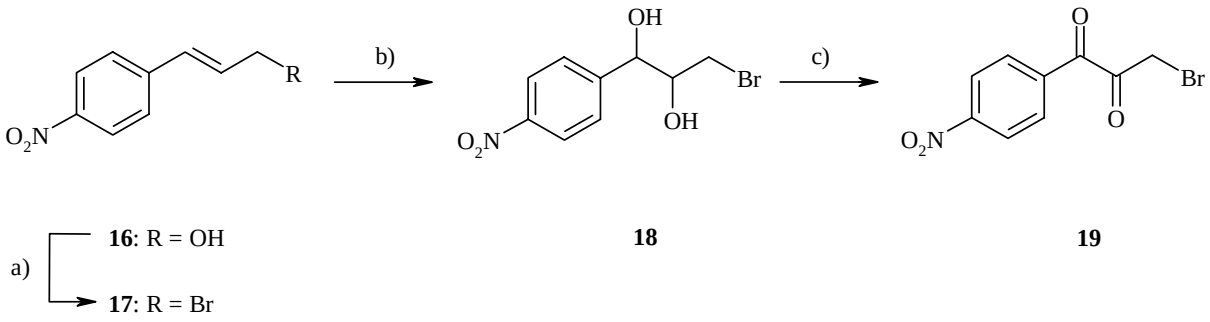


13 **14** **15**

Scheme 2.15

Asymmetrically functionalized α-diketone from SeO_2 oxidation. Reagents and Conditions: a) Zn, CuCN·LiCl, THF, -25 to 0°C, 10h, 48%. b) SeO_2, AcOH, H_2O, dioxane, 100°C, 4h

A more reliable method was found by sequential use of a dihydroxylation step and a *Swern* oxidation. Commercially available 4-nitrocinnamyl alcohol **16** was converted into the corresponding bromide **17** in good yield (Scheme 2.16). Alkene **17** was further submitted to dihydroxylation using OsO_4 and N-methylmorpholine N-oxide (NMO). The obtained diol **18** was then oxidized to diketone **19** using a standard *Swern* oxidation.

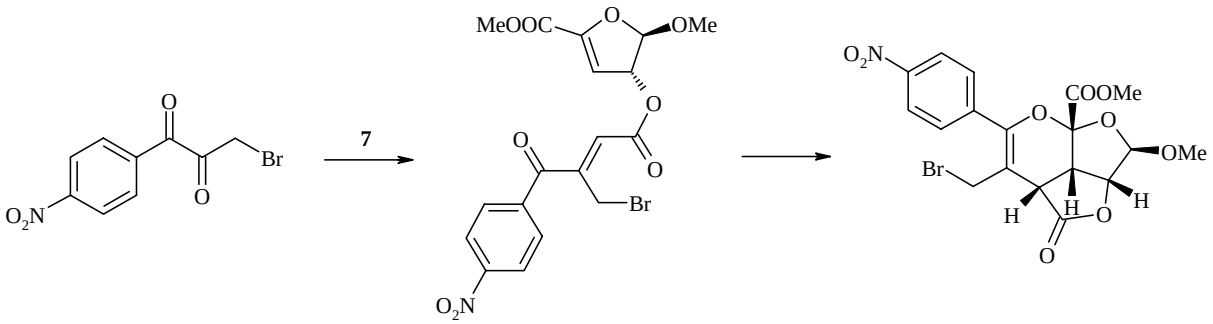


18 **19**

Scheme 2.16

Dihydroxylation / Swern oxidation sequence to diketone **19**. Reagents and Conditions: a) PPh_3, CBr_4, Et_2O, 0°C, 15 min. 74%. b) OsO_4, NMO, t-BuOH, acetone, H_2O, rt, 45 min. 79%. c) DMSO, TFAA, Et_3N, CH_2Cl_2 33%

Diketone **19** should react with phosphonate **7** yielding acylacryl ester **10b** combining the properties of ester **10a** containinging a halogen and ester **3c** with a 4-nitrophenyl group (Scheme 2.17). For sterical reasons formation of only one regioisomer in the *HWE* reaction to **10b** is expected. Cyclisation of **10b** yielding **11b** shold proceed as usual. The possible use diketone **19** in such a manner is currently being investigated in our research group.



19 **10b** **11b**

Scheme 2.17

Possiple application of diketon **19** in a *Horner-Wadsworth- Emmons reaction* followed by cyclisation to multi-functionalized scaffold **11b**.

2.1.7 Reductive Demethoxylation of the Methyl Acetal

The acetal and ketal functionalities present in the scaffolds may bear considerable instability towards acidic conditions. Indeed the scaffold **4a** decomposes completely when stirred at 50°C in 1N HCl / THF (5:4) during 3 - 19 h. At rt the same conditions induce only little decomposition over 3 hours. Little or on decomposition is observed at pH values > 3 (see Table 2.5).

Time / temperature	1N HCl / THF (5:4)	Phosphate buffer (pH3) / THF 5:4	Citrate–NaOH buffer (pH 5) / THF 5:4
2 h / r.t.	o	o	o
3 h / 50°C	o/x	o	o
19h /50°C	x	n/a	o
20h / 80°C	n/a	x	o

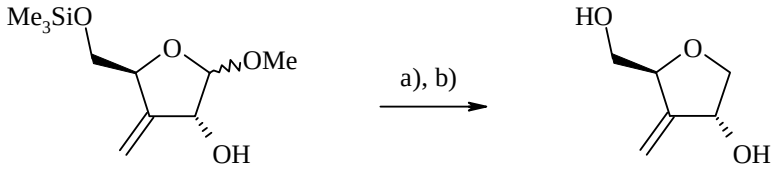
Table 2.5

Stability of scaffold **4a** to acidic conditions. o = no reaction; x = complete decomposition

This acid lability sets limitations to normal synthetic methods as well as to the use of the scaffold in a solid support synthesis since acidic conditions are often necessary to cleave products from the support. Part of the problem might be solved by elimination of the acetal in furanoside **1**. This would eventually just leave one ketal function in the scaffold which should be considerably more stable to acid.

Initial experiments showed that the reduction of the enol ether double bond could be readily achieved by catalytic hydrogenation. This aspect will discussed in chapter 2.2.1. To explore

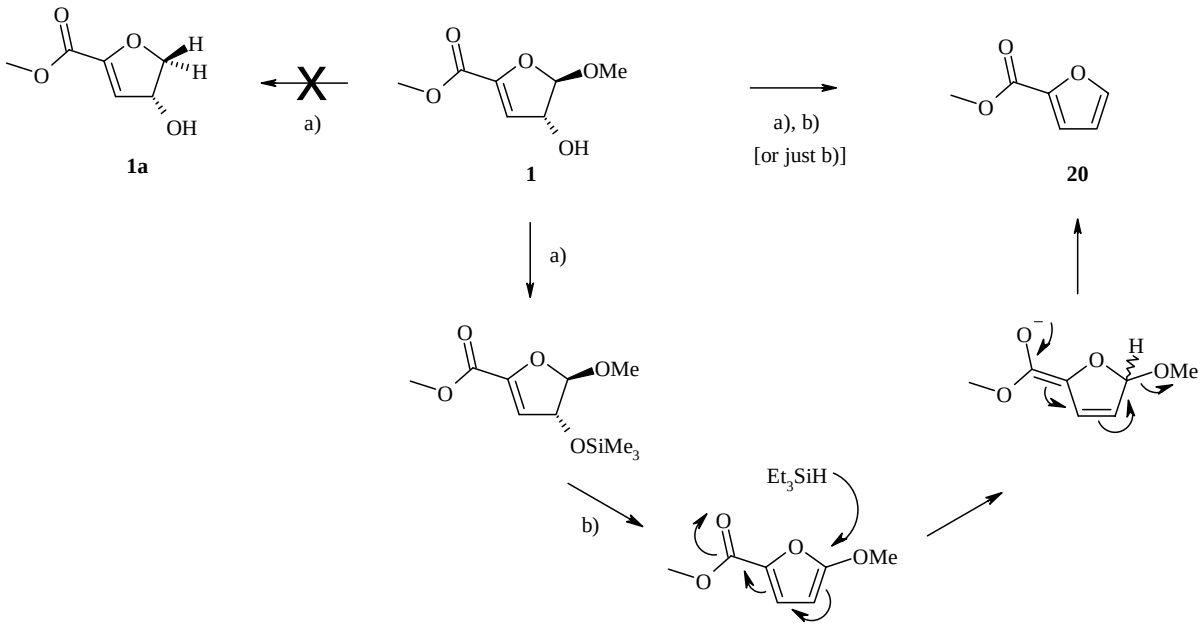
the reduction of the acetal moiety, we carried out a series of test experiments. A known method for converting acetals into ethers is reductive demethoxylation. It is a standard method used predominately in sugar chemistry as shown in the example of Nair and Bera[95] (Scheme 2.18).



Scheme 2.18

Example of reductive demethoxylation. Reagents and conditions: a) Me_3SiCl, HMDS, r.f. 17h. b) Et_3SiH, $Me_3SiOSO_2CF_3$, CH_3CN, RT, 78%

In the case of dihydrofuranoside **1** the outcome was not as expected. Instead of the reduced dihydrofuranoside **1a** the elimination product **20** (Scheme 2.19) was found after reaction using the same conditions like in the example outlined in Scheme 2.18. Product **20** is commercially available and of no interest for our purposes.



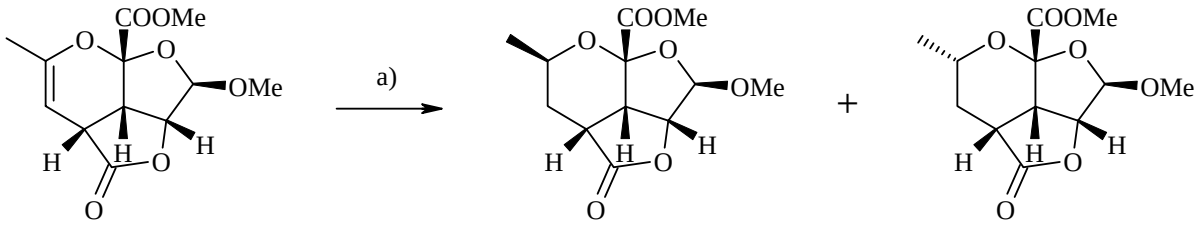
Scheme 2.19

Unexpected outcome of reductive demethoxylation on furanoside **1.** reagents and conditions: a) Me_3SiCl, HMDS, r.f. 17h. b) Et_3SiH, $Me_3SiOSO_2CF_3$, CH_3CN, or $CDCl_3$, rt.

Product **20** was also found when submitting **1** directly to Et_3SiH and $Me_3SiOSO_2CF_3$ omitting silylation by HMDS. This method was used to get samples for characterisation. The outcome of the reaction can be explained by an elimination of the alcohol group as trimethylsilylated- or a tosylated leaving group followed by a nucleophilic addition / elimination by hydride from triethylsilane as shown in Scheme 2.19.

Since the scaffold **4a** has no potential leaving group next to the acetal, we tried anyway to achieve the goal in this way. This time, instead of reductive demethoxylation, the enol ether was reduced (Scheme 2.20). The two diastereomers **21** were found as a 2/1 mixture of, while no efforts have been made to to separate them.

At this point, attempts aimed at improving the scaffold's stability towards acidic conditions were discontinued. Later results (see chapter 2.2.2 and 2.2.4) had shown the scaffold to be stable enough to the conditions applied for cleavage from the solid support.



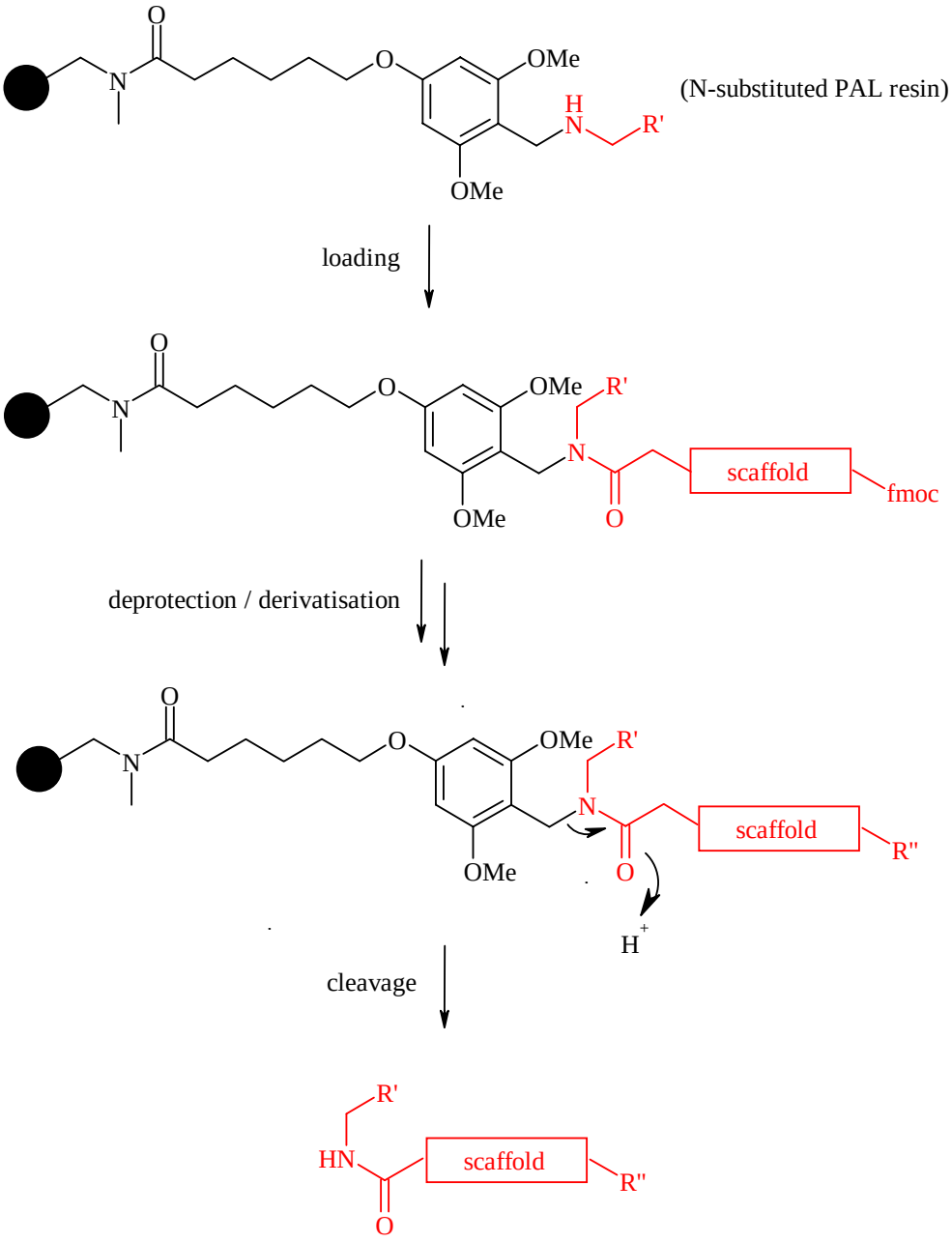
4a 6R-**21** 6S-**21**

Scheme 2.20

Attempted reductive demethoxylation on **4a**. Reagents and conditions: a) Et_3SiH (3 eq.), $Me_3SiOSO_2CF_3$ (3 eq.), CH_2Cl_2, rt, 24h, 86%

2.2 Solid Support Assisted Library Synthesis

For the synthesis of combinatorial compound libraries derived from the scaffold we decided to use N-substituted PAL resin (see introduction, chapter 1.3.3). To attach the scaffold to this anchor a carboxylic acid moiety is needed in some distance to the scaffold to avoid sterical hindrance during the coupling step. The N-substituted PAL resin features the advantage of derivatising the carboxylic acid moiety in the coupling step by secondary amide formation (Scheme 2.21).



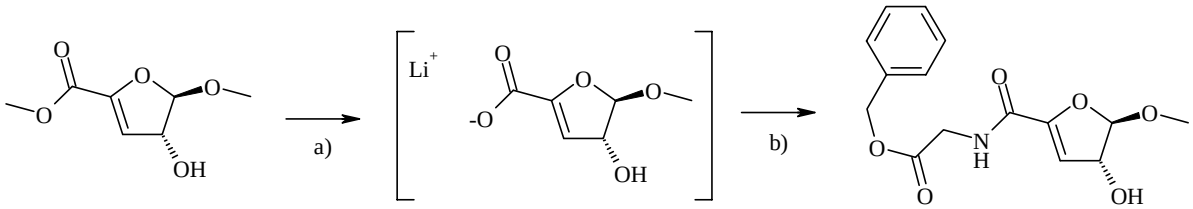
Scheme 2.21

Synthetic operations on the N-substituted PAL solid support.

In the conventional examples like polyamide synthesis the scaffold carries a fmoc protecting group to prevent side reactions during the coupling step. Any functional groups orthogonal to coupling reactions involving activated carboxylic acids do not need to be protected. A capping step with acetic acid anhydride of the unoccupied amine groups on the solid support is carried out after loading. Then follow the chemical transformations with the support bound scaffold. This can include several deprotection and derivatisation steps. At the end of the synthesis, the immobilised product is cleaved from the support using aq. TFA. Thus the scaffold has to be stable towards exposure to TFA (20% in CH_2Cl_2) at rt.

2.2.1 Preparation of a Scaffold Containing a Linker Group and a Protected Amine - Function

To have a versatile building block for scaffolds with a carboxylic acid linker in hand, the modified furanoside **23** was made from the original furanoside **1** (Scheme 2.22). Since different acylacrylic acids can be used for ester formation with **23,** a variety of scaffolds ready for immobilisation on solid support can be made. The synthesis of amide **23** via the hydrolysed intermediate **22**, which can be used without further purification, is high yielding. Amide bond formation was accomplished by benzotriazol-1-yloxy - tris(dimethylamino) phosphoniumhexa - fluoro-phosphate (BOP) activation of the lithium carboxylate **22.**



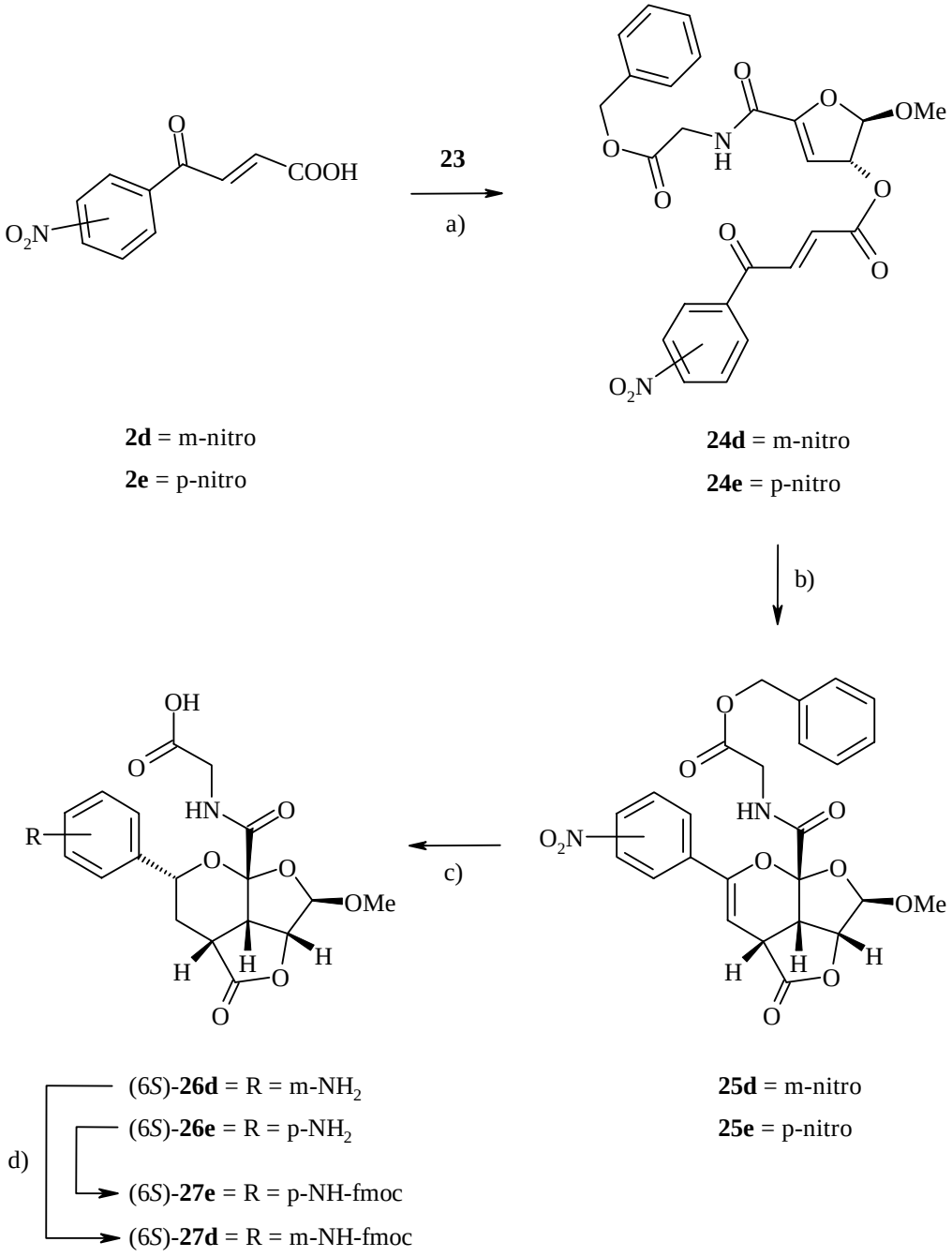
1 **22** **23**

Scheme 2.22

Synthesis of a furanoside with protected glycine linker moiety. Reagents and Conditions: a) 0.5N LiOH, Dioxane/H_2O, quant. b) Glycine benzylester, BOP, N,N Diisopropylethylamine , AcCN, rt, 4 hours, 97%

Alcohol **23** was reacted with acylacrylic acids **2d** and **2e** to give esters **24d** and **24e**, respectively (Scheme 2.23). Reaction times longer than 2 hours give lower yield due to decomposition (see above). Ester **24d** and **24e** can be cyclised at 100°C in 24h giving the products in yields of 45%. This cyclisation could be further optimised using $LiClO_4$ in AcCN

as a catalyst at a temperature of 50°C. Yields of over 55% were obtained under these conditions. This cyclisation will be discussed in more detail in chapter 2.3.2. Hydrogenation of the scaffolds **25d** and **25e** involved three processes in one reaction: Reduction of the benzylester, the nitro group as well as the enol ether moiety to give (6*S*)-**26d** or (6*S*)-**26e** as single products.



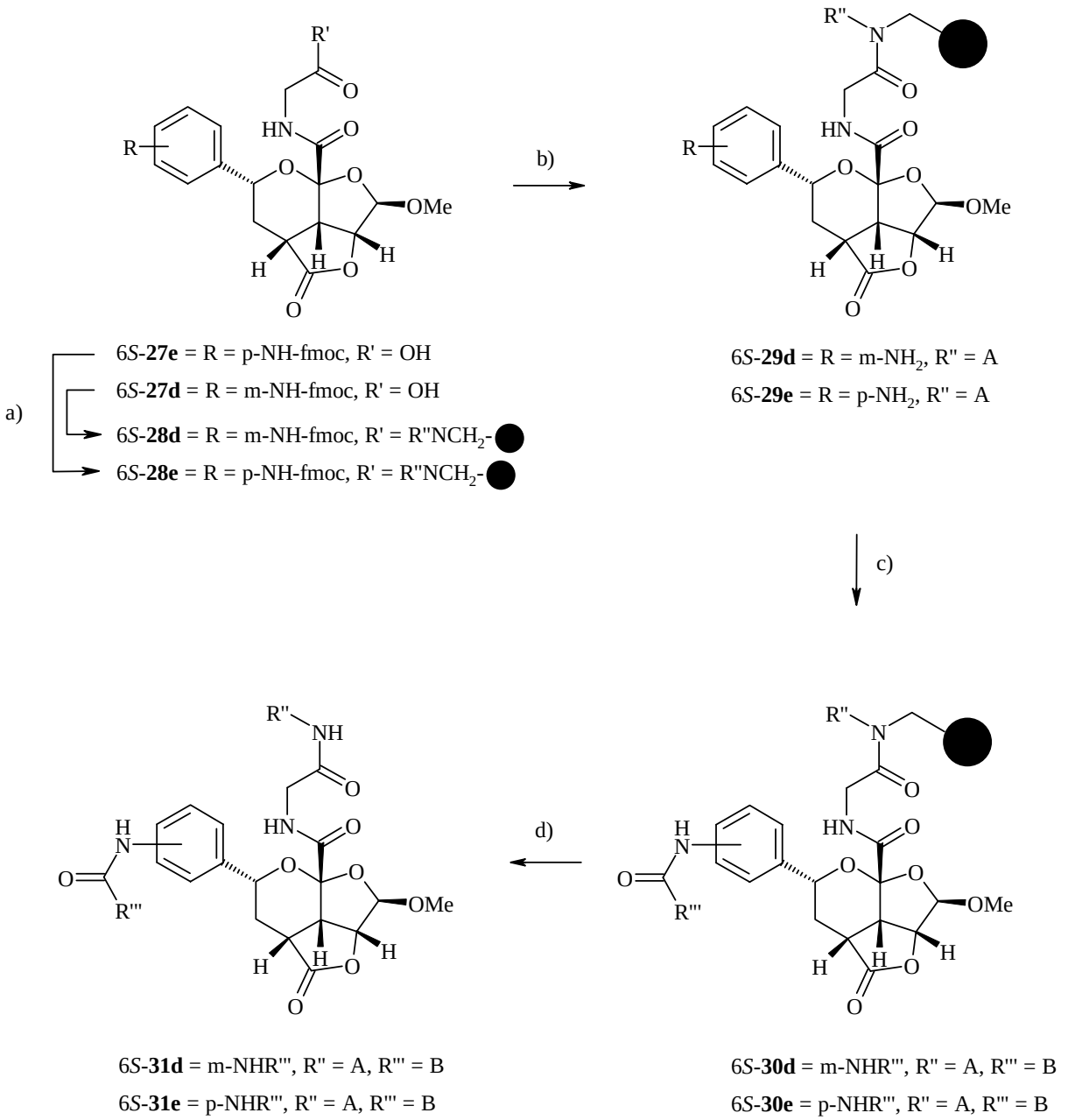
Scheme 2.23

Synthesis of the fmoc-protected aniline acid scaffold **27d** and **27e**. Reagents and conditions: a) Piv Cl, Et_3N, DMAP, 1,2-dichloroethane, 0°C, 2h, 45%. b) $LiClO_4$, CH_3CN, 50h, 50°C, 55%. c) Pd/C (10%), H_2 , THF d) Fmoc-Cl, $NaHCO_3$, dioxane/H_2O, 95%.

The hydrogenation is carried out in THF since some methyl ester formation could be observed using the same conditions in MeOH. The anilines **26d** and **26e** are protected with Fmoc-Cl. Purification of the fmoc protected scaffolds **27d** and **27e** was first attempted using RP-HPLC. The purity of the products was, however, not sufficient. Crystallisation from methanol/MTBE proved to be much better and gave good yields of over 60% based on **25d** and **25e.**

2.2.2 Elaboration of Conditions for the Solid Phase Synthesis

To immobilize the scaffold efficiently onto the solid support, coupling conditions needed to be optimized. It is common to use several equivalents of the compound to be immobilized in order to obtain maximum coupling yields. Methods involving the coupling reagents HATU (2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate), chlor-enamine or TFFH (tetramethylfluoroformamidium hexafluorophosphate) were not successful enough. The combination of HCTU (1H-Benzotriazolium 1-[bis(dimethylamino)methylene]-5-chloro, hexa- fluorophosphate(1-),3-oxide) and HOBT (1-hydroxybenzotriazole) in N-methyl pyrrolidone (NMP) was eventually best with coupling efficiencies (see exp. Section, chapter 4.1) of up to 70%. The purity of the acids **27d** and **27e** was crucial for a good coupling reaction. The solid support beads were rinsed with a sequence of different solvents after each reaction step to wash away any by-products or excess reagents. The immobilized anilines **28d** and **28e** were deprotected using 30 ml of 20% pyperidine in DMA, forming piperidine dibenzofulvene from the fmoc group. By measuring UV absorbance of an aliquot of the piperidine / DMA / dibenzofulvene-piperidine solution, the loading of the support (percentage of amino groups on the support coupled with the scaffold) was determined. Before the acylation step of **29d** and **29e** (see Scheme 2.24) the solid support beads have to be rinsed with absolute CH_2Cl_2 several times since traces of humidity lead to precipitation of the carboxylic acids formed from its corresponding acid chloride. It's important at any time in the synthesis to ensure good suspension of the support. Precipitates or agglutination of the beads may cause lower yields or incomplete conversion in the reaction steps. The acylated products **30d** and **30e** are cleaved from the support using 20% aq. TFA in CH_2Cl_2 yielding **31d** or **31e**. The crude product solution is left in a stream of argon to "air off" TFA and CH_2Cl_2. Before this cleaving step it's again important to rinse with absolute CH_2Cl_2, otherwise less volatile solvents like DMA, used in the washing steps, may be hard to evaporate from the cleaving solution.



Scheme 2.24

Solid support synthesis with scaffold **28d** or **28e**. Reagents and conditions: a) HCTU/HOBT, N,N-diisopropyl-ethylamine, R''-solid-support, A = combinatorial rest, NMP. b) 20% Piperidine/DMA. c) Acyl-chloride (20 eq.), B =combinatorial acyl chloride derivative, Pyridine/DCM 8:2. d) 6 x 20% TFA aq./DCM

Earlier experiments on **4a** (see chapter 2.1.7) had shown considerable acid lability of the scaffold at pH 1 at 50°C. Therefore doubts whether the conditions in the cleaving step would be endured by the library products had always been present. To our delight, the scaffold proved to be completely stable. The crude products were purified using normal phase HPLC and the pure products were fully characterized.

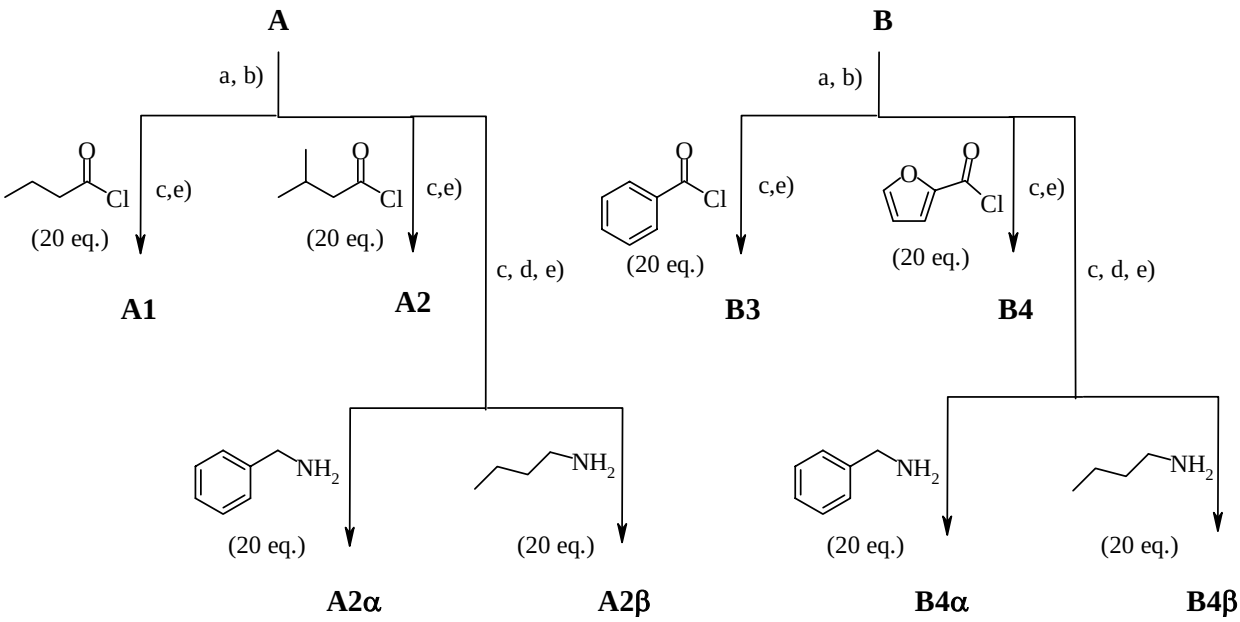
2.2.3 Synthesis of a Small Model Library

Two examples of solid support mediated libraries were next made from fmoc protected aniline acid **27d**. In these model libraries, presented in the following, two different N-substituted PAL resin (see introduction) were used. Support **A** containinging a benzyl amine and support **B** with a 2-methoxy ethylamine rest (Scheme 2.25).

Scheme 2.25

Two types of solid supports used

The synthesis started with two equal batches of support **A** and **B.** After coupling and deprotection of **27d** each batch was split into two unequal portions of ¼ and ¾ . Acylation was then performed as shown in Scheme 2.26. The smaller portions were cleaved from the support directly after acylation, leading to the products **A1** through **B4,** while the bigger portions were split again into two equal portions to be submitted to aminolysis of the lactone. The structures of the obtained products are shown in Table 2.6.



Scheme 2.26

Library Synthesis. Reagents and conditions: a) HCTU/HOBT, N,N-diisopropyl-ethylamine, **27d**, NMP. b) 20% Piperidine/DMA. c) Pyridine/DCM 8:2. d) 2-hydroxy pyridine (5 eq), THF. e) 6 x 20% TFA aq./DCM

The loading of the solid supports used in this example, was 56-59%, as determined by UV spectrometry. The crude products contained up to 45% of the “capping product” araising from uncoupled amino groups on the support. Purification was done by normal phase HPLC using CH_3CN isocratically as the eluent. Retention times were between 8 and 11 min. The pure products were obtained as white solids in yields of 40 - 70% (based on the loading). The structures of the products were confirmed by ^{1}H- and ^{13}C-NMR analysis as well as by MS.

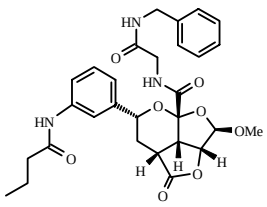
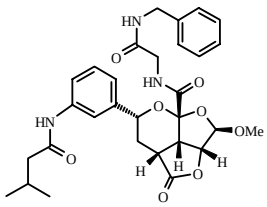
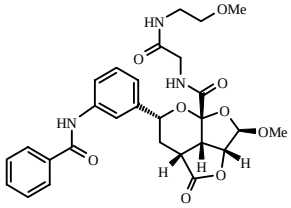
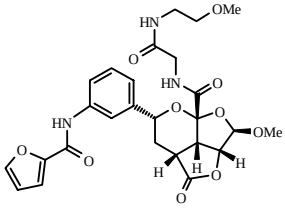
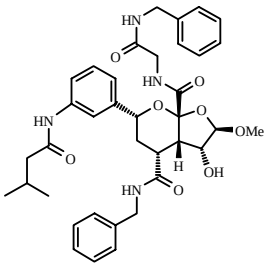
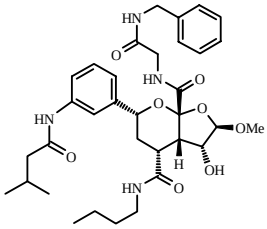
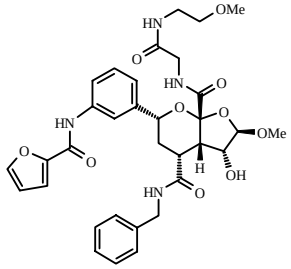
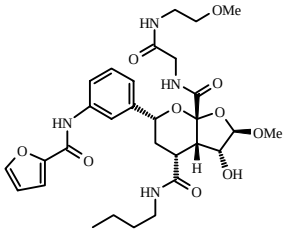
Synthesized on support **A**		Synthesized on support **B**	
A1 MW: 551.6 Yield: 55%	**A2** MW: 565.6 Yield: 54%	**B3** MW: 553.6 Yield: 59%	**B4** MW: 543.5 Yield: 71%
			
A2α MW: 672.8 Yield: 46%	**A2β** MW: 638.8 Yield: 39%	**B4α** MW: 650.7 Yield: 70%	**B4β** MW: 616.7 Yield: 63%
			

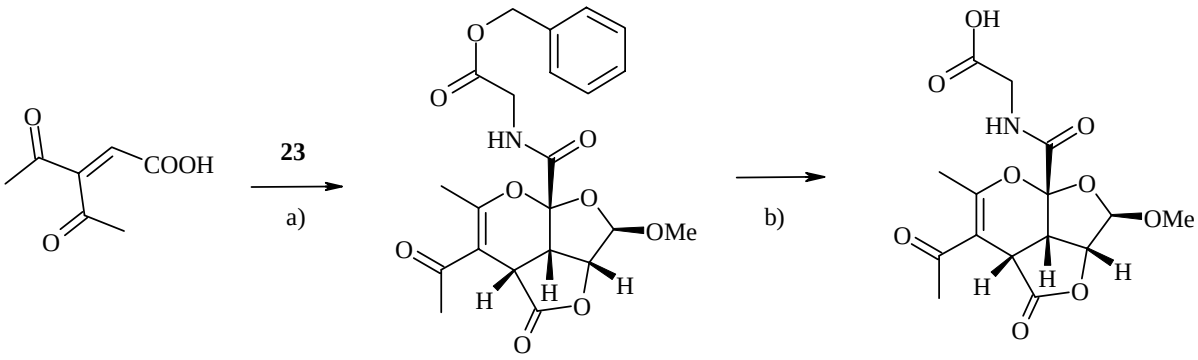
Table 2.6

Structures of library products (yields based on loading)

The compounds obtained through this synthesis show considerable polar character. With up to five hydrogen bond donors and a mass of over 500 au the *Lipinski’s rule of five* are partially violated. Improvement of this library could thus be achieved by developing scaffolds of smaller molecular weight.

2.2.4 An Alternative Approach Towards the Library Through a *Wittig* Olefination

The synthesis of fmoc protected acids **27d** and **27e** is rather long (4 steps from ribose derivative **23**). A more straightforward approach was found by implementing the synthesis of **4i** with alcohol **23** (see above, Scheme 2.22). The cyclisation of the ester made from **23** and **3i** proceeded at rt and saved one step in the synthesis (Scheme 2.27). Hydrogenation of the resulting tricycle **32** proceeded in high yields and provides ketone **33** with a glycine linker for immobilisation. To our surprise the same conditions like in the case of the hydrogenation of ketone **4i** to **5** did not reduce the enol ether in the case of **32**. The double bond was still present in acid **33**. The only difference of **32** in comparison to **4i** is the replacement of the methyl ester with a glycine ester. Therefore this different substituent must somehow take account for the change in reactivity and might sterically hinder the hydrogenation. On the other hand, the same glycine benzylester does not prevent hydrogenation of the enol ether in the reduction of **25d** and **25e.**



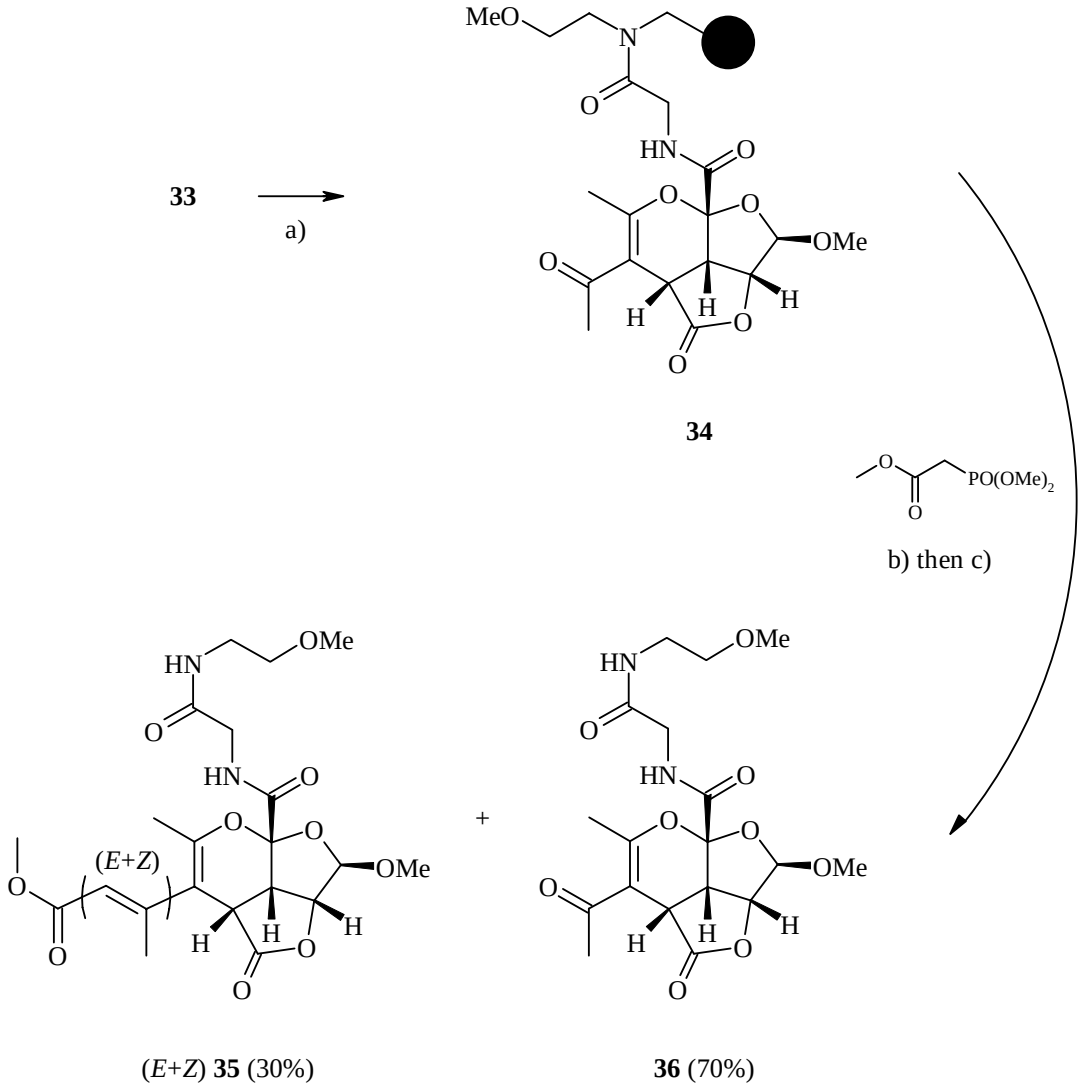
2i **32** **33**

Scheme 2.27

Synthesis of ketone **33** with a glycine linker for immobilisation. Reagents and conditions: a) Piv Cl, Et_3N, DMAP, 1,2-dichloroethane, 0°C, 20h, 20%. b) Pd/C 10%, H_2, THF, 2h, rt, 94%.

Ketone **33** can be recrystallized from hot methanol in a more efficient manner than in the case of **27**. Because of the absence of an amino group in **33** compared to **27** no protection step with fmoc is required before immobilisation. The derivatisation of **33** renders 5-substituted products (see chapter 1.3.4 and 1.4) accessible in a straightforward way through *Wittig* olefinations.

We have seen in chapter 2.1.4 that ketone **4i** does not react with a phosphonate if the adjunct enol ether is not reduced. Since on solid support the use of excess reagents is possible, we wanted to see if *HWE* reaction could be forced to take place on immobilized ketone **33**. Immobilisation of scaffold **33** was carried out using the same conditions as in the case of scaffold **27d** and **27e** using HCTU and HOBT. The immobilized product **34** (Scheme 2.28) can be submitted directly to derivatisation. Capping steps are not necessary since the remaining free amino groups on the solid support are not reactive to the conditions of the *HWE* reaction. Of course also the initial deprotection step, which is necessary in the case of fmoc protected amines, is not required.



Scheme 2.28

Horner Wadsworth Emmons reaction on solid support. Reagents and Conditions: a) HCTU/HOBT, N,N-diisopropylethylamine, MeO-ethyl-PAL resin, NMP. b) LiHMDS, THF, 20°C. c) 20% TFA aq./DCM.

The use of 3 equivalents of phosphonate ylide during 18 hours only gave traces of olefin **35**. The increase to 20 equivalent within a reaction time of 18 hours eventually led to 30% conversion of the ketone to olefin **35** as a mixture of (*E*)- and (*Z*)-isomers with an approximate ratio of 1:4 respectively. The combined yield of the two products **35** and **36** is high enough to exclude decomposition of the scaffold by the acidic conditions used during the cleaving step. This is surprising since we assumed that the use of 20% TFA in DCM was only tolerated due to prior hydrogenation of the enol ether double bond. The conditions needed for total conversion of **34** in a Wittig reaction are currently still locked for. Synthesis of a second small library involving the approach described in this chapter will then follow.

2.3 Scope and Limitations of the Hetero *Diels-Alder* Reaction

2.3.1 Influence of Diene- and Dienophile- Substituents on the Reaction Rate

In the chapter 1.3.2 the influence of electronic properties of diene and dienophile on the rate of the hetero *Diels-Alder* reaction was discussed (see Scheme 1.14). In the case of the inverse electron demand HDA reaction electron withdrawing groups on the diene accelerate the reaction while systems with donor groups on the diene require higher cyclisation temperatures. In Table 2.7, the observed cyclisation conditions required for *intramolecular* HDA reactions described in chapter 2.1 are arranged according to their approximate reaction rate.

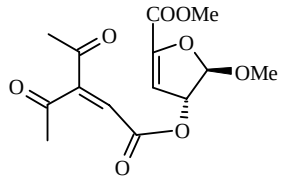
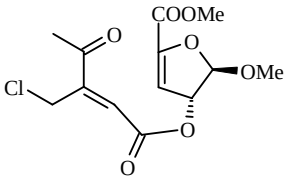
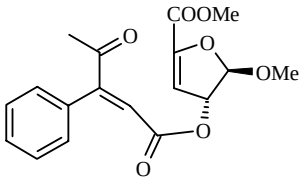
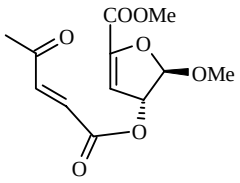
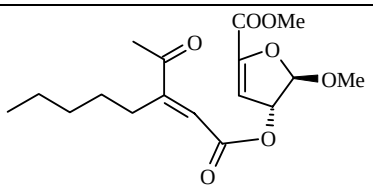
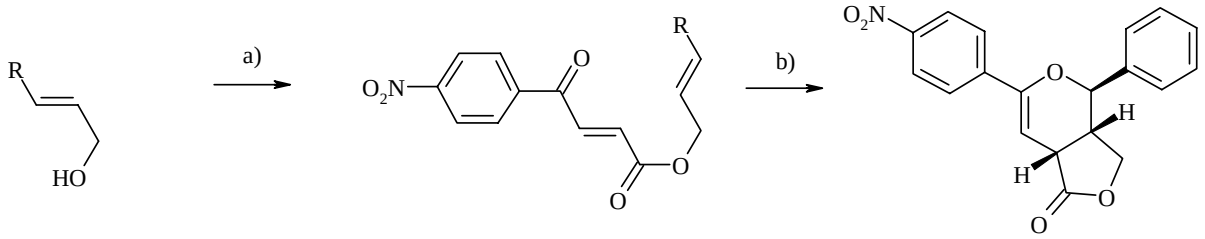
Reaction	Structure of HDA system	conditions
3i → 4i		rt, 20h
10a → 11a		100°C, 5h
3f → 4f		100°C, 21h
3a → 4a		145°C, 17h
3h → 4h		180°C, 5h

Table 2.7

Influence of diene-substitution on the reactivity of HDA systems.

These observations are well in accordance with theory. Thus our (D)-ribose derived furanoside behaves as an electron rich, rather than an electron poor dienophile. This was not clear in the first place considering that the carbomethoxy group is electron withdrawing and renders the dienophile a captodative moiety.[96,97,98] The influence of the carbomethoxy group is, however overridden by the donor effect of the alkoxy group. This becomes even more obvious in a comparison between esters **38a** and **38b,** which show different substitution of the dienophile. The esters **38a** and **38b** have been prepared according to Scheme 2.29 from the cinnamoyl alcohol **37a** and 4-hydroxy-methyl crotonate **37b**.



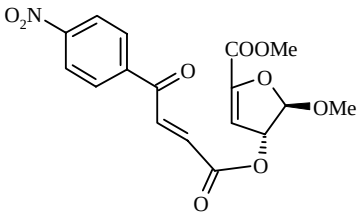
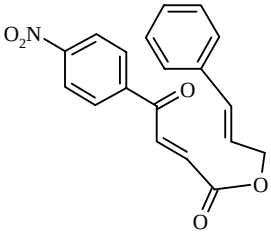
37a, R = C_6H_5 **38a**, R = C_6H_5 **39**

37b, R = COOMe **38b**, R = COOMe

Scheme 2.29

Esters from allyl alcohols with donor or acceptor group on the dienophile. Reagents and Conditions: a) Et_3N, **2e,** pivaloyl chloride, DMAP, 2h, 0°C → rt, 63% for **a** and 44% for **b**. b) o-Xylene, 145°C, 22h

While **3e** and **38a** have similar HOMO energies for their dienophiles and cyclise at 145°C, the acceptor substituted ester **38b** does not undergo cyclisation even at high temperatures (Table 2.8). The cyclisation of **38a** gives one specific cycloadduct **39**.

Ester	structure	conditions
3e		145°C, 3h
38a		145°C, 22h

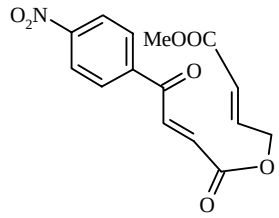
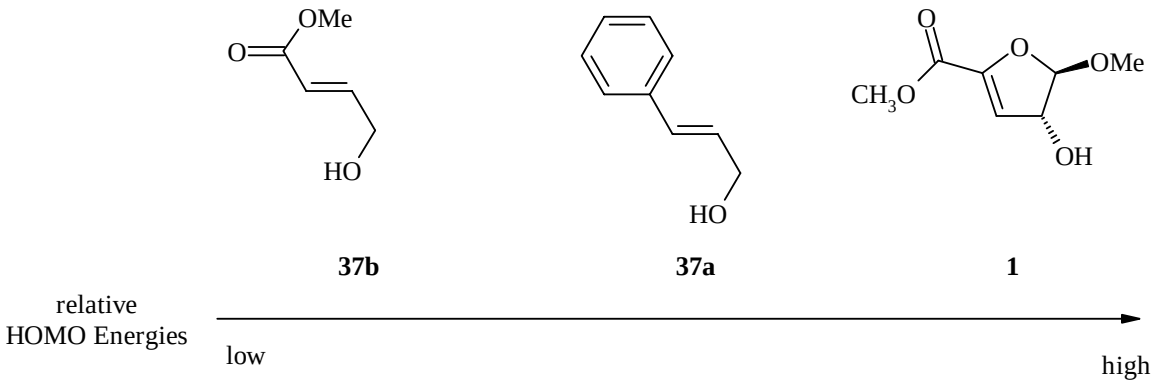
38b		n.o.

Table 2.8

Influence of diene-substitution on the reactivity of HDA systems. n.o. = no reaction observerd

From these findings, a rough estimation on the HOMO energies of the dienophiles of compounds **37a**, **37b** and **1** can be made.Theory predicts that **37b** has a lower HOMO than **1**. It is more surprising on the other hand that even though **37a** carries a donor group, its HOMO is still lower in energy than the one of **1** eith its captodative character. One would expect to find the HOMO energy of **1** somewhere between the one of **37a** and **37b**. From these observations a rough assessment of the individual relative HOMO energies of **1**, **37a** and **37b** can be made however, revealing **1** to be a rather electron rich dienophile (see Scheme 2.30).



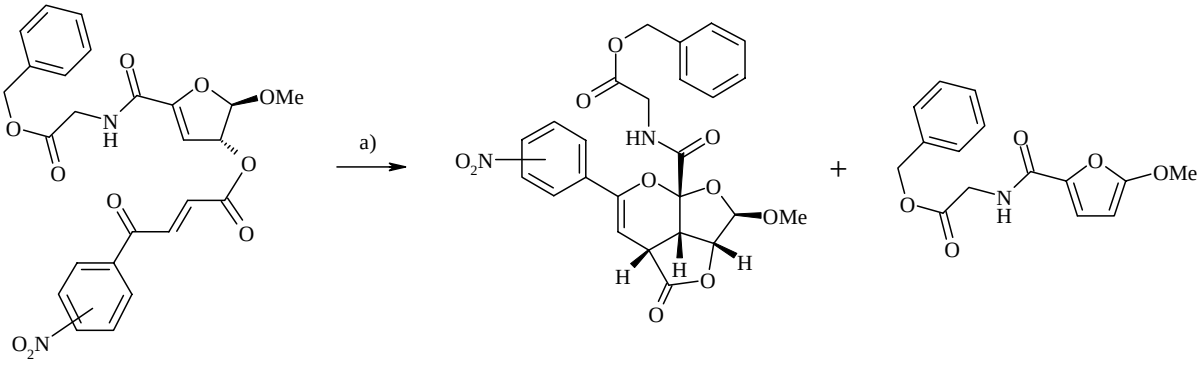
Scheme 2.30

HOMO energies of different dienophiles

2.3.2 Rate Acceleration of the Hetero *Diels-Alder* Reaction by Lithium Perchlorate

The HDA cyclistations of esters **3a – h** proceeded at different temperatures depending on the substitution of the diene. The higher the temperature required for cyclisation to take place, the larger was the amount of by-product **40a** found in the product mixture. The formation of the elimination product is even more pronounced in the cyclisation of **24d** and **24e** at 100°C (see Scheme 2.31). Up to 40% of by-product **40a** has been found in these examples. Due to this

rather large degree of undesired side-reaction, we started to look into improvements of the intramolecular HDA reaction.



24d = m-nitro
24e = p-nitro

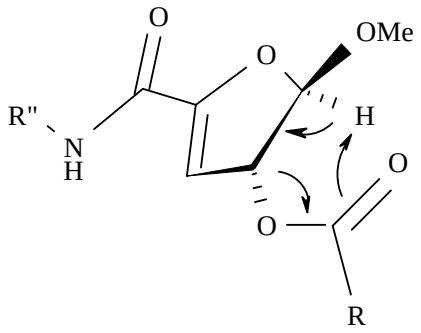
25d = m-nitro
25e = p-nitro

40a

Scheme 2.31

Elimination side reaction in the cyclisation of esters **24d** and **24e**. Reagents and conditions: a) toluene, 2,6-lutidine, 100°C, 24h, 49% for **25d** or **25e**.

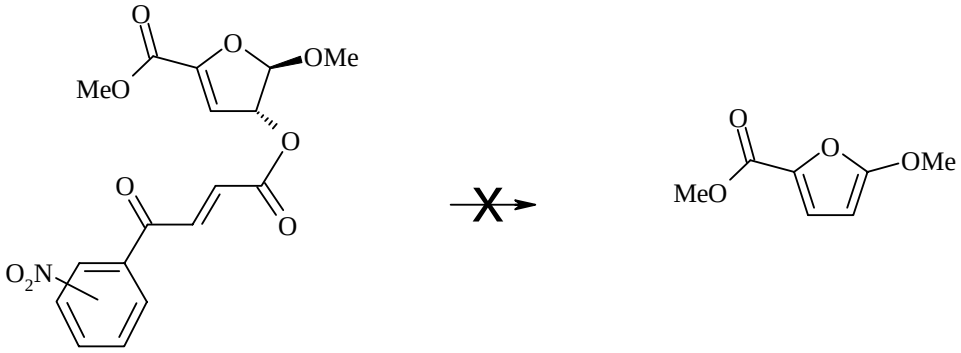
A likely explanation for the elimination reaction is shown in Scheme 2.32. Thus the reaction proceeds through a thermal *syn*-elimination[99,100] According to literature the process follows the mechanism shown in Scheme 2.32 and is believed to be concerted.



Scheme 2.32

Thermal *syn* elimination. R’ = acylacryl rest, R’’ = glycine benzylester

In the course of the project, we found that esters **3d** and **3e,** bearing a methyl ester were much less prone to give this by product **40b** (Scheme 2.33) than the corresponding glycine amide analogs **24d** and **24e**.



3d = m-niro
3e = p-nitro

40b

Scheme 2.33

No elimination side reaction occurs in the cyclisation of the esters **3d** and **3e**

We reasoned that the addition of a Lewis acid could resolve the problem by suppressing the H-bond acceptor effect of the carboxylic ester and, at the same time, lower the cyclisation temperature of the HDA reaction by Lewis acid catalysis[101]. In preliminary experiments, we found that $LiClO_4$[102,103] in CH_3CN showed the best results. This Lewis acid was, therefore, further investigated.

The effect of different concentrations of $LiClO_4$ in CH_3CN was monitored taking samples for NMR analysis at different times. The proportion of starting material over the course of the reaction was determined by integration of the corresponding signals. No elimination was observed in any of the experiments carried out at 50°C. A comparison of the disappearance of the starting meterial in dependence of the $LiClO_4$ concentration used is given in Table 2.9.

time (min)	$LiClO_4$ [0M]	$LiClO_4$ [0.05M]	$LiClO_4$ [0.5M]	$LiClO_4$ [1.5M]	$LiClO_4$ [1.5M]
0	100	100	100	100	100
4			85		
18	99	84		33	2
42		64			
50			12	3	
69			6		

Table 2.9

Percentage of starting material after a certain time at 50°C at different concentrations of $LiClO_4$ in CH_3CN

A graphical representation of the values shows how dramatic the reaction rate increases with higher perchlorate concentrations. The values correspond nicely with their fitted curves (see figure 2.4) of a first order reaction. In two cases the reaction yield has been determined after column chromatography. In both cases 55% of product was isolated.

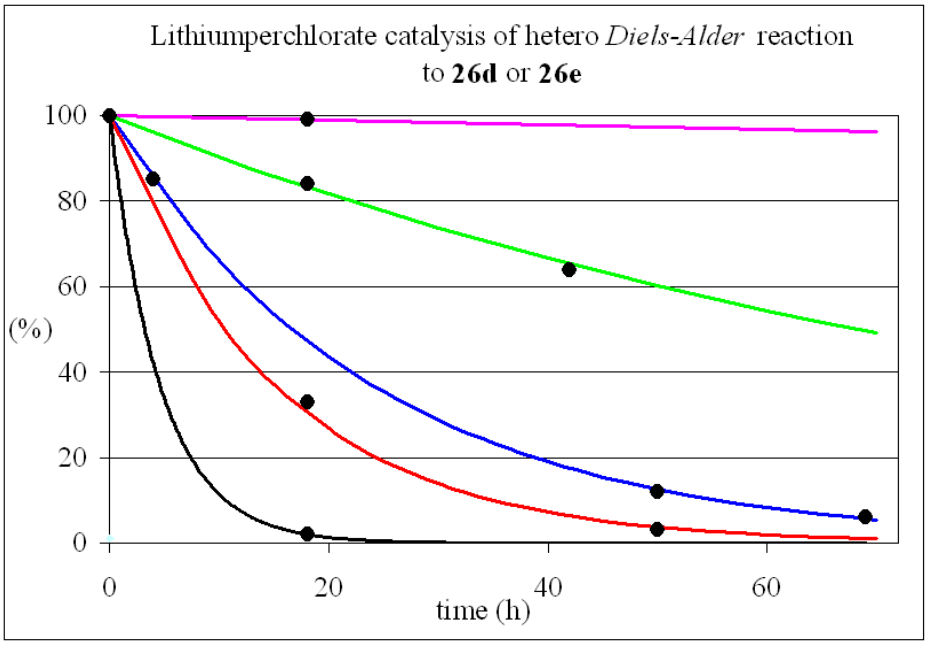
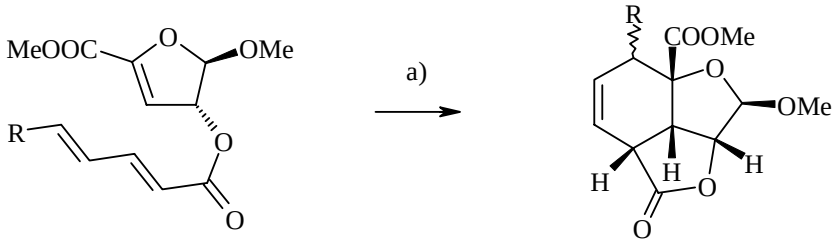


Figure 2.4

Decrease of ester content in cyclisation with $LiClO_4$. Concentrations: ■ = 0M, ■ = 0.05M, ■ = 0.5M, ■ = 1M ■ = 1.5M. From the values measured a mean reaction rate was calculated assuming first order kinetics. The curves in color are first order exponential decays according to the calculated rates.

2.3.3 Normal Electron Demand *Diels Alder* Reactions Involving Dienophile 1

In a preceding diploma work[70] intramolecular *Diels-Alder* reactions of (*E*)-pentadienic acid esters had been studied. As in the case of the hetero *Diels-Alder* reactions, the cyclisation of ester **41a** only yields one diastereomeric product. The reaction goes through an *endo-E* transition state to afford the product **42a** (Scheme 2.34). In the case of ester **41b**, two products were formed, which differ in the configuration of the additional methyl group.



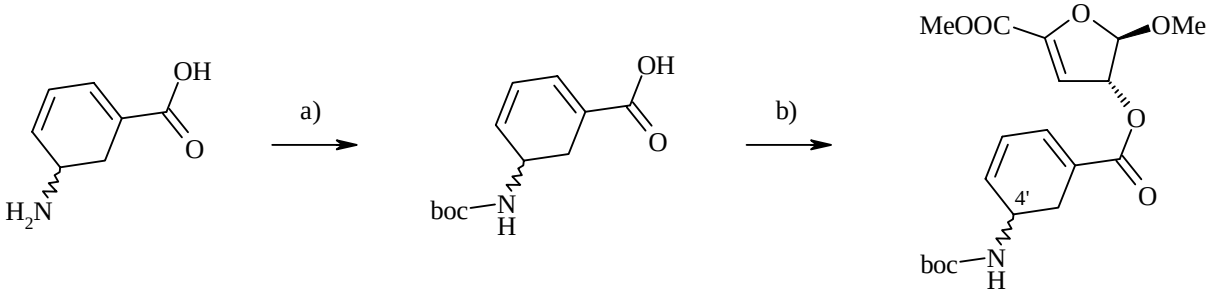
41a, R = H
41b, R = Me

42a, R = H,
42b, R = Me

Scheme 2.34

Diels Alder reactions of pentadienic acids esters of furanoside **1**. Reagents and conditions: a) toluene, 170°C, 17h, 33%. The reaction was carried out in a sealed, Teflon®-coated steel autoclave.

The yields of these reactions are rather low, mostly due to the harsh reaction conditions. The essence is however, that normal electron-demand *Diels-Alder* reactions are also possible with the captodative dienophile **1**. The substitution on the double bond of **1** has, as stated above, more of a donor character. For this reason the use of **1** as an electron rich dienophile like in the cases discussed so far is actually more promising. On the other hand if dienes are used in a normal electron demand DA reaction, they have to be very electron rich to proceed smoothly.
To further study the use of dienophile **1** in combination with carbodienes, (+/-) *gabaculine* was chosen to serve as dienic acid. The cycloadducts obtained from such an approach would be bridged tricycles with a protected amine functionality for further derivatisation. Boc protection of the amine in (+/-) *gabaculine* was achieved with quite good yields after recrystallisation of the crude product (Scheme 2.35).



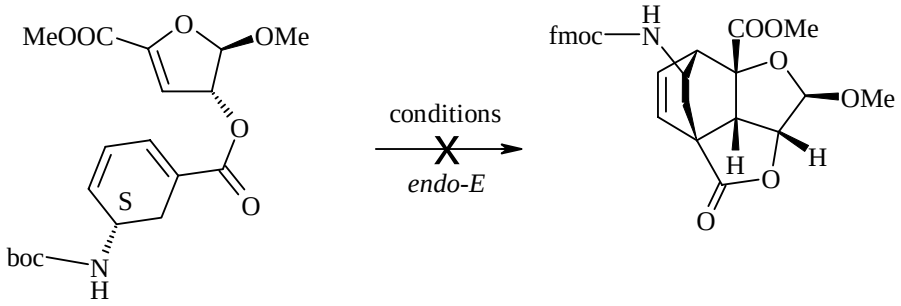
(+/-) gabaculine **(+/-) 43** (4'*S*)/(4'*R*) **44**

Scheme 2.35

Synthesis of a *Diels-Alder* reaction precursor from (+/-) *gabaculine.* Reagents and conditions: a) $(BOC)_2O$, Et_3N, MeOH, 1h, rt, 65% from recryst. b) Et_3N, pivaloyl chloride, **1**, DMAP, 2h, 0°C, 83%.

The yield for the formation of the ester bond to give **44** was higher than in the case of acylacrylic acids, using the same conditions. The ester **44** was obtained as diastereomeric mixture of (4'*R*)-**44** and (4'*S*)-**44**.

Efforts were made to cyclize **44** using various conditions. First normal thermal cyclisation was tried by heating in o-xylene. While after 4 hours at 145°C still big amounts of ester **44** could be found, heating for longer periods or heating to 170°C in a pressure autoclave led to decomposition of the starting material. Lewis acid catalysis involving $AlCl_3$, Me_2AlCl, SnCl, $BF_3{\cdot}Et_2O$ and $LiClO_4$ did not succeed under different conditions.

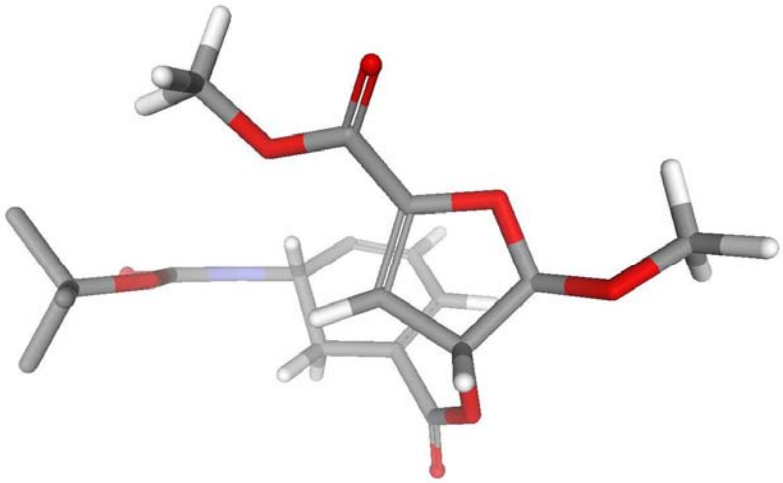


4'S 44

Scheme 2.36

Expected cyclisation reaction of (4'*S*)-**44** to form a tricyclic bridged product.

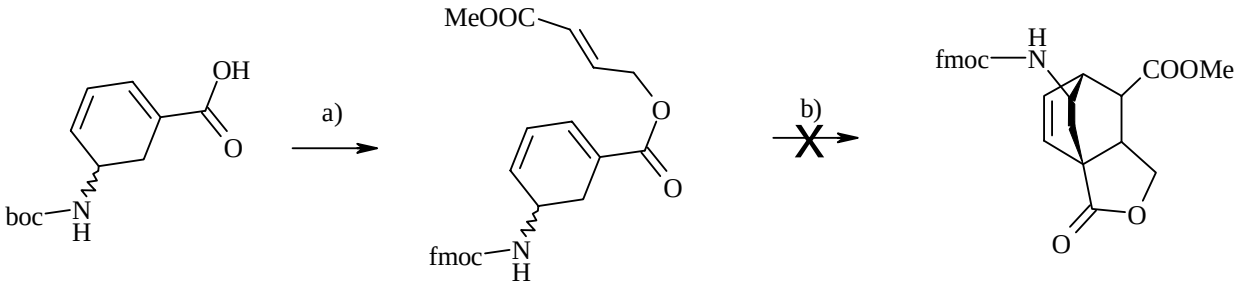
Considering the electronic properties of the diene in **44** we should expect a similar or higher reaction rate than in the case of **41**. The diene system has an additional weak electron donor substituents, i.e. the alkyl substituent in α-position. The reason for its low reactivity must, therefore, reside rather in steric constraints. The product expected from an *endo* transition state has the structure drawn in scheme 2.36. Since in all cases of *E*-configured dienes in this work an *endo* cyclisation could be observed, the same should be expected from the cyclisation of **44**, too. As a three dimensional model of **44** in Scheme 2.37 shows, a cyclisation going through an *endo* conformation is only possible for (4'*S*)-**44**. In the case of (4'*R*)-**44** the amino-boc substituent would sterically interfere with the methoxy carbonyl group. The structure of (4'*S*)-**44** calculated by a semi empirical modelling program suggest that the required overlap of the orbitals involved in the cycloaddition is possible. It is questionable, however, if in the further course of bond formation none of the substituents start to get into each others way.



Scheme 2.37

Semiempirical model of (4'*S*)-**44** generated with Hyperchem®

To exclude some of the presumed sterical hinderence from the system and to eliminate the donor effect of the acetal in the dienophile, ester **45** was synthesized from alcohol **37b** and boc-protected (+/-)-gabaculine **43** (Scheme 2.38). Ester **45** could be obtained in moderate yield using the usual mixed anhydride method. A reaction of this cyclisation precoursor should be possible through both an *endo-E* as well as an *exo-E* transition state. For the latter transition state, no sterical interference of the methoxy carbonyl group with the boc protection group would be expected for either diastereomer. Unfortunatelly both the improved electronic properties of the ene/diene pair as well as the removal of possible sterical hinderance from the system did not bring the expected result.



(+/-) 43 **45**

Scheme 2.38

Synthesis of ester **45** and attempted cyclisation thereof. Reagents and conditions: a) Et_3N, pivaloyl chloride, **37b** DMAP, 2h, 0°C, 44%. b) o-xylene, 145°C, several days.

Even at prolonged reaction times at 145°C no cyclisation could be observed. Instead, some double bond isomerisation of the allylic ester was observed.

A similar example in literature suggests that temperatures of 275°C and high pressures are required.[104] The scaffold described in this example differs from the one in Scheme 2.38 only by the absence of the boc protected amine and the methoxy group.

3 Conclusions and Outlook

A short and facile route to a tricyclic scaffold with high structural similarity to several bioactive natural products has been worked out. The key step of the synthesis involves a *intramolecular* hetero *Diels-Alder* reaction. The reaction proceeds with very high diastereoselectivity through an *E-endo or Z-exo* transition state, as established on the basis of X-ray structural analysis of the products. The scope and limitations of a ribose derived furanoside used as dienophile has been fully evaluated. The dienophile was shown to react in inverse electron *Diels-Alder* reactions as well as in normal electron demand *Diels-Alder* reactions involving carbodienes. The electronic nature of the dienes was found to be essential for their reactivity in a cycloaddition in accordance with the literature. The problem of thermal syn elimination in some acylacrylic esters during cyclisation was solved by $LiClO_4$ catalysis of the hetero *Diels-Alder* reaction.

Further elaboration of the scaffold to gain access to a variety of derivatives with different functional groups has been made. Thus, derivatives containing aniline groups in C(6) position and either a ketone or chloromethyl functionality in C(5) position were synthesised. With the elaboration of a synthetic route involving asymmetrical functionalized 1,2-diketones a way to scaffolds containing functional groups both in C(6) and C(5) position was prepared. With a reliable route to asymmetrically functionalized 1,2-diketones in hand the synthesis of dihydro furo pyranones ready for diversification is in hand.

The value of dienophile **1** for the construction of natural product-like scaffolds has been increased by the preparation of a benzyl protected glycine linker replacing the original methoxy carbonyl group. This linker enables the immobilisation of scaffolds derived from dienophile **1** on different solid supports containing an amine functionality. The potential of such immobilized tricyclic scaffolds has been demonstrated by the synthesis of a small test library of 8 different compounds. All products were isolated and fully characterized. Sufficient stability of the scaffold containing a double ketal/acetal structure to acidic cleavage conditions used for release from N-protected PAL solid supports has been proven. Solvolysis of the lactone in solution as well as on solid support gave access to a new bicyclic structure still open for further modification.

The single compounds produced in the course of this work as well as the library products are interesting structures that are currently investigated in biological activity tests.

The compounds produced in the small test library presented in this work might be too polar to match biological criteria. Synthesis of an immobilized scaffold containing a keto function, however, opens the way to more lipophilic compounds. Initial experiments showed that *Wittig* olefination products can be obtained. Further optimisation is required, however.

4 Experimental Part

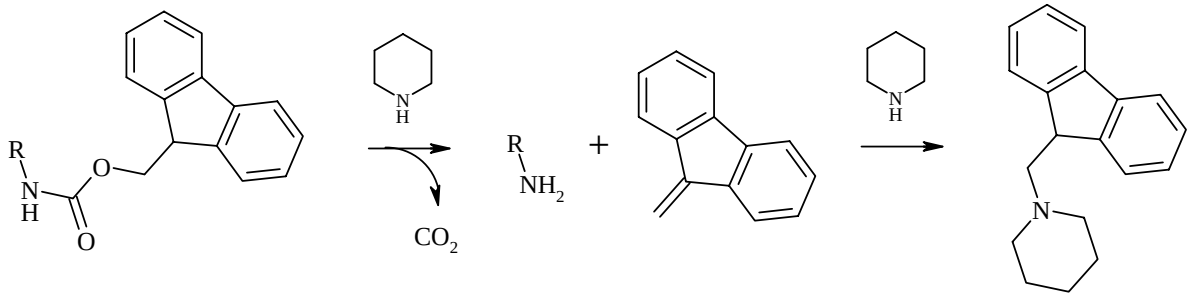
4.1 Definitions

4.1.1 Loading Efficiency and -Capacity

Each type of solid support and even each batch of a specific resin is different regarding its loading capacity. The loading capacity is the maximum amount (mol/g) of an ideal coupling partner that can be bound onto the surface of a certain quantity of solid support.
When immobilizing a substrate on a solid support only a fraction of the available functional groups get occupied, depending on the substrate and the conditions. The loading efficiency is expressed as the ratio of [loading capacity (mol/g) / bound substrate (mol/g)]·100%.

4.1.2 UV-Spectrometric Quantification of the Loading Efficiency

In the case of immobilized substrates containing chromophoric protection groups (e.g. fmoc) the loading efficiency can be determined accurately by UV spectrometric quantification. In the case of an fmoc protecting group cleaved with piperidine, the dibenzovulvene-piperidine adduct forms froms from dibenzovulvene[105] (λ = 302 nm, ε = 7800, see Scheme 4.1).



dibenzovulven-piperidine adduct

Scheme 4.1

Deprotection of the 9-fluorenylmethoxycarbonyl amino protecting group using piperidine.

The absorbance (*A*) of an aliquot of the cleaving solution is measured to get exact concentration of the cleaving product (see chapter 2.4.4 general method C). The quantity of substrate bound on the support derived from this method is put into relation with the loading capacity as described above.

4.1.3 Absorbance and Extinction Coefficient

The absorbance (*A*) is the logarithm to base ten of the reciprocal of the spectral internal transmittance (*T*).

$$A = -\log T$$

The reading displayed by most commercially available photometers is the absorbance, because it is proportional to the concentration according to the Lambert-Beer Law.
The extinction coefficient is the constant used in the Beer-Lambert Law which relates the concentration (*c*) of the substance being measured (in moles) and the path length (*d*) to the absorbance of the substance in solution at a specific wavelength.

$$\varepsilon = A / (c * d)$$

4.2 Instrumentation

4.2.1 NMR-, UV- and IR Spectroscopy

NMR Spectroscopy

1H-NMR spectra were recorded on a *Bruker* AC 300 MHz or a *Bruker* DRX 500 MHz spectrometer and are reported in δ from Me_4Si (δ = 0.00 ppm) or from $CDCl_3$ (δ = 7.26 ppm). The ^{1}H-NMR chemical shifts and coupling constants were determined assuming first-order behaviour. Multiplicities are reported using the following abbreviations: *s* (singlet), *d* (doublet), *dd* (doublet of doublets), *dt* (doublet of triplets), *t* (triplet), *q* (quartet). Where coupling behaviour of higher order has to be assumed the abbreviations m (multiplet) or br (broad) have been used. The list of coupling constants (*J*; reported to the nearest 0.1 Hz) corresponds to the order of the multiplicity assignment.

13C-NMR spectra were recorded on a *Bruker* AC 300 MHz or a *Bruker* DRX 500 MHz spectrometer with the chemical shifts relative to the signals of the NMR-solvent[106].
The NMR data was evaluated with the *Bruker* programs, 1D WIN-NMR and 2D WIN-NMR, version 6.0.

UV Spectroscopy

UV spectra were recorded with UV/VIS Spectrometer Lambda 16 of *Perkin Elmer*. The blank, spectra of pure solvent or buffer with the same UV-cell, was subtracted from measured spectra to receive corrected spectra.

IR Spectroscopy

IR spectra were recorded as pure substance (solid or oil) using a *Jasco* FT/IR-460 plus spectrometer, with a Golden Gate Mk II ATR Accessory with Diamond Top-plate and KRS-5 lenses, and processed with the Spectra Manager of *Jasco*. Peaks are reported between 3500 and 900 cm^{-1}.

4.2.2 Mass Spectrometry

All mass spectrometric measurements were carried out by the Analytic Research Service (ARS) of Dr. S. Schürch and Dr. J. Schaller (Departement für Chemie und Biochemie, Universität Bern)

Electron Ionization Mass Spectrometry (EI-MS)

Instrument: Micromass Autospec Q (*Waters / Micromass*), Ionization mode: electron impact, Ionization energy: 70 eV, Sample inlet: solids probe, Acceleration voltage: 8 kV, Mass resolving power: >1000 (10% valley), Calibration: External calibration using perfluorokerosene (PFK).

Electrospray Mass Spectrometry (ESI-MS)

Instrument: Micromass Platform (quadrupole mass spectrometer), Injection: Loop injection, injection volume: 10 µl, flow rate: 10 µl/min, Capillary potential: +3500 V (positive ion mode); -3000 V (negative ion mode), Curtain gas: nitrogen, Calibration: External calibration with myoglobin. Measured mostly in CH_3CN or CH_3CN/H_2O/formic acid 50:49:1.

Accurate Mass Determination in Combination with EI and ESI

Accurate mass determinations using electron ionization are performed on the Micromass Autospec Q mass spectrometer. The mass accuracy is of the order of ± 2 ppm. Accurate mass determinations using electrospray ionization are performed on the QStar Pulsar instrument. Mass accuracy is better than ± 5 ppm. See the basic instrumental parameters for the corresponding low resolution analyses. The following internal standards are used for accurate mass determination:

EI: perfluorokerosene (PFK)

ESI positive ion mode: caesium iodide (Cs+) and reserpine [M+H]+

ESI negative ion mode: caesium iodide (I-) and taurocholic acid [M-H]-

4.2.3 Analytical TLC and Preparative Column Chromatography

All reactions were monitored by thin layer chromatography (TLC), which was carried out on 0.25 mm Macherey-Nagel silica gel-25 UV_{254} precoated plates. The following reagents were used as detectors (dipping followed by heating):

Anisaldehyde reagent: 1 mL of anisaldehyde and 2 mL of concentrated sulfuric acid dissolved in100mL of glacial acetic acid.

Potassium permanganate reagent: 3.0 g $KMnO_4$, 20 g K_2CO_3, 5.0 ml 5% NaOH and 300ml water.

Cer reagent: 5.0 g phosphomolybdic acid hydrate and 16 ml concentrated phosphoric acid were dissolved in 200 ml water. Finally 2.0 g cer(IV)-sulfate was added.

Bromokresol green reagent : 40 mg of bromokresol green indicator (3,3',5,5'-tetrabromo-m-kresolsulfon-phthalein) was dissolved in 100 mL of ethanol and treated with 0.1 M aqueous NaOH until a blue color appeared. Basic compounds give a deep blue, acid or weak acid compounds a yellow color.

Ninhydrine reagent: 0.2 g of ninhydrine was dissolved in 100mL of ethanol.

Vanillin reagent: 8.6 g vanillin and 2.5 ml concentrated sulfuric acid were dissolved in 200 ml ethanol.

Preparative liquid chromatography (LC) was performed with silica 60 A, 40-63 nm, from sds (France). Silica gel was suspended, in starting eluent, before filled into column and then covered with cristobalite (seesand). After the dissolved crude material was added, solvent,

isocratic or gradient, was pumped through the column using nitrogen from the pressure bottle. Collected fractions were controlled by TLC.

4.2.4 High Performance Liquid Chromatographie (HPLC)

BIO-TEK Kontron Instruments: pump system 525, diode array detector 545V.
Soft ware: Galaxie Chromatography Data System (Varian).

RP-HPLC: LiChrospher® 100-RP-18 (7µm); Merck; A: 0.1 M triethyl ammonium acetate in water, B: acetonitrile; 40 °C.
NP-HPLC: LiChrospher® Si 60 (10 µm), Merck; Acetonitrile isocratic, 2 ml/min, rt.

4.2.5 X-Ray Crystal Structure Analysis

The X-ray crystal structure analysis was carried out by the BENEFRI-small molecule crystallography service (Prof. Helen Stoeckli-Evans), Institute of Chemistry, University of Neuchâtel, Switzerland. Crystallographic data (exluding structure factors) for **4a**, **4b** and **4h** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications numbers CCDC 248308, CCDC 248309, and CCDC 248310, respectively.

The intensity data were collected at 153K (-120°C) on a Stoe Mark II-Image Plate Diffraction System[107] equiped with a two-circle goniometer and using MoKα graphite monochromated radiation. Image plate distance 100mm, ω rotation scans 0 - 148° at ϕ 0°, step Δω = 1.2°, 2θ range 3.2 – 51.0°, $d_{min} – d_{max}$ = 12.91 - 0.83 Å.
The structure was solved by Direct methods using the programme SHELXS-97[108]. The refinement and all further calculations were carried out using SHELXL-97[109]. The H-atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2.
The molecular structure and crystallographic numbering scheme are illustrated in the PLATON[110] drawing.

In the crystal symmetry related molecules are connected by an intermolecular C-H…O hydrogen bond forming a chain extending in the *a* direction.

4.2.6 Autoclave

A high pressure reactor made of high-alloy, SS 316 TI stainless steel with PTFE lining by *Berghof* was used. Type: HR-100; 150 ml, 100 bar, 250°C. The autoclave is equipped with a rupture disc to reliably limit maximum pressure, clamping ring for tool-free opening and closing, thermometer, pressure gauge and liquid and/or gas sample extraction device.

4.3 Solvents, Chemicals and Consumables

Chemicals used for organic synthesis were of highest quality obtainable from commercially suppliers (Fluka, Aldrich, Merck and Acros).

Solvents used in organic synthesis were of the quality needed from commercially suppliers.Solvents for work up and liquid chromatography were of technical quality and distilled prior to use. Silica Gel 40-63 µm from *SDS* (France) was used. Organic solvents used in HPLC were of super purity solvent (SPS) quality from Romil (Methanol 205, Acetonitril 190, Chloroform, EtOAc, n-hexane 95%). Ion exchange Water was used for synthesis work up. Deuterated solvents for NMR were from various suppliers.

Syringes and needles used were from *Braun AG*.

Protecting gas Ar 48 from *Garbagas* was used.

Solid supports and compound **1** were a generous gift by the Novartis Institutes of BioMedical Research

4.4 General Methods

General method A: Ester formation

In a three-neck flask the acylacrylic acid was suspended in absolute 1,2-dichloroethane (3.5 ml / mmol). The suspension was cooled to 0°C before triethylamine (1.55 eq.) was added within 8 min. To the thus obtained yellow brown solution pivaloyl chloride (1.46 eq.) was added during 10 min in 1,2-dichloroethane (0.15 ml/mmol) and the mixture was stirred at 0°C for 30 min. Then the alcohol (1 eq.) in 1,2-dichloroethane (1 ml/mmol) and, shortly after, DMAP (0.15 eq.) was added. Stirring was continued at 0°C for 2 h.

General Method B: Pd/C Hydrogenation

In an absolute 3 neck flask with two cocks (for vacuum and H_2) the benzyl ester protected enol ether was dissolved in THF (40 – 50 ml / mmol). Under argon and stirring Pd/C 10% (200 – 250 mg / mmol) was added. The flask was evacuated and filled with hydrogen (twice). Stirring is continued for 2 – 3 hours. The reaction was quenched with argon and filtered through THF-soaked Celite. The celite was washed twice more with THF.

General Method C: Test Library

Coupling Step

Resin **A** (153 mg, 110 μmol, max. loading = 0.72 mmol/g, benzylamin-rest) and Resin **B** (180 mg, 110 μmol, max. loading = 0.61 mmol/g, methoxyethyl-amin-rest) were each weighed into a syringe with filter fritt.

Each Resin was treated with 2-3 ml NMP (N-methyl-pyrollidon), stirred well with a spatula and left to swell for 30 min in a syringe with filter fritt. The following was done for each of the two portion of solid support separately.

HCTU (100 mg, 241.6 μmol) together with HOBT (33 mg, 241.6 μmol) was dissolved in 1 ml NMP and **28d (**148 mg, 241.6 μmol) was dissolved in 1 ml NMP. The NMP from the swelling was sucked off. The Teflon® cock was replaced with a cover which had to by firmly closed. The prepared solutions and DIPEA (148 μl, 880 μmol) were added to the resins. Sometimes addition of some more NMP is necessary so the resin can float inside the syringe freely. The suspensions were agitated over night.

The solution were sucked off and a fresh coupling-solution (HCTU (68 mg, 165 μmol) together with HOBT (22 mg, 165 μmol) dissolved in 1 ml NMP and **28d** (101.2 mg, 164.8

μmol) dissolved in 1 ml NMP.) was added to the resin together with DIPEA (148 μl, 880 μmol). No washing step is necessary here. The suspension was stirred for 4-5h.

Washing/Deprotection:

The solutions were sucked off. The resins were washed with portions (around 1 ml) of 5x DMA (degased), 1x isopropanol, 3x DMA, 5x isopropanol, 2x DCM and 2x DMA.
During 30 min 30 ml 20% piperidin/DMA solution was added continuously to each resin. The solution was collected in a clean 100 ml graduated flask and diluted to 100 ml with methanol. In an additional flask a reference solution of 30 ml 20% piperidin/DMA was diluted with 70 ml of methanol. Both solutions are measured for UV absorption, where absorption between 320 nm and 230nm is measured. The fmoc maximum is found between 299.9 and 300.1. The value of the blank measured at 320 was subtracted from the one of the sample measured at 302nm. From this value the percentage of loading on the resin was calculated. $\varepsilon = 7800 \Rightarrow c = A/\varepsilon$ (see 4.1.2)

For resin **A** absorption of 1.275 corresponding to **59% loading** was found.
For resin **B** absorption of 1.205 corresponding to **56% loading** was found.

Washing/Splitting/Derivatisation:

The resin was washed with portions of 5x DMA, 1x isopropanol, 3x DMA, 5x isopropanol, 2x DCM and 2x DMA. At the end rinsing with DCM abs. was necessary.
Resin **A** was split into 2 unequal portions of ¼ (**A1**) and ¾ (**A2**) while suspended in DCM.
Resin **B** was split into 2 unequal portions of ¼ (**B3**) and ¾ (**B4**) while suspended in DCM.

A1 was treated with butyryl chloride (57μl, 550μmol, 20 eq.) in 400 μl absolute DCM/pyridine 8:2.
A2 was treated with isovaleryl chloride (201 μl, 1.65 mmol, 60 eq.) in 1.2 ml absolute DCM/pyridine 8:2.
B3 was treated with benzoyl chloride (64 μl, 550μmol, 20 eq.) in 400 μl absolute DCM/pyridine 8:2.
B4 was treated with 2-furoyl chloride (129 μl, 1.65 mmol, 60 eq.) in 1.2 ml absolute DCM/pyridine 8:2.

The suspensions were agitated for 3h on the rotor. (**close syringe well!!**)

Washing/Splitting

The resin were washed with portions of 5x DMA (degased), 1x isopropanol, 3x DMA, 5x isopropanol, 2x DCM and 2x DMA. At the end rinsing with DCM abs. was necessary.

A1 and **B3** were put aside for the cleaving step in the end. **A2** and **B4** were split into 3 equal portions while suspended in DCM. One third of **A2** and **B4** are also put aside for the cleaving step in the end. The other two thirds of **A2** (**A2α** and **A2β**) and the 2/3 of **B4** (**B4α** and **B4β**) were treated as follows:

Aminolysis:

A2α and B4α were each treated with benzylamine (75 µl, 687 µmol) together with 2-hydroxy pyridine (13 mg, 137 µmol) in 0.5 ml THF.

A2β and **B4β** were both treated with butylamine (68 µl, 687 µmol) together with 2-hydroxy pyridine (13 mg, 137 µmol) in 0.5 ml THF.

Cleaving:

In 5 repetitions 0.6 ml of a 20% TFA aq. (95%TFA in water)/DCM solution was left to react with the resins for 15 min per repetition and portion. The thus obtained solutions were collected in a sample flask. TFA and DCM were aired off with a stream of argon. The remaining oil was dissolved in MeOH and evaporated fully. The samples were redissolved in C_6D_6 and evaporated once again before measuring crude NMR.

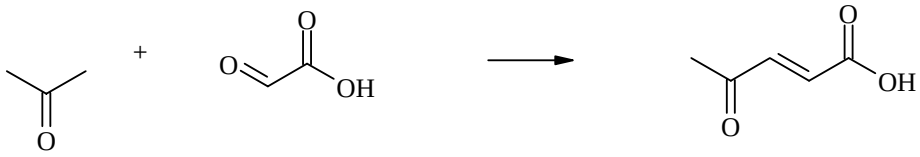
HPLC:

The samples were dissolved in AcCN. Some insoluble material remains still suspended and is removed by filtration through syringe filters. Separation on the normal phase LiChrospher® Si 60 (10 µm) column with AcCN isocratic. UV detection was messured between 220 and 320 nm.

4.5 Experimental Procedures and Characterisation Data

4.5.1 Acylacrylic Acids 2a – 2i

(*E*)-4-Oxo-pent-2-enoic acid (2a).



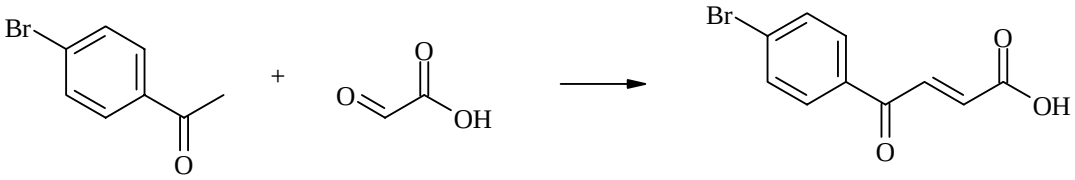
C_3H_6O	$C_2H_2O_3$	$C_5H_6O_3$
58.08	92.06	114.10
		2a

To a solution of glyoxylic acid monohydrate (50 g, 0.53 mol) in 500 ml acetone, morpholine.HCl (66.4 g, 0.54 mol) were added and stirring was applied for one hour. The now clear solution was refluxed for three days. At –10°C, morpholine HCl was crystallised and filtered off over Hyflo, which is rinsed with 200 ml of acetone. After evaporation of the solvents, the obtained brown oil was washed with 200 ml of water and extracted 5 times with 160 ml of diethylether. The org. Phases were dried over Na_2SO_4 and solvents evaporated. The obtained solid was stirred with 155 ml EtOAc and filtered off after 10 min. This yielded 39.3 g (0.34 mol, 65 %) of a yellow solid.

^{1}H–NMR (300 MHz, CD_3OD): 6.94 (1H, *d*, *J* = 16.2), 6.69 (1H, *d*, *J* = 16.2), 2.36 (3H, *s*); ^{13}C-NMR (75 MHz, CD_3OD): 200.7, 169.1, 141.7, 134.0, 28.5; IR (KBr): 3066s, 2930s, 2704m, 2584m, 2518m, 1670s, 1644s, 1623s, 1439s, 1409s, 1361s, 1304s, 1294s, 1277s, 1258s, 1236s, 1217s, 1104w, 1026m, 1005s, 930m, 894m.

(*E*)-3-Benzoylacrylic acid (2b) was obtained from Aldrich

(*E*)-4-(4-Bromo-phenyl)-4-oxo-but-2-enoic acid (2c)

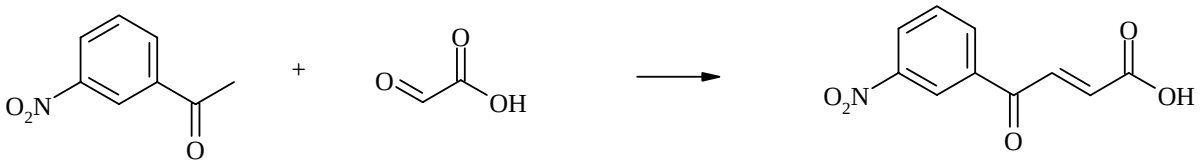


C_3H_6O	$C_2H_2O_3$	$C_5H_6O_3$
58.08	92.06	114.10
		2c

4-Bromo-acetophenon (5,65 g, 27.8 mmol) weas suspended in 50 ml acetic acid and 5ml HCl conc. After addition of glyoxylic acid monohydrate (2.65 g, 27.8 mmol) the mixture was refluxed for 15 h. Solvents were removed from the orange solution, the solid yellow residue was taken up in EtOAc and filtered. After evaporation of the EtOAc the procedure was repeated once. Drying afforded 2.52 g (9.89 mmol, 35,7 %) of a pale yellow solid.

^{1}H-NMR (300MHz, $CDCl_3$): 7.95 (1H, *d*, *J* = 15.5), 7.88 (2H, *m*), 7.68 (2H, *m*), 6.90 (1H, *d*, *J* = 15.5,); ^{13}C-NMR (75 MHz $CDCl_3$): 188.1, 170.1, 137.7, 135.1, 132.4, 131.8, 130.3, 129.6; IR (KBr): 3038 (s, br), 2678 (m), 2579 (m), 1693 (s), 1668 (s), 1634 (s), 1584 (s), 1568 (m), 1486 (m), 1417 (s), 1398 (s), 1297 (s), 1193 (s), 1106 (m), 1071 (s), 1007 (s), 979 (s), 916 (m), 837 (s), 763 (s), 717 (m), 654 (s).

(*E*)-4-(3-Nitro-phenyl)-4-oxo-but-2-enoic acid (2d).



$C_8H_7NO_3$ + $C_2H_2O_3$ → $C_{10}H_7NO_5$

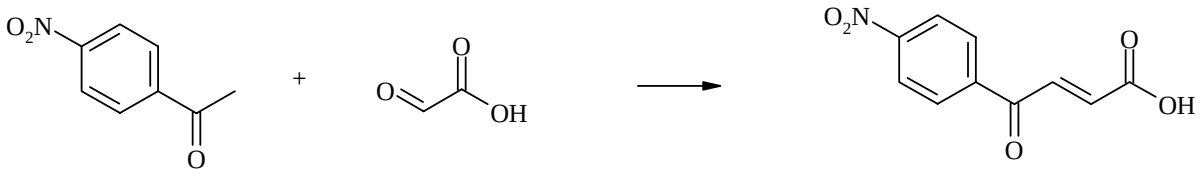
165.15 + 92.06 → 221.17

2d

3-nitro-acetophenon (16.85 g, 0.1 mol) was suspended in 30 ml of acetic acid. After adding glyoxylic acid monohydrate (9.49 g, 0.1 mol) under stirring, the mixture was refluxed for 15 h. The solution was cooled to RT and the obtained yellow brown solid was filtered. The filtrate was washed with ethanol to obtain 10.57 g (47.8 mmol, 47.8%) product which was used without further purification.

^{1}H-NMR (300MHz, DMSO): 8.68-8.61 (1H, *m*), 8.53-8.40 (2H, *m*), 7.90 (1H, *d*, *J* = 15.4), 7.89-7.81 (1H, *m*), 6.73 (1H, *d*, *J* = 15.8); ^{13}C-NMR: (75MHz, DMSO) 188.5, 166.4, 148.3, 137.5, 135.9, 135.1, 134.1, 131.0, 128.2, 123.3; IR (KBr): 3081 (m, br), 2680 (m, br), 1683 (s), 1615 (s), 1580 (m), 1532 (s), 1480 (m), 1418 (s), 1347 (s), 1306 (s), 1199 (m), 1091 (m), 1037 (m), 980 (m), 942 (m), 809 (m), 775 (m), 730 (s), 666 (s), 634 (s).

(*E*)-4-(4-Nitro-phenyl)-4-oxo-but-2-enoic acid (2e).



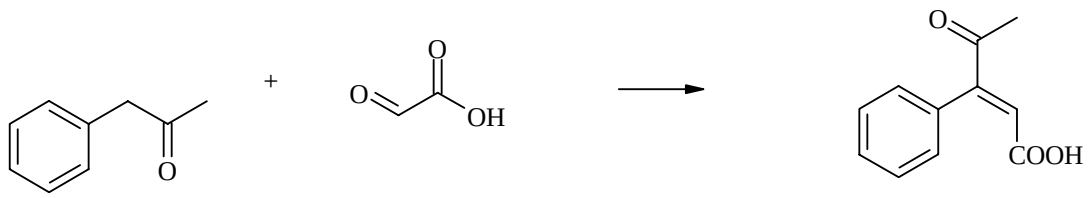
$C_8H_7NO_3$ 165.15 + $C_2H_2O_3$ 92.06 → $C_{10}H_7NO_5$ 221.17

2e

4-nitro-acetophenon (36.5 g, 0.21 mol) was dissolved in 300 ml of toluene. After adding glyoxylic acid monohydrate (22.4 g, 0.243 mol) and p-toluenesulfonic acid (841 mg, 4.4 mmol) under stirring, the mixture was refluxed for 4.5 h in an apparatus with $CaCl_2$-tube and water separator. The solution was cooled to 50°C and 400 ml of 5% aq. Na2CO_3 solution was added. The toluene phase was separated and washed once more with water. Under stirring the water phases were slowly treated with 30 ml of 36% HCl. The so obtained precipitation was filtered off and washed three times with water. After drying 22.9 g (47%) whitish crystals are obtained. Recrystalization from first $CHCl_3$, then $CHCl_3$/1,2-dichloroethane 3/5, and last 1,2-dichloroethane gave 20.8 g (42,5%) of 2e as yellow crystals.

^{1}H-NMR (300MHz, DMSO): 8.35 (2H, *d*, *J* = 8.8), 8.24 (2H, *d*, *J* = 8.8), 7.85 (1H, *d*, *J* = 15.4), 6.70 (1H, *d*, *J* = 15.4); ^{13}C-NMR (75MHz, DMSO): 189.2, 166.4, 150.4, 141.0, 136.0, 134.1, 130.5, 124.2; IR (KBr) 2982 (m, br), 2868 (m, br), 2678 (m), 2580 (m), 1696 (s), 1672 (s), 1606 (s), 1532 (s), 1420 (s), 1351 (s), 1316 (s), 1191 (s), 1113 (m), 1009 (m), 981 (s), 944 (m), 857 (s), 826 (m), 782 (m), 733 (s), 687 (m), 656 (m).

(*E*+*Z*)-4-Oxo-3-phenyl-pent-2-enoic acid (2f)

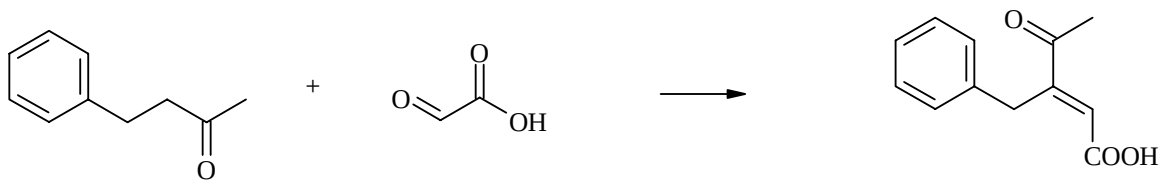


$C_9H_{10}O$	$C_2H_2O_3$	$C_{11}H_{10}O_3$
134.18	92.06	190.20
		2f

To a solution of glyoxylic acid monohydrate (1.84 g, 0.02 mol) in phenyl-aceton (4.0 ml, 0.03 mol) 3 ml of orthophosphoric acid (85%) was poured. The mixture was first heated for 4h at 80°C and then just stirred at room temperature for 24 more hours. The mixture was poured on brine and extracted three times with CH_2Cl_2/diethylether 1:1. The organic phases were washed two more times with brine and then extracted twice with 50 ml sat. aq. Na_2CO_3. The basic water phase was brought to pH = 2 with 6N HCl and extracted three timed with CH_2Cl_2. This gave 2.76 g (15 mmol, 72%) of a yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$): 7.82 – 7.78 (2H, *m*), 7.51 – 7.48 (3H, *m*), 6.30 (1H, *s*) 2.28 (3H, *s*) and 7.41 – 7.37 (3H, *m*), 7.20 - 7.17 (2H, *m*) 6.7 (1H, *s*) 1.83 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 198.9, 187.2, 169.2, 152.8, 134.1, 128.3, 128.2, 124.8, 28.2; IR: 3030, 1710, 1685, 1629, 1574, 1495, 1443, 1403, 1356, 1229, 1202, 1167, 1075, 1021, 1001, 944, 930, 885, 860, 841; EI-MS: 190 (M^+), 147, 145, 134, 130.

(*E*+*Z*)-3-Acetyl-oct-2-enoic acid (2g).

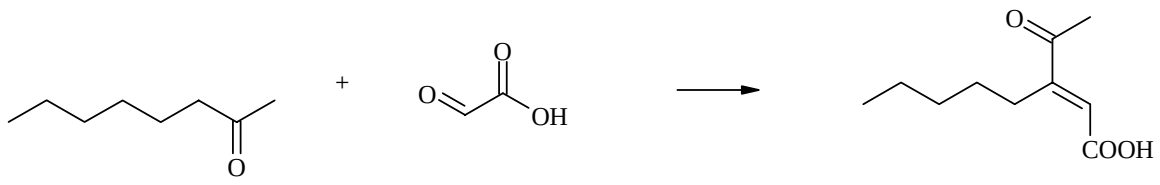


$C_{10}H_{12}O$	$C_2H_2O_3$	$C_{12}H_{12}O_3$
148.21	92.06	204.23
		2g

To a solution of glyoxylic acid monohydrate (3.31 g, 36 mmol) in 4-phenyl-2-butanone (9.86 ml, 63 mmol) 3 ml of orthophosphoric acid (85%) was poured. The mixture was first heated for 4h at 90°C and then just stirred at room temperature for 18 more hours. The reaction mixture was extracted three times with 10-15 ml of CH_2Cl_2/diethylether = 1:1. The organic phases were washed with 20 ml of brine. After drying (Na_2SO_4), evaporating the solvents and distilling at 40°C (0.1 Torr) 3.462g (18.8 mmol, 28%) of 2g as a colorless oil was obtained.

^{1}H-NMR (300MHz, $CDCl_3$): 6.51 (1H, *s*), 2.79-2.74 (2H, *m*), 3.18 (3H, *s*), 1.40-1.28 (6H, *m*), 0.90- 0.86 (3H, *m*); ^{13}C-NMR (75MHz, $CDCl_3$): 200, 170.9, 157.9, 124.5, 31.9, 28.9, 26.8, 26.7, 22.3, 13.9; IR: 2957, 2929, 2860, 1686, 1636, 1415, 1359, 1245, 1181, 1126, 878, 737; EI-MS: 184 (M^+), 169, 167,166, 137, 138, 124.

(*E*+*Z*)-3-Acetyl-oct-2-enoic acid (2h).



$C_8H_{16}O$ + $C_2H_2O_3$ → $C_{10}H_{16}O_3$

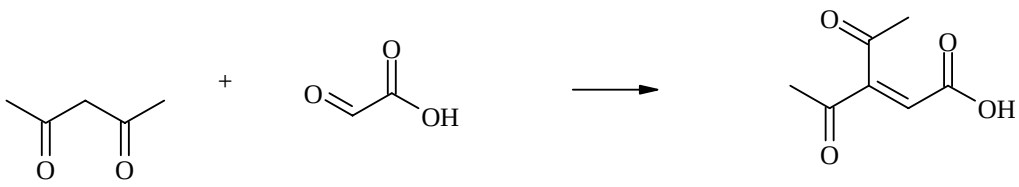
128.22 + 92.06 → 184.24

2h

To a solution of glyoxylic acid monohydrate (3.31 g, 36 mmol) in 4- phenyl-2-butanon (9.46 ml, 63 mmol) 3 ml of orthophosphoric acid (85%) was poured. The mixture was first heated for 4h at 90°C and then just stirred at room temperature for 18 more hours. The reaction mixture was extracted three times with 10-15 ml of CH_2Cl_2:diethylether = 1:1. The organic phases were washed with 20 ml of brine. After drying (Na_2SO_4), evaporating the solvents and distilling at 165°C (0.29 Torr) 2.37g (11 mmol, 32%) of 2f as a colorless oil was obtained.

^{1}H-NMR (300MHz, $CDCl_3$): 7.37-7.11 (5H, *m*), 6.66 (1H, *s*), 2.34 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 199.4, 170.6, 155.1, 137.7, 128.9, 128,5, 126.5, 125.0, 32.1, 27.0; IR: 3062, 3029, 1679, 1628, 1604, 1495, 1453, 1418, 1369, 1258, 1233, 1186, 1076, 1030, 1015, 934, 905, 782, 739, 694, 667; EI-MS: 204 (M^+), 187, 186, 172, 171, 159.

3-Acetyl-4-oxo-pent-2-enoic acid (2i).



$C_5H_8O_2$ + $C_2H_2O_3$ → $C_7H_{18}O_4$

100.12 + 92.06 → 156.14

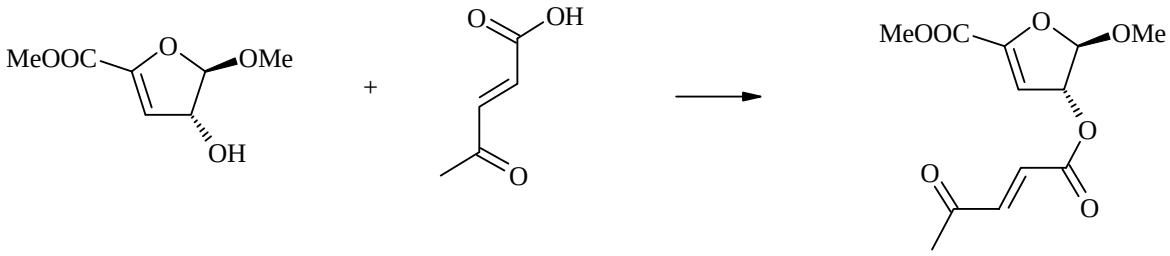
2i

To a solution of glyoxylic acid monohydrate (5 g, 54.3 mmol) in 50 ml acetic acid, acetylaceton (5.6 ml, 54.3 mmol) were added. The mixture was heated to 80°C for 5h or until no more acetylaceton was detectable by TLC. Acetic acid and the water formed were evaporated and fully removed at 0.1 mbar and 155°C. This afforded 7.8 g (50 mmol, 92%) of **2i** as a yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$: 6.55 (1H, *s*), 2.52 (3H, *s*), 1.84 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 193.4, 169.0, 159.4, 126.7, 106.7, 28.7, 24.6; IR: 3104, 3004, 1748, 1685, 1419, 1370, 1324, 1211, 1131, 1085, 1022, 930, 860, 741, 678, 658, 614; EI-MS: 156 (M^+), 141, 138, 114.

4.5.2 Acylacrylate Esters 3a – 3i

(4*R*,5*R*)-5-Methoxy-4-((*E*)-4-oxo-pent-2-enoyloxy)-4,5-dihydro-furan-2-carboxylic acid methyl ester (3a)

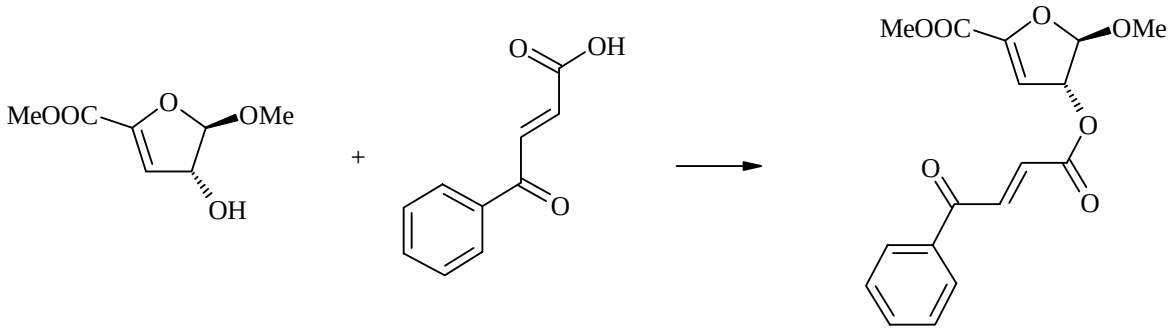


$C_7H_{10}O_5$	$C_5H_6O_3$	$C_{12}H_{14}O_7$
174.15	114.10	270.24
1	**2a**	**3a**

To a suspension of 2a (2.28 g, 20 mmol) in 1,2-dichloroethane, triethylamine (3.1 ml, 22 mmol) was added at 0°C. The addition of pivaloyl chloride (2.65 g, 22 mmol) was followed by dihydrofuranoside 1 (3.48 g, 20 mmol). After 3 h DMAP (310 mg, 2.5 mmol) was added and thus all remaining starting material converted. The reaction mixture was washed with 200 ml of sat. aq. $NaHCO_3$ and extracted three times with 200 ml EtOAc. After drying (Na_2SO_4), evaporating the solvent and separation of the crude on 200 g of silicagel (ethylacetate/hexane 3:7) 3.27 g (12.1 mmol, 60.5%) of 3a as a white solid was obtained.

TLC (EtOAc/hexane 3:7): R_f 0.24; ^{1}H-NMR (300MHz, $CDCl_3$): 7.04 (1H, *d*, *J* = 15.8), 6.63 (1H, *d*, *J* = 16.2), 6.06 (1H, *d*, *J* = 2.9), 5.66 (1H, *dd*, *J* = 1.3, *J* = 2.8), 5.44 (1H, *d*, *J* = 1.5), 3.86 (3H, *s*), 3.59 (3H, *s*), 2.36 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 197, 164, 160, 152, 141, 130, 110, 107, 81, 57, 52, 28; IR (KBr): 3064, 3041, 3004, 2954, 2844, 1732, 1716, 1677, 1648, 1626, 1456, 1440, 1373, 1331, 1312, 1272, 1256, 1228, 1202, 1165, 1135, 1107, 1074, 1023, 1008, 980, 969, 921, 906, 896; EI-MS: 270 (M^+), 238 , 211.

(4*R*,5*R*)-5-Methoxy-4-((*E*)-4-oxo-4-phenyl-but-2-enoyloxy)-4,5-dihydro-furan-2-carboxylic acid methyl ester (**3b**)**.**

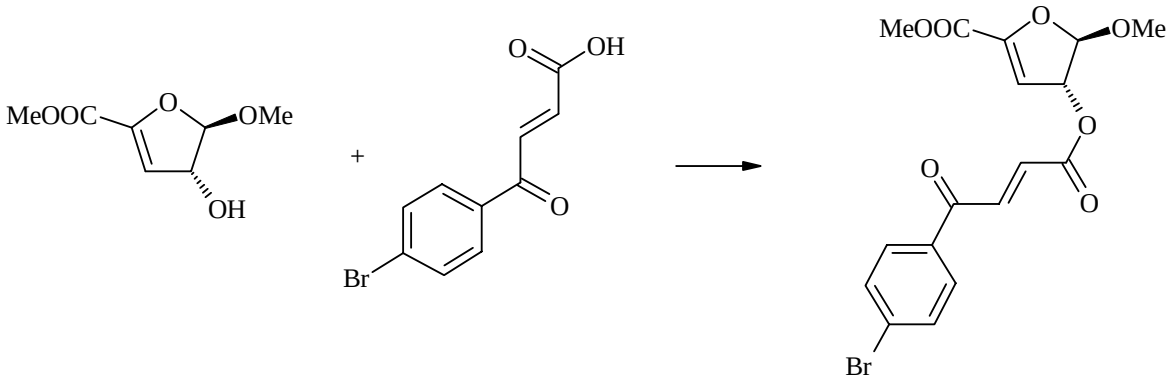


$C_7H_{10}O_5$	$C_{10}H_8O_3$	$C_{17}H_{16}O_7$
174.15	176.17	332.31
1	**2b**	**3b**

In an absolute three-neck flask 2b (1.2 g, 6.6 mmol) was suspended in 9ml of absolute 1,2-dichloroethane under argon. The suspension was cooled to 0°C before triethylamine (0.95 ml, 6.9 mmol) was added. To the now yellow solution pivaloyl chloride (0.78 ml, 6.3 mmol) was added slowly in 2 ml 1,2-dichloroethane and after stirring for some minutes **1** (1 g, 5.7 mmol) was added in another 4ml of 1,2-dichloroethane. After adding DMAP (140 mg, 1.15 mmol) and warming to RT the mixture was stirred for 3 h. The red turbid mixture was washed with 100 ml sat. aq. $NaHCO_3$ and extracted with diethylether. The solvents were evaporated and the crude was purified on silicagel (EtOAc/hexane 9:1, 6:1, 3:1). This yielded 1.30 g (3.9 mmol, 68.6%) of **3b** as a yellow oil.

TLC (EtOAc/hexane 2:3): R_f 0.59; ^{1}H-NMR (300MHz, $CDCl_3$): 8.02-7.95 (2H, *m*), 7.91 (1H, *d*, *J* = 15.8), 7.68-7.59 (1H, *m*), 7.55-7.48 (2H, *m*), 6.85 (1H, *d*, *J* = 15.8), 6.08 (1H, *d*, *J* = 2.6), 5.69 (1H, *dd*, *J* = 2.9 and 1.5), 5.47 (1H, *d*, *J* = 1.1), 3.86 (3H, *s*), 3.59 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 189.0, 164.4, 159.9, 152.0, 137.5, 136.3, 134.0, 131.2, 128.8, 109.7, 107.3, 81.3, 57.0, 52.6; IR (Film on NaCl): 3128, 3064, 3006, 2956, 2849, 1732, 1674, 1633, 1598, 1581, 1449, 1370, 1291, 1252, 1222, 1164, 1109, 1005, 923, 899, 792, 758, 731, 690.

(4*R*,5*R*)-4-[(*E*)-4-(4-Bromo-phenyl)-4-oxo-but-2-enoyloxy]-5-methoxy-4,5-dihydro-furan-2-carboxylic acid methyl ester (3c).

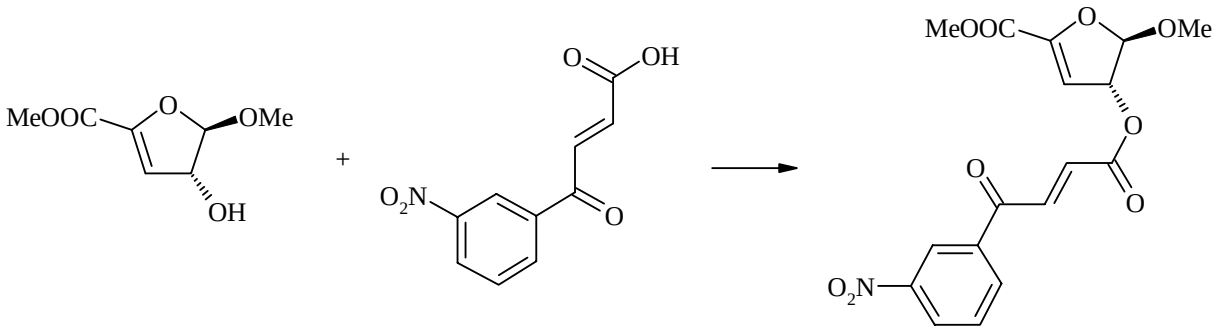


$C_7H_{10}O_5$	$C_{10}H_7BrO_3$	$C_{17}H_{15}BrO_7$
174.15	255.07	411.21
1	**2c**	**3c**

In a three neck flask **2c** (0.79 g, 3.1 mmol, 1.1 eq) was suspended in 10 ml of absolute 1,2-dichloroethane. The suspension was cooled to 0°C before triethylamine (0.45 ml, 3.2 mmol) was added. To the thus obtained yellow brown solution pivaloyl chloride (0.38 ml, 3.1 mmol) was added slowly in 3 ml 1,2-dichloroethane and the mixture was stirred at RT for 1h. After cooling again to 0°C **1** (0.49 g, 28 mmol) in 3 ml 1,2-dichloroethane was added dropwise. Shortly after, DMAP (68 mg, 0.56 mmol) was added and the cooling bath was removed. After 4 h the mixture was washed with 50 ml sat. aq. $NaHCO_3$ and extracted three times with diethylether. After drying over Na_2SO_4 and evaporation of the solvents the orange crude was purified on silicagel (hexane/EtOAc 9:1, 6:1). This yielded 0.78 g (1.89 mmol, 67.2%) of **3c** as a yellow solid.

TLC (hexane/EtOAc 3:2): R_f 0.68-0.71; ^{1}H-NMR: (300 MHz, $CDCl_3$) 7.87 (1H, *d*, *J* = 15.8), 7.85 (2H, *d*, *J* = 8.8), 7.66 (2H d, *J* = 8.5), 6.86 (1H, *d*, *J* = 15.8), 6.08 (1H, *d*, *J* = 2.6), 5.69 (1H, *dd*, *J* = 2.9 and 1.5,), 5.47 (1H, *d*, *J* = 1.5), 3.86 (3H, *s*), 3.59 (3H, *s*); ^{13}C-NMR: (75 MHz, $CDCl_3$): 188.0, 164.3, 159.9, 152.1, 136.9, 135.1, 132.3, 131.7, 130.3, 129.5, 109.7, 107.2, 81.4, 57.1, 52.6; IR: (KBr) 3127, 3081, 2958, 2851, 1729, 1673, 1630, 1580, 440, 1400, 1370, 1328, 1308, 1291, 1667, 1220, 1155, 1108, 1071, 998, 975, 933, 927, 895, 846, 760, 751.

(4*R*,5*R*)-5-Methoxy-4-[(*E*)-4-(3-nitro-phenyl)-4-oxo-but-2-enoyloxy]-4,5-dihydro-furan-2-carboxylic acid methyl ester (3d).

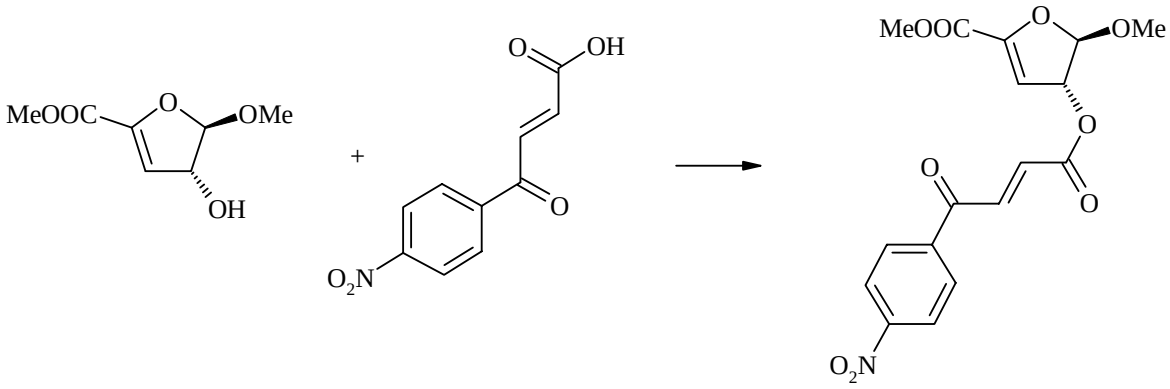


$C_7H_{10}O_5$	$C_{10}H_7NO_5$	$C_{17}H_{15}NO_9$
174.15	221.17	377.31
1	**2d**	**3d**

In a three neck flask **2d** (3.5 g, 15.8 mmol) was suspended in 43 ml of absolute 1,2-dichloroethane. The suspension was cooled to 0°C before triethylamine (2.3 ml, 16.4 mmol) was added during 5 min. To the thus obtained yellow brown solution pivaloyl chloride (1.9 ml, 15.4 mmol) was added within 10 min in 1.8 ml 1,2-dichloroethane. The mixture was stirred at 0°-15°C for 40 min. After cooling again to 5°C **1** (1.22 g, 7 mmol) in 4 ml 1,2-chloroethane was added dropwise. Shortly after, DMAP (0.222 g, 1.82 mmol) of were added and the cooling bath was removed. After 4 h the mixture was washed with sat. aq. $NaHCO_3$ and extracted three times with diethylether. After drying over Na_2SO_4 and evaporation of the solvents the orange crude was purified on silicagel (hexane/EtOAc 6:1 -> 2:1). This yielded 1.67 g (4.4 mmol, 63%) of **3d** as a yellow oil.

TLC (hexane/EtOAc 3:2): R_f 0.34; ^{1}H-NMR (30MHz, $CDCl_3$): 8.83-8.78 (1H, *m*), 8.55-8.45 (1H, *m*), 8.35-8.28 (1H, *m*), 7.92 (1H, *d*, *J* = 15.4), 7.75 (1H, t, *J* = 7.9), 6.94 (1H, *d*, *J* = 15.4), 6.09 (1H, *d*, *J* = 2.6), 5.70 (1H, *dd*, *J* = 2.9 and 1.5), 5.49 (1H, *d*, *J* = 1.1), 3.87 (3H, *s*), 3.60 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 187.0; 164.0; 159.9, 152.1, 148.6, 137.6, 135.9, 134.2, 132.9, 130.3, 128.1, 123.6, 109.6, 107.1, 81.6, 57.1, 52.6; IR (Film on NaCl): 3088, 2958, 2850, 1733, 1679, 1634, 1615, 1535, 1480, 1440, 1352, 1309, 1291, 1252, 1222, 1165, 1108, 1006, 976, 924, 900, 814, 758, 727, 677.

(4*R*,5*R*)-5-Methoxy-4-[(*E*)-4-(4-nitro-phenyl)-4-oxo-but-2-enoyloxy]-4,5-dihydro-furan-2-carboxylic acid methyl ester (**3e**)**.**

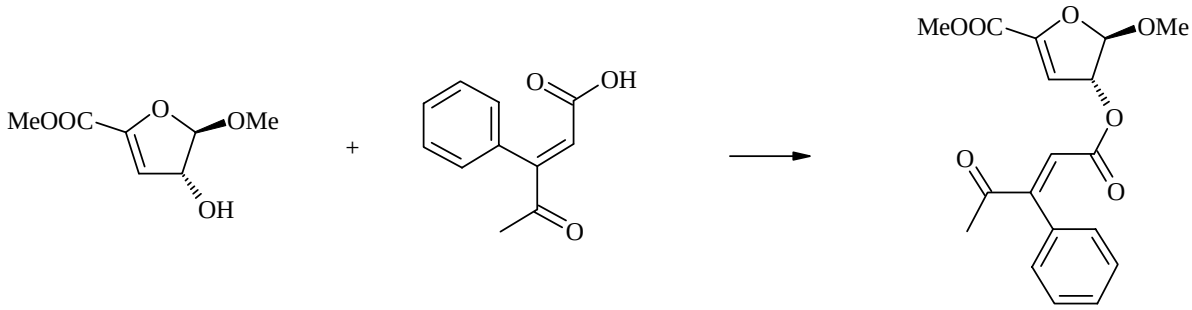


$C_7H_{10}O_5$	$C_{10}H_7NO_5$	$C_{17}H_{15}NO_9$
174.15	221.17	377.31
1	**2e**	**3e**

In a three-neck flask **2e** (3.0 g, 13.6 mmol) was suspended in 38 ml of absolute 1,2-dichloroethane. The suspension was cooled to 0°C before triethylamine (1.9 ml, 14.0 mmol) was added within 8 min. To the thus obtained yellow brown solution pivaloyl chloride (1.6 ml, 13.2 mmol) was added during 10 min in 1.5 ml 1,2-dichloroethane and the mixture was stirred at 0°C for 30 min. Then **1** (1.57 g, 9.04 mmol) in 5 ml 1,2-dichloroethane and, shortly after, DMAP (0.188 g, 1.54 mmol) of was added. Stirring was contioued at 0°C for 2.5 h. The mixture was poured on sat. aq. $NaHCO_3$ and extracted twice with diethylether. After drying over Na_2SO_4 and evaporation of the solvents the brown crude was purified on silicagel (EtOAc/hexane 1:3). This yielded 2.65 g (7.0mmol, 78%) of **3e** as a yellow oil.

TLC (hexane/EtOAc 3:2): R_f 0.52; ^{1}H-NMR: (300 MHz, $CDCl_3$) 8.37 (2H, *d*, *J* = 8.8), 8.14 (2H, *d*, *J* = 8.8), 7.89 (1H, *d*, *J* = 15.5), 6.92 (1H, *d*, *J* = 15.5), 6.08 (1H, *d*, *J* = 2.9), 5.70 (1H, *dd*, *J* = 2.9 and 1.5), 5.48 (1H, *d*, *J* = 1.1), 3.87 (3H, *s*), 3.60 (3H, *s*); ^{13}C-NMR: (75 MHz, $CDCl_3$) 187.7, 164.0, 159.9, 152.2, 150.7, 140.8, 136.2, 132.9, 129.8, 124.1, 109.7, 107.1, 81.6, 57.1, 52.7; IR (KBr): 3114, 3080, 2956, 2851, 1732, 1678, 1633, 1604, 1529, 1441, 1349, 1320, 1289, 1252, 1222, 1165, 1108, 1006, 977, 923, 898, 858, 841, 757, 731.

(4*R*,5*R*)-5-Methoxy-4-[(*E*+*Z*)4-oxo-3-phenyl-pent-2-enoyloxy]-4,5-dihydro-furan-2-carboxylic acid methyl ester (3f)



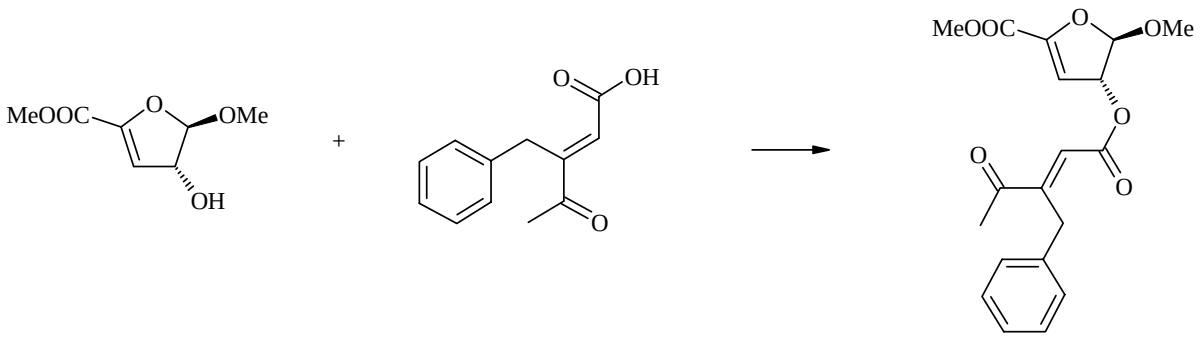
C7H10O5	C11H10O3	C18H18O7
174.15	190.20	346.34
1	**2f**	**3f**

The product was synthesised according to general method A.

The mixture was washed with cold sat. $NaHCO_3$ and extracted twice with CH_2Cl_2. The organic phases were washed once more with aq. sat. NH_4Cl. After drying (Na_2SO_4), evaporating the solvents and separation of the black crude on silicagel (EtOAc/hexane 1:4) 836 mg (2.41 mmol, 69%) of a yellow oil was obtained.

TLC (EtOAc/hexane = 1:3): R_f 0.31; ^{1}H-NMR (300MHz, $CDCl_3$): 7.41 – 7.37 (3H, *m*), 7.17 – 7.14 (2H, *m*), 5.85 (1H, *d*, *J* = 2.8), 5.41 (1H, *dd*, *J* = 2.9 and 1.4), 4.93 (1H, *d*, *J* = 1.5), 3.84 (3H, *s*), 3.46 (3H, *s*) 2.30 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 198.5, 164.4, 159.9, 152.1, 151.7, 134.6, 128.6, 128.4, 128.2, 125.5, 109.5, 107.2, 80.8, 56.9, 52.5, 28.1; IR: 2954, 1732, 1697, 1630, 1494, 1442, 1362, 1311, 1204, 1151, 1104, 1005, 926, 898; EI-MS: 346 (M^+), 287, 259, 255, 227, 213, 190, 174, 173.

(4*R*,5*R*)-4-((*E*)-3-Benzyl-4-oxo-pent-2-enoyloxy)-5-methoxy-4,5-dihydro-furan-2-carboxylic acid methyl ester (3g).



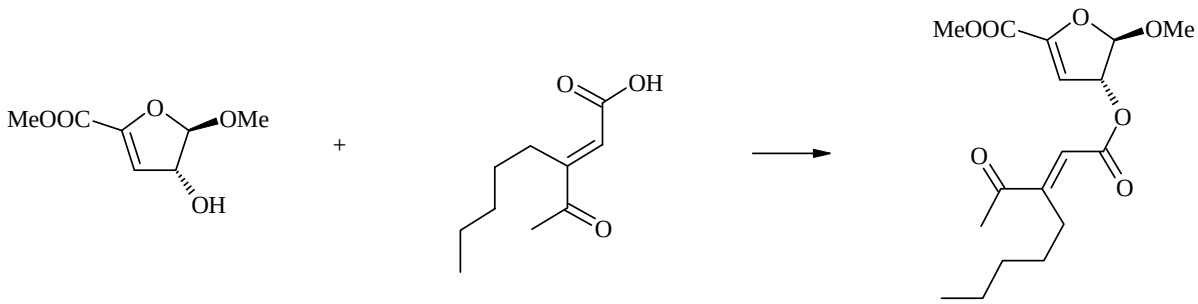
$C_7H_{10}O_5$	$C_{12}H_{12}O_3$	$C_{19}H_{20}O_7$
174.15	204.23	360.37
1	**2g**	**3g**

The product was synthesised according to general method A.

The mixture was washed with cold sat. $NaHCO_3$ and extracted twice with diethylether. The organic phases were washed once more with brine. After drying (Na_2SO_4), evaporating the solvents and separation of the black crude on silicagel (EtOAc/hexane 1:4) 735 mg (2.04 mmol, 75%) of a yellow oil was obtained.

TLC (EtOAc/hexane = 2:8): R_f 0.24; ^{1}H-NMR (300MHz, $CDCl_3$): 7.23-7.18 (5H, *m*), 6.60 (1H, *s*), 6.07 (1H, *d*, *J* = 3.0), 5.59 (1H, *dd*, *J* = 1.3 and 2.8), 5.41 (1H, *d*, *J* = 1.3), 4.19 (2H, *s*), 3.87 (3H, *s*), 3.58 (3H, *s*), 2.32 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 199.2, 164.8, 159.9, 154.4, 151.9, 137.9, 128.8, 128.5, 126.4, 125.0, 109.7, 107.4, 81.0, 57.1, 52.6, 31.9, 26.8; IR: 2954, 2359, 1730, 1684, 1632, 1602, 1495, 1439, 1370,1310, 1247, 1220, 1202, 1158, 1104, 1007, 917, 897; ESI-MS: 383 ($M+Na^+$), 361 (M^+), 329, 313, 311, 227, 209.

(4*R*,5*R*)-4-((*E*)-3-Acetyl-oct-2-enoyloxy)-5-methoxy-4,5-dihydro-furan-2-carboxylic acid methyl ester (3h)



$C_7H_{10}O_5$	$C_{10}H_{16}O_3$	$C_{17}H_{24}O_7$
174.15	184.24	340.38
1	**2h**	**3h**

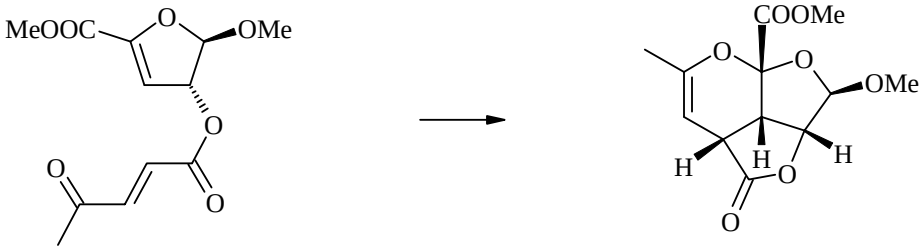
The product was synthesised according to general method A.

The mixture was washed with cold sat. aq. $NaHCO_3$ and extracted twice with diethylether. The organic phases were washed once more with brine. After drying (Na_2SO_4), evaporating the solvents and separation of the black crude on silicagel (EtOAc/hexane 1:4) 443 mg (1.3 mmol, 60%) of a yellow oil was obtained.

TLC (EtOAc/hexane = 2:8): R_f 0.24; ^{1}H-NMR (300MHz, $CDCl_3$): 6,46 (1H, *s*), 6.08 (1H, *d*, *J* = 2.8), 5.65 (1H, *dd*, *J* = 1.3 and 2.8), 5.44 (1H, *d*, *J* = 1.1), 3.86 (3H, *s*), 3.60 (3H, *s*), 2.77-2.72 (2H, *m*), 2.38 (3H, *s*), 1.40-1.24 (6H, *m*), 0.91-0.86 (3H, *m*); ^{13}C-NMR (75MHz, $CDCl_3$): 199.6, 164.7, 160.0, 157.2, 151.9, 124.3, 109.8, 107.6, 80.7, 57.0, 52.6, 32.0, 29.0, 26.9, 26.6, 22.4, 14.0; IR: 2957, 2931, 2859, 1730, 1685, 1631, 1439, 1366, 1309, 1244, 1204, 1163, 1104, 1064, 1009, 919, 897, 756; ESI-MS: 363 ($M+Na^+$), 3341 (M^+), 309, 281.

4.5.3 Scaffolds 4a – 4h

(2*R*,2a*R*,4a*R*,7a*S*,7b*S*)-2-Methoxy-6-methyl-4-oxo-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid methyl ester (4a)



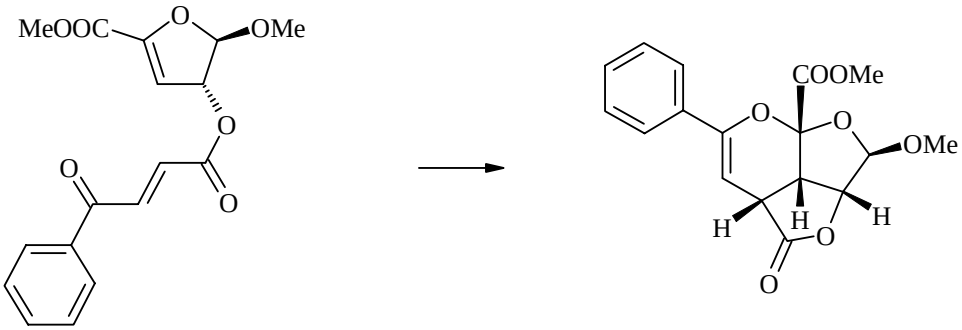
$C_{12}H_{14}O_7$
270.24
3a

$C_{12}H_{14}O_7$
270.24
4a

A solution of **3a** (5 g, 18.5 mmol) in 500 ml o-xylene was heated to reflux for 17 h. Evaporation of the solvent and recrystalisation from methanol/H_2O 9:1 gave 2.66 g (9.83 mmol, 53%) of white crystals.

TLC (EtOAc/hexane 4:6): R_f 0.47; ^{1}H-NMR (300MHz, $CDCl_3$): 5.08 (1H, *m*), 5.06 (1H, *s*), 4.98 (1H, *d*, *J* = 7.7), 4.03 (1H, *dd*, *J* = 7.4 and 11.8), 3.87 (3H, *s*), 3.42 (3H, *s*), 3.29 (1H, dm, *J* = 11.5), 1.89 (3H, *m*); ^{13}C-NMR (75MHz, $CDCl_3$): 175, 168, 148, 106, 103, 93, 85, 56, 53, 36, 34, 20; IR (KBr): 3039, 2963, 2943, 2847, 1789, 1745, 1707, 1432, 1380, 1334, 1307, 1291, 1269, 1237, 1200, 1186, 1163, 1126, 1099, 1069, 1042, 1013, 985, 949, 930, 886, 829, 810; EI-MS: 271 (50, M^+), 239 (45), 211 (60).

(2*R*,2a*R*,4a*R*,7a*S*,7b*S*)-2-Methoxy-4-oxo-6-phenyl-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxacyclopenta[cd]indene-7a-carboxylic acid methyl ester *(*4b*)*.



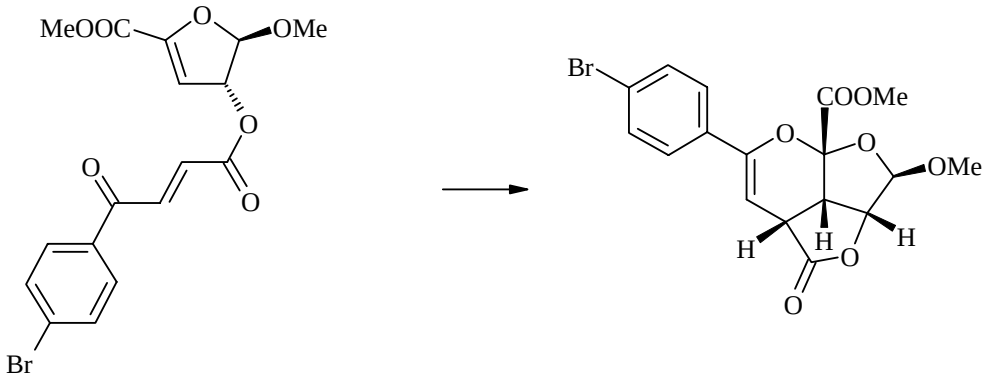
$C_{17}H_{16}O_7$
332.31
3b

$C_{17}H_{16}O_7$
332.31
4b

A solution of **3b** (1.28 g, 3.88 mmol) in 38 ml of o-xylene was stirred at 150°C for 5 h. The obtained solution was cooled to 70°C and the solvent was evaporated. After drying on the HV a yellow crystalline product was obtained which was further purified by recrystallization from methanol. Thus 0.94 g (2.83 mmol, 72.9 %) of a pale yellow product was obtained.

TLC (Toluol/EtOAc 5:1): R_f 0.45; ^{1}H-NMR: (300 MHz, $CDCl_3$) 7.67-7.58 (2H, *m*), 7.42-7.32 (3H, *m*), 5.86 (1H, *d*, *J* = 4.4), 5.11 (1H, *s*), 5.04 (1H, *d*, *J* = 7.7), 4.17 (1H, *dd*, *J* = 11.6 and 7.5), 3.90 (3H, *s*), 3.52 (1H, *dd*, J=11.6 and 4.6), 3.44 (3H, *s*); ^{13}C-NMR (75 MHz, $CDCl_3$): 175.0, 168.1, 148.6, 133.1, 129.3, 128.4, 125.0, 106.7, 103.4, 94.1, 85.0, 56.0, 53.3, 37.5, 35.0; IR (KBr): 3090, 3008, 2967, 2938, 2844, 1971, 1794, 1742, 1676, 1580, 1498, 1444, 1374, 1319, 1279, 1235, 1164, 1108, 1075, 1018, 985, 924, 858, 826, 806, 773, 747, 721, 693; EI-MS: 332 (M^+, 34), 301, 273, 229, 215, 201, 187, 185, 159, 157, 131, 127, 115, 105, 85, 77, 59, 45.

(2*R*,2a*R*,4a*R*,7a*S*,7b*S*)-6-(4-Bromo-phenyl)-2-methoxy-4-oxo-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxacyclopenta[cd]indene-7a-carboxylic acid methyl ester *(4c)*.



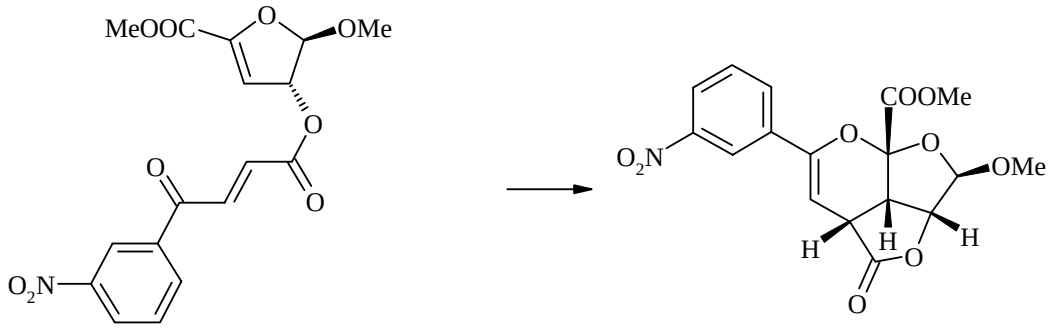
$C_{17}H_{16}BrO_7$
411.21
3c

$C_{17}H_{16}BrO_7$
411.21
4c

In a round bottom flask equipped with a reflux condensor, **3c** (1.0 g, 2.43 mmol) was dissolved in 24 ml of o-xylene and stirred at 150°C for 18 h. The obtained solution was cooled to 70°C and the solvent was evaporated. After purification on silicagel (hexane/EtOAc 5:1, 3:1, 1:1) and drying on the HV, 0.447 g (1.1 mmol, 45%) of a yellow oil was obtained.

TLC (hexane/EtOAc 2:1): R_f 0.33; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.49 (4H, *m*), 5.87 (1H, *d*, *J* = 4.8), 5.11 (1H, *s*), 5.04 (1H, *d*, *J* = 7.7), 4.17 (1H, *dd*, *J* = 11.6 and 7.5,), 3.91 (3H, *s*), 3.51 (1H, *dd*, *J* = 11.6 and 4.2,), 3.45 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 174.8, 167.9, 147.7, 132.0, 131.6, 126.5, 123.5, 106.7, 103.4, 94.7, 85.0, 56.0, 53.4, 37.5, 35.0; IR (Film on NaCl): 2954, 2847, 1790, 1752, 1677, 1589, 1490, 1439, 1399, 1376, 1282, 1242, 1174, 1106, 1073, 1008, 981, 927, 823, 808, 788, 730; EI-MS: 412 (M^+, 36), 410, 381, 379, 353, 351, 339, 337, 309, 307, 295, 293, 281, 279, 267, 265, 239, 237, 235, 211, 209, 185, 183, 157, 155.

(2*R*,2a*R*,4a*R*,7a*S*,7b*S*)-2-Methoxy-6-(3-nitro-phenyl)-4-oxo-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxacyclopenta[cd]indene-7a-carboxylic acid methyl ester (4d).



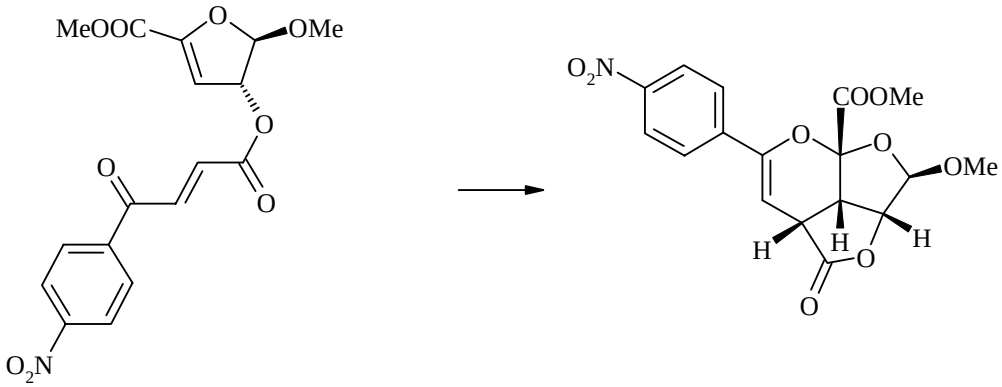
$C_{17}H_{15}NO_9$
377.31
3d

$C_{17}H_{15}NO_9$
377.31
4d

In a round bottom flask equipped with a reflux condensor, **3d** (2.5 g, 6.63 mmol) was dissolved in 45 ml of toluene and stirred at reflux for 20 h. The obtained solution was cooled to 70°C and the solvent was evaporated. After drying on the HV 2.41g (6.38 mmol, 96%) of a brown solid was obtained which was used without further purification.

TLC (toluene/EtOAc 5:1): R_f 0.39 ^{1}H-NMR (300 MHz, $CDCl_3$): 8.48 (1H, *s*), 8.21 (1H, *dd*, *J* = 8.3 and 1.3), 7.94 (1H, *d*, *J* = 8.1), 7.56 (1H, *t*, *J* = 8.0), 6.04 (1H, *d*, *J* = 4.4), 5.13 (1H, *s*), 5.06 (1H, *d*, *J* = 7.7), 4.20 (1H, *dd*, *J* = 11.8 and 7.7), 3.93 (3H, *s*), 3.58 (1H, *dd*, *J* = 11.6 and 4.6), 3.46 (3H, *s*); ^{13}C-NMR (75 MHz, $CDCl_3$): 174.4, 167.7, 148.4, 146.6, 134.8, 130.7, 129.5, 123.9, 120.0, 106.8, 103.5, 96.9, 85.0, 56.1, 53.5, 37.7, 35.0; IR (Film on NaCl): 3091, 2956, 1790, 1752, 1616, 1532, 1439, 1351, 1275, 1243, 1174, 1106, 1077, 1025, 981, 930, 789, 741, 724; EI- MS: 377 (M+, 22), 346, 318,304, 290, 274, 260, 246, 232, 214, 204, 176, 150, 138, 106, 104, 91, 84, 59.

(2*R*,2a*R*,4a*R*,7a*S*,7b*S*)-2-Methoxy-6-(4-nitro-phenyl)-4-oxo-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxacyclopenta[cd]indene-7a-carboxylic acid methyl ester (4e).



$C_{17}H_{15}NO_9$ | $C_{17}H_{15}NO_9$

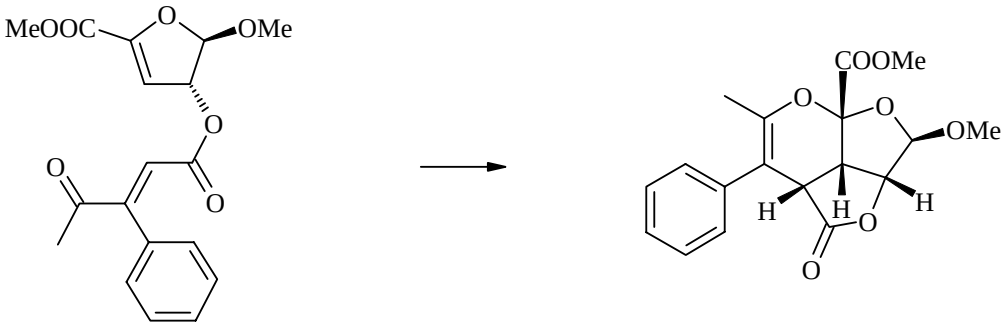
377.31 | 377.31

3e | **4e**

In a round bottom flask equipped with a reflux condensor, **3e** (1.0 g, 2.65 mmol) was dissolved in 12 ml of o-xylene and stirred at reflux for 3 h. After evaporation of the solvents 990 mg (2.62 mmol, 99%) of crude material was obtained, which was used without further purification.

TLC (hexane/EtOAc 3:2): R_f 0.52; ^{1}H-NMR (300 MHz, $CDCl_3$): 8.23 (2H, *d*, *J* = 9.2), 7.79 (2H, *d*, *J* = 9.2), 6.08 (1H, *d*, *J* = 4.8), 5.12 (1H, *s*), 5.06 (1H, *d*, *J* = 7.4), 4.20 (1H, *dd*, *J* = 11.6 and 7.5,), 3.92 (3H, *s*), 3.58 (1H, *dd*, *J* = 11.4 and 4.8), 3.45 (3H, *s*); ^{13}C-NMR (75 MHz, $CDCl_3$): 174.2, 167.7, 148.1, 146.8, 138.9, 125.8, 123.8, 106.9, 103.5, 98.3, 85.0, 56.1, 53.5, 37.6, 35.2; IR: 3104, 3006, 2962, 2926, 2855, 1791, 1747, 1683, 1599, 1516, 1451, 1429, 1379, 1349, 1323, 1289, 1245, 1223, 1183, 1099, 1072, 1041, 1019, 982, 969, 928, 858, 848, 806, 743, 721; EI-MS: 377 (M^+, 22), 346, 318, 307, 274, 260, 246, 230, 214, 204, 176, 150, 139, 127, 104, 85, 76, 59, 45.

(2*R*,2a*R*,4a*R*,7a*S*,7b*S*)-2-Methoxy-6-methyl-4-oxo-5-phenyl-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid methyl ester (4f)



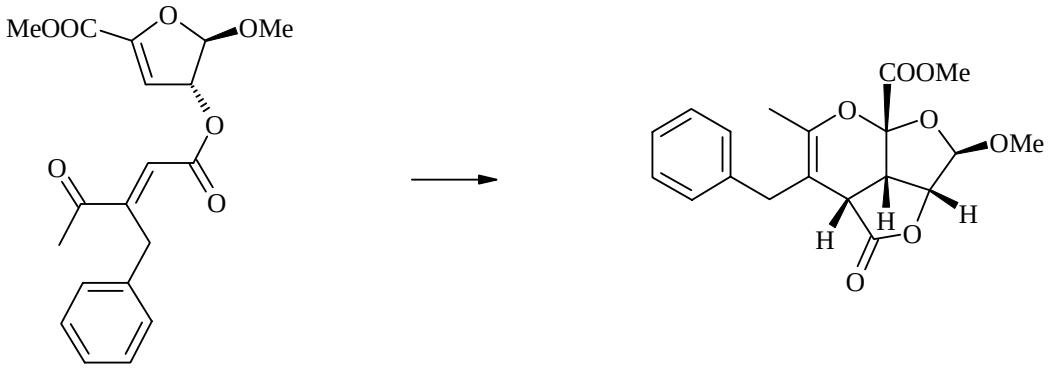
$C_{18}H_{18}O_7$
346.34
3f

$C_{18}H_{18}O_7$
346.34
4f

Under an argon atmosphere ester LM333 (48 mg, 139 µmol) was dissolved in 5 ml toluene and stirred at 100°C for 21 hours. The solvent was evaporated and the crude oil separated on silicagel using EtOAc/hexane 1:4. This yielded 19 mg (55 µmol, 39%) product.

TLC (EtOAc/hexane = 1:4): R_f 0.22; ^{1}H-NMR (300MHz, $CDCl_3$): 7.37 – 7.27 (5H, *m*), 5.39 (1H, *s*), 4.92 (1H, *d*, *J* = 6.6), 4.03 (1H, *dd*, *J* = 9.5 and 6.7), 3.88 (3H, *s*), 3.70 (1H, *d*, *J* = 9.8), 3.50 (3H, *s*), 1.96 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 174.7, 149.3, 138.2, 129.2, 128.8, 127.5, 112.3, 108.2, 83.6, 56.3, 53.7, 46.4, 42.0, 18.0; IR: 3023, 2953, 2926, 2847, 1786, 1750, 1495, 1439, 1382, 1206, 1148, 1112, 1064, 977, 933; EI-MS: 348, 347, 346 (M^+), 315, 287, 282, 255.

(2*R*,2a*R*,4a*R*,7a*S*,7b*S*)-5-Benzyl-2-methoxy-6-methyl-4-oxo-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid methyl ester (4g)



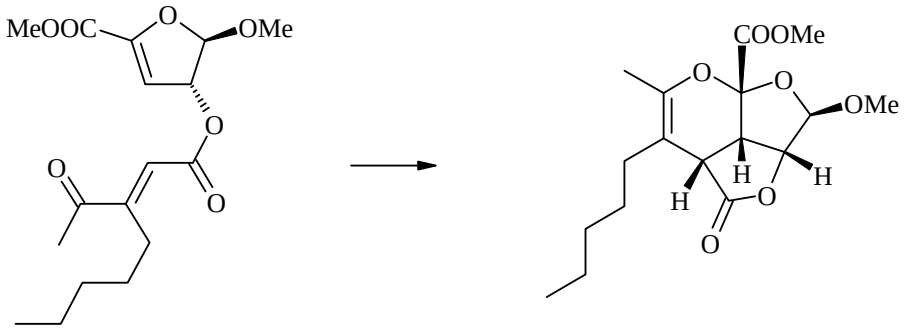
$C_{19}H_{20}O_7$
360.37
3g

$C_{19}H_{20}O_7$
360.37
4g

A solution of **3f** (168 mg, 0.46 mmol) in 15 ml of toluene was heated in an autoclave at 180°C for over 3 h. After evaporation of the solvent and separation on 15 g silicagel (EtOAc/hexane 1:9 to 2:8) **4f** (40 mg, 0.11 mmol, 24%) was obtained as a yellow oil.

TLC (EtoAc/Hex = 2:8): R_f: 0.33; ^{1}H-NMR (300MHz, $CDCl_3$): 7.37-7.19 (5H,m), 5.18 (1H,s), 4.82 (1H, d, *J* = 7.0), 3.86 (3H,s), 3.78 (1H, *dd*, *J* = 7.5 and 11,2), 3.75 (1H, *d*, *J* = 4.8), 3.44 (3H,s), 3.09 (1H, *dd*, *J* = 10.7 and 1.1), 2.04 (3H,s); ^{13}C-NMR (75MHz, $CDCl_3$): 174.5, 168.3, 145.34, 128.9, 128.7, 128.6, 128.5, 126.6, 106.8, 105.4, 103.7, 83.5, 56.0, 53.2, 41.0, 3.2, 34.6, 16.6; IR: 2952, 2844, 2359, 1747, 1697, 1494, 1453, 1436, 1382, 1250, 1197, 1151, 1107, 1065, 1040, 972, 910, 728, 700; ES-MS: 360 (M^+), 301, 269, 243, 217, 186; HR-MS: Calcd. for $C_{19}H_{20}O_7$: 360.12090; measured: 360.12088.

(2*R*,2a*R*,4a*R*,7a*S*,7b*S*)-2-Methoxy-6-methyl-4-oxo-5-pentyl-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid methyl ester (4h)



$C_{17}H_{24}O_7$
340.38
3h

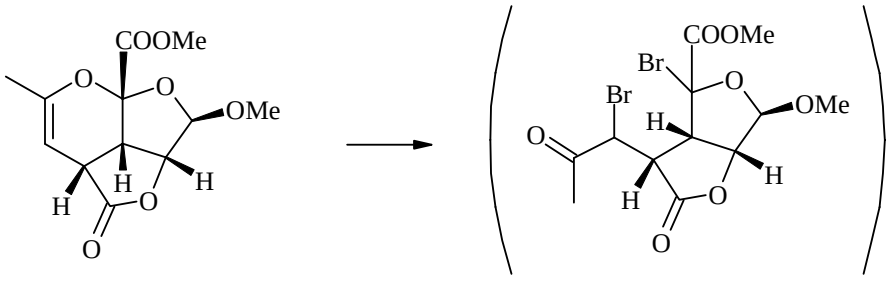
$C_{17}H_{24}O_7$
340.38
4h

A solution of **3g** (300 mg, 0.88 mmol) in 30 ml of toluene was heated in an autoclave at 180°C for 5 h. After evaporation of the solvent and separation on silicagel (EtOAc/Hex 2:8) 88 mg (0.26 mmol, 30%) of colorless oil was obtained which was further purified by crystallization from hexane for analytical purposes.

TLC (EtOAc/hexane = 2:8): R_f 0.34; ^{1}H-NMR (300MHz, $CDCl_3$): 5.22 (1H,s), 4.87 (1H, *d*, *J* = 6.8), 3.94 (1H, *dd*, *J* = 7.0 and 10.4), 3.83 (3H, *s*), 3.44 (3H, *s*), 3.29 (1H, *dd*, *J* = 10.5 and 1.0), 2.45-2.37 (1H, *m*), 2.23-2.13 (1H, *m*), 1.87 (3H, *s*), 1.55-1.23 (6H, *m*), 0.92-0.87 (3H, *m*); ^{13}C-NMR (75MHz, $CDCl_3$): 174.5, 168.4, 144.7, 107.4, 107.1, 104.3, 83.4, 55.9, 53.1, 42.3, 37.5, 31.4, 29.2, 27.4, 22.5, 16.2, 14.1; IR: 2955, 2932, 2857, 2365, 2256, 1747, 1439, 1378, 1248,1201, 1152, 1108, 1061, 973, 910, 729, 647; ES-MS: 340 (M^+), 283, 281, 253, 223, 197, 195; HR-MS: Calcd. for $C_{17}H_{24}O_7$: 340.15220; measured: 340.15213.

4.5.4 Derivative 4a-Br

(2*R*,2a*R*,4a*R*,7b*S*)-4-Bromo-3-(1-bromo-2-oxo-propyl)-6-methoxy-2-oxo-hexahydro-furo[3,4-*b*]furan-4-carboxylic acid methyl ester (4a-Br)



$C_{12}H_{14}O_7$ | $C_{12}H_{14}Br_2O_7$

270.24 | 430.05

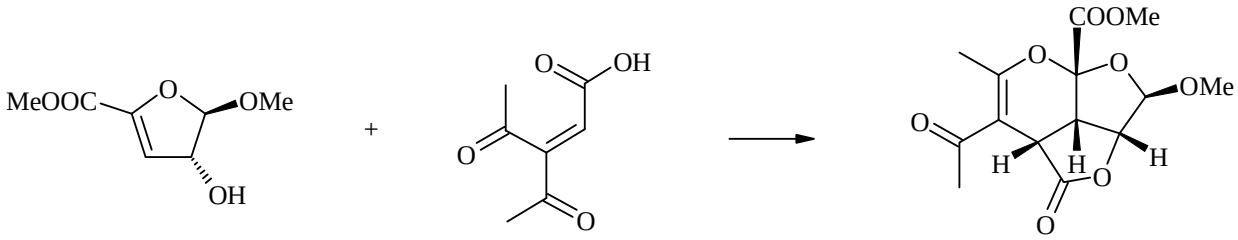
4a | **4a-Br**

In a two neck flask **4a** (200 mg, 0.74 mmol) was dissolved in 2 ml $CHCl_3$ and cooled to O°C. A suspension of N-Bromo-succinimide (138 mg, 0.77 mmol) in 1.5 ml $CHCl_3$ was added to the stirred above solution. The cooling was removed and stirring continued for 20 hours. The reaction mixture was washed with H_2O and extracted with CH_2Cl_2 three times. The organic phases were dried with Na_2SO_4 and the solvents evaporated. After column chromatographie with EtOAc/hexane 2:8, **4a-Br** (74 mg, 23%) was obtained as a white solid.

TLC (EtOAc/hexane = 1:1): R_f 0.45; ^{1}H-NMR (300MHz, $CDCl_3$): 5.26 (1H, *s*), 5.02 (1H, *d*, *J* = 2.8), 4.80 (1H, *d*, *J* = 6.8), 4.11 (1H, *dd*, *J* = 10.4 and 6.8), 3.82 (1H, *dd*, *J* = 10.0 and 3.2), 3.85 (3H, *s*), 3.44 (3H, *s*), 2.28 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 203.0, 175.1, 167.1, 116.2, 109.4, 91.6, 82.9, 55.6, 53.2, 50.7, 45.2, 26.0; ES-MS: 350, 348, 309, 308, 307, 306, 289, 286, 271, 244, 243, 227;

4.5.6 Scaffolds 4i, 5 and 6

(2*R*,2a*R*,4a*R*,7a*S*,7b*S*)-5-Acetyl-2-methoxy-6-methyl-4-oxo-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxacyclopenta[cd]indene-7a-carboxylic acid methyl ester (4i).

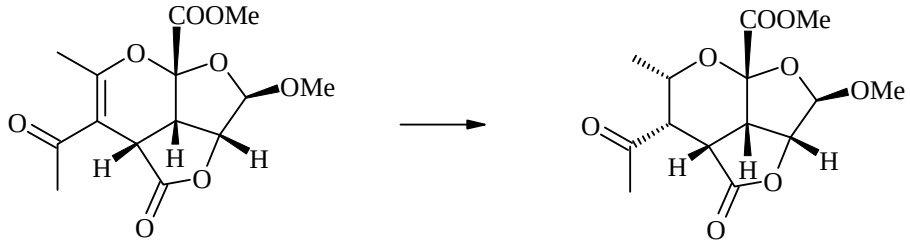


$C_7H_{10}O_5$	$C_7H_8O_4$	$C_{14}H_{16}O_8$
174.15	156.14	312.28
1	**2i**	**4i**

Under an argon atmosphere, **2h** (1.49 g, 9.5 mmol) was suspended in 60 ml 1,2-dichloroethane. At 0°C Et_3N (1.39 ml, 9.9mmol) was added drop wise within 3min. Over 15 min. pivaloyl chloride (1.14 ml, 9.3 mmol) was added in 12.8 ml 1,2-dichloroethane and stirring was continued for an other 20 min. During 15 min dihydrofuranoside **1** (1.108 g, 6.4 mmol) was given to the mix in 13 ml 1,2-dichloroethane. Shortly after cooling to –20°C DMAP (116 mg, 0.95 mmol) was added. After stirring 3 hours at 0°C the reaction was left to warm to RT over night (total 20h reaction time). The reaction mixture was washed with sat. aq. $NaHCO_3$ and extracted twice with ether and once with CH_2Cl_2. After drying (Na_2SO_4), evaporating the solvents and separation of the black crude on silicagel (hexane/EtOAc 6:4 -> 1:1) 1.0 g (3.2 mmol, 51% from **1**) of a yellow solid were obtained.

TLC (CH_2Cl_2/ether 9:1): R_f 0.38; ^{1}H-NMR (300MHz, $CDCl_3$): 5.32 (1H, *s*), 4.97 (1H, *d*, *J* = 6.3), 4.23 (1H, *d*, = 10.3), 3.87 (1H, *dd*, *J* = 10.5 and 6.8), 3.84 (3H, *s*), 3.49 (3H, *s*), 2.46 (3H, *s*), 2.32 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$):196.2, 173.7, 167.5, 162.2, 112.3, 107.5, 105.5, 83.1, 56.0, 53.6, 43.8, 36.3, 30.2, 20.5; IR: 2927, 2848, 1787, 1734, 1686, 1629, 1604, 1439, 1374, 1236, 1151, 1107, 1059, 1017, 970, 930; EI-MS: 312 (M^+), 253, 211, 207, 195; HR-MS: Calcd. for $C_{14}H_{16}O_8$: 312.08451; measured: 312.08472.

(2*R*,2a*R*,4a*S*,5*S*,6*S*,7a*S*,7b*S*)-5-Acetyl-2-methoxy-6-methyl-4-oxo-hexahydro-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid methyl ester (5).



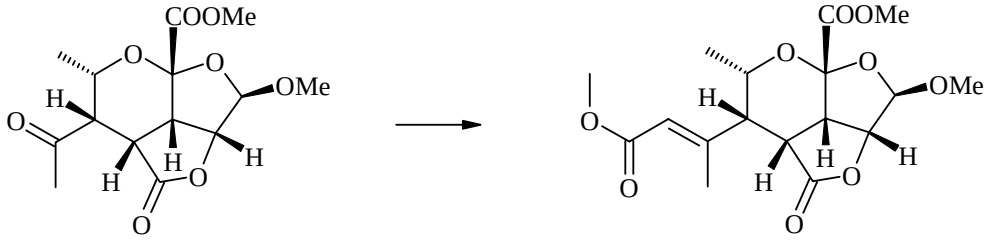
$C_{14}H_{16}O_8$
312.28
4i

$C_{14}H_{18}O_8$
314.29
5

The product was synthesised according to general method B.
Solvents were evaporated to afford 86 mg of crude **4i** as single diastereomer. This was further purified by column chromatographie using EtOAc/hexane 2:3 → 1:1. After drying (Na_2SO_4) and evaporation of the Solvents 79 mg (0.25 mmol, 78%) of a clear oil was obtained.

TLC (EtOAc/hexane 1:1): R_f 0.30; ^{1}H-NMR (300MHz, $CDCl_3$): 5.24 (1H, *s*), 4.89 (1H, *d*, *J* = 6.0), 4.00 (1H, q, *J*=6.2), 3.86 (1H, *dd*, *J* = 6.3 and 9.5), 3.82 (3H, *s*), 3.38 (3H, *s*), 3.35 (1H, *dd*, J = 9.6 and 2.6), 3.15 (1H, *dd*, *J* = 6.0 and 2.6), 2.26 (3H, *s*) 1.45 (3H, *d*, *J* = 6.4); ^{13}C-NMR (75MHz, $CDCl_3$): 206.0, 175.9, 167.9, 106.4, 104.5, 84.2, 68.7, 55.5, 53.0, 51.2, 38.3, 37.4, 29.1, 22.4; IR: 2934, 1782, 1742, 1711, 1439, 1376, 1358, 1237, 1155, 1112, 1049, 972, 922; ES$^+$-MS: 629 (M^+·2), 491, 337 (M+Na^+), 315 (M^+), 283, 241.

(2*R*,2a*R*,4a*S*,5*S*,6*S*,7a*S*,7b*S*)-2-Methoxy-5-[(*E*)-2-methoxycarbonyl-1-methyl-vinyl]-6-methyl-4-oxo-hexahydro-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid methyl ester (6).



$C_{14}H_{16}O_8$
312.28
5

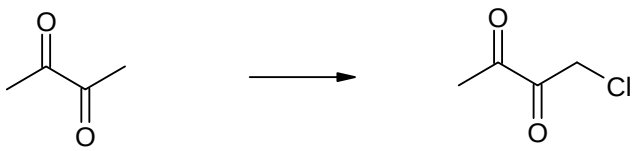
$C_{14}H_{18}O_8$
314.29
6

Under argon atmosphere at 0°C BuLi 1.6M (398 µl, 636 µmol) and shortly after HMDS (133 µl, 636 µmol) was added to 1 ml of THF. The solution was stirred for 30 min. at 0°C. After this methyl-diethyl-phosphonoacetat (166 µl, 636 µmol) was added. After an other 30 min **5** (200 mg, 636 µmol) was added drop wise and cooling is removed. The solution was stirred for 2h, then another 4 eq. of BuLi were treated with 4eq. HMDS in 0.5 ml THF at 0°C in a separate reaction vessel. Again 4eq. methyl-diethyl-phosphonoacetat are added to this fresh prepared LiHMDS solution. After stirring for 15 min the solution is added to the reaction. Monitoring the reaction by TLC showed that after a further hour no more starting material was present. The mixture was washed with brine and extracted twice with diethylether. The organic phase was washed once more with sat. aq. $NaHCO_3$ .After drying (Na_2SO_4) and removing of the solvents 130 mg of yellow oil was obtained containing one isomer of the product. column chromatographie using EtOAc/hexane 3:7 yielded 23 mg (62 µmol, 10%) of colorless oil.

TLC (EtOAc/hexane 1:1): R_f 0.55; ^{1}H-NMR (300MHz, $CDCl_3$): 5.88 (1H, *s*), 5.22 (1H, *s*), 4.86 (1H, *d*, *J* = 6.2), 3.95 (1H, *dd*, *J* = 6.3 and 9.5), 3.86 (3H, *s*), 3.54 (1H, *dd*, *J* = 6.2 and 8.9), 3.39 (3H, *s*), 2.93 (1H, *dd*, *J* = 9.6 and 2.6), 2.85 (1H, *dd*, *J* = 8.9 and 2.6), 2.20 (3H, *s*), 1.29 (3H, *d*, *J* = 6.2); ^{13}C-NMR (75MHz, $CDCl_3$): 175.5, 168.9, 166.4, 156.0, 119.1, 106.0, 105.3, 83.4, 70.2, 55.5, 53.2, 51.2, 49.2, 40.2, 38.3, 20.6, 16.5; IR: 2952, 1783, 1739, 1716, 1649, 1437, 1379, 1223, 1154, 1128, 1109, 1053, 1039, 972, 920; ES^+-MS: 741(M·2), 407 ($M+K^+$), 393 ($M+Na^+$), 371 (M^+), 339, 307.

4.5.7 Compounds for the Tricyclic Scaffold Involving 1,2 Diketones

1-Chloro-butane-2,3-dione (9a)



$C_4H_6O_2$ | $C_4H_6ClO_2$

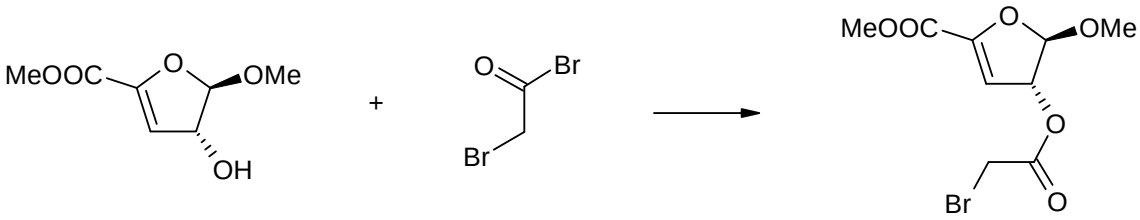
86.09 | 120.54

9a

To a stirred solution of butane-2,3-dione (3.44 ml, 40 mmol) in 2 ml of benzene sulfuryl chloride (3.26 ml, 40 mmol) was added drop wise within 2 hours 40 min. During this and for a further hour after the addition the solution was held at 60°C, then it was heated to 80-90°C for 2,5 hours. Benzene was removed under reduced pressure (the use of cooling traps is recommended). Then the unreacted butane-2,3-dione is destilled at 55°C, 20 mbar. Further distillation at 55°C and 0.1 mbar afforded 1.87g (15.5 mmol, 39%) of **9a** as yellow liquid.

^{1}H-NMR (300MHz, $CDCl_3$): 4.59 (2H, *s*), 2.43 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 195.9, 186.4, 44.8, 24.1; IR: 1715, 1419, 1393, 1360, 1223, 1154, 1133, 1050, 1011, 942, 758; EI^+-MS: 122, 120 (M^+), 105, 97, 95, 79, 77.

(4*R*,5*R*)-4-(2-Bromo-acetoxy)-5-methoxy-4,5-dihydro-furan-2-carboxylic acid methyl ester (8)

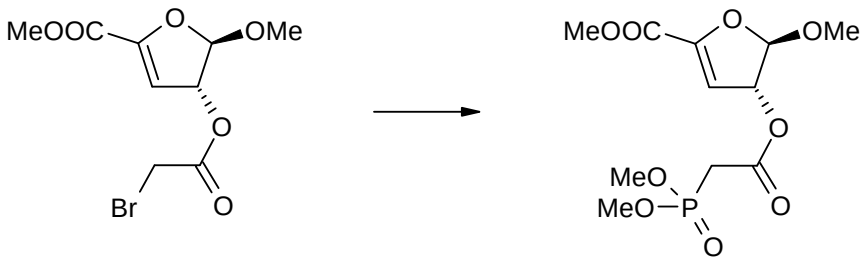


$C_7H_{10}O_5$	$C_2H_2Br_2O$	$C_9H_{11}BrO_6$
174.15	201.85	295.09
1		**8**

To a stirred solution of **1** (8.3 g, 47.7 mmol) in 80 ml MTBE at 0°C, pyridine (4.2 ml, 52.4 mmol) was added slowly. Shortly after bromoacetyl bromide (4.1 ml, 47.7 mmol) was added drop wise to get a yellow-white suspension. After stirring at 0°C for 3 hours 50 min some more bromoacetyl bromide (0.4 ml, 4.7 mmol) was added. The Suspension was poured on H_2O after a total of 4.5 hours. The organic phase is collected and washed once more with brine. The water phases are extracted once with MTBE. After drying (Na_2SO_4) and evaporation of the solvents 13.73 g crude product were obtained. Separation using column chromatographie using EtOAc/hexane 1:3 → 2:1 yielded 12.47 g (42.3 mmol, 88.7%) product as a colorless oil.

TLC (EtOAc/hexane 3:7): R_f 0.50; ^{1}H-NMR (300MHz, $CDCl_3$): 6.05 (1H, *d*, *J* = 2.9), 5.61 (1H, *dd*, *J* = 2.9 and 1.5), 4.43 (1H, *d*, *J* = 1.1), 3.86 (3H,s), 3.84 (2H, *s*), 3.58 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 166.3, 159.9, 152.2, 109.5, 106.9, 82.1, 57.0, 52.6, 25.3; IR: 2955, 1733, 1631, 1439, 1368, 1308, 1248, 1204, 1101, 1004, 923, 896; EI$^+$-MS: 296 (M^+), 294 (M^+), 266, 264, 237, 235.

(4*R*,5*R*)-4-[2-(Dimethoxy-phosphoryl)-acetoxy]-5-methoxy-4,5-dihydro-furan-2-carboxylic acid methyl ester (7)



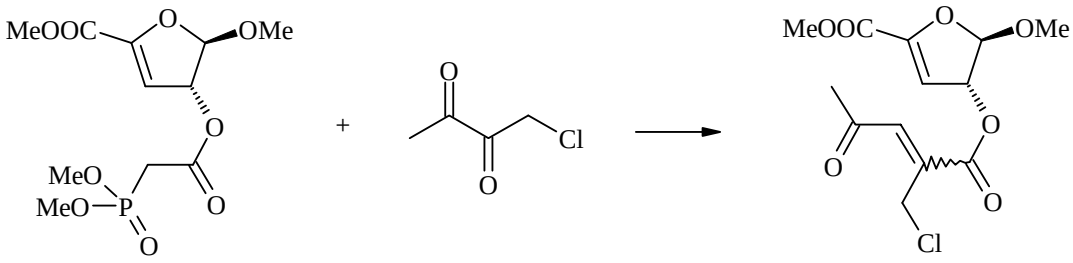
$C_9H_{11}BrO_6$
295.09
8

$C_{11}H_{17}O_9P$
324.23
7

In a two neck flask with magnetic stirrer and cooler **8** (5.62 g, 19.1 mmol) was dissolved in 60 ml THF. At rt trimethylphosphite (3.37 ml, 28.6 mmol) were added. The mixture is heated for several days at a oil bath temperature of 80°C. After one day an other 0.5 ml of trimethylphosphite was added. Completion of the reaction was monitored using TLC (EtOAc/hexane 1:1). The solvent was evaporated and the obtained crude oil is further dried on the high vacuum over 24h. This yielded 5.89 g (18.1 mmol, 95%) **7,** which was used without further purification.

TLC (EtOAc/hexane 1:1) R_f 0.10; ^{1}H-NMR (300MHz, $CDCl_3$): 6.02 (1H, *d*, *J* = 3.0), 5.60 (1H, *dd*, *J* = 2.8 and 1.3), 5.40 (1H, *d*, *J* = 1.3), 3.85 (3H, *s*), 3.56 (3H, *s*), 3.00 (2H, *d*, *J* = 21.5); ^{13}C-NMR (75MHz, $CDCl_3$): 164.8, 159.9, 152.0, 109.6, 107.1, 81.5, 57.0, 52.6, 34.2, 32.4; IR: 2956, 2853, 1736, 1632, 1440, 1368, 1308, 1245, 1220, 1104, 1021, 912; ESI^+-MS (+TOF MS): 671 ($M\cdot2+Na^+$), 649 ($M\cdot2$), 377, 347 ($M+Na^+$), 191.

(4*R*,5*R*)-4-[(*E*/*Z*)-3-Chloromethyl-4-oxo-pent-2-enoyloxy]-5-methoxy-4,5-dihydro-furan-2-carboxylic acid methyl ester (10a)

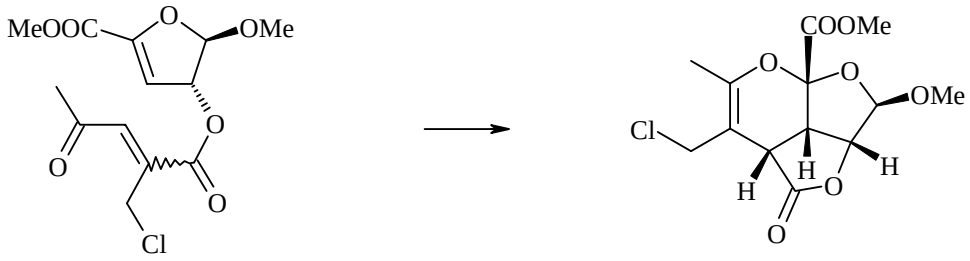


$C_{11}H_{17}O_9P$	$C_4H_6ClO_2$	$C_{13}H_{15}ClO_7$
324.23	120.54	318.71
7	**9a**	**(*E*)/(*Z*) 10a**

Under an argon atmosphere at 0°C BuLi 1.6M (2.93 ml, 4.7 mmol) and then HMDS (0.977 ml, 4.7 mmol) was added to 5 ml of THF. The solution was stirred for 30 min. at 0°C. Then **7** (1.52 g, 4.7 mmol) in 15 ml THF was added drop wise. The mixture was cooled to -70°C and **9a** (565 mg, 4.7 mmol) was slowly given to the solution. After 1 hour and 20 min the mixture is washed with sat. aq. NH_4Cl and extracted three times with CH_2Cl_2. The organic phases were washed with brine. This yielded 1.34 g of crude product which was further purified by column chromatographie using EtOAc/CH_2Cl_2/hexane 1:3:6. After complete evaporation of the solvents 817 mg of **(*E*)/(*Z*) 10a** (2.56 mmol, 55%) were obtained. The isomers could not be separated. According to ^{1}H-NMR the product has a *E*/*Z* ratio of 63/37.

TLC (EtOAc/CH_2Cl_2/hexane 1:3:6): R_f 0.32; (*E*)-isomer: ^{1}H-NMR (300MHz, $CDCl_3$): 6.61 (1H, *s*), 6.07 (1H, *d*, *J* = 2.8), 5.69 (1H, *dd*, *J* = 2.8 and 1.3), 5.46 (1H, *d*, *J* = 1.3), 4.77 (2H, *s*), 3.87 (3H, *s*), 3.60 (3H, *s*), 2.46 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 196.7, 163.5, 159.8, 152.2, 149.7, 126.9, 109.5, 107.0, 81.5, 56.9, 52.5, 34.5, 26.4; (*Z*)-isomer: ^{1}H-NMR (300MHz, $CDCl_3$): 6.03 (1H, *d*, *J* = 2.9), 6.02 (1H, *d*, *J* = 2.2), 5.59 (1H, *dd*, *J* = 2.9 and 1.4), 5.41 (1H, *d*, *J* = 1.3), 4.21 (2H, *d*, *J* = 2.2), 3.86 (3H, *s*), 3.57 (3H, *s*), 2.45 (3H, *s*); (*E*)-isomer: ^{13}C-NMR (75MHz, $CDCl_3$): 196.7, 163.5, 159.8, 152.2, 149.7, 118.7, 109.6, 107.0, 81.3, 57.0, 52.6, 43.5, 30.7; (*Z*)-isomer: ^{13}C-NMR (75MHz, $CDCl_3$): 202.6, 163.7, 159.8, 155.1, 152.0, 118.7, 109.5, 107.0, 81.5, 56.9, 52.5, 34.5, 26.4; IR: 2954, 1735, 1694, 1439, 1374, 1249, 1193, 1156, 1104, 1051, 970, 932, 892, 845, 826; EI$^+$-MS: 349, 318 (M^+), 283, 266,

(2*R*,2a*R*,4a*S*,7a*S*,7b*S*)-5-Chloromethyl-2-methoxy-6-methyl-4-oxo-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid methyl ester (11a)



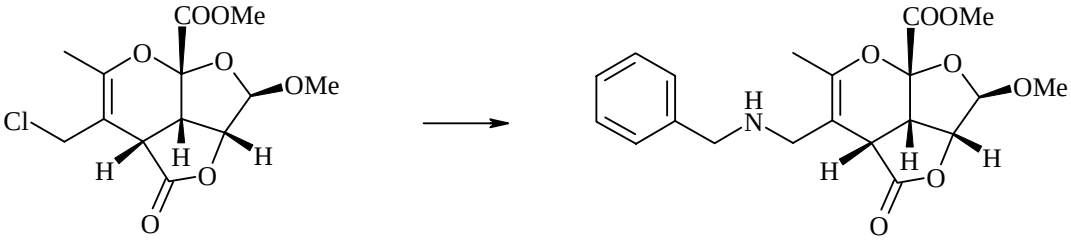
$C_{13}H_{15}ClO_7$
318.71
(*E*)/(*Z*) 10a

$C_{13}H_{15}ClO_7$
318.71
11a

A solution of **10a** (500mg, 1.57 mmol) in 50 ml of dry toluene was heated for 3h30min at 90°C and an other 2 hours at 100°C. Evaporation of the toluene afforded 522 mg of crude product, which was purified by column chromatographie using TEA/hexane/EtOAc 1:15:8 → 1:13:10. This afforded 68 mg (213 µmol, 14%). No other product could be isolated after column chromatographie even flushing with polar solvents.

TLC (TEA/hexane/EtOAc 1:15:8): R_f 0.33; ^{1}H-NMR (300MHz, $CDCl_3$): 5.11 (1H, *s*), 4.98 (1H, *d*, *J* = 7.1), 4.78 (1H, *d*, *J* = 12.0), 4.39 (1H, *d*, *J* = 12.0), 4.05 (1H, *dd*, *J* = 11.4 and 7.2), 3.86 (3H, *s*), 3.60 (1H, *dd*, *J* = 11.3 and 1.5), 3.45 (3H, *s*), 2.02 (3H, *d*, *J* = 1.0); ^{13}C-NMR (75MHz, aceton-d6): 175.2, 168.7, 150.2, 107.4, 104.6, 104.5, 84.6, 56.0, 53.4, 43.9, 41.0, 35.7, 16.5; EI-MS: 318 (M+), 283, 259, 223.

(2*R*,2a*R*,4a*S*,7a*S*,7b*S*)-5-(Benzylamino-methyl)-2-methoxy-6-methyl-4-oxo-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid methyl ester (12)



$C_{13}H_{15}ClO_7$ | $C_{20}H_{23}NO_7$

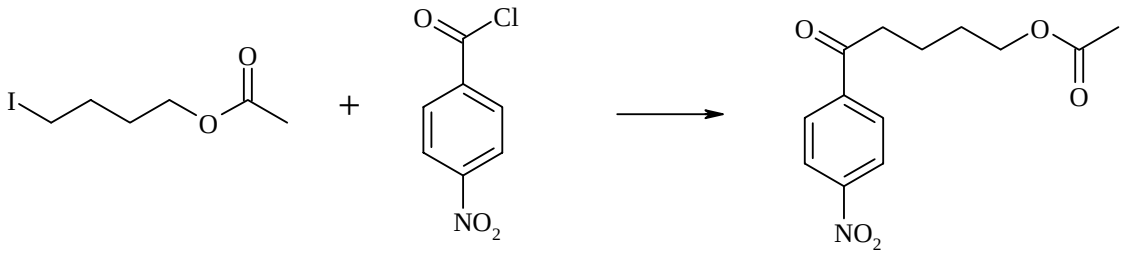
318.71 | 389.41

11a | **12**

To a solution of **11a** (68 mg, 0.21 mmol) in 1 ml of CH_3CN, benzylamine (23 µl, 0.21 mmol) in 0.5 ml CH_3CN was added. The mixture was stirred for 19h at rt while a white precipitate forms. The solvents were evaporated and the crude separated by column chromatographie using EtOAc/hexane 7:3. This yielded **12** (49 mg, 60%) as a yellow oil.

TLC (EtOAc/hexane 7:3): R_f 0.31; ^{1}H-NMR (300MHz, aceton-d6): 7.32 – 7.23 (5H, *m*), 4.96 (1H, *s*), 4.46 (2H, *m*), 4.25 (1H, *d*), 3.87 (2H, *m*), 3.79 (3H, *s*), 3.35 – 3.32 (2H, *m*), 3.34 (3H, *s*), 1.67 – 1.65 (3H, *m*); ^{13}C-NMR (75MHz, $CDCl_3$): 172.9, 168.7, 143.0, 136.0, 128.8, 128.0, 127.7, 111.7, 105.5, 105.4, 75.4, 55.4, 53.0, 47.2, 46.5, 42.9, 37.2, 16.7; EI^+-MS: 389 (M+), 330, 316, 300, 298, 258, 241, 223, 215.

Acetic acid 5-oxo-5-(4-nitro-phenyl)-pentyl ester (14)



$C_6H_{12}IO_2$	$C_7H_4ClNO_3$	$C_{13}H_{15}NO_5$
242.06	185.6	265.27
13		**14**

Zinc dust (817 mg, 12.5 mmol) was weighted into a first three neck flask and suspended in 1 ml THF. The flask was flushed with argon and 1,2 dibromoethane (85µl, 1 mmol) was added. This mixture was set to boil with a heat gun and cooled back to rt in 5 repetitions. Me_3SiCl was added and everything stirred for 15 more minutes. Then a solution of 4-iodobutylacetate in 5 ml THF was added gently so the temperature remained between 35-40°C. This suspension was stirred during 4 hours at 35°C then stirring was stopped and the suspension allowed settling for 15 min. Meanwhile a mixture of CuCN (448 mg, 5 mmol) and LiCl (424 mg, 10 mmol) was weighed into a second flask and dried for 2 hours under vacuum (0.1 mbar) at 150°C. The salts were then cooled to rt., the flask flushed with argon and everything dissolved in 5 ml THF to obtain a yellow/green solution. At -10°C the solution of the alkylzinc iodide was added rapidly and stirring was continued at 0°C for another 10 min. At -25°C 4-nitro benzoyl chloride (696 mg, 3.75 mmol) was added. The mixture was stirred over night at 0°C. Water was then added to the reaction and extracted with diethyl ether. The organic phases were dried over Na_2SO_4 and solvents were removed to obtain 1g of a yellow oil. This was further purified by column chromatographie using MTBE/Hex 3:7 → 1:1. Removal of the solvents yielded 484 mg (1.82 mmol, 49) of a clear yellow oil.

TLC (MTBE/Hex 3:7): R_f 0.38; ^{1}H-NMR (300MHz, $CDCl_3$): 8.35 – 8.30 (2H, *m*), 8.14 – 8.10 (2H, *m*), 4.14 (2H, t, *J* = 6.2), 3.08 (2H, t, *J* = 7.1), 2.06 (3H, *s*), 1.91 – 1.70 (4H, *m*); ^{13}C-NMR (75MHz, $CDCl_3$):198.0, 171.1, 150.2, 141.2, 128.9, 123.8, 63.9, 38.4, 27.9, 20.9, 20.2; EI^+-MS : 311, 283, 265 (M^+), 205, 170, 155, 150;

(*E*)-1-(3-Bromo-propenyl)-4-nitro-benzene (17)

$C_9H_9NO_3$ — $C_9H_8BrNO_2$

179.15 — 242.05

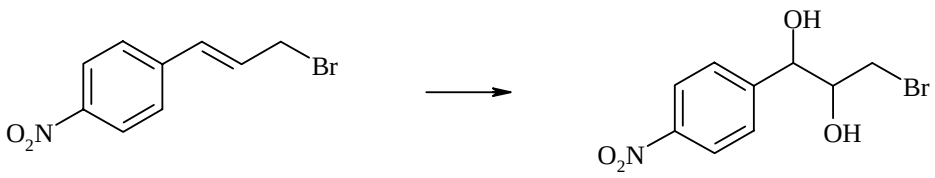
16 — **17**

4-Nitrocinnamoyl alcohol 98% was available from Lancaster UK Prod.# 7302.

In a dry reaction vessel **16** (1 g, 5.58 mmol) is dissolved in 3 ml CH_2Cl_2. Under magnetic stirring CBr_4 (2.22 g, 6.7 mmol) is added in 2 ml CH_2Cl_2 to the solution. After cooling to 0°C PPh_3 (1.61 g, 6.14 mmol) is added slowly so the temperature is allowed to rise to 30°C (exothermic). The turbid reaction mixture turns clear and is stirred for then another 15 min. The solution is poured on water and extracted with EtOAc. The organic phases are washed once more with aq. sat. NaCl. and then dried over Na_2SO_4. Column chromatographie using EtOAc / hexane 2:3 and evaporation of the solvents yields 1 g (4.31 mmol, 74%) of solid product.

TLC (EtOAc/hexane 2:3): R_f 0.29; ^{1}H-NMR (300MHz, $CDCl_3$): 8.23 – 8.18 (2H, *m*), 7.56 – 7.51 (2H, *m*), 6.71 (1H, *d*, *J* = 15.5), 6.59 (1H, dt, *J* = 15.5 and 7.6), 4.17 (2H, *dd*, *J* = 7.4 and 0.8); ^{13}C-NMR (75MHz, $CDCl_3$): 147.4, 142.2, 132.2, 129.9, 127.3, 124.1, 31.9; IR: 1590, 1484, 1438, 1311, 1186, 1118, 1072, 1026, 996, 940, 862; EI^+-MS: 243 and 241 (M^+), 162, 145, 131, 117, 116, 115, 104, 103.

3-Bromo-1-(4-nitro-phenyl)-propane-1,2-diol (18)



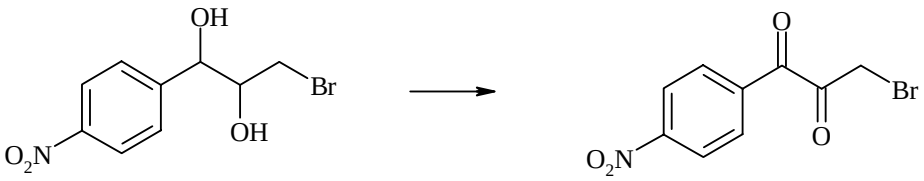
$C_9H_8BrNO_2$ — 242.05 — **17**

$C_9H_{10}BrNO_4$ — 276.09 — **18**

In a two neck flask NMO (613 mg, 4.54 mmol) was dissolved in 10 ml H_2O. 5 ml Aceton were added to the solution and shortly after OsO_4 (300 µl, 0.65 M in t-BuOH). The solution was stirred at RT for 10 min. Meanwhile **17** was dissolved in 1 ml t-BuOH and 5 ml acetone and added to the reaction. The suspension was stirred under Ar at RT for 45 min. TLC control was used to determine completion of the by then clear reaction. The solution was worked up between water and EtOAc (extract only once) and dried over Na_2SO_4. The crude product was further purified by column chromatographie. This yielded 0.9 g (3.26 mmol, 79%) of a light gray solid.

TLC (EtOAc/hexane 1:1) R_f: 0.53; ^{1}H-NMR (300MHz, aceton-d6): 8.24 – 8.19 (2H, *m*), 7.76 – 7.72 (2H, *m*), 5.06 – 5.03 (1H, *m*), 4.03 – 3.95 (1H, *m*), 3.67 (1H, *dd*, *J* = 4.9 and 10.4), 3.32 (1H, *dd*, *J* = 10.5 and 6.5); ^{13}C-NMR (75MHz, aceton-d6): 150.9, 148.2, 128.7, 123.8, 76.0, 74.2, 35.7; EI$^+$-MS: 276 (M^+), 198, 195, 182, 153, 152, 136; IR: 1600, 1512, 1436, 1411, 1342, 1291, 1234, 1196, 1178, 1138, 1089, 1054, 1036, 1023, 917, 872, 862, 841, 802;

3-Bromo-1-(4-nitro-phenyl)-propane-1,2-dione (19)



$C_9H_{10}BrNO_4$ | $C_9H_6BrNO_4$

276.09 | 272.06

18 | **19**

To DMSO (304 µl, 4.28 mmol) in 3 ml CH_2Cl_2 at – 70°C was added TFAA (595 µl, 4.28 mmol) in 2 ml CH_2Cl_2. After 15 min. **18** (591 mg, 2.14 mmol) was added slowly in 5 ml THF. Stirring was continued for another 40 min. then Et_3N (597 µl, 4.28 mmol) in 1 ml CH_2Cl_2 was added. After 15 min. cooling was removed and the reaction was stirred for another 15 min. By then TLC control didn't show any more starting material.

Water was poured into the reaction mixture and extracted with CH_2Cl_2 (strong odor!). The organic phases were washed once with Brine, HCL 1N and aq. sat. $NaHCO_3$ consecutively. After drying over Na_2SO_4 a brown crude oil was obtained.

Column chromatographie with EtOAc/hexane 1:9 -> 2:8 yields 135 mg (0.49 mmol, 23%) of **19** as a yellow oil.

TLC (EtOAc/hexane 2:8) R_f: 0.5 – 0.6; ^{1}H-NMR (300MHz, $CDCl_3$): 8.38 – 8.34 (2H, *m*), 8.25 – 8.21 (2H, *m*) 4.41 (2H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 189.9, 188.0, 136.5, 131,4, 129.7, 124.0, 29.7; IR: 1794, 1718, 1683, 1602, 1521, 1407, 1345, 1319, 1228, 1169, 1108, 1047, 1012, 933, 904, 849.

4.5.8 Acid stability test of 4a

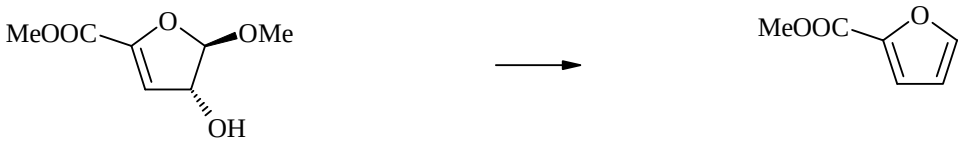
Experiment A: 113 mg **4a** were dissolved in 400µl THF and treated with 500 µl HCl 1N. The resulting white suspension was stirred for 3h at rt. After this time TLC control of the reaction showed only very little new product at the baseline of the TLC plate. The reaction was stirred at 50°C for another 2.5 h. Half of the mixture was extracted with EtOAc. After drying of the organic phase with Na_2SO_4 and evaporation of the solvents 18 mg of an oil containing starting material among two new more polar product was obtained. The remaining half of the reaction mixture was stirred at 50°C for 16 more hours. After this period no more **4a** could be detected by TLC.

Experiment B: 109 mg **4a** were dissolved in 400µl THF and treated with 500 µl phosphate buffer pH 3. The resulting white suspension was stirred for 2h at rt. After this time TLC control of the reaction showed no new products. The reaction was then stirred at 50°C for 4.5 h. Still no change could be observed by TLC. After another 20h at 80°C complete decomposition had taken place.

Experiment C: 109 mg **4a** were dissolved in 400µl THF and treated with 500 µl citrate / NaOH buffer pH 5. The resulting suspension was stirred for 2h at rt. After this time TLC control of the reaction showed no new products. The reaction was then stirred at 50°C for 4.5 h. No change could be observed by TLC after this time. After another 20h at 80°C **4a** was still clearly detectable by TLC.

4.5.9 Compounds 20 and 21

Furan-2-carboxylic acid methyl ester (20)



$C_7H_{10}O_5$ | $C_6H_6O_3$

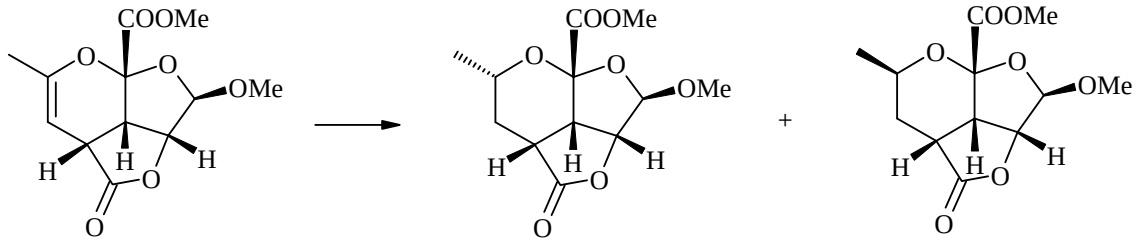
174.15 | 126.11

1 | **20**

In a 1 ml Eppendorf tube **1** (100 mg, 0.56 mmol) was dissolved in 0.5 ml $CDCl_3$. In a second Eppendorf tube triethyl silane (0.092 ml, 0.56 mmol) and trimethyl silyl triflate (0,126 ml, 0.56 mmol) were mixed in 0.5 ml $CDCl_3$. Both tubes were cooled to 0°C and then mixed in a testtube. The now yellow reactionmixture was left to react at 0°C and mixed once in a while. After 20 min. 1 ml brine was added to the suspension. The tube was well agitated and the water phase was removed fully. The remaining phase was passed over 1 g of basic alox. The now colorless solution was used directly for NMR measurements. For mass spectroscopy the same procedure was repeated but instead of $CDCl_3$, C_6D_6 was used.

TLC (EtOAc/hexane = 1:1): R_f 0.71; ^{1}H-NMR (300MHz, $CDCl_3$): 7.58 (1H, *m*), 7.19 (1H, *m*), 6.52 (1H, *m*), 3.91 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 156.3, 143.5, 143.0, 115.2, 109.2, 48.7; EI-MS: 239, 217, 189, 161, 126 (M^+), 105, 95.

(2*R*,2a*R*,4a*S*,6*S*,7a*S*,7b*S*) and (2*R*,2a*R*,4a*S*,6*R*,7a*S*,7b*S*)-2-Methoxy-6-methyl-4-oxo-hexahydro-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid methyl ester and (21)



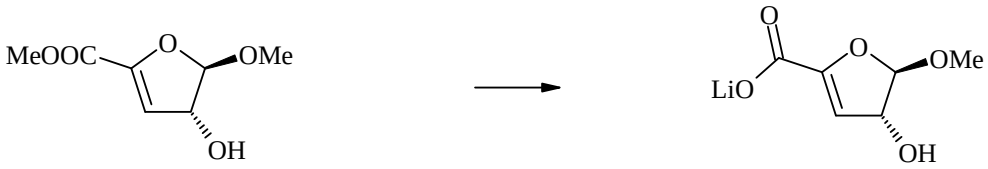
$C_{12}H_{14}O_7$	$C_{12}H_{16}O_7$	$C_{12}H_{16}O_7$
270.24	272.26	272.26
4a	6S-**21**	6R-**21**

Under an argon atmosphere, **4a** (150 mg, 555 µmol) was dissolved in 1 ml CH_2Cl_2 and Et_3SiH (265 µl, 1.66 mmol) were added. The solution was cooled to 0°C and trimethyl silyl triflate (226 µl, 1.25 mmol) were added drop wise. Cooling was removed and stirring continued for 24h at RT. and an other 24 hours at 30°C. The mixture was then poured on sat. aq. $NaHCO_3$ and extracted twice with CH_2Cl_2. After drying (Na_2SO_4) and evaporating the solvents 172 mg of crude **21** as a diastereomeric mixture of approximately 2/1 was obtained. Separation of the white solid crude on silicagel (EtOAc/hexane 3:7 -> 4:6) ylieded 71 mg (261 µmol, 47%) of one and 28 mg (103 µmol, 19%) of the other diastereomer. Another 27 mg (99 µmol, 18%) were obtained as mixture of the two diastereomers.

TLC (EtOAc/hexane 3:7): R_f 0.4 and 0.26; ^{1}H-NMR (300MHz, $CDCl_3$): 5.03 (1H, *s*), 4.86 (1H, *d*, *J* = 7.0), 3.90 (1H, *dd*, *J* = 11.6 and 7.17), 3.83 (3H, *s*), 3.81 – 3.74 (1H, *m*), 3.40 (3H, *s*), 3.08 – 3.01 (1H, *m*), 2.12 – 2.06 (1H, *m*), 1.68 – 1.58 (1H, *m*), 1.28 – 1.26 (3H, *m*) and 5.17 (1H, 4.84 (1H, *d*, *J* = 6.6), 3.84 – 3.78 (1H, *m*), 3.83 (3H, *s*), 3.39 (3H, *s*), 3.05 – 2.97 (1H, *m*), 2.13 – 1.94 (2H, *m*), 1.32 – 1.30 (3H, *m*); ^{13}C-NMR (75MHz, $CDCl_3$): 177.1, 169.1, 105.0, 104.7, 83.6, 64.9, 55.6, 53.1, 35.7, 34.3, 28.4, 20.8 and 177.0, 168.8, 106.2, 105.0, 84.0, 68.0, 55.6, 53.0, 38.4, 34.8, 26.8, 22.2; EI-MS: 271 (M^+), 241, 213, 195.

4.5.10 Compounds for the Scaffolds for library Synthesis

Lithium; (4*R*,5*R*)-4-hydroxy-5-methoxy-4,5-dihydro-furan-2-carboxylate (22)



$C_7H_{10}O_5$ | $C_6H_7LiO_5$

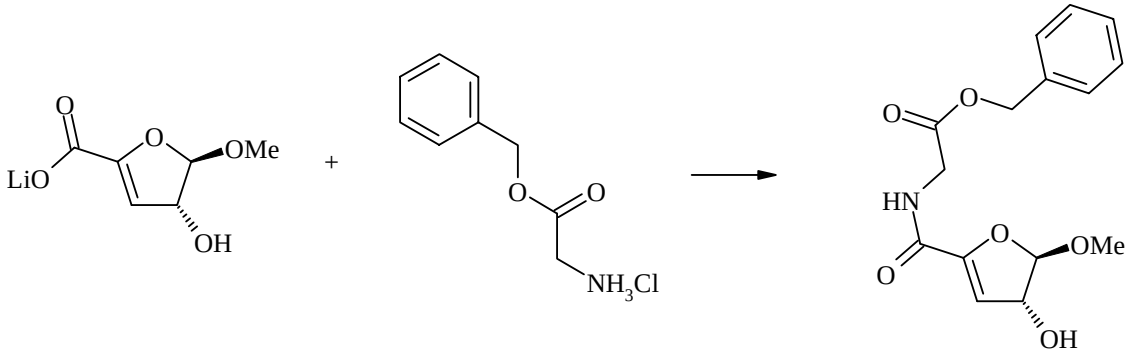
174.15 | 166.06

1 | **22**

To a solution of **1** (4.4g, 25.3 mmol) in 40 ml dioxane 8 ml of H_2O were added. At 10-15°C LiOH 0.5N (55.6 ml, 27.8 mmol) was added during 20 min. The yellow solution was stirred for 2 hours at rt. Then the solvents were evaporated and twice 15-20 ml AcCN was added and evaporated. This gave 4.21g (25.3, 100%) white crude product which was used without further purification.

^{1}H-NMR (300MHz, $CDCl_3$): 5.66 (1H, *d*, *J* = 2.8), 5.14 (1H, *d*, *J* = 1.3), 4.53 (1H, *dd*, *J* = 2.6 and 1.5), 3.50 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 167.8, 157.0, 114.0, 107.2, 80.0, 56.5; IR: 1595, 1410, 1336, 1266, 1202, 1106, 1039, 977, 913; EI$^+$-MS: 157 (M^+), 149, 129, 121, 115, 113, 84.

[((4*R*,5*R*)-4-Hydroxy-5-methoxy-4,5-dihydro-furan-2-carbonyl)-amino]-acetic acid benzyl ester (23)

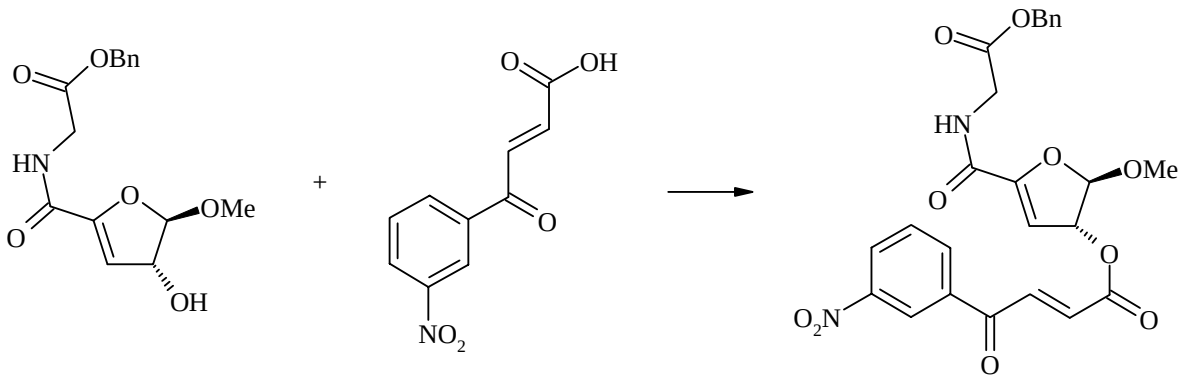


$C_6H_7LiO_5$	$C_9H_{12}ClNO_2$	$C_{15}H_{17}NO_6$
166.06	201.65	307.31
22		***23***

Under an argon atmosphere **22** (4.21 g, 25.4 mmol) and BOP (14.57 g, 33 mmol) were dissolved in 63 ml abs. CH_3CN. After stirring for 10 min DIPEA (21.7 ml, 126 mmol) was added over 20 min. Then the apparatus was opened briefly to add glycine-benzyl ester HCl (7.66 g, 38 mmol). The mixture was stirred at rt for 4 hours and then poured on cold H_2O to be extracted three times with EtOAc. The organic phases were washed once more with sat. aq. NaCl. After evaporation of the solvents 23.22 g of crude product was obtained. Column chromatographie using EtOAc/hexane 3:2 → 4:1 yields 7.56 g (24.6 mmol, 96.8%) **23** as a white foam.

TLC (EtOAc): R_f 0.62; ^{1}H-NMR (300MHz, $CDCl_3$): 7.37 (5H, *s*), 7.09 (1H, *m*), 6.01 (1H, *d*, *J* = 2.6) 5.29 (1H, *s*), 5.21 (2H, *s*), 4.70 (1H, t, *J* = 1.3), 4.28 (1H, *dd*, 18.4 and 5.9), 4.07 (1H, *dd*, 18.6 and 5.2), 3.50 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 170.7, 162.1, 152.8, 136.9, 129.6, 129.5, 129.5, 129.3, 129.2, 129.1, 114.6, 109.2, 79.3, 67.9, 56.8, 41.8; IR: 1738, 1669, 1532, 1455, 1390, 1357, 1199, 1157, 1115, 1079, 1041, 1008, 978, 912, 835; EI$^+$-MS: 307 (M^+), 290, 289, 167, 155, 129.

(4*R*,5*R*)-4-(3-Nitro-phenyl)-(*E*)-4-oxo-but-2-enoic acid 5-(benzyloxycarbonylmethyl-carbamoyl)-2-methoxy-2,3-dihydro-furan-3-yl ester (24d)



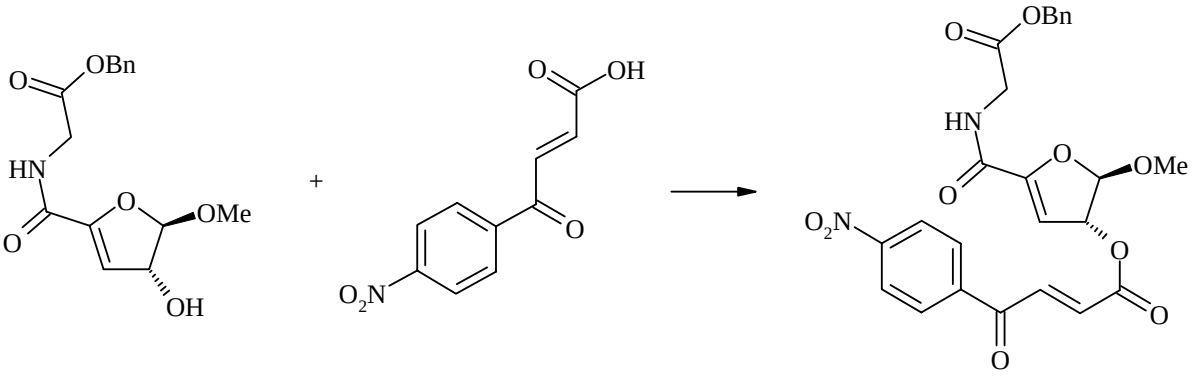
$C_{15}H_{17}NO_6$	$C_{10}H_7NO_5$	$C_{25}H_{22}N_2O_{10}$
307.31	221.17	510.46
23	**2d**	**24d**

The product was synthesised according to general procedure A.

The mixture was poured on cold $NaHCO_3$ sat. and washed. The organic phase was then separeted and washed once more with NaCl sat./H_2O (1:1). The aquaous phases are extracted with diethylether. The organic phases are then dried with Na_2SO_4 and the solvents evaporated. This yields a crude black oil which was separaed on silicagel with EtOAc/Hex 2:3. Upon evaporation of the solvents an orange foam with a yield of 44.5 % was obtained.

TLC (EtOAc/Hex 2:1) R_f: 0.66 UV_{254}, Cer/Molybdenic acid reagent; ^{1}H-NMR (300MHz, $CDCl_3$): 8.81 (1H, t, *J* = 1.7), 8.49 (1H, *d*, *J* = 8.1), 8.32 (1H, *d*, *J* = 7.7), 7.91 (1H, *d*, *J* = 15.5), 7.75 (1H, t, *J* = 8.0), 7.36 (5H, *s*), 6.94 (1H, *d*, *J* = 13.9), 6.91 (1H, *m*), 6.07 (1H, *d*, *J* = 2.8), 5,72 (1H, *dd*, *J* = 2.5 and 0.9), 5.52 (1H,s), 5.22 (2H, *s*), 4.28 – 4.11 (2H, *m*), 3.58 (3H,s); ^{13}C-NMR (75MHz, $CDCl_3$): 187.0, 169.1, 164.0, 158.5, 154.0, 140.8, 135.8, 134.2, 133.0, 130.3, 128.7, 128.4, 124.1, 123.6, 110.3, 103.8, 81,8, 67.5, 57.0, 41.0; IR: 1726, 1674, 1613, 1528, 1455, 1386, 1349, 1320, 1288, 1256, 1192, 1161, 1114, 999, 904; EI^+-MS: 510 (M^+), 480, 389, 318, 289.

(4*R*,5*R*)-4-(4-Nitro-phenyl)-(*E*)-4-oxo-but-2-enoic acid 5-(benzyloxycarbonylmethyl-carbamoyl)-2-methoxy-2,3-dihydro-furan-3-yl ester (24e)



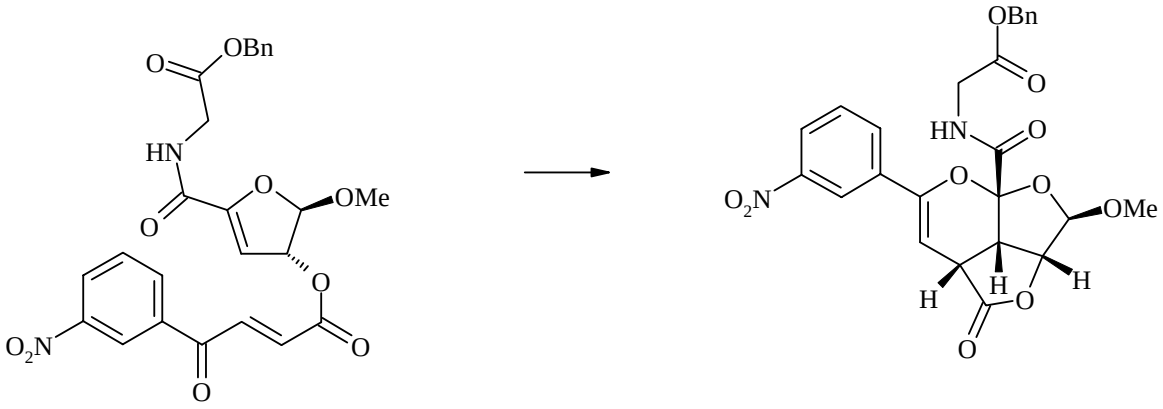
$C_{15}H_{17}NO_6$	$C_{10}H_7NO_5$	$C_{25}H_{22}N_2O_{10}$
307.31	221.17	510.46
23	**2e**	**24e**

The product was synthesised according to general procedure A.

The mixture was poured on cold $NaHCO_3$ sat. and washed. The organic phase was then separeted and washed once more with NaCl sat./H_2O (1:1). The aquaous phases are extracted with diethylether. The organic phases are then dried with Na_2SO_4 and the solvents evaporated. This yields a crude black oil which was separaed on silicagel with EtOAc/Hex 2:3. Upon evaporation of the solvents an orange foam with a yield of 44.5 % was obtained.

TLC (EtOAc/Hex 2:1) R_f: 0.66 UV_{254}, Cer/Molybdenic acid reagent; ^{1}H-NMR (300MHz, $CDCl_3$): 8.30 (2H, dm, *J* = 8.9), 8.08 (2H, dm, *J* = 8.5), 7.81 (1H, *d*, *J* = 15.6), 7.36 (5H, *s*), 6.87 (1H, t, *J* = 5.4), 6.85 (1H, *d*, *J* = 15.5), 6.08 (1H, *d*, *J* = 3.0), 5.72 (1H, *dd*, *J* = 2.6 and 1.3), 5.51 (1H, *d*, *J* = 1.3), 5.22 (2H, *s*), 4.30 – 4.12 (2H, *m*); ^{13}C-NMR (75MHz, $CDCl_3$): 187.8, 169.1, 164.0, 158.5, 154.0, 140.8, 136.1, 133.0, 129.9, 128.7, 128.4, 124.1, 110.3, 103.9, 81,7, 67.5, 57.0, 41.0; IR: 1728, 1674, 1602, 1521, 1455, 1386, 1347, 1318, 1286, 1259, 1164, 1114, 1069, 970, 908; EI^+-MS: 510 (M^+), 480, 389, 318, 289.

(2*R*,2a*R*,4a*S*,7a*S*,7b*S*)-{[2-Methoxy-6-(3-nitro-phenyl)-4-oxo-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxa-cyclopenta[cd]indene-7a-carbonyl]-amino}-acetic acid benzyl ester (25d)



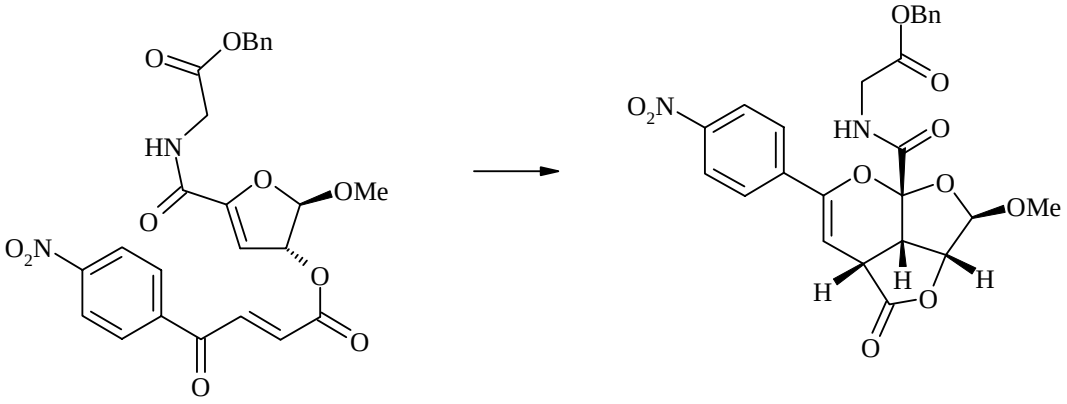
$C_{25}H_{22}N_2O_{10}$
510.46
24d

$C_{25}H_{22}N_2O_{10}$
510.46
25d

In an absolute apparatus a solution of **24e** (1.48 mg, 2.9 mmol) in 140 ml Toluene and 2,6-lutidine (0.96 ml, 8.2 mmol) is stirred at 100°C for 24 h. The crude oil was separated on silicagel using $CHCl_3$/diethylether/hexane 2:2:1. Upon evaporation of the solvents 666 mg (1.3 mmol, 45%) of an orange foam was obtained.

TLC (diethylether/$CHCl_3$/hexane 2:2:1): R_f 0.37; ^{1}H-NMR (300MHz, $CDCl_3$): 8.45 – 8.44 (1H, *m*), 8.23 – 8.20 (1H, *m*), 7.93 – 7.90 (1H, *m*), 7.58 – 7.54 (1H, *m*), 7.39 – 7.35 (1H, *m*), 7.14 – 7.12 (1H, *m*), 6.04 (1H, *d*, *J* = 4.8), 5.24 (2H, *s*), 5.21 (1H, *s*), 5.05 (1H, *dd*, *J* = 8.0 and 0.7), 4.27 – 4.14 (2H, *m*), 4.17 (1H, *dd*, *J* = 11.3 and 8.2), 3.59 (1H, *dd*, *J* = 11.4 and 4.9), 3.51 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 174.4, 169.0, 167.7, 148.5, 147.6, 135.0, 134.9, 130.7, 129.5, 128.7, 128.5, 123.9, 120.0, 108.7, 105.2, 97.5, 85.4, 67.6, 57.0, 41.6, 39.0, 35.5; IR: 3406, 2838, 1785, 1747, 1691, 1528, 1455, 1382, 1348, 1321, 1267, 1176, 1108, 1066, 969; EI^+-MS: 511, 510 (M^+), 480, 450, 318, 304.

(2*R*,2a*R*,4a*S*,7a*S*,7b*S*)-{[2-Methoxy-6-(4-nitro-phenyl)-4-oxo-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxa-cyclopenta[cd]indene-7a-carbonyl]-amino}-acetic acid benzyl ester (25e)



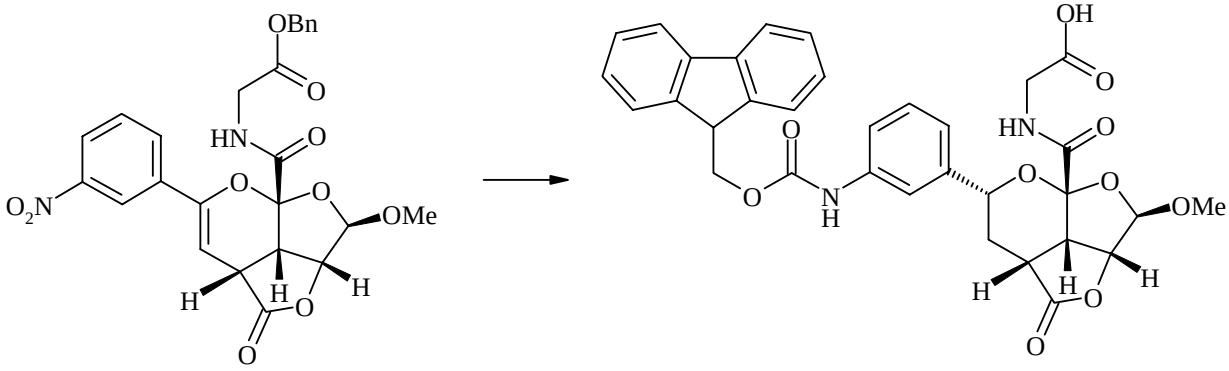
$C_{25}H_{22}N_2O_{10}$
510.46
24e

$C_{25}H_{22}N_2O_{10}$
510.46
25e

In an absolute apparatus a solution of **24e** (100 mg, 0.196 mmol) in 5 ml AcCN and $LiClO_4$ (795 mg, 7.5 mmol) is stirred at 50°C for 50 h. When cooling the solution to rt again part of the LIClO4 recrystallizes. CH3CN is added until a solution is obtained. The reaction mixture is washed with sat. aq. $NaHCO_3$ and extracted twice with diethylether. The organic phases are washed once more with H_2O/brine 1:1. The organic phase is dried with Na_2SO_4 and solvents are evaporated. The crude oil was separated on approx. 10g silicagel with $CHCl_3$/diethylether/hexane 2:2:1. Upon evaporation of the solvents 55 mg (0.108 mmol, 55%) of an orange foam was obtained.

TLC (diethylether/$CHCl_3$/hexane 2:2:1): R_f 0.37; ^{1}H-NMR (300MHz, $CDCl_3$): 8.22 (2H, dm, *J* = 8.9), 7.76 (2H, dm, *J* = 9.1), 7.38 (5H, *s*), 7.09 (1H, *m*), 6.07 (1H, *d*, *J* = 4.8), 5.24 (2H, *m*), 5.21 (1H, *s*), 5.05 (1H, *d*, *J* = 7.9), 4.19 (2H, *m*), 4.17 (1H, *dd*, *J* = 11.2 and 7.9), 3.59 (1H, *dd*, *J* = 11.4 and 4.9), 3.50 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 174.3, 169. 0, 167.7, 148.0, 147.7, 139.1, 134.8, 128.7, 128.5, 125.7, 123.7, 108.6, 105.1, 98.8, 85.4, 67.6, 57.0, 41.6, 38.8, 35.6; IR: 3404, 2925, 2852, 2359, 2344, 1785, 1747, 1687, 1598, 1516, 1455, 1410, 1386, 1345, 1319, 1290, 1175, 1108, 1064, 965; EI^+-MS: 510 (M^+), 481, 480, 450, 419, 393, 318

(2*R*,2a*R*,4a*S*,6*S*,7a*S*,7b*S*)-({6-[3-(9H-Fluoren-9-ylmethoxycarbonylamino)-phenyl]-2-methoxy-4-oxo-hexahydro-1,3,7-trioxa-cyclopenta[cd]indene-7a-carbonyl}-amino)-acetic acid (27d)



$C_{25}H_{22}N_2O_{10}$
510.46
25d

$C_{33}H_{30}N_2O_{10}$
614.61
27d

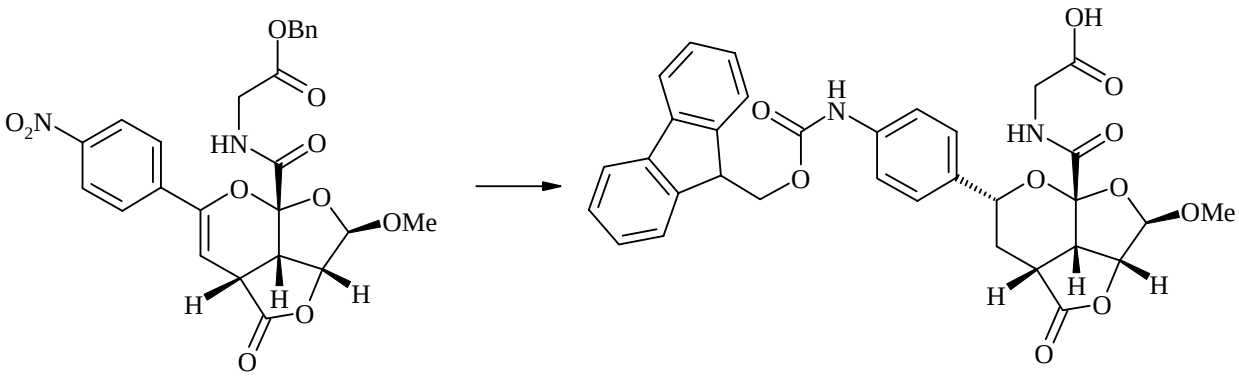
The product was synthesised according to general method B.

The solvents are removed and 363 mg (0.926 mmol, 86%) crude brown foam is obtained.

The crude material is dissolved in 35 ml/35 drops Dioxane/H_2O. $NaHCO_3$ (75 mg, 0.89 mmol) is added first then Fmoc-Cl (231 mg, 0.89 mmol). The turbid solution is stirred at rt for 4 h. The solvents are then removed and after drying on the HV, 728 mg of a red brown foam is obtained. The crude material is dissolved in THF at 40°C and filtered. From the obtained clear solution the THF is removed fully. The thus obtained foam is recrystallised form MeOH/MTBE. This gave 236 mg (0.384 mmol, 35.7%) of white solid.

^{1}H-NMR (300MHz, THF-d8): 8.90 (1H, *s*), 7.81 – 7.79 (2H, *m*), 7.78 – 7.74 (1H, *m*), 7.71 – 7.68 (2H, *m*), 7.39 – 7.26 (6H, *m*), 7.20 – 7.15 (1H, m), 7.02 – 7.00 (1, *m*), 5.20 (1H, *s*), 4.79 (1H, *d*, *J* = 6.2), 4.67 (1H, t, *J* = 8.1), 4.48 (2H, *d*, *J* = 6.6), 4.27 (1H, t, *J* = 6.7), 3.95 (1H, *dd*, *J* = 9.2 and 6.2), 3.88 (2H, *m*), 3.35 (3H, *s*), 3.18 – 3.11 (1H, *m*), 2.24 – 2.19 (2H, *m*); ^{13}C-NMR (75MHz, THF-d8): 174.6, 168.3, 166.5, 151.4, 142.4, 140.8, 139.5, 137.6, 126.4, 125.5, 124.9, 123.0, 118.8, 117.8, 115.6, 114.4, 105.1, 104.7, 81.9, 70.4, 52.6, 45.4, 38.4, 36.0, 33.7, 25.6; IR: 3348, 2940, 2359, 1770, 1726, 1657, 1613, 1542, 1496, 1448, 1430, 1404, 1377, 1307, 1254, 1217, 1167, 1118, 1080, 1052, 1013, 977, 942, 924, 877; ES^+-MS: 1228 (2xM), 637 ($M+Na^+$), 615 (M^+), 582.

(2*R*,2a*R*,4a*S*,6*S*,7a*S*,7b*S*)-({6-[4-(9H-Fluoren-9-ylmethoxycarbonylamino)-phenyl]-2-methoxy-4-oxo-hexahydro-1,3,7-trioxa-cyclopenta[cd]indene-7a-carbonyl}-amino)-acetic acid (27e)



$C_{25}H_{22}N_2O_{10}$
510.46
25e

$C_{33}H_{30}N_2O_{10}$
614.61
27e

The product was synthesised according to general method B.

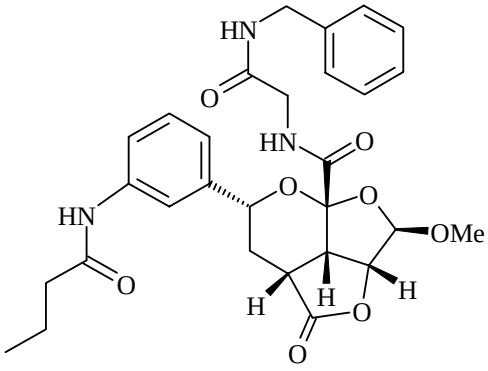
The solvents are removed and 1.3 g (3.3 mmol, 85%) crude brown foam is obtained.

The crude material is dissolved in 120 ml dioxane and 12 ml H_2O. $NaHCO_3$ (277 mg, 3.3 mmol) is added first then Fmoc-Cl (853 mg, 3.3 mmol). The turbid solution is stirred at RT for 4 h. The solvents are then removed and after drying on the HV, 931 mg of a red brown foam is obtained. The crude material is dissolved in THF at 40°C and filtered. From the obtained clear solution the THF is removed fully. The thus obtained foam is recrystallised form MeOH/MTBE. This gave 598 mg (0.97 mmol, 25% from **25e**) of white solid.

^{1}H-NMR (300MHz, THF-d8): 8.79 (1H, *s*), 7.82 (1H, *m*), 7.79 (2H, dm, *J* = 7.5), 7.68 (2H, dm, *J* = 7.4), 7.43 – 7.26 (9H, *m*), 5.19 (1H, *s*), 4.77 (1H, *d*, *J* = 6.2), 4.65 (1H, t, *J* = 8.6), 4.51 (2H, *d*, *J* = 6.4), 4.26 (1H, t, *J* = 6.3), 3.95 (1H, *dd*, *J* = 9.0 and 6.2), 4.04 – 3.76 (2H, *m*), 3.33 (3H, *s*), 3.14 (1H, dt, *J* = 3.2 and 8.7), 2.32 - 2.12 (2H, *m*); ^{13}C-NMR (75MHz, THF-d8):177.1, 172.8, 169.2, 143.7, 143.6, 141.4, 127.8, 127.7, 127.1, 124.9, 120.1, 106.8, 106.6, 84.0, 72.7, 55.8, 47.0, 40.8, 37.9, 36.0, 26.9; IR: 3307, 2935, 2360, 1785, 1692, 1666, 1600, 1537, 1449, 1414, 1376, 1319, 1235, 1150, 1111, 1056, 1020, 982, 950, 917; ES$^+$-MS: 1229(2xM), 653 (M+K$^+$), 634 (M+Na$^+$), 615 (M$^+$), 583.

4.5.11 Componds from Solid Phase Synthesis

(2*R*,2a*R*,4a*S*,6*S*,7a*S*,7b*S*)-6-(3-Butyrylamino-phenyl)-2-methoxy-4-oxo-hexahydro-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid (benzylcarbamoyl-methyl)-amide (A1)



$C_{29}H_{33}N_3O_8$

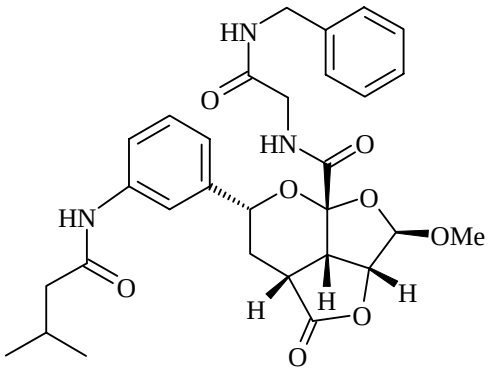
551.60

A1

The product was synthesised according to general method C. Yield: 5 mg (55% based on 59% loading)

TLC (AcCN): R_f 0.73; HPLC: t_R = 10.76, λ_{max} = 244 nm; ^{1}H-NMR (300MHz, aceton-d6): 7.79 – 7.76 (1H, *m*), 7.50 – 7.49 (1H, *m*), 7.30 – 7.20 (6H, *m*), 7.07 – 7.04 (1H, *m*), 5.26 (1H, *s*), 4.91 (1H,m),, 4.77 (1H, *m*), 4.45 -4.31 (2H, *m*), 4.06 – 3.92 (2H, *m*), 3.40 – 3.35 (1H, *m*), 3.37 (3H, *s*), 2.40 – 2.13 (4H, *m*), 1.74 – 1.57 (2H, *m*), 0.92 (3H, t); ^{13}C-NMR (75MHz, aceton-d6): 177.1, 173.1, 169.3, 168.3, 148.4, 141.4, 138.7, 138.6, 137.8, 129.6, 129.0, 128.1, 127.9, 127.8, 121.9, 120.0, 117.9, 107.3, 106.7, 84.5, 73.5, 56.3, 44.8, 43.9, 43.3, 39.9, 38.9, 38.3, 35.9, 27.6, 22.8, 19.3, 14.0; ESI-MS (positive mode): 574 ($M+Na^+$), 552 (M^+), 502, 273, 200, 178, 91; HR-MS: Calcd. for $C_{29}H_{34}N_3O_8Na$: 574.2165; measured: 574.2160.

(2*R*,2a*R*,4a*S*,6*S*,7a*S*,7b*S*)-2-Methoxy-6-[3-(3-methyl-butyrylamino)-phenyl]-4-oxo-hexahydro-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid (benzylcarbamoyl-methyl)-amide (A2)



$C_{30}H_{35}N_3O_8$

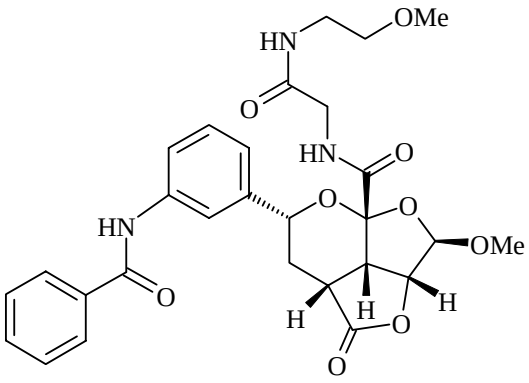
565.6

A2

The product was synthesised according to general method C. Yield: 5 mg (54% based on 59% loading)

TLC(AcCN): R_f 0.78; HPLC: t_R = 8.57, λ_{max} = 277 nm; ^{1}H-NMR (300MHz, aceton-d6): 7.80 – 7.77 (1H, *m*), 7.50 – 7.49 (1H, *m*), 7.30 – 7.21 (6H, *m*), 7.07 – 7.04 (m, 1H) 5.26 (1H, *s*), 4.91 (1H, *m*), 4.77 (1H, *m*), 4.46 – 4.31 (2H, *m*), 4.05 – 3.92 (3H, *m*), 3.40 – 3.31 (1H, *m*), 3.37 (3H, *s*), 2.40 – 2.11 (5H, *m*), 0.96 (6H, d); ^{13}C-NMR (75MHz, aceton-d6): 178.1, 172.5, 169.7, 168.1, 143.4, 140.6, 140.1, 129.6, 129.3, 129.2, 128.4, 127.9, 127.7, 121.9, 119.6, 119.5, 118.0, 118.9, 107.9, 107.7, 84.9, 73.4, 55.9, 47.0, 46.1, 43.6, 43.4, 39.0, 36.4, 30.9, 28.5, 26.8, 22.8; ESI-MS (positive mode): 589 ($M+Na^+$), 566 (M^+), 534, 303, HR-MS: Calcd. for $C_{30}H_{35}N_3O_8Na$: 588.2321; measured: 588.2338.

(2*R*,2a*R*,4a*S*,6*S*,7a*S*,7b*S*)-6-(3-Benzoylamino-phenyl)-2-methoxy-4-oxo-hexahydro-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid [(2-methoxy-ethylcarbamoyl)-methyl]-amide (B3)



$C_{28}H_{31}N_3O_9$

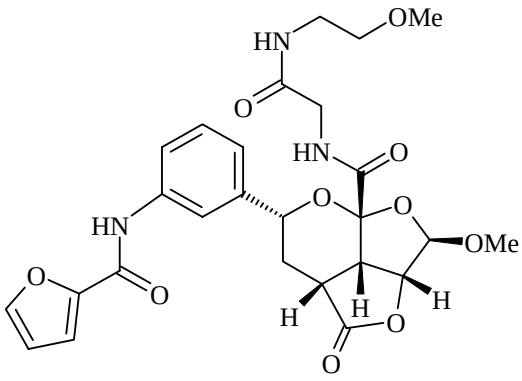
553.6

B3

The product was synthesised according to general method C. Yield: 5 mg (59% based on 56% loading)

TLC (AcCN): R_f 0.50; HPLC: t_R = 8.50, λ_{max} = 277 nm; ^{1}H-NMR (300MHz, aceton-d6): 7.91 – 7.88 (2H, *m*), 7.84 – 7.80 (1H, *m*), 7.61 – 7.60 (1H, *m*), 7.48 – 7.35 (3H, *m*), 7.24 – 7.19 (1H, *m*), 7.05 – 7.03 (1H, *m*), 5.15 (1H, *s*), 4.81 – 4.79 (1H, *m*), 4.70 – 4.65 (1H, *m*), 3.89 – 3.73 (3H, *m*), 3.29 – 3.16 (5H, *m*), 3.29 (3H, *s*), 3.20 – 3.16 (4H, *m*), 3.10 (3H, *s*), 2.32 – 2.07 (2H, *m*); ^{13}C-NMR (75MHz, aceton-d6): 178.1, 169.6, 169.3, 166.3, 143.3, 140.5, 136.4, 132.4, 129.6, 129.5, 128.3, 122.5, 120.6, 120.5, 119.3, 119.2, 108.0, 107.7, 84.9, 73.4, 71.8, 58.7, 55.9, 43.3, 39.9, 39.0, 36.4, 28.3; ESI-MS (positive mode): 576 ($M+Na^+$), 554 (M^+), 522. 296; HR-MS: Calcd. for $C_{28}H_{31}N_3O_9Na$: 576.1957 ; measured: 576.1974

(2R,2aR,4aS,6S,7aS,7bS)-6-{3-[(Furan-2-carbonyl)-amino]-phenyl}-2-methoxy-4-oxo-hexahydro-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid [(2-methoxy-ethylcarbamoyl)-methyl]-amide (B4)



$C_{26}H_{29}N_3O_{10}$

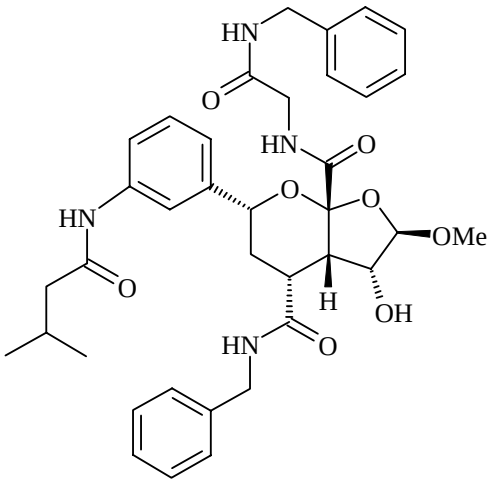
543.5

B4

The product was synthesised according to general method C. Yield: 6 mg (71% based on 56% loading)

TLC(AcCN): R_f 0.46; HPLC: t_R = 8.55, λ_{max} = 276 nm; ^{1}H-NMR (300MHz, aceton-d6): 7.94 – 7.90 (1H, *m*), 7.76 – 7.75 (1H, *m*), 7.73 – 7.72 (1H, *m*), 7.70 (1H, *m*), 7.37-7.31 (1H, *m*), 7.24 – 7.23 (1H, *m*), 6.66 – 6.64 (1H, *m*), 5.28 (1H, *s*), 4.94 – 4.92 (1H, *m*), 4.83 – 4.78 (1H, *m*), 4.01 – 3.86 (3H, *m*), 3.42 (3H, *s*), 3.42 – 3.34 (5H, *m*), 3.24 (3H, *s*), 2.44 – 2.19 (2H, *m*); ^{13}C-NMR (75MHz, aceton-d6): 178.1, 169.6, 169.2, 157.1, 146.0, 143.4, 139.8, 129.7, 122.7, 120.5, 120.4, 119.2, 115.4, 113.0, 107.7, 84.9, 73.4, 71.8, 58.7, 55.9, 43.3, 39.8, 39.0, 36.4, 28.3; ESI-MS (positive mode): 566 ($M+Na^+$), 544 (M^+), 512; HR-MS: Calcd. for $C_{26}H_{29}N_3O_{10}Na$: 566.1750; measured: 566.1769

(2*R*,3*R*,3a*S*,4*S*,6*S*,7a*S*)-3-Hydroxy-2-methoxy-6-[3-(3-methyl-butyrylamino)-phenyl]-hexahydro-furo[2,3-b]pyran-4,7a-dicarboxylic acid 4-benzylamide 7a-[(benzylcarbamoyl-methyl)-amide] (A2*α*)



$C_{37}H_{44}N_4O_8$

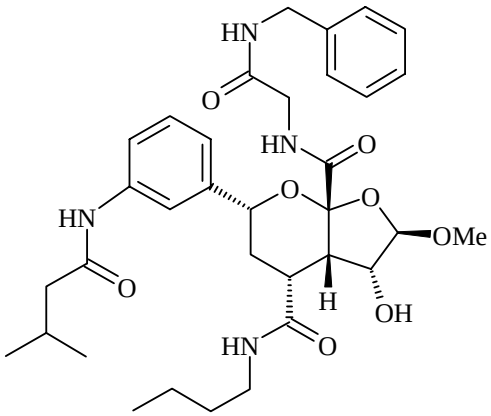
672.79

A2*α*

The product was synthesised according to general method C. Yield: 5 mg (46% based on 59% loading)

TLC(EtOAc): R_f 0.55 ; HPLC: t_R = 8.51, λ_{max} = 275 nm; ^{1}H-NMR (300MHz, aceton-d6): 7.68 – 7.66 (1H, *m*), 7.36 – 7.35 (1H, *m*), 7.23 – 7.07 (13H, *m*), 6.94 – 6.91 (1H, *m*), 4.98 (1H, *s*), 4.77 – 4.72 (1H, *m*), 4.36 – 4.34 (2H, *m*), 4.29 – 4.27 (2H, *m*), 4.15 – 4.13 (1H, *m*), 3.93 – 3.75 (2H, *m*), 3.24 – 3.15 (1H, *m*), 3.19 (3H, *s*), 2.80 – 2.76 (1H, *m*), 2.24 – 2.01 (4H, *m*), 1.70 – 1.63 (1H, *m*), 0.85 – 0.83 (6H, d); ^{13}C-NMR (75MHz, aceton-d6): 175. 1, 171.4, 169.9, 169.3, 143.7, 140.5, 140.1, 129.4, 129.3, 129.2, 128.4, 128.3, 128.0, 127.9, 122.2, 119.4, 119.3, 117.8, 117.7, 112.2, 106.4, 78.6, 78.5, 76.0, 55.6, 47.0, 44.9, 43.6, 43.5, 43.0, 41.4, 34.6, 26.8, 22.8; ESI-MS (positive mode): 696 ($M+Na^+$), 642; HR-MS: Calcd. for $C_{37}H_{44}N_4O_8Na$: 695.3056; measured: 695.3040

(2*R*,3*R*,3a*S*,4*S*,6*S*,7a*S*)-3-Hydroxy-2-methoxy-6-[3-(3-methyl-butyrylamino)-phenyl]-hexahydro-furo[2,3-b]pyran-4,7a-dicarboxylic acid 7a-[(benzylcarbamoyl-methyl)-amide] 4-butylamide (A2β)



$C_{34}H_{46}N_4O_8$

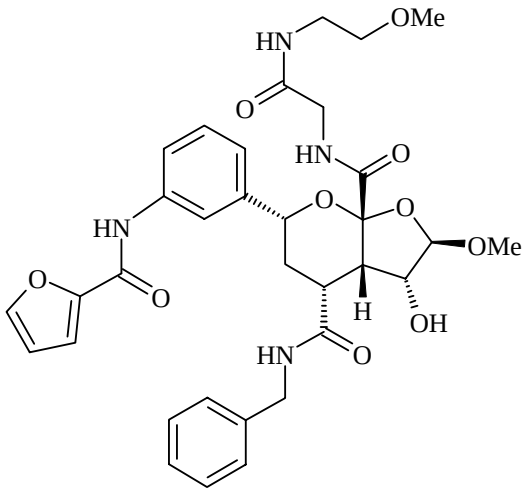
638.77

A2β

The product was synthesised according to general method C. Yield: 4 mg (39% based on 59% loading)

TLC (EtOAc): R_f 0.55; HPLC: t_R = 8.51, λ_{max} = 277 nm; ^{1}H-NMR (300MHz, aceton-d6): 7.82 – 7.79 (1H, *m*), 7.48 (1H, *m*), 7.30 – 7.20 (6H, *m*), 7.06 – 7.04 (1H, *m*), 5.11 (1H, *s*), 4.88 – 4.84 (1H, *m*), 4.43 – 4-41 (2H, *m*), 4.25 – 4.23 (1H, *m*), 4.06 – 3.88 (2H, *m*), 3.31 (3H, *s*), 3.30 – 3.16 (3H, *m*), 2.85 – 2.82 (1H, t), 2.28 – 2.14 (4H, *m*), 1.75 – 1.69 (1H, *m*), 1.58 – 1.31 (4H, *m*), 0.97 (6H, d), 1.90 (3H, t); ^{13}C-NMR (75MHz, aceton-d6): 175.5, 171.4, 169.9, 169.3, 143.7, 140.5, 140.2, 129.4, 129.3, 128.4, 127.9, 122.2, 119.4, 119.3, 117.8, 117.7, 112.1, 106.3, 78.7, 75.9, 55.6, 47.0, 43.6, 43.0, 42.9, 42.0, 41.5, 39.8, 34.6, 32.3, 26.8, 22.8, 20.7, 14.1; ESI-MS (positive mode): 661 ($M+Na^+$), 640 (M^+), 609, 608; HR-MS: Calcd. for $C_{34}H_{46}N_4O_8Na$: 661.3213; measured: 661.3213

(2*R*,3*R*,3a*S*,4*S*,6*S*,7a*S*)-6-{3-[(Furan-2-carbonyl)-amino]-phenyl}-3-hydroxy-2-methoxy-hexahydro-furo[2,3-b]pyran-4,7a-dicarboxylic acid 4-benzylamide 7a-{[(2-methoxy-ethylcarbamoyl)-methyl]-amide} (B4*α*)



$C_{33}H_{38}N_4O_{10}$

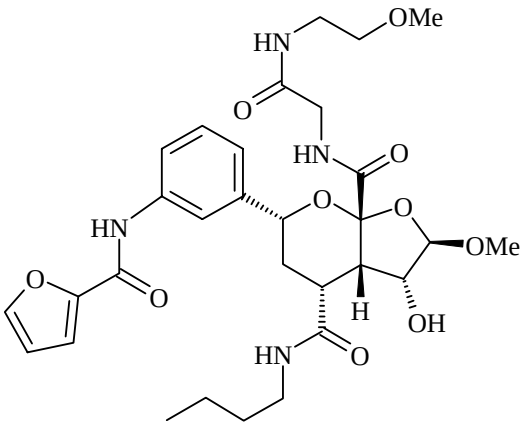
650.69

B4*α*

The product was synthesised according to general method C. Yield: 7 mg (70% based on 56% loading)

TLC (EtOAc): R_f 0.15; HPLC: t_R = 8.61, λ_{max} = 277 nm; ^{1}H-NMR (300MHz, aceton-d6): 8.29 – 8.25 (1H, *m*), 7.75 – 7.74 (1H, *m*), 7.73 – 7.72 (1H, *m*), 7.37 – 7.18 (8H, *m*), 6.65 – 6.63 (1H, *m*), 5.13 (1H, *s*), 4.95 – 4.90 (1H, *m*), 4.49 (2H, *s*), 4.29 – 4.27 (1H, *m*), 3.98 – 3.82 (2H, *m*), 3.38 – 3.36 (5H, *m*), 3.36 (3H, *s*), 3.24 (3H, *s*), 2.93 – 2.89 (1H, *m*), 2.43 – 2.31 (1H, *m*), 1.88 – 1.82 (1H, *m*); ^{13}C-NMR (75MHz, aceton-d6): 175.0, 169.8, 169.2, 157.0, 149.3, 146.0, 143.8, 140.1, 139.6, 129.5, 129.4, 128.4, 127.9, 123.0, 120.3, 119.0, 115.5, 115.3, 113.1, 113.0, 112.2, 106.7, 106.4, 78.5, 76.0, 71.8, 58.7, 55.7, 43.8, 42.8, 42.0, 41.4, 39.7, 34.3; ESI-MS (positive mode): 674 ($M+Na^+$), 651 (M^+), 621, 620; HR-MS: Calcd. for $C_{33}H_{38}N_4O_{10}Na$: 637.2485; measured: 673.2480

(2*R*,3*R*,3a*S*,4*S*,6*S*,7a*S*)-6-{3-[(Furan-2-carbonyl)-amino]-phenyl}-3-hydroxy-2-methoxy-hexahydro-furo[2,3-b]pyran-4,7a-dicarboxylic acid 4-butylamide 7a-{[(2-methoxy-ethylcarbamoyl)-methyl]-amide} (B4β)



$C_{30}H_{40}N_4O_{10}$

616.67

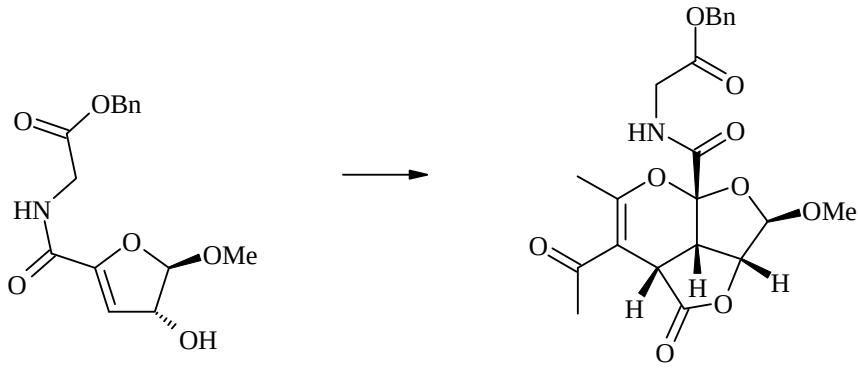
B4β

The product was synthesised according to general method C. Yield: 6 mg (63% based on 56% loading)

TLC (EtOAc): R_f 0.15; HPLC: t_R = 8.41, λ_{max} = 276 nm; ^{1}H-NMR (300MHz, aceton-d6): 7.91 – 7.88 (1H, *m*), 7.82 (1H, *m*) 7.75 (1H, *m*), 7.72 (1H, *m*), 7.34 – 7.29 (1H, *m*), 7.23 – 7.22 (1H, *m*), 7.20 – 7.17 (1H, *m*), 6.65 – 6.63 (1H, *m*), 5.13 (1H, *s*), 4.93 – 4.88 (1H, *m*), 4.26 – 4.25 (1H, *m*), 4.00 – 3.82 (2H, *m*), 3.39 – 3.36 (4H, *m*), 3.36 (3H, *s*), 3.29 – 3.18 (3H, *m*), 3.25 (3H, *s*), 2.87 – 2.83 (1H, *m*), 2.39 – 2.26 (1H, *m*), 1.81 – 1.74 (1H, *m*), 1.58 – 1.29 (4H, *m*), 0.93 – 0.88 (3H, *m*); ^{13}C-NMR (75MHz, aceton-d6): 175.0, 169.8, 169.2, 157.0, 149.3, 145.9, 143.8, 139.6, 129.5, 123.0, 120.3, 119.0, 115.3, 113.0, 112.1, 106.4, 78.6, 75.9, 71.9, 58.7, 55.7, 46.7, 42.8, 42.1, 41.5, 39.8, 39.7, 34.4, 32.3, 30.9, 30.7, 20.7, 14.1; ESI-MS (positive mode): 539 ($M+Na^+$), 517 (M^+), 586, 585; HR-MS: Calcd. for $C_{30}H_{40}N_4O_{10}Na$: 639.2642; measured: 639.2619.

4.5.12 Compounds for Library Synthesis Through *Wittig* Olefination (32-35)

(2*R*,2a*R*,4a*S*,7a*S*,7b*S*)-[(5-Acetyl-2-methoxy-6-methyl-4-oxo-2a,4,4a,7b-tetrahydro-2H-1,3,7-trioxa-cyclopenta[cd]indene-7a-carbonyl)-amino]-acetic acid benzyl ester (32)



$C_{15}H_{17}NO_6$
307.31
23

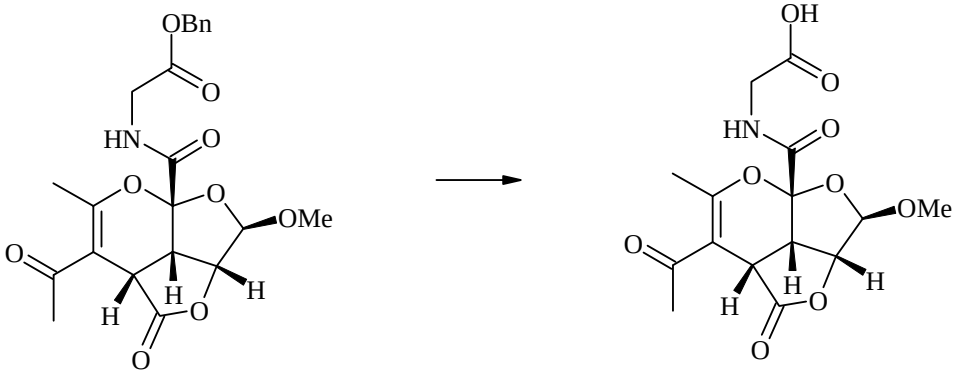
$C_{22}H_{23}NO_9$
445.43
32

Under an argon atmosphere, **3i** (2.63 g, 16.8 mmol) was suspended in 160 ml 1,2-dichloroethane. At 0°C Et_3N (2.44 ml, 17.4mmol) in 4 ml 1,2-dichloroethane was added drop wise within 3min. Over 15 min. pivaloyl chloride (2.0 ml, 16.4 mmol) was added in 30 ml 1,2-dichloroethane and stirring was continued for an other 30 min. During 15 min dihydrofuranoside **23** (3.45 g, 11.2 mmol) was given to the mix in 30 ml 1,2-dichloroethane. Shortly after cooling to –20°C DMAP (205 mg, 1.68 mmol) in 1 ml 1,2-dichloroethane was added. After stirring 3 hours at 0°C the reaction was left to warm to rt over night (total 20h reaction time). The reaction mixture was washed with sat. aq. $NaHCO_3$ and extracted twice with ether and once with CH_2Cl_2. After drying (Na_2SO_4), evaporating the solvents and separation of the black crude on silicagel (hexane/EtOAc 6:4 -> 1:1) 1 g (2.25 mmol, 20% from **23**) of a colorless oil was obtained.

TLC (CH_2Cl_2/ether 9:1): R_f = 0.43; ^{1}H-NMR (300MHz, $CDCl_3$): 7.40 – 7.33 (6H, *m*), 7.09 – 7.06 (1H, *m*), 5.40 (1H, *s*), 5.20 (2H, *s*), 4.92 (1H, *d*, *J* = 6.5), 4.31 (1H, *d*, *J* = 9.6), 4.15 – 3.99 (2H, *m*), 3.79 (1H, *dd*, *J* = 9.7 and 6.3), 3.56 (3H, *s*), 2.44 (3H, *s*), 2.34 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 195.3, 173.7, 168. 9, 167.5, 164.2, 134.8, 128.8, 128.7, 128.5, 113.8, 108.8, 107.6, 83.0, 67.6, 57.1, 46.0, 41.5, 37.0, 30.2, 21.0; IR: 1774, 1742, 1686, 1600, 1530, 1498, 1435, 1389, 1376, 1360, 1318, 1289, 1274, 1225, 1193, 1157, 1128, 1105, 1070, 1051, 1019,

973, 958, 925, 858, 829, 799; ES^+-MS: 913 ($2xM+Na^+$), 891($2xM^+$), 468 ($M+Na^+$), 446 (M^+), 420, 372, 311;

(2*R*,2a*R*,4a*S*,7a*S*,7b*S*)-[(5-Acetyl-2-methoxy-6-methyl-4-oxo-hexahydro-1,3,7-trioxa-cyclopenta[cd]indene-7a-carbonyl)-amino]-acetic acid (33)



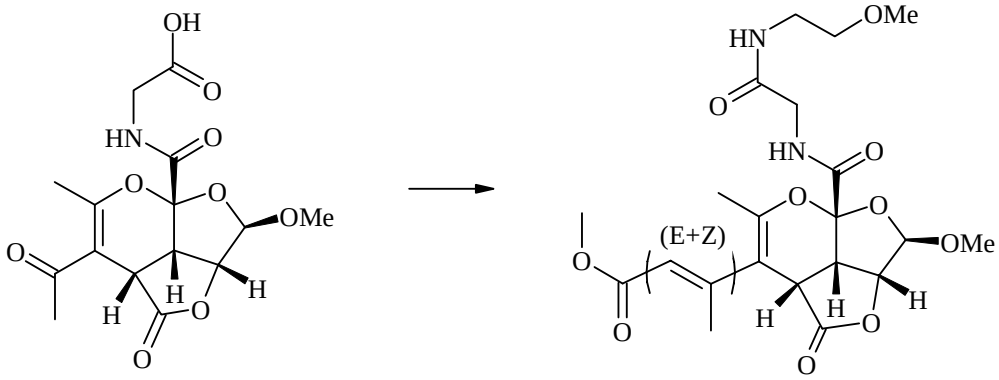
$C_{22}H_{23}NO_9$
445.43
32

$C_{15}H_{19}NO_9$
357.32
33

The product was synthesised according to general method B.
After evaporation of the solvents and drying on the HV 168 mg (0.47 mmol, 94 %) of a white solid was obtained, this was used without further purification.

TLC (EtOAc/MeOH 1:1): R_f 0.5; ^{1}H-NMR (300MHz, dmso-d6): 12.59 (1H, COOH), 8.34 – 8.30 (1H, *m*), 5.48 (1H , *s*), 5.01 (1H, *d*, *J* = 6.0), 4.46 (1H, *d*, *J* = 9.6), 3.90 (1H, *dd*, *J* = 9.5 and 6.3), 3.85 – 3.68 (2H, *m*), 3.42 (3H, *s*), 2.31 (3H, *s*), 2.21 (3H, *s*); ^{13}C-NMR (75MHz, dmso-d6): 195.6, 174.5, 170.0, 166.6, 162.6, 113.3, 107.0, 106.9, 82.4, 55.3, 44.5, 40.53, 36.7, 29.3, 19.5; IR: 1774, 1741, 1686, 1665, 1570, 1555, 1415, 1376, 1361, 1319, 1291, 1274, 1211, 1163, 1127, 1107, 1069, 1051, 1019, 987, 971, 958, 925, 842, 800; ESI$^+$-MS: 733 (2xM+Na$^+$), 711(2xM$^+$), 378 (M+Na$^+$), 356 (M$^+$), 323, 281;

(2*R*,2a*R*,4a*S*,7a*S*,7b*S*)-5-(2-butenoic acid methyl ester)-methoxy-4-oxo-hexahydro-1,3,7-trioxa-cyclopenta[cd]indene-7a-carboxylic acid [(2-methoxy-ethylcarbamoyl)-methyl]-amide (35)



$C_{15}H_{19}NO_9$
357.32
33

$C_{21}H_{28}N_2O_{10}$
468.46
35

Coupling Step

Resin **B** (30 mg, 24 μmol, max. loading = 0.80 mmol/g, methoxyethyl-amin-rest) was weighed into a syringe with filter fritt. The resin was treated with 0.5 ml NMP (N-methyl-pyrrolidon), stirred well with a spatula and left to swell for 30 min in a syringe with filter fritt. HCTU (23 mg, 56 μmol) together with HOBT (7.5 mg, 56 μmol) was dissolved in 0.25 ml NMP and **33 (**20 mg, 56 μmol) was dissolved in 0.25 ml NMP. The NMP from the swelling was sucked off. The Teflon® cock was replaced with a cover which had to by firmly closed. The prepared solutions and DIPEA (32 μl, 192 μmol) were added to the resins. The suspensions were agitated over night.

Without washing step the coupling procedure with fresh HCTU/HOBT and **33** is repeated once more. The suspension was stirred for 4-5h this time.

Washing/Derivatisation:

The resin was washed with portions of 5x DMA, 1x isopropanol, 3x DMA, 5x isopropanol, 2x DCM and 2x DMA. At the end rinsing with DCM abs. was necessary.

To a prepared solution of Buthyllithium (300 μl, 480 μmol) and HMDS (100 μl, 480 μmol) in a glass vessel in 0.5 ml THF abs. methyl-diethyl-phosphonoacetate (87 μl, 480 μmol) was added at 0°C. This solution was stirred for 30 min at 0°C and then added to the washed solid support. The suspension was agitated for 18h on the rotor.

Washing/Cleaving:

The resin were washed with portions of 5x DMA (degased), 1x isopropanol, 3x DMA, 5x isopropanol, 2x DCM and 2x DMA. At the end rinsing with DCM abs. was necessary.

In 5 repetitions 0.6 ml of a 20% TFA aq. (95%TFA in water)/DCM solution was left to react with the resin for 15 min per repetition. The thus obtained solutions were collected in a sample flask. TFA and DCM were aired off with a stream of argon. The remaining oil was dissolved in MeOH and evaporated fully. The samples were redissolved in C_6D_6 and evaporated once again before measuring crude NMR.

HPLC:

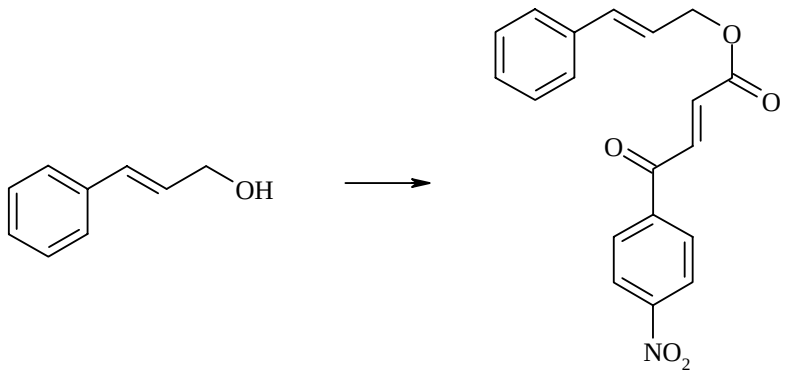
The sample was dissolved in EtOAc. Separation was carried out on NP HPLC with EtOAc→AcCN 35 min. UV detection was not possible, instead 1 minute fractions were collected and the products detected using cer reagent.

^{1}H-NMR (300MHz, $CDCl_3$): 5.97 (0.2H, *s*), 5.87 (0.8H, *s*), 5.55 (1H, *s*), 4.84 (1H, *d*), 4.18 – 3.29 (2H, *m*), 3.58 (3H, *s*), 3.45 – 3.33 (8H, *m*), 3.37 (3H, *s*), 2.90 (1H, *d*), 2.22 (3H, *s*), 1.75 (3H, *s*);

EI-MS: 468 (M^+), 394, 370, 354, 353; ESI^+-MS: 491($M+Na^+$), 469 (M^+), 435.

4.5.13 Compounds 37 - 45

(*E*)-4-(4-Nitro-phenyl)-4-oxo-but-2-enoic acid 3-phenyl-allyl ester (38a)



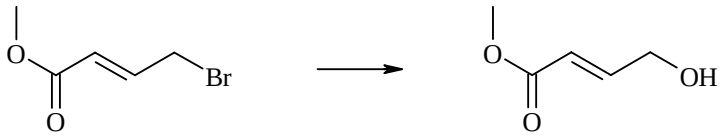
$C_9H_{10}O$	$C_{19}H_{15}NO_5$
134.18	337.34
37a	**38a**

The product was synthesised according to general method A.

The mixture was washed with cold sat. $NaHCO_3$ and extracted twice with diethylether. After drying (Na_2SO_4), evaporating the solvents and separation of the black crude on silicagel (EtOAc/hexane 1:4) 643 mg (1.90 mmol, 63%) of a yellow oil was obtained.

TLC (EtOAc/hexane 1:1): R_f 0.8; ^{1}H-NMR (300MHz, CDCl3): 8.39 – 8.35 (2H, *m*), 8.18 – 8.14 (2H, *m*), 7.91 (1H, *d*, *J* = 15.5), 7.44 – 7.29 (5H, *m*), 6.99 (1H, *d*, *J* = 15.5), 6.74 (1H, *d*, *J* = 15.5), 6.35 (1H, *dd*, *J* = 15.8 and 6.6), 4.93 (1H, *dd*, *J* = 6.5 and 1.2);

(*E*)-4-Hydroxy-2-butenoic acid methyl ester (37b)



$C_5H_7BrO_2$ → $C_5H_8O_3$

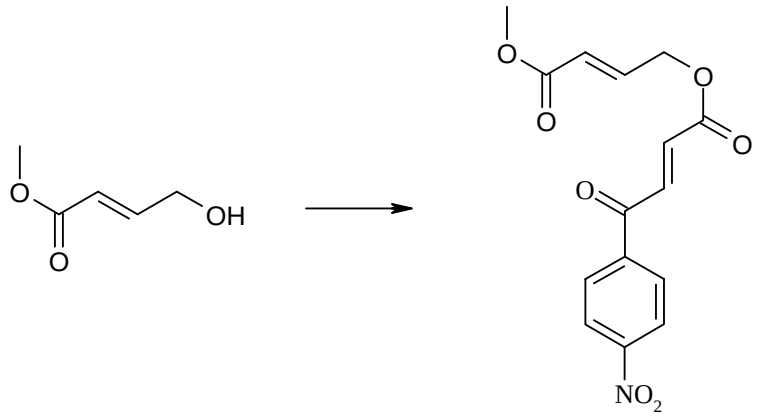
179.01 → 116.12

37b

In a reaction vessel Ag_2O (4.36 g, 18.8 mmol) was suspended in 40 ml H_2O. To this well stirred mixture Methyl-γ-bromocrotonate 90% (5 ml, 37.6 mmol) was added. After stirring at RT for 20 hours the reaction was heated to 60°C for another 5.5 hours. The turbid mixture was filtered over Celite before the water was evaporated. Distillation of the colorless oil at 0.5 mbar, 105 C° yielded 1.532 g (13.2 mmol, 31.6%) of **37b** as colorless oil.

TLC (EtOAc/hexane 3:7): R_f 0.19; ^{1}H-NMR (300MHz, $CDCl_3$): 7.05 (1H, dt, *J* = 15.8 and 4.0), 6.11 (1H, *d*, *J* = 15.7), 4.36 (2H, *dd*, *J* = 4.0 and 2.1), 3.75 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 167.3, 147.9, 119.4, 61.5, 51.7; IR: 1775, 1717, 1660, 1437, 1300, 1274, 1193, 1168, 1094, 1036, 1009, 957, 927, 907; EI^+-MS: 113, 115 (M^+), 99, 87, 85;

(*E*)-4-(4-Nitro-phenyl)-4-oxo-but-2-enoic acid 3-methoxycarbonyl-allyl ester (38b)



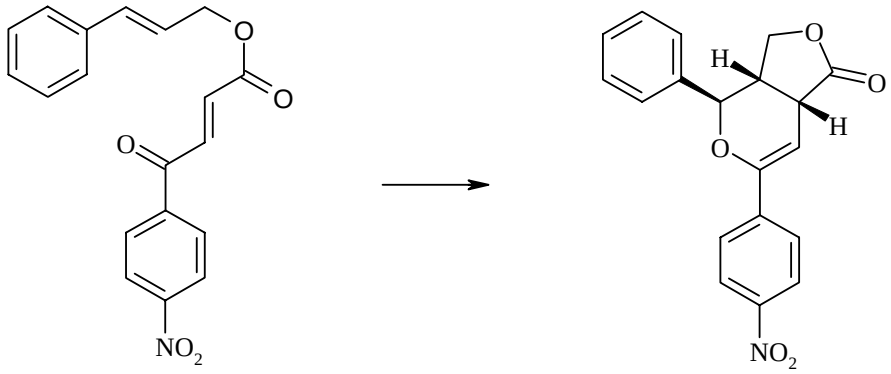
$C_5H_8O_3$	$C_{15}H_{13}NO_7$
116.12	319.27
37b	**38b**

The product was synthesised according to general method A.

The mixture was washed with cold sat. $NaHCO_3$ and extracted twice with diethylether and once with CH_2Cl_2. After drying (Na_2SO_4) of the prganic phases, evaporating the solvents and separation of the black crude on silicagel (EtOAc/hexane 1:4) 122 mg (380 µmol, 44 %) of a yellow solid was obtained.

TLC (EtOAc/hexane 1:4): R_f 0.28; ^{1}H-NMR (300MHz, $CDCl_3$): 8.39 – 8.36 (2H, *m*), 8.18 – 8.14 (2H, *m*), 7.96 (1H, *d*, *J* = 15.4), 7.04 (1H, *dt*, *J* = 15.8 and 4.8), 7.02 (1H, *d*, *J* = 15.4), 6.13 (1H, *dt*, *J* = 15.8 and 1.9), 4.97 (2H, *dd*, *J* = 4.7 and 1.9).

(4-Nitro-phenyl)-4-phenyl-3a,7a-dihydro-3*H*,4*H*-furo[3,4-*c*]pyran-1-one (39)



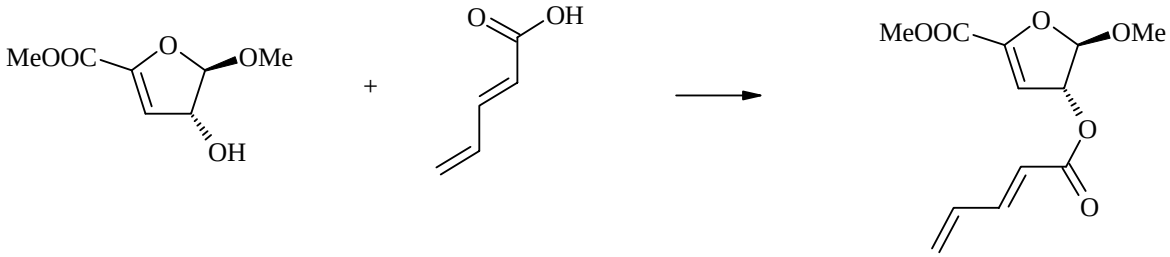
$C_{19}H_{15}NO_5$
337.34
38a

$C_{19}H_{15}NO_5$
337.34
Rac-39

Compound **38a** (600 mg, 1.78 mmol) was dissolved in 30 ml o-xylene and refluxed for 22 h. The solution was cooled to rt. and added to cold sat. $NaHCO_3$. This was exreacted twice with EtOAc. The organic phases were washed with sat. NaCl and dried over Na_2SO_4. After evaporation of the solvents 1.31 an orange solid was obtained, which was further purified by column chromatographie using $CHCl_3$/Et_2O/hexane 1:1:1. This afforded 330 mg (978 µmol, 55%) of **39** as a racemic mixture.

TLC ($CHCl_3$/Et_2O/hexane 1:1:1): R_f 0.28; ^{1}H-NMR (300MHz, $CDCl_3$): 8.21 – 8.16 (2H, *m*), 7.78 – 7.74 (2H, *m*), 7.51 – 7.42 (5H, *m*), 6.03 (1H, *d*, *J* = 5.1), 4.56 (1H, *d*, *J* = 11.1), 4.35 (1H, *dd*, *J* = 10.1 and 6.3), 4.14 (1H, *d*, *J* = 10.2 and 0.8), 3.52 (1H, *dd*, *J* = 7.7 and 4.9), 2.99 – 2.90 (1H, *m*); ES-MS: 337 (M^+), 307, 293, 279, 278, 252, 232, 205, 202, 189, 187, 150;

(4*R*,5*R*) 4-((E)-Penta-2,4-dienoyloxy)-5-methoxy-4,5-dihydro-furan-2-carboxylic acid methyl ester (41a).

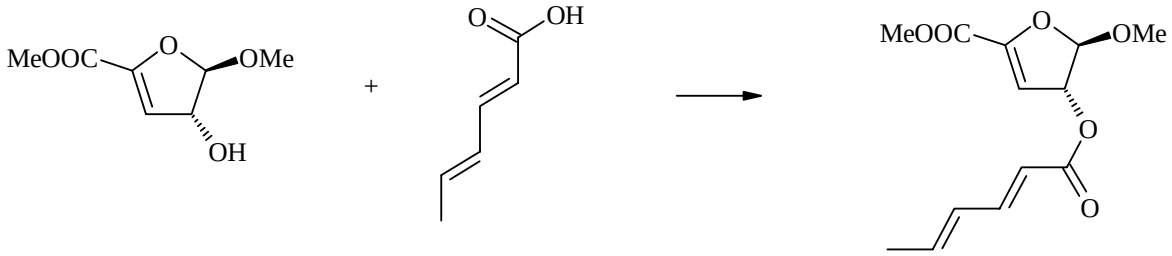


$C_7H_{10}O_5$	$C_5H_6O_2$	$C_{12}H_{14}O_6$
174.15	98.10	254.24
1	pentadienic acid	**41a**

To a solution of pentadienic acid (1.28 g, 13.1 mmol) in 1,2-dichloroethane, triethylamine (1.9 ml, 13.5 mmol) was added slowly. The reaction mixture was cooled to 0°C and pivalic acid (1.53 g, 12.7 mmol) was added. After letting the solution warm to rt dihydrofuranoside **1** (2 g, 11. 5 mmol) and DMAP (184 mg, 1.5 mmol) were added. The solution was stirred for 3h under nitrogen and then washed with 100 ml of cold $NaHCO_3$ sat. and extracted 3 times with 100 ml ethylacetate. The organic phase was washed once with 200 ml water and twice with 100 ml Brine. After drying (Na_2SO_4) and evaporating of the solvent the oil obtained was separated by column chromatography on 160 g of silikagel with ethylacetate/hexane 1:9. The Product was always stored in solution with little BHT to prevent polymerisation. Therefore no yield was determined.

TLC (EtOAc/hexane 3:7): R_f 0.47; ^{1}H-NMR (300MHz, $CDCl_3$): 7.27 (1H, *dd*, *J* = 11.2 and 15.3), 6.44 (1H, *dt*, *J* = 16.9 and 10.5), 6.05 (1H, *d*, *J* = 2.6), 5.88 (1H, *d*, *J* = 15.4), 5.63 (1H, *d*, *J* = 16.9), 5.62 (1H, *dd*, *J* = 1.3 and 2.6), 5.52 (1H, *d*, *J* = 9.9), 5.41 (1H, *d*, *J* = 1.5), 3.84 (3H, *s*), 3.56 (3H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 165, 160.1, 151.6, 146.1, 134.5, 126.6, 120.9, 110.0, 108.0, 80.3, 57.0, 52.5; IR (NaCl): 2924*w*, 1719*s*, 1636*w*, 1439*w*, 1309*m*, 1252*s*, 1199*s*, 1137*s*, 1106*s*, 1013*m*, 921*w*, 759*w*.

(4*R*,5*R*) 4-((E)-Hexa-2,4-dienoyloxy)-5-methoxy-4,5-dihydro-furan-2-carboxylic acid methyl ester (41b).

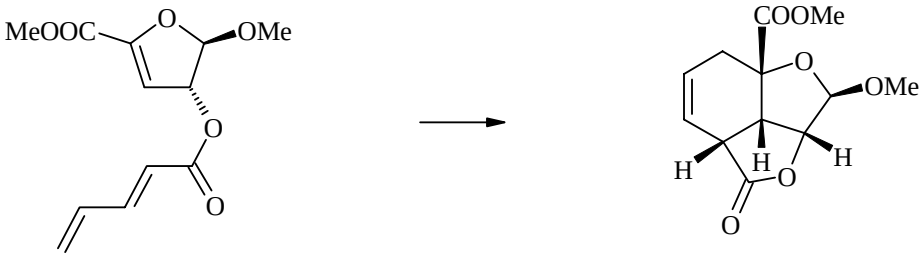


$C_7H_{10}O_5$	$C_6H_8O_2$	$C_{13}H_{16}O_6$
174.15	112.13	268.27
1	sorbic acid	**41b**

To a solution of sorbic acid (367 mg, 3.3 mmol) in 1,2-dichloroethane, triethylamine (0.47 ml, 3.4 mmol) was added slowly. The reaction mixture was cooled to 0°C and pivalic acid (384 g, 3.2 mmol) were added. After letting the solution warm to rt. of dihydrofuranoside **1** (500 mg, 2.9 mmol) and DMAP (46 mg, 0.4 mmol) were added. The solution was stirred for 3h under nitrogen and then washed with 10 ml of cold $NaHCO_3$ sat. and extracted 3 times with 10 ml diethylether. The organic phase was washed once with 10 ml water and twice with 10 ml Brine. After drying (Na_2SO_4), evaporating the solvent and separation of the crude by column chromatography on 60 g of silicagel with ethylacetate/hexane 1:9 **41b** was obtained as a yellow oil (207 mg, 0.77mmol).

TLC (EtOAc/hexane 3:7): R_f 0.36; ^{1}H-NMR (300MHz, $CDCl_3$): 7.3-7.2 (1H, *m*), 6.20 (1H, *m*), 6.18 (1H, *d*, *J* = 1.8), 6.06 (1H, *d*, *J* = 2.9), 5.74 (1H, *d*, *J* = 15.1), 5.63 (1H, *dm*, *J* = 1.5), 5.42 (1H, *d*, *J* = 1.5), 3.85 (3H, *s*,), 3.57 (3H, *s*), 1.87 (3H, *m*); ^{13}C-NMR (75MHz, $CDCl_3$): 166, 160, 151, 146, 140 130, 118, 110, 108, 80, 57, 52, 19; IR (NaCl) = 2955*w*, 1734*s*, 1636*w*, 1441*w*, 1374*w*, 1310*m*, 1251*m*, 1165*m*, 1108*s*, 1006.

(2*R*,2a*R*,4a*R*,7a*R*,7b*R*)-2,2a,4a,7,7a,7b-Hexahydro-7a-methoxycarbonyl-2-methoxy-4H-Furo[2,3,4-cd]benzofuran-4-one (42a).



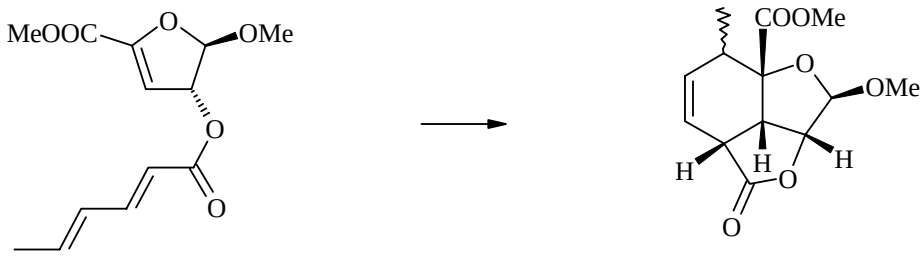
$C_{12}H_{14}O_6$
268.27
41a

$C_{12}H_{14}O_6$
268.27
42a

The solution of pentadienic acid ester **41a** (see above) stabilized with BHT in EtOAc/Hexane was coevaporated with 50 ml toluene to remove the more volatile solvents. The remaining concentrated solution was treated with 150 ml toluene and placed in an autoclave. The cyclisation was carried out at approx. 165°C over 14 h. Evaporation of the toluene and separation on 210 g silicagel with EtOAc/hexane 2:8 → 4:6 gave 670 mg (2.63 mmol, 23% from **1**) of a colorless oil.

TLC (EtOAc/hexane 4:6): R_f 0.56; ^{1}H-NMR (300MHz, $CDCl_3$): 6.02-5.92 (1H, *m*), 5.89-5.79 (1H, *m*), 4.99 (1H, *d*, *J* = 7.7), 4.97 (1H, *s*) 4.07 (1H, *dd*, *J* = 7.7 and 11.8), 3.77 (3H, *s*) 3.36 (3H, *s*) 3.36-3.27 (1H, *m*), 2.71 (1H, *dd*, *J* = 18.2 and 5.7) 2.25 (1H, *ddd*, *J* = 18.3, 5.8 and 2.8); ^{13}C-NMR (75MHz, $CDCl_3$): 176, 174, 123, 121, 108, 87, 82, 56, 53, 39, 37, 30. EI-MS: 255 (M^+), 223, 221, 195.

(2*R*,2a*R*,4a*R*,7a*R*,7b*R*)-2,2a,4a,7,7a,7b-Hexahydro-7a-methoxycarbonyl-2-methoxy-7-methyl-4H-Furo[2,3,4-cd]benzofuran-4-one (42b).



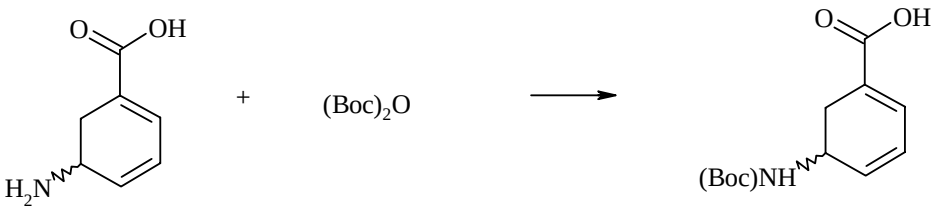
$C_{13}H_{16}O_6$
254.24
41b

$C_{13}H_{16}O_6$
254.24
42b

Sorbic acid ester **41b** (300mg, 1.15 mmol) was dissolved in 30 ml toluene and heated at 170°C for 16 h. Evaporation of the toluene and separation on 15 g silicagel with EtOAc/hexane 3:7 gave 97 mg (0.36 mmol, 32%) of a colorless oil. The compound was obtained as diastereomeric mixture 7*R*/7*S* = 2:1.

TLC (EtOAc/hexane 1:2): R_f 0.36; ^{1}H-NMR (300MHz, $CDCl_3$): 7*R*–diastereomer: 6.00-5.81 (1H, *m*), 5.61-5.56 (1H, *m*), 4.99 (1H, *m*), 4.91 (1H, *m*), 4.15-4.02 (1H, *m*), 3.77 (3H, *s*), 3.39 (3H, *s*), 3.31-3.25 (1H, *m*), 2.48-2.45 (1H, *dm*, *J* = 7.4), 1.24 (3H, *d*, *J* = 7.4); 7*S*–diastereomer: 6.00-5.81 (1H, *m*), 5.61-5.56 (1H, *m*), 4.99 (1H, *m*), 4.91 (1H, *m*), 4.15-4.02 (1H, *m*), 3.77 (3H, *s*) 3.34 (3H, *s*), 3.31-3.25 (1H, *m*), 2.80-2.71 (1H, *dm*, *J* = 6.8), 0.87 (3H, *d*, *J* = 7.0); EI-MS: 255 (M^+), 223, 221, 195, 155, 147, 137, 133.

Boc-5-amino-1,3-cyclohexadiene-1-carboxylic acid (43)



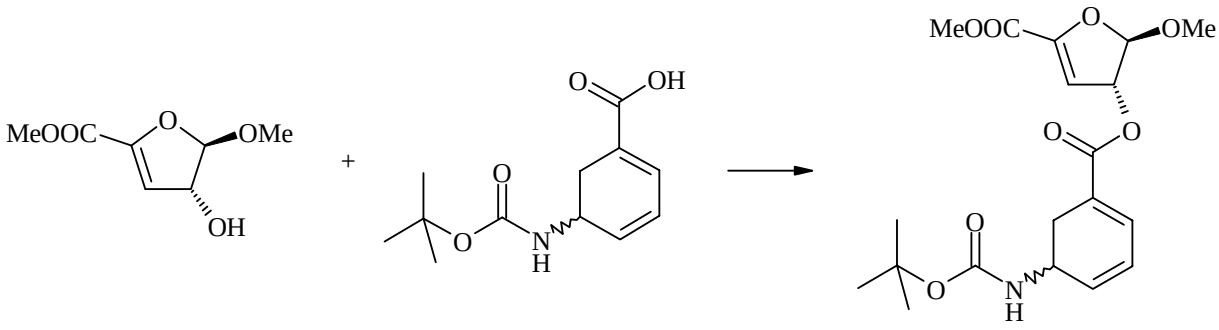
$C_7H_9NO_2$	C10H18O5	$C_{12}H_{17}NO_4$
139.16	218.25	239.27
(+/-) gabaculine		**43**

Commercially available through AnaSpec Inc. Cat #26211 or made from (+/-) gabaculine.

In a glass vessel (+/-) gabaculine (500 mg, 2.84 mmol) was dissolved in 15 ml MeOH. To this triethylamine (1.5 ml, 10.7 mmol) and shortly after $(BOC)_2O$ (1.3 g, 5.97 mmol) was added. The solution is stirred for 2 hours. After evaporation of the solvents the residue was stirred with 20 ml diluted HCl (pH = 2.15, 0°C) and extracted 4 times with EtOAc. The organic phases were dried with Na_2SO_4 and the solvent evaporated. After recrystallisation from diethylether/chloroform 443 mg (1.85 mmol, 65%) **43** was obtained.

^{1}H-NMR (300MHz, $CDCl_3$): 7.19 – 7.18 (1H, m), 6.22 – 6.20 (2H, m), 4.69 – 4.66 (1H, m), 4.49 – 4.46 (1H, m), 2.79 – 2.63 (2H, m); ^{13}C-NMR (75MHz, $CDCl_3$): 171.6, 154.8, 133.9, 133.7, 126.1, 124.8, 79.8, 43.4, 28.4.

(4*R*,5*R*)-4-(Boc-5-amino-1,3-cyclohexadiene-1-carboxylic acid)-5-methoxy-4,5-dihydro-furan-2-carboxylic acid methyl ester (44)



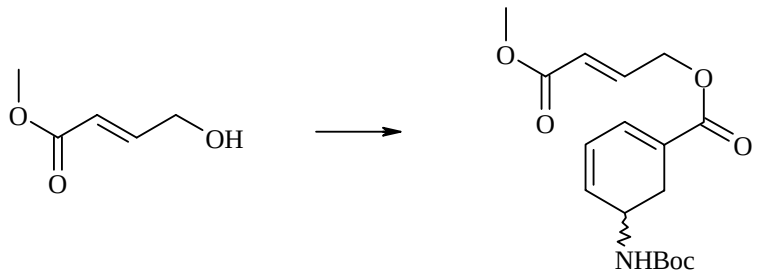
$C_7H_{10}O_5$	$C_{12}H_{17}NO_4$	$C_{19}H_{25}NO_8$
174.15	239.27	395.41
1	**43**	**44**

The product was synthesised according to general method A.

The mixture was washed with cold sat. $NaHCO_3$ and extracted three times with diethylether. After drying (Na_2SO_4), evaporating the solvents and separation on silicagel (EtOAc/hexane 1:4 -> 3:7) 196 mg (0.495 mmol, 82%) of a colorless oil was obtained.

TLC (EtOAc/hexane 2:8): R_f 0.23; ^{1}H-NMR (300MHz, $CDCl_3$): 7.06 - 7.04 (1H, *m*), 6.17 – 6.15 (2H, *m*), 6.07 – 6.05 (1H, *m*), 5.64 – 5.61 (1H, *m*), 5.43 (1H, *m*), 4.67 - 4.64 (1H, *m*), 4.45 -4.42 (1H, *m*), 3.85 (3H, *s*), 3.57 (3H, *s*), 2.74 – 2.58 (2H, *m*), 1.43 (9H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 165.7, 160.1, 154.8, 151.6, 133.5, 133.1, 125.9, 124.6, 109.9, 108.0, 82.7, 80.6, 56.7, 52.5, 43.1, 28.4, 27.7; ES$^+$-MS: 791 (2xM^+), 396 (M^+), 30

5-(Boc-5-amino-1,3-cyclohexadiene-1-carboxylic acid)-(*E*)-3-methoxycarbonyl-allyl ester (45)



$C_5H_8O_3$	$C_{13}H_{16}O_4$
116.12	236.27
37b	**45**

The product was synthesised according to general method A.

The mixture was washed with cold sat. $NaHCO_3$ and extracted three times with diethylether. After drying (Na_2SO_4), evaporating the solvents and separation on silicagel (EtOAc/hexane 1:4 -> 3:7) 93 mg (0.275 mmol, 44%) of a colorless oil was obtained.

TLC (EtOAc/hexane 3:7): R_f 0.37; ^{1}H-NMR (300MHz, $CDCl_3$): 7.14 – 7.11 (1H, *m*), 7.04 – 6.96 (1H, *m*), 6.23 – 6.18 (2H, *m*), 6.09 – 6.03 (1H, *m*) 4.86 – 4.84 (2H, *m*), 4.66 – 4.64 (1H, *m*), 4.48 – 4.46 (1H, *m*), 3.77 (3H, *s*), 2.82 – 2.64 (2H, *m*), 1.45 (9H, *s*); ^{13}C-NMR (75MHz, $CDCl_3$): 166.2, 166.0, 154.8, 141.5, 133.3, 132.8, 126.1, 124.7, 121.8, 80.1, 62.7, 51.7, 43.0, 28.8, 28.3;

5 Appendix

5.1 Abbreviations

abs	absolute
Abs_x	absorption at x nanometers
Ac	acetyl
AcOAc	acetic anhydride
AcOH	acetic acid
au	atomic unit
Bn	benzyl
Boc	tert.-butylcarbamate
$(Boc)_2O$	di-tert.- butyldicarbonate
BOP	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluoro-phosphate
bp	boiling point
Bu	butyl
Bz	benzoyl
°C	degrees Celsius
CBr_4	tetrabromomethan
CCl_4	carbon tetrachloride
$CDCl_3$	deuterochloroform
$CH2Cl_2$	dichloromethane
CH3CN	acetonitrile
$CHCl_3$	chloroform
^{13}C-NMR	carbon NMR
d	day(s)
d	doublet
DA	*Diels-Alder*
DCC	dicyclohexyl-carbodiimide
DCM	dichloromethane
dd	doublet of doublets
DIPEA	diisobutylethylamine
D_2O	deuterated water
DMA	dimethylacetamide
DMAP	4-(N,N-dimethylamino)pyridine

DMF	dimethylformamide
DMSO	dimethylsulphoxide
DNA	desoxy ribonucleic acid
dt	doublet of triplets
ε	extinction coefficient
EI	MS electron spray MS
Eq.	equivalent(s)
ESI	MS electron spray ionisation MS
Et	ethyl
EtOAc	ethylacetate
Et_2O	diethylether
g	gram
EtOH	ethanol
Fmoc	(9 fluorenylmethoxy) carbonyl
h	hour(s)
HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
H_2O	water
HOBT	1-hydroxybenzotriazole
HCl	acid hydrochloricum
HCTU	1H-Benzotriazolium 1-[*bis*(dimethylamino)methylene]-5-chloro,hexafluorophosphate(1-),3-oxide
Hex	hexane
HMDS	hexamethyldisilane
^{1}H-NMR	proton NMR
HPLC	high performance liquid chromatography
HV	high vacuum
Hz	hertz
i	iso
IR	infrared
J	coupling
l	liters
LC	liquid chromatography
M	molar (moles / liter)
Me	methyl
MeOD	deuteromethanol
MeOH	methanol
mg	milligramms

min	minute(s)
ml	milliliters
mp	melting point
MS	mass spectrometry
m	multiplet
mw	molecular weight
Na_2CO_3	di sodium carbonate
NaH	sodium hydride
$NaHCO_3$	sodium hydrogen carbonate
NBS	N-bromo-succinimide
NMP	N-methyl pyrrolidon
NMR	nuclear magnetic resonance
NP HPLC	normal phase HPLC
PEG	polyethylene glycol
Ph	phenyl
q	quartet
R_f	retention factor
r.f.	reflux
RP	reverse phase
rt	room temperature
s	singlet
sat.	saturated
t	triplet
tBME	*tert*-butylmethylether
tBu	*tert*-butyl
tBuOH	*tert*-butanol
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoracetic acid anhydride
TFFH	tetramethylfluoroformamidium hexafluorophosphate
THF	tetrahydrofuran
THF-d8	deuterated THF
TLC	thin layer chromatography
TMS-Cl	trimethylsilyl chloride
t_R	retention time
UV	ultraviolet
µl	microliters

5.2 Literature References

[1] M.S. Lesney, Patents and Potions: “Entering the Pharmaceutical Century”, *The Pharmaceutical Century: Ten decades of Drug Discovery Supplement to American Chemical Society* **2000**, pp. 18-31.

[2] J.B. Miller, “Antibiotics and Isotopes: Swingtime”, *The Pharmaceutical Century: Ten decades of Drug Discovery Supplement to American Chemical Society* **2000,** pp. 52-72.

[3] B.D. Tweedy, M.S.Lesney, “Prescriptions and Polio: Postwar Progress”, *The Pharmaceutical Century: Ten decades of Drug Discovery Supplement to American Chemical Society* **2000,** pp. 72-91.

[4] C.A. Lipinski et al. “Experimental and computational approaches to estimate solubility and permeability in drug discovery and developmental settings“, *Advanced Drug Deliv. Rev.* **1997,** *23*, 3-29.

[5] D. Bailey, D. Brown, “High-throughput chemistry and structure-based design: survival of the smartest“. *Drug Discovery Today* **2001**, *6*, 57-59.

[6] K.H. Bleicher, H.J. Bohm, K. Muller, A.I. Alanine, “Hit and lead generation: Beyond high-throughput screening“. *Nature Reviews Drug Discovery* **2003**, *2*, 369-378.

[7] A.W. Czarnik, “Encoding strategies for combinatorial chemistry“. *Curr. Opin. Chem. Biol.* **1997**, *1*, 60–66.

[8] J.M. Reichert, “Trends in development and approval times for new therapeutics in the United States“. *Nature Reviews Drug Discovery* **2003**, *2*, 695-702.

[9] R. Breinbauer, I.R. Vetter, H. Waldmann, “From protein domains to drug candidates - Natural products as guiding principles in the design and synthesis of compound libraries“. *Angew.Chem.-Int.Ed.* **2002**, *41*, 2879-2890.

[10] J.Y. Ortholand, A. Ganesan, “Natural products and combinatorial chemistry: back to the future“. *Curr.Opin.Chem.Biol.* **2004**, *8*, 271-280.

[11] A.M. Piggott, P. Karuso, “Quality, not quantity: The role of natural products and chemical proteomics in modern drug discovery“. *Combinatorial Chemistry & High Throughput Screening* **2004**, *7***,** 607-630.

[12] D.J. Newman, G.M.Cragg, K.M. Snader, “The influence of natural products upon drug discovery“. *Natural Product Reports* **2000**, *17*, 215-234.

[13] K.H. Lee, “Current developments in the discovery and design of new drug candidates from plant natural product leads“. *J.Nat.Prod.* **2004**, *67*, 273-283.

[14] A. Harvey, “Strategies for discovering drugs from previously unexplored natural products“. *Drug Discovery Today* **2000**, *5*, 294-300.

[15] M. Tulp, L. Bohlin, “Functional versus chemical diversity: is biodiversity important for drug discovery ?“ *Trends in pharmacological sciences* **2002**, *23*, 225-231.

[16] D.J. Newman, G.M. Cragg, K.M. Snader, “Natural products as sources of new drugs over the period 1981-2002“. *J.Nat.Prod.* **2003**, *66*, 1022-1037.

[17] M.D. Burke, S.L. Schreiber, “A planning strategy for diversity-oriented synthesis“. *Angew.Chem.-Int.Ed.* **2004**, *43*, 46-58.

[18] D.R. Spring, “Diversity-oriented synthesis; a challenge for synthetic chemists“. *Organic & Biomolecular Chemistry* **2003**, *1*, 3867-3870.

[19] D.S. Tan, M.A. Foley, M.D. Shair, S.L. Schreiber, “Stereoselective synthesis of over two million compounds having structural features both reminiscent of natural products and compatible with miniaturized cell-based assays“. *J.Am.Chem.Soc.* **1998**, *120*, 8565-8566.

[20] K.C. Nicolaou, J.A. Pfefferkorn, A.J. Roecker, G.Q. Cao, S. Barluenga, H.J. Mitchell, “Natural product-like combinatorial libraries based on privileged structures. 1. General principles and solid-phase synthesis of benzopyrans“. *J.Am.Chem.Soc.* **2000**, *122*, 9939-9953.

[21] R.W. DeSimone, K.S. Currie, S.A. Mitchell, J.W. Darrow, D.A. Pippin, “Privileged structures: Applications in drug discovery“. *Combinatorial Chemistry & High Throughput Screening* **2004**, *7*, 473-493.

[22] Muller G, “Medicinal chemistry of target family-directed masterkeys“. *Drug Discovery Today* **2003**, *8*, 681-691.

[23] G. Mehta, V. Singh, “Hybrid systems through natural product leads: An approach towards new molecular entities“. *Chem.Soc.Rev* **2002**, *31*, 324-334.

[24] L.F. Tietze, H.P. Bell, S. Chandrasekhar, “Natural product hybrids as new leads for drug discovery“. *Angew.Chem.Int.Ed Engl.* **2003**, *42*, 3996-4028.

[25] A.M. Boldi, “Libraries from natural product-like scaffolds“. *Curr.Opin.Chem.Biol.* **2004**, *8*, 281-286.

[26] J. Nielsen, “Combinatorial synthesis of natural products“. *Curr.Opin.Chem.Biol.* **2002**, *6*, 297-305.

[27] Liao Y, Hu YH, Wu H, Zhu Q, Donovan M, Fathi R, Yang Z: “Diversity oriented synthesis and branching reaction pathway to generate natural product-like compounds“. *Current Medicinal Chemistry* **2003**, *10*, 2285-2316.

[28] Abreu PM, Branco PS: “Natural product-like combinatorial libraries“. *Journal of the Brazilian Chemical Society* **2003**, *14*, 675-712.

[29] K.C. Nicolaou, J.A. Pfefferkorn, “Solid phase synthesis of complex natural products and libraries thereof“. *Biopolymers* **2001**, *60*, 171-193.

[30] K. Knepper, C. Gil, S. Brase, “Natural product-like and other biologically active heterocyclic libraries using solid-phase techniques in the post-genomic era“. *Combinatorial Chemistry & High Throughput Screening* **2003**, *6*, 673-691.

[31] D.S. Tan, “Current progress in natural product-like libraries for discovery screening“. *Combinatorial Chemistry & High Throughput Screening* **2004**, *7*, 631-643.

[32] R. Messer, C.A. Fuhrer, R. Häner, “Natural product-like libraries based on non-aromatic, polycyclic motifs“. *Current Opinions in Chemical Biology* **2005**, in press (and references therein)

[33] P.M. Dewick, “Medicinal Natural Products“, 2nd ed.; *J. Wiley & Sons: Chichester, UK*, **2003**.

[34] K.H. Lee, *J. Nat. Prod.* **2004**, *67*, 273-283.

[35] F. Alonso, E. Lorenzo, J. Melendez, M. Yus, *Tetrahedron* **2003**, *59*, 5199-5208.

[36] E. Lorenzo, F. Alonso, M. Yus, *Tetrahedron Lett.* **2000**, *41*, 1661-1665.

[37] (a) F. Dini, G. Guella, P. Giubbilini, I. Mancini, F. Pietra, F. *Naturwissenschaften* **1993**, *80*, 84. (b) G. Guella, F. Dini, A. Tomei, F. Pietra, *J. Chem. Soc. P. T. 1* **1994**, *17*, 161. (c) G. Guella, F. Dini, F. Pietra, F. *Helv.Chim. Acta* **1996**, 79, 710.

[38] T. Nakatsu, B.N. Ravi, D. Faulkner, *J.Org. Chem.* **1981**, *46*, 2435-2438.

[39] Y. Ge, S. Kondo, Y. Odagaki, S. Katsumura, K. Nakatani, S. Isoe, *Tetrahedron Lett.* **1993**, *34*, 2621-2624.

[40] Y. Ge, S. Kondo, Y. Odagaki, S. Katsumura, K. Nakatani, S. Isoe, *Tetrahedron* **1993**, *49*, 10555-10567.

[41] Y. Ge, K. Nakatani, S. Isoe, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1085-1088.

[42] J.E. Little, D.B. Johnstone, *Arch. Biochemistry* **1951**, *30*, 445.

[43] S.M.Kupchan, A. Desserti, B.T. Blaylock, R.F. Bryan, *J. Org. Chem.* **1974**, *39*, 2477-2482.

[44] J.E. Anderson, C.-J. Chang, J.L. McLaughlin, *J. Nat. Prod.* **1988**, *51*, 307-308.

[45] L.B.S. Kardono, S.Tsauri, K. Padmawinata, J.M. Pezzuto, A.D. Kinghorn, *J. Nat. Prod.* **1990**, *53*, 1447-1455.

[46] Y. Endo et al. *Chem. Pharm. Bull.* **1994**, *42*, 1198-1201.

[47] C.A. Wood, K. Lee, A.J. Vaisberg, D.G.I. Kingston C.C.Neto, G.B. Hammond, *Chem. Pharm. Bull.* **2001**, *49*, 1477-1478.

[48] H.J. Koo, Y.S. Song, H.J.Kim, Y.H. Lee, S.M. Hong, S.J. Kim, B.C. Kim, C. Jin, C.J. Lim, E.H. Park, *European Journal Of Pharmacology* **2004**, *495*, 201-208.

[49] R. Aquino, N. De Tommasi, M. Tapia, M.R. Lauro, L. Rastelli, *J. Nat. Prod.* **1999**, *62*, 560-562.

[50] D.H. Lee, I.G. Cho, M.S. Park, K.N. Kim, I.M. Chang, W.C. Mar, *Archives Of Pharmacol Research* **2001**, *24*, 55-63.

[51] R.A. Aungst, R.L. Funk, *J. Am. Chem. Soc.* **2001**, *123*, 9455-9456.

[52] J.K. Whitesell, M. Fisher, P. Da Silva Jardine, *J. Org. Chem.* **1983**, *48*, 1557-1559.

[53] B.M. Trost, Balkovec, M.K.-T. Mao, *J. Am. Chem. Soc* **1983**, *105*, 6755-6757.

[54] O. Diels, K. Alder, *Liebigs Ann. Chem.* **1928**, *460*, 98.

[55] I. Fleming, "Frontier Orbitals and Organic Chemical Reactions"; *J. Wiley & Sons: Chichester, UK*, **1976**.

[56] W. Oppolzer, *Angew.Chem.Int.Ed.Engl.* **1977**, *16*, 10-23.

[57] G. Desimoni, G. Tacconi, *Chem.Rev.* **1975**, *75*, 651-692.

[58] R.R. Schmidt, *Acc. Chem. Res.* **1986,** *19*, 250-259.

[59] H. Waldmann, *Synthesis* **1994**, 535-551.

[60] K.A. Jorgensen, *Angew.Chem.Int.Ed.* **2000**, *39*, 3558-3588.

[61] L.F. Tietze, G. Kettschau, "Hetero Diels-Alder Reactions in Organic Chemistry"; *Topics in Current Chemistry, Springer Verlag*, **1997**, *189*, 1 – 120.

[62] L.F. Tietze *Chem. Ber.* **1974**, *107*, 2491.

[63] Coda A.C.; Desimoni G.; Righetti P.P.; Tacconi G.; Butlafava A.; Martinotti-Fracitano F. *Tetrahedron* 1983, 39, 331

[64] A. Marglin, R.B.Merrifield, *J. Am. Chem. Soc.* **1966**, *88*, 5051-5052.

[65] S.-S.Wang, *J. Am. Chem. Soc.*, **1973**, *95*, 1328.

[66] H. Rink, *Tetrahedron lett.* **1987**, *28*, 3787 - 3790.

[67] G. Barany et al. *J.* Org. *Chem.* **1990**, *55*, 3730-3743.

[68] S.K. Sharma, M.F. Songster, T.L. Colpitts, P. Hegyes, G. Barany, F.J. Castellino, *J. Org. Chem.* **1993**, *58*, 4993-4996.

[69] D.H. Rich, S.K. Gurwara, *J. Am. Chem. Soc.* **1975**, *97*, 1575 - 1579.

[70] R. Messer Diplomawork **2000.**

[71] R.K. Pandey et al *J.Org. Chem*. **2004**, *69*, 6165-6172.

[72] R.R. Schmidt, D. Heermann, K.J. Jung, *Liebigs Ann. Chem.* **1974**, 1856-1863.

[73] J.J. Bourguignon, A. Schoenfelder, M. Schmitt, C.G. Wermuth, V. Hechler, B. Charlier, M. Maitre, *J.Med.Chem.* **1988**, *31*, 893-897.

[74] D. Papa, E. Schwenk, F. Villani, E. Klingsberg, *J. Am. Chem. Soc*. **1948**; *70*, 3356-3357.

[75] R.R. Schmidt, *Acc. Chem. Res.* **1986,** *19*, 250-259.

[76] K.A. Jorgensen, *Angew.Chem.Int.Ed.* **2000**, *39*, 3558-3588.

[77] Kim, K. S.; Cho, I. H.; Joo, Y. H.; Yoo, I. Y.; Song, J. H.; Ko, J. H. *Tetrahedron Lett.* **1992**, *33*, 4029-4032

[78] C. Fuhrer, R. Messer, R. Häner, *Tetrahedron Lett.* **2004**, *45*, 4297-4300.

[79] W.M.F. Fabian, K. Bowden, *Eur. J. Org. Chem.* **2001**, *2*, 303-309

[80] K. Naresh, R.R. Wayne, Patent WO 02/00639

[81] The X-ray data sets were measured by the BENEFRI Small Molecule Crystallography Service directed by Prof. Helen Stoeckli-Evans

[82] F. Effenberger, R. Maier, K.H. Schoenwaelder, T. Ziegler, *Chemische Berichte* **1982**, *8*, 115.

[83] M. Hojo, R. Masuda, S. Sakaguchi, M. Takagawa, *Synthesis* **1986**, *12*, 1016-17.

[84] J. S. Clark, J. G. Kettle *Tetrahedron* **1999**, *55*, 8231-8248.

[85] D. Obrecht, *Helv Chem. Acta* **1991**, *74*, 27 – 46.

[86] R.Messer, A. Schmitz, L. Moesch, R.Häner, *J. Org. Chem.* **2004**, *69*, 8558-8560

[87] Patent CH-657613

[88] L.F. Tietze, T. Brumby, M. Pretor, G. Remberg, *J. Org. Chem.* **1988**, *53*, 810–820.

[89] L.F. Tietze, T. Brumby, M. Pretor, *Synthesis* **1987**, 700–703.

[90] S. Tews, R. Miethchen, H. Reinke, *Synthesis* **2003**, *5*, 707–716.

[91] F. Effenberger F. *Chem. Ber*. **1965**, *98*, 2260.

[92] M.P. Sib, M. Marvin, R. Sharma, *J.Org. Chem.* **1995,** *60***,** 5016-5023.

[93] H. L. Riley, J. F. Morley and N. A. Friend, *J. Chem. Soc.* **1932**, 1875

[94] X. Linghu, J. S. Johnson, *Angew. Chem.*, **2003**, *115*, 2638-2640. (and literature therein)

[95] S. Bera, V. Nair, *Helv. Chem.Acta* **2000**, *83*, 1398-1407.

[96] W. R. Roush and D. A. Barda *J. Am. Chem. Soc.* **1997**, *119*, 7402-7403.

[97] J. Tamariz et al. *J. Org. Chem.* **1990**, *55*, 1024-1034.

[98] B.C. Söderberg, D. Jones, A. Modelli, H.A. Jiménez-Vazquez, R. Herrera, J. Tamariz, *Eur. J. Org Chem.* **2001**, 4657 - 4669

[99] C.D. Hurd, F.H. Blunck, *J. Am. Chem. Soc.* **1938**, *60*, 2419-2425.

[100] J. A. Erickson, S. D. Kahn, *J. Am. Chem. Soc.* **1994**, *116*, 6271-6276.

[101] H. Yamamoto, Lewis acids in organic synthesis, *Wiley-VCH*, **2000**

[102] G. Desimoni, G. Faita, G. Tacconi, P.P. Righetti *Tetrahedron* **1991** *39*, 8399 - 8406

[103] A. Casaschi, G. Desimoni, G. Faita, A.G. Invernizzi, S. Lanati, P.P. Righetti, *J. Am. Chem. Soc.* **1993**, *115*, 8002 - 8007

[104] T.M. Swarbrick, L. Kennard, I.E. Marko, *Tetrahedron Letters,* **1991**, *32*, 2549 – 2552.

[105] L.A. Carpino, G.Y. Han, *J. Org. Chem.* **1972**, *37*, 3404.

[106] H.E. Gottlieb, V. Kotlyar, A. Nudelman: NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities *J. Org. Chem.* **1997,** *62*, 7512-7515.

[107] Stoe. **2002**. *X-Area V1.17 & X-RED32 V1.04 Software*. Stoe & Cie GmbH, Darmstadt, Germany.

[108] G. M. Sheldrick: "SHELXS-97 - Program for Crystal Structure Determination", *Acta Crystallogr*. **1990,** *A46*, 467 473.

[109] G. Sheldrick, **1999** "SHELXL-97", Universität Göttingen, Göttingen, Germany.

[110] A.L Spek, *J.Appl.Cryst.* **2003,** *36*, 7-13

Acknowledgment

Special thanks go to Prof. Dr. Robert Häner for the opportunity to work in his research group, for the interesting assignment, support and the efforts to effect collaborations with the Novartis Institutes for BioMedical Research.

Special thanks also go to Prof. Dr. Philippe Renaud for his efforts as a reviewer of this work.

Many thanks to Dr. Rolf Tona and Simon Langenegger for the excellent working environment in our lab and the helpful practical and theoretical discussions during breaks.

Sincere thanks go to Dr. Jürg Zimmermann and Dr. Andreas Marzinzik and their team at the Novartis Institutes for BioMedical Research for the successful collaborations, the instructive internships and the helpful suggestions.

Thanks a lot to our technician Luzia Moesch for the preparation of many of the compounds.

Thanks to the teams of Prof. Dr. H. Stöckli-Evans for x-ray crystallographic analysis, the team of Prof. Dr. P. Bigler for any NMR elucidations, the team of Dr. S. Schürch for mass spectrometric measurements, the technical services and the administration of the Department of Chemistry and Biochemistry for various help.

Last but not least, I'd like to thank all the past and current members of the Häner Group for help, support and good spirits.

Curriculum Vitae

2001 – 2005	PhD at the University of Bern Chemistry Department.
2001	Webmaster for swissinfo (SRG SSR idée suisse)
2001	Master of Science in Chemistry (lic. Phil. Nat.)
2000 – 2001	Diploma work with Prof. R. Häner in organic chemistry.
1996 – 2000	Study of Chemistry at the University of Bern
1992 – 1993	Exchange Year Central High School in East Corinth, Maine, USA
1990 – 1996	Realgymnasium Bern-Neufeld
1982 – 1990	Primarschule Hilterfingen and Sekundarschule Hünibach
1975	Born in Thun BE as the first of two children of Marianne and Richard Messer

Publications

Elaboration of D-(-)-Ribose into a Tricyclic, Natural Product like Scaffold R. Messer, A. Schmitz, L. Moesch, R. Häner, *J. Org. Chem.* **2004**, *69*, 8558-8560.

Stereoselective Synthesis of 3a,7a-Dihydro-3H,4H-furo[3,4-c]pyran-1-ones via Intramolecular Hetero-Diels-Alder Reaction C. Fuhrer, R. Messer, R. Häner, *Tetrahedron Lett.* **2004**, *45*, 4297-4300.

Natural product-like libraries based on non-aromatic, polycyclic motifs. Roland Messer, Cyril A. Fuhrer and Robert Häner, *Curr.Opin.Chem.Biol.* **2005**, in press