Electroorganic Reactions in Polymer Supported Organic Synthesis

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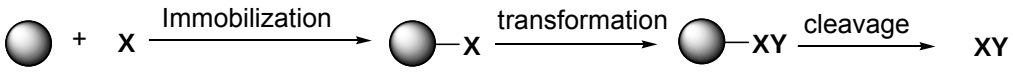
1. Introduction

An important application of organic chemistry is the design and synthesis of new molecules for potential use in medicine[1] or material sciences.[2] Drug discovery requires the synthesis of numerous individual analogues of a biologically active compound in order to improve on activity, bioavailability, or selectivity. It has been estimated that for each new drug approved this process requires the synthesis of thousands of compounds, which is laborious, and time consuming. With the advent of combinatorial chemistry this problem can be solved. In addition, the capability of combinatorial chemistry to produce large numbers of compounds rapidly makes it a powerful tool not only for drug discovery but also for inventing new materials and the development of new catalysts for industrial applications. Combinatorial synthesis may be performed either in solution or on solid support. Each having their own advantages and disadvantages, both methods have been widely used in the construction of various compound libraries.

Nowadays, combinatorial chemistry via solid phase synthesis enables chemists to produce analogues of a particular compound in a much more efficient and rapid way. More than three decades ago, Merrifield introduced the concept of solid phase peptide synthesis, which was used by chemists regularly for automated solid phase synthesis of libraries of polypeptides and oligonucleotides. Recently, solid phase synthesis of nonoligomeric, small organic molecules has been developed due to the demand for diverse compound libraries to be tested in biological assays. Solid phase organic synthesis (SPOS) has several advantages. The most important one is the appreciable simplified reaction procedure: time-consumption for purification and isolation steps are reduced to simple filtration as both substrate and product are attached to solid support. This process can easily be automated and run in parallel. Nevertheless, in a final step the bond between the target product and the linker has to be cleaved selectively under mild conditions, without destroying the product (Scheme 1).



Scheme 1. Solid phase chemistry

In many cases higher yields than in solution can be obtained by using a large excess of reagents, when the conditions are chosen carefully so that no undesired side reactions such as multisubstitutions can take place. In addition, other reactions such as cross linking and multiple couplings can be suppressed by using high dilute condition (using low loading supports <0.8 mmol/g, which serve to isolate the reactive sites). Although, sometimes the supports are costly, it is not an important factor in the multistep synthesis of expensive

products. However, these positive features are opposed by some drawbacks: adapting a standard solution phase reaction to solid phase frequently gives problems associated with finding suitable, robust and versatile points of attachment for the linker in the starting material. This inherent feature limits the choice of suitable reaction conditions. Furthermore, the selection of solvents is restricted due to the variation of swelling properties of different resins in different solvents. Also the temperature that can be applied is restricted: +100°C is generally at or beyond the upper limit of most solid phase systems. Chemistry involving heterogeneous catalysts such as palladium on charcoal is incompatible with solid phase synthesis methods. Another drawback is that, the on-bead analysis is still not satisfying, although NMR and IR as well as MS techniques have been improved. Despite of all these disadvantages, solid phase chemistry is applied to the elegant and powerful “split-and-pool” synthesis strategy for combinatorial chemistry.

Another approach of combinatorial chemistry is via dendritic polymers, which has its own characteristics both in soluble form and insoluble hybrid polymeric form. For combinatorial synthesis hybrid resins are attractive, because they have several favorable material properties (e.g. good swelling properties, high loading capacities). Dendritic soluble polymers are promising candidates due to their high loading capacities as well as they provide homogeneous reaction conditions and allow easy monitoring of reaction process. However, they have some drawbacks due to their laborious separation techniques compared to solid phase supports.

Combinatorial synthesis via solid phase chemistry has made tremendous progress during the last decade. Previously combinatorial libraries have produced poor hit and lead structures due to inappropriate library design which relied on a very limited number of reaction types applicable to SPOS. Recently it has been recognized that biological relevance, design and diversity of the library is important. Therefore, more complex and more diverse libraries are the aim of the combinatorial chemists. In order to achieve this goal, new methods have to be developed that ultimately all known reactions which make organic synthesis so powerful can be applied to solid phase.[3]

2. Aim of the thesis

Combinatorial synthesis via solid phase chemistry is of great potential for library production in muliparallel synthesis. To obtain high quality libraries, high yielding reactions are required for each step in the synthetic sequence. In addition, mild reaction conditions are always favourable. In organic synthesis electrochemical reductions and oxidations have numerous advantages over conventional methods. For example, mild reaction conditions can be achieved to get high selectivity, raw materials can be used in a better way, and isolation of the products is easy. Since the pioneering work of Merrifield, organic chemists have transferred almost all organic reactions known in solution onto the solid phase.[4] However, notable exceptions are electroorganic reactions, which are a powerful tool for organic synthesis and even are applied in large-scale industrial processes.[5] Although the parallelization of electrochemical reactions for solution-phase electroorganic synthesis has been addressed recently,[6] and electroorganic reactions have been carried out with substrates bound to modified electrodes,[7] solid-phase electroorganic synthesis using conventional polymeric beads has not been reported yet.

In this regard, the objective of this thesis was to adapt electrosynthetic methodology to solid supports to make it available for combinatorial applications. For this purpose electrochemical oxidation of furans was chosen as a model reaction, as it has industrial relevance and the resulting 2,5-dimethoxy-2,5-dihydrofurans are useful starting materials in organic synthesis. It was believed that an indirect electrochemical method via a mediator (Figure 1) should enable the electron transfer between the electrode and the solid supported substrate as a direct contact between electrode and substrate is impossible due to steric reasons.

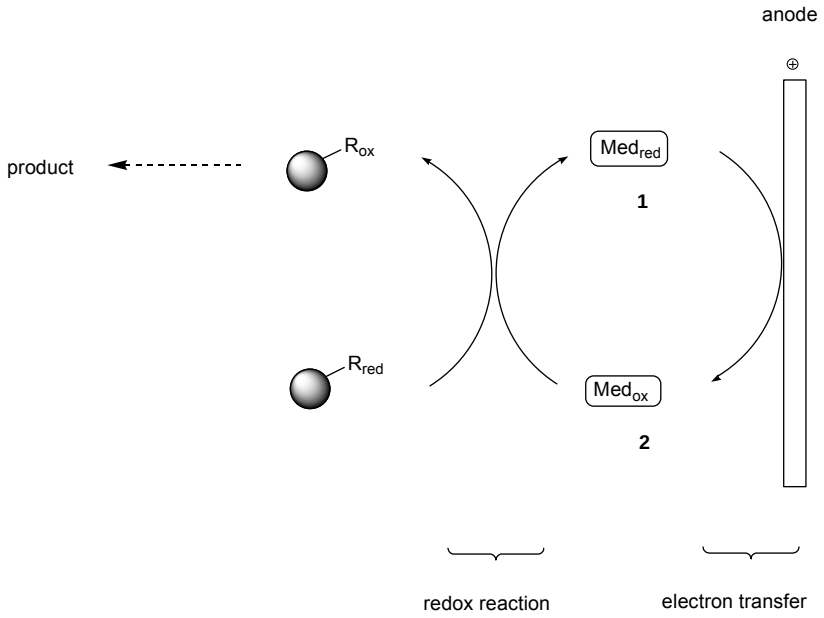


Figure 1. Indirect anodic oxidation with solid supported substrate

Solid phase electroorganic synthesis would allow the integration of electrochemical reactions, with its advantages of complementary reactivity and mild reaction conditions, into the pool of organic reactions used for solid-phase library synthesis. On this basis another goal was to exploit the intermediates prepared by electrosynthesis on solid phase for further diversification. Through the preparation of new organic small molecules by using these synthetic intermediates on solid phase the usefulness of electroorganic synthesis on solid phase for multistep synthesis should be demonstrated.

Recenty dendritic soluble polymeric supports have been used for the parallel synthesis approach which can overcome some of the problems associated with solid beads such as low loadings and problems due to the heterogeneous nature of the reactions. Another aim of this thesis was to show that high loading soluble polymeric supports are suitable for electrosynthesis. The goal of this project was to show that multistep synthesis of a small library of *N*-subtituted pyrroles which are interesting drug like structures can be achieved via an electrochemical reaction by using a dendritic polyglycerol support.

3 Theoretical background

3.1 Electroorganic synthesis on solid phase

3.1.1 Introduction

Solid-phase organic synthesis (SPOS) has become an invaluable tool in the quest for the synthesis of large compound libraries.[8] During the last decade preparative organic electrochemistry has bloomed and a very optimistic view on the synthetic possibilities of the new method both for laboratory and technical applications was expressed which motivate us to apply this area on solid phase chemistry. In this thesis, the principle of indirect electrolysis was applied to solid phase synthesis. As a great deal of progress has recently been made in the application of organic electron transfer agents in solution phase electrochemistry, compounds have been found that are sufficiently stable in both the reduced as well as the oxidized state. By taking advantage of these substances we were able to establish solid phase electroorganic chemistry.

3.1.2 Indirect anodic oxidation

The electrochemical formation and regeneration of redox agents for organic synthesis (*indirect electrolysis*) widens the potential of electrochemistry, as higher or totally different selectivities can often be obtained while at the same time the energy input can be lowered significantly. The principle of this method is described below.

In electroorganic reactions, an active species is generated on the electrode surface by electron transfer between a substrate molecule and the electrode. The substrate molecule is transformed to a cation radical or an anion radical, depending on the direction of the electron transfer. Hence, the formation of active species is highly controlled by the oxidation and reduction potentials of the substrates. If these potentials are beyond the range accessible by the usual electrochemical technique, then the direct electron transfer between the substrate and electrode hardly takes place as described in the direct oxidation of aliphatic saturated alcohols. Therefore, it is necessary to devise some other methods to oxidize or reduce the substrates. Also even if the oxidation and reduction potentials of the substrates are in the accessible range of the electrochemical method, it is more desirable to oxidize or reduce them at much lower potentials than those applied in the direct method. This is achieved by the electroorganic synthesis using mediators. The oxidative reaction system using a mediator is schematically represented in Figure 2.

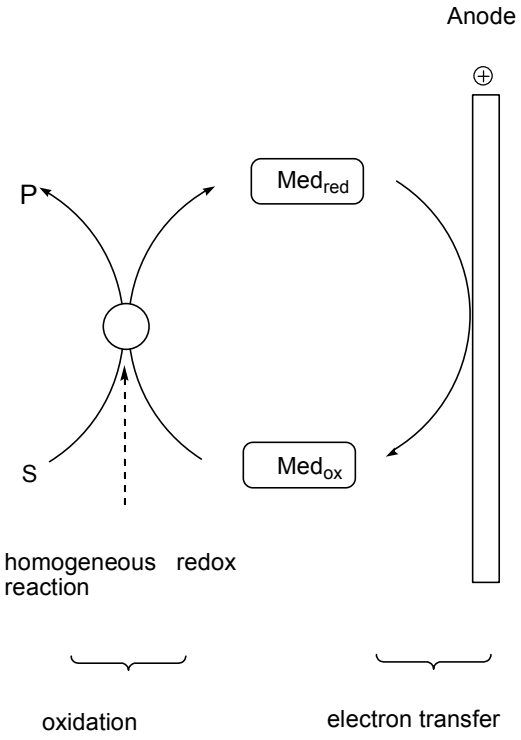


Figure 2. Mediatory system

The oxidation potential of the substrate S in Figure 2 is beyond the range accessible by the electrochemical method so that direct electron transfer from substrate to the anode hardly occurs, and also the high oxidation potential necessary for the direct oxidation of S causes unexpected side reactions involving oxidation of the solvent or supporting electrolyte. However, when a compound M_{red} (a reduced form of M) which may be oxidized at a sufficiently lower potential than S is added to the reaction system, the oxidation of M_{red} to M_{ox} (an oxidized form of M) will take place prior to the oxidation of S. Provided that M_{ox} is able to oxidize S to product P, the oxidation of S will be achieved at a potential lower than that necessary for its direct oxidation. The compound M is called mediator or an electron carrier, since M mediates electron transfer between S and the anode. When M_{ox} oxidizes S in solution, M_{ox} is reduced to M_{red} which is again oxidized at the anode to regenerate $M_{ox.}$ Thus if the lifetime of the redox system $M_{ox} \leftrightarrow M_{red}$ is sufficiently long, only a catalytic amount of mediator is required to initiate the entire reaction. As a matter of course, the concept of the mediatory system is not only applicable to oxidations, as illustrated by Figure 2 but also to reductions. Although the term mediator or electron carrier has been introduced recently, many types of reaction systems involving a compound which behaves as a mediator were already known.

Indirect electrochemical processes are, in a certain sense, hybrids: They combine an electrochemical and therefore heterogeneous electron transfer reaction with a homogeneous

redox process. The redox agent reacts with the substrate in a homogeneous reaction and is subsequently regenerated in its active form at the electrode.

Redox catalyst

The redox catalyst (mediator) holds a key position in indirect chemical electrolysis since it is involved in both the heterogeneous as well as the homogeneous redox reaction. To be suitable for both types of reactions the mediators must fulfill the following conditions:

1) Both reduced and oxidized forms must be chemically stable. Even a slight side reaction to give compounds no longer convertible into the active form leads to a rapid loss of catalytic activity.

2) Electron exchange with the electrode and reaction with the substrate must be fast and as reversible as possible, otherwise larger and therefore more expensive electrode surface is necessary. In addition side reactions are often favored.

3) Redox reactions with other than the desired compounds, for instance with the solvent, must not take place or must be suppressed.

4) Both redox systems must be sufficiently soluble in the chosen supporting electrolyte.

5) The redox catalyst should be easily separable from the product and its purification before the electrolysis and after should be easy.

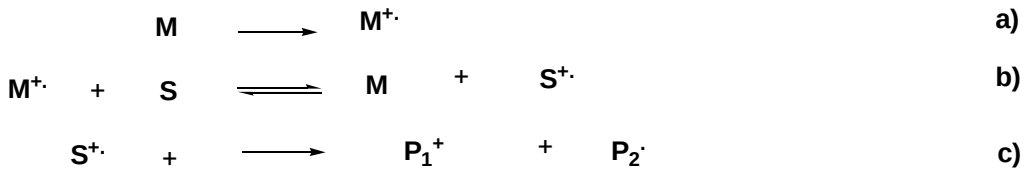
Inorganic ions, metal salts and some metal complexes usually fulfill the condition of chemical stability more easily than organic mediators, however the electron transfer is often too slow, as it is in many cases connected with a change of a complex structure. On the other hand, metal ions often have the advantage of moderating the reactivity of intermediates that are formed during the electron transfer by coordination or complexation and thereby enable specific and selective reactions. Moreover, in the case of transition metal complexes, the redox potential can easily be influenced by choice of the central atoms or the ligands. These redox reagents are often capable of undergoing selective redox reactions with a large number of organic substrates. By simply varying the reaction conditions a large variety of products can be obtained, since such redox processes are usually not simple electron transfer reactions

Organic mediators in their active form, e.g. as radical ions, are sometimes not sufficiently stable in many media. They often react irreversibly with the solvent, with the electrolyte, or with the intermediates that are formed during the redox reaction. The number of stable electron transfer agents is therefore limited and their availability is often restricted to certain electrolytes. Nevertheless, great progress has been made in this field recently. In most cases the use of these reagents is reasonable from an economic and ecological point of view only if the redox catalysts can be generated.

In principle the redox catalyst can be classified in two groups according to their reaction mechanisms they undergo in the homogeneous redox step.

Homomediatory system

The homogeneous redox reaction consists of a pure electron transfer. Such a process is called homomediatory system. The homomediatory system is represented by equations **a**) to **c**), (Scheme 2) in which the mediator **M** is first oxidized to $\mathbf{M}^{+\bullet}$ at a relatively lower potential. The next step involves a homogeneous electron transfer from **S** to $\mathbf{M}^{+\bullet}$ to form $\mathbf{S}^{+\bullet}$; this step is a reversible reaction. In the final step, $\mathbf{S}^{+\bullet}$ is transformed to the products $\mathbf{P_1}^{+}$ and $\mathbf{P_2}^{\bullet}$ by an irreversible reaction.



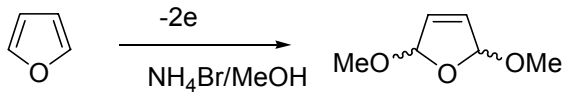
Scheme 2. Reactions in homomediatory system

Since the oxidation potential of **S** is more positive than that of **M**, the equilibrium in equation **b)** is largely shifted to the left hand side. Hence the rate of the whole reaction greatly depends on the rate of the irreversible reaction in equation **c)**. In fact, the oxidation described by equation **a)** proceeds effectively only when $\mathbf{S}^{+\bullet}$ is transformed sufficiently fast to products $\mathbf{P_1}^{+}$ and $\mathbf{P_2}^{\bullet}$.

When the oxidation potential of **S** is much more positive than that of **M** the equation illustrated by equation **a)** is almost impossible, even though the irreversible reaction of $\mathbf{S}^{+\bullet}$ is fast. In such a case, some further activation of $\mathbf{M}^{+\bullet}$ is necessary to make the oxidation possible.

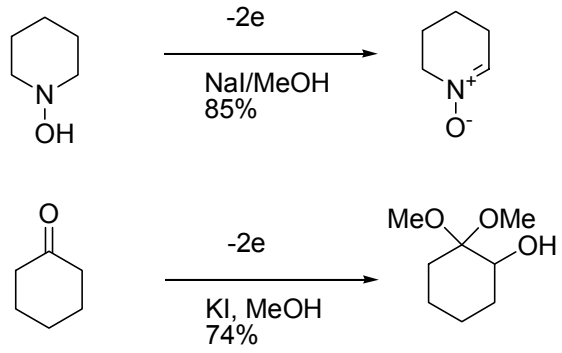
Heteromediatory system

In Heteromediatory system, the homogeneous redox reaction is combined with a chemical reaction. That means, the substrate **S** is not oxidized by direct electron transfer from **S** to $\mathbf{M_{ox}}$ but by chemical reaction between **S** and $\mathbf{M_{ox.}}$. Many of the mediatory systems which are useful in organic synthesis may be classified in this category. Among a variety of mediators, the redox system consisting of a halide ion and a positive halogen species in one of the most interesting mediators used in organic synthesis. One of the earliest synthetic reactions in which the halide anion was used as a mediator is the anodic methoxylation of furan, in the presence of 0.05 equiv. of ammonium bromide (Scheme 3).[9]



Scheme 3. Anodic oxidation of furan

After this early investigation, a variety of oxidations using the redox system halide ion/positive halogen species as the mediator have been studied. Some of these oxidation systems are shown below in equations (Scheme 4). [10, 11]



Scheme 4. Example of heteromediatory system

Double mediatory system

As described above, the mediatory system is an effective tool to oxidize the substrates that cannot be readily oxidized by the direct method. Further development of this concept has led to the combination of two types of mediators (Figure. 3). As a result, the oxidation of substrates is achieved at a potential which is far lower than that required when the system contains only one type of mediator.[12]

In this system, the potential, (E_p= 1.1 versus SCE) of the oxidation of Br^- to Br^+ is the lowest, and the oxidation of R'_2S to $R'_2S^{+\bullet}$ does not take place at this potential. For example, alcohols such as RRCHOH are oxidized to $R'_2S^{+\bullet}$, whereas Br^+ itself is not sufficiently reactive to oxidize alcohols to ketones in satisfactory yields. When both mediators are combined as depicted in Figure. 3, however, the oxidation of alcohols may be achieved at a considerably lower potential than that necessary for the oxidation of R'_2S to $R'_2S^{+\bullet}$.

The yields of the obtained ketones are in the range of 80-94%. The mediatory system in Figure 3 can be called a double mediatory system. A double mediatory system containing the redox systems $Pd^0 \leftrightarrow Pd^{2+}$ and quinine↔hydroquinone has been reported.[13]

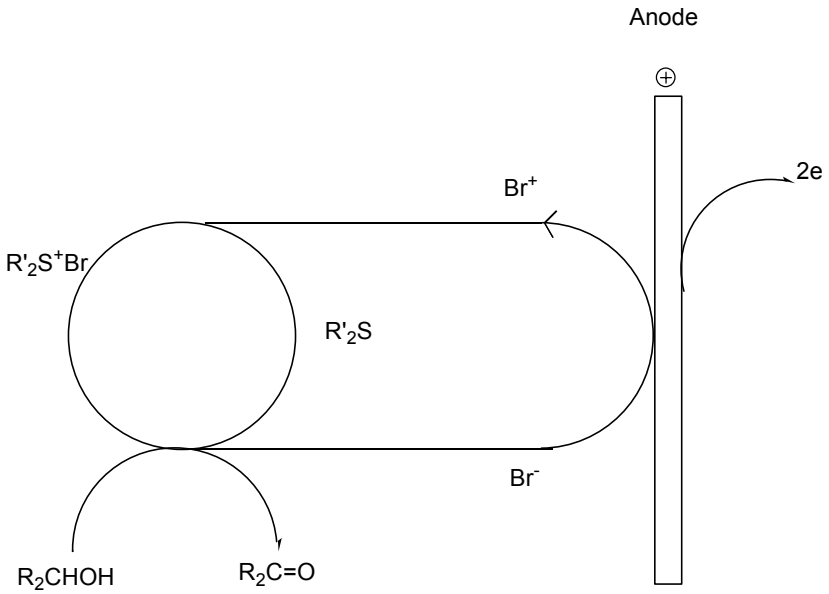


Figure 3. Double mediatory system

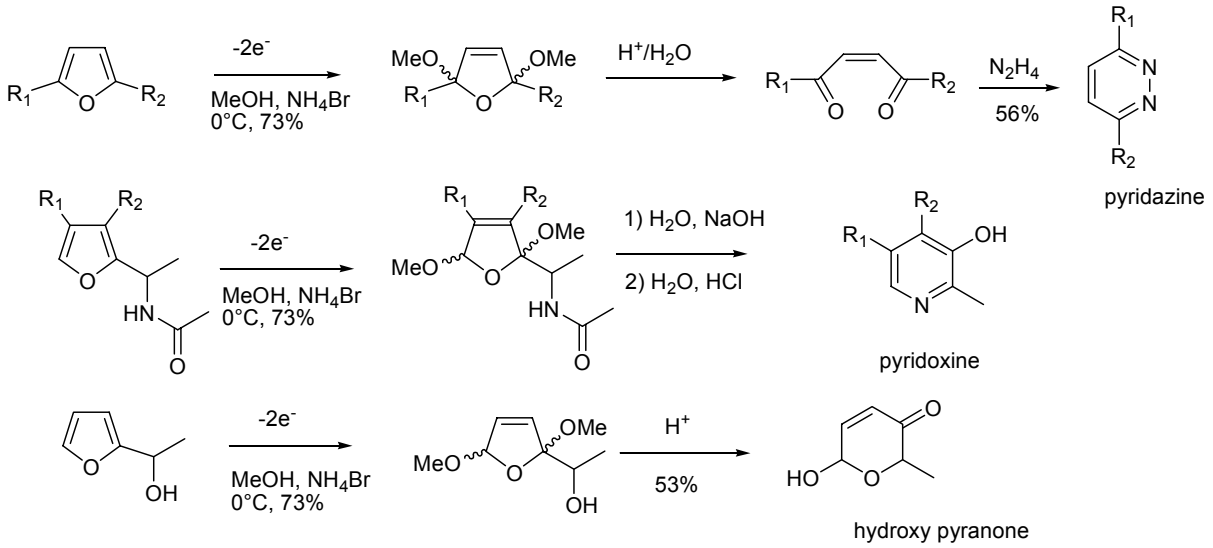
Indirect electrochemical synthesis has become the subject of intensive study and a host of new possibilities for its application is emerging nowadays. The particular advantages of this technique are its lower burden on the environment, the favourable exploitation of energy because of the acceleration of electrode reactions, and high selectivity of many of the syntheses. In addition, in a direct electrolysis method, overpotentials have to be applied to a smaller or larger extent, but in indirect electrolysis no overpotentials are encountered as long as reversible redox systems are used as mediators. In indirect electrolysis there is also no direct contact between substrate and the electrode, therefore this process is completely independent of the potential of the substrate. All these advantages make this method a useful tool for organic chemists.

3.1.3 Application of electrochemistry in organic synthesis

In organic synthesis electrochemical reductions and oxidations offer numerous advantages over conventional methos: mild reaction conditions, which often guarantee a high selectivity, better use of raw materials, an easier isolation of products.

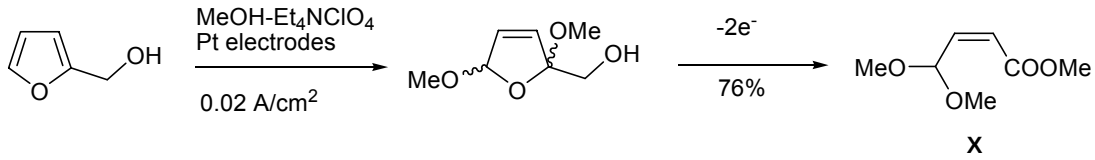
Electrochemistry is a clean and convenient method for the generation of many reactive intermediates (radical ions, radicals, carbanions, and carbocations) on preparative scale. Several conditions have been devised for selective and useful chemical conversions. Many well-established electrosynthetic reactions proceed with little or no byproducts. Particularly useful and versatile are carbon-carbon bond forming reactions such as those involving the Kolbe reaction, electrohydrodimerisations, which are diificult to achieve by other routes.[14] Another advantage of electrosynthesis over conventional chemical methods is the selective transformation of functional groups by controlling the applied potential. For example, nitroalkenes can be selectively reduced to hydroxyl amines or amines.[15] The *in situ* electrogeneration and regeneration of redox reagents in non stoichiometric amounts, and the related redox catalysis, is providing an attractive indirect, electrosynthetic approach.

The industrial application of electroorganic synthesis bagan in the 1950s with the anodic methoxylation of furan and furan derivatives to 2,5-dihydro-2,5-dimethoxyfurans by Clauson-Kaas *et al*.[9] (Scheme 5). Such compounds are derivatives of 1,4-dicarbonylbutene and as such are readily transformed to other compounds. A number of heterocyclic compounds have been prepared from 1,4-dicarbonyl-2-butenes.[16] The reaction is performed on industrial scale by BASF and Otsuka Chemicals in methanolic solution using ammonium bromide as supporting electrolyte as well as a redox catalyst.



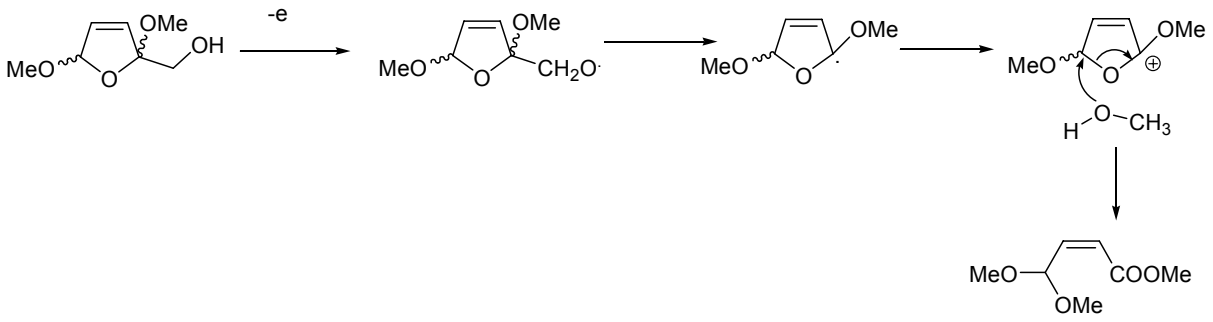
Scheme 5. Preparation of heterocyclic compounds via anodic oxidation of furan

Torii *et al*. described a convenient preparation of methyl (*E*) and (*Z*)-4,4-dimethoxy-2-butenoates by electrolysis of furfuryl alcohol (Scheme 6), [17] which have been recognized as powerful Michael acceptors in the synthesis of the plant antitumor agent campthothecin[18] and which also can serve as an unusual Diels-Alder dienophile.[19] They observed that the selectivity of the product formation was affected by the amount of the passed charge and by the current density. A selective transformation of furfuryl alcohol to its dimethoxy-dihydro derivative is achieved at current densities smaller than 0.05 A/cm^2 and a charge of 2 F/mol. When the electrolysis was prolonged to charge magnitudes of 4-6 F/mol the ring was opened, and afforded 2-butenoate **X** (Scheme 6). However, at higher current density the product selectivity was decreased as well.



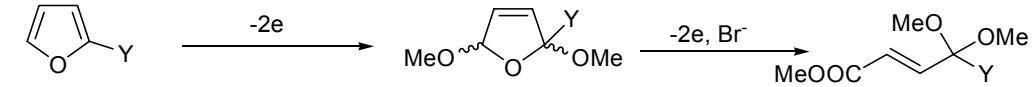
Scheme 6. Formation of methyl-4,4-dimethoxy-2-butenoates

A plausible mechanism of the anodic conversion is depicted in Scheme 7. One electron oxidation of 2,5-dimethoxy-2,5-dihydro furfuryl alcohol could be considered to generate an alkoxy radical which undergoes elimination of formaldehyde and successive one-electron oxidation. Subsequent nucleophilic attack by methanol would produce the ring opening product via the cation intermediate.[20] The conversion should require 4 electrons at the anode.



Scheme 7. Mechanism of the formation of methyl-4,4-dimethoxy-2-butenoates

The concentration of the bromide ion plays also an important role on the ring opening product. Torii *et al*. have described a novel oxidative ring opening of 2-substituted furans, which can be achieved without loosing C(2)-substituents (Y), by a Br^+ mediated electrolysis (Scheme 8).[21]

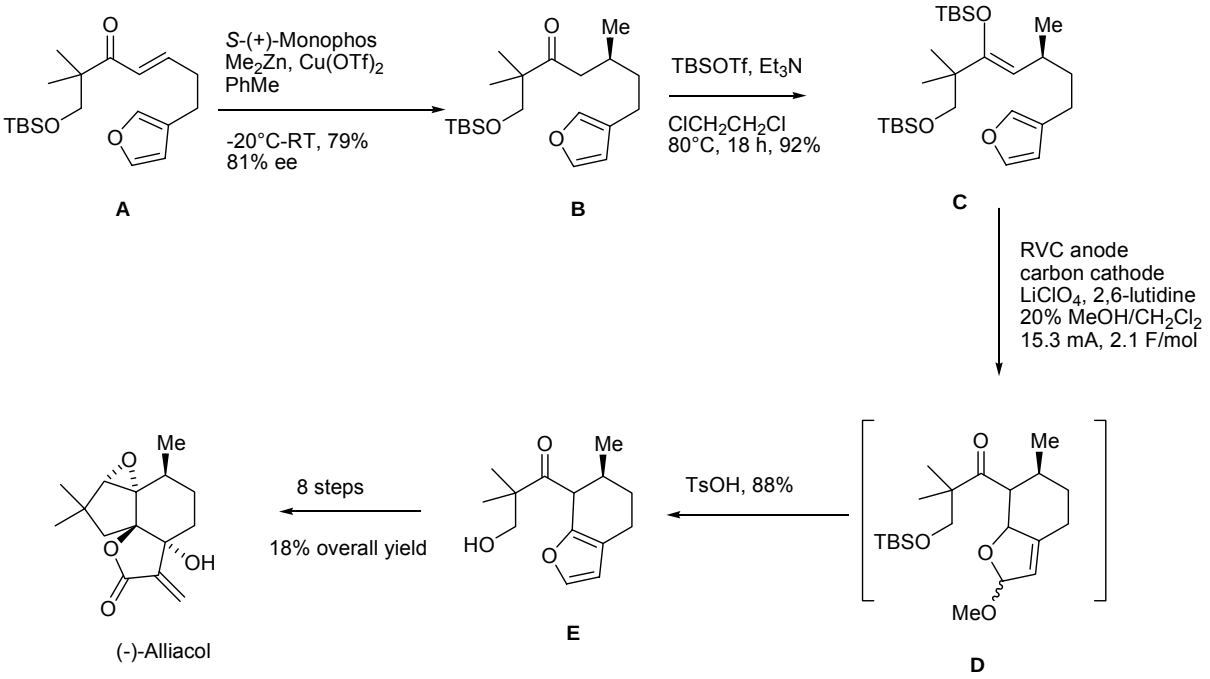


Y = COOMe, CHO, CH_2OH etc.

Scheme 8. Effect of Br^- concentration on methoxylation of furan

According to their observation at lower Br^- concentration (0.03-0.1 M), the ring-opening reaction takes place after passage of 13 F/mol of electricity, while at higher Br^- concentration (>0.2 M), the generation of Br_2 predominates and gives the 2,5-dimethoxy-2,5-dihydrofuran derivatives as a major product.

Recently this anodic methoxylation of furan was successfully applied by Moeller and coworkers[22] for the asymmetric synthesis of (-)-alliacol A (Scheme 9) which displays a moderate antimicrobial activity and inhibits DNA synthesis in the ascetic form of Ehrlich carcinoma.[23]



Scheme 9. Asymmetric synthesis of (-)-alliacol A via electrochemical cyclization

A tandem electrochemical cyclization-Friedel-Crafts alkylation strategy was used to rapidly complete the asymmetric synthesis of alliacol A. The anodic oxidation reaction allowed for the generation of a new bond between two nucleophiles. They have prepared substrate **C** enantioselectively which underwent electrolysis in 20% methanol/dichloromethane (reticulated vitreous carbon anode and a carbon rod cathode) to form the bicyclic product **D** which was not isolated. The crude **D** was treated with 5 equiv of *p*-toluenesulfonic acid at room temperature for 17 h to afford **E** in 88% yield (over two steps) and, finally after eight steps the desired (-)-alliacol A was isolated in 18% overall yield. The anodic coupling reaction of two nucleophiles in **C** was used as key step and the electrochemical reaction proceeded in high yield.

3.1.4 Electrochemical methods in combinatorial chemistry

Recent advance in combinatorial electrochemistry include new methods for parallel construction of small organic molecules, synthesis of conducting materials, electroactive solid supports and heterogeneous catalysts. In addition, new instrumentation for high-throughput electrosynthesis and analysis continues to be developed.[24] The first example of combinatorial electrochemistry appeared in 1998 which described an automated method for generating large libraries of metal alloy catalysts for methanol oxidation.[25] The first example of parallel electrosynthesis of small organic molecules on a preparative scale was documented by

Yudin and co-workers.[26] They have designed and fabricated a 16-well (4 by 4 arrays) spatially addressable electrolysis platform (SAEP, Figure 4). In this method, each one of the 16 electrolysis cells was equipped with a tubular stainless-steel cathode and a graphite rod anode. The stainless-steel cathodes were welded into a stainless-steel plate, which acted as a common terminal for the connection to the current source. The graphite anodes served as working electrodes and were insulated from each other and from the cathodes. Parallel connection of the wells was achieved using this set-up. When the electrolysis parameters (solvent, supporting electrolyte, surface area of electrode, and temperature) are identical for each cell, the current is distributed evenly amongst the cells. However this method requires high technological background for the instrumentation and also the SAEP is not good for large scale reactions.

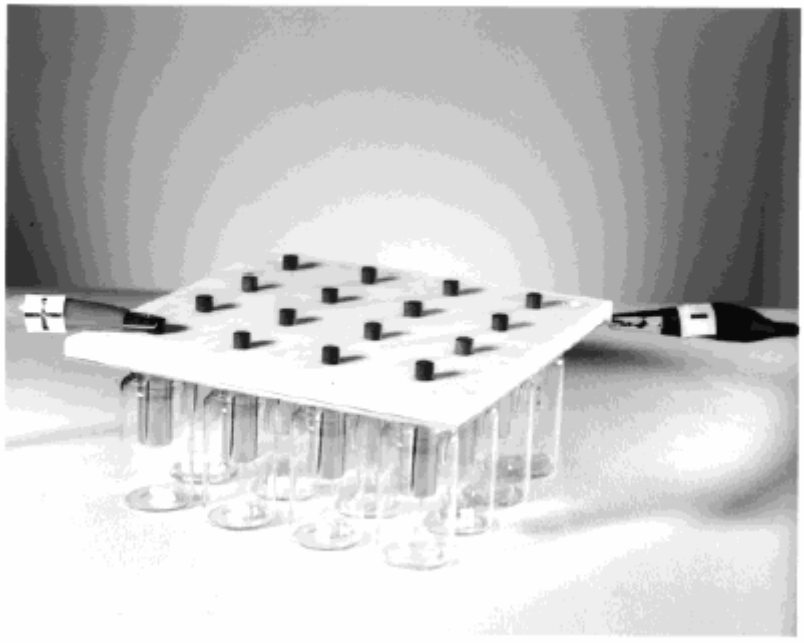
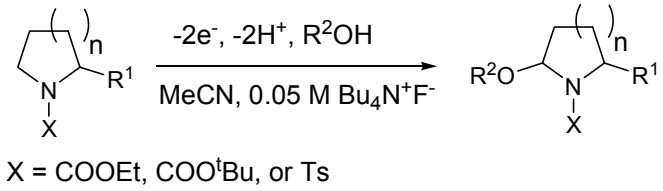


Figure 4. Experimental SAEP setup with glass reactors after electrode assembly (picture taken from reference[32])

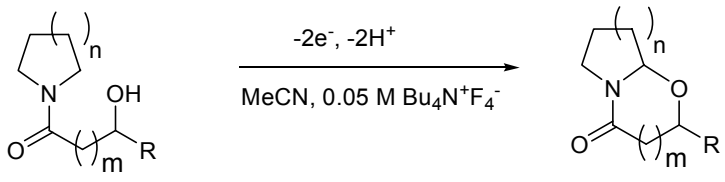
As a first application they carried out the anodic oxidation of carbamates using the SAEP to afford libraries of α-alkoxycarbamates (Scheme 10). An alternative way of making the derivatized α-alkoxycarbamates is through the reduction of *N*-alkoxycarbonylactams which requires cooling of the reaction mixture (-6 °C) and relatively long reaction time (4-5 h).[27] The electrochemical method can essentially be performed at room temperature, and a typical reaction time is only 10 min for a reaction on a 1 mmol scale. The corresponding α-alkoxycarbamates are versatile synthetic intermediates and can be further elaborated into valuable products. The highest yield (65-95%, by GC) and selectivity of the products were

achieved by using a current density of 80 mA/cm^2 at 30 °C in a 50:50 (by volume) acetonitrile/alcohol mixture.



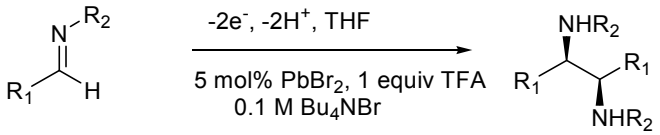
Scheme 10. Parallel electrochemical formation of α-alkoxycarbamates

Similarly, parallel electrochemical intramolecular cyclization of hydroxyamides provided diverse hetero-bicyclic compounds in high yields (Scheme 11).



Scheme 11. Parallel electrochemical intramolecular cyclization of hydroxyamides

Recently, reductive hydrocoupling of aldimines (Scheme 12) was also performed by Yudin *et al*.[24] using the SAEP to generate vicinal diamines.

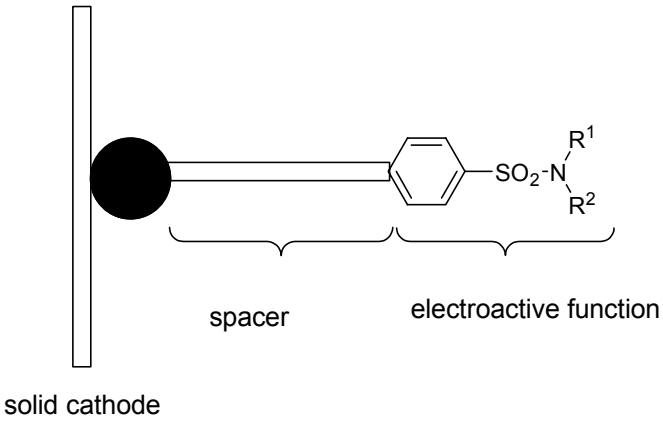


Scheme 12. Parallel electroreductive hydrocoupling of adimines

These examples highlight the advantages that electrochemistry offers to combinatorial synthesis of valuable small molecules and it can be concluded that combinatorial chemistry and parallel synthesis can benefit from the power and simplicity intrinsic to electrochemical approaches.

In the area of electrosynthesis on conducting supports, electrochemically generated polythiophenes were evaluated by Pilard *et al*. as Merrifield like resins for anchoring various amine-containing molecules.[28] For aryl sulfonamide a mild and selective electrochemical

cleavage of S-N bond is already reported.[29] Pilard and co-workers described the potential of these conducting polymers bearing an arylsulfonamide moiety as Merrifield-like resins for allowing a facile and highly selective cathodic S-N bond scission according to the following configuration (Figure 5).



R^1, R^2 = H, alkyl, benzyl.

Figure 5. Electrosynthesis on conducting support

Immobilization of electrochemically cleavable protecting reagents on a conducting polymer support, developed by Pilard *et al*. provides a novel solid-phase synthesis process. The polythiophene film acts as a solid support and as an electron-transfer interface for the electrochemical reaction. This process requires an attachment of the conducting support on the electrode (platinum) surface, which limits its application to small-scale electrosynthesis.

Polythiophene was substituted in the 3-position with a fully regenerable aromatic sulfonamide moiety (Figure 6, substrate **A)**. The S-N bonds were cleaved with high selectivity under very mild conditions with concomitant liberation of deprotected amines by an indirect method using pyrene as a mediator. A recycling process of the polymer matrix allows further grafting of various amines (Figure 6).

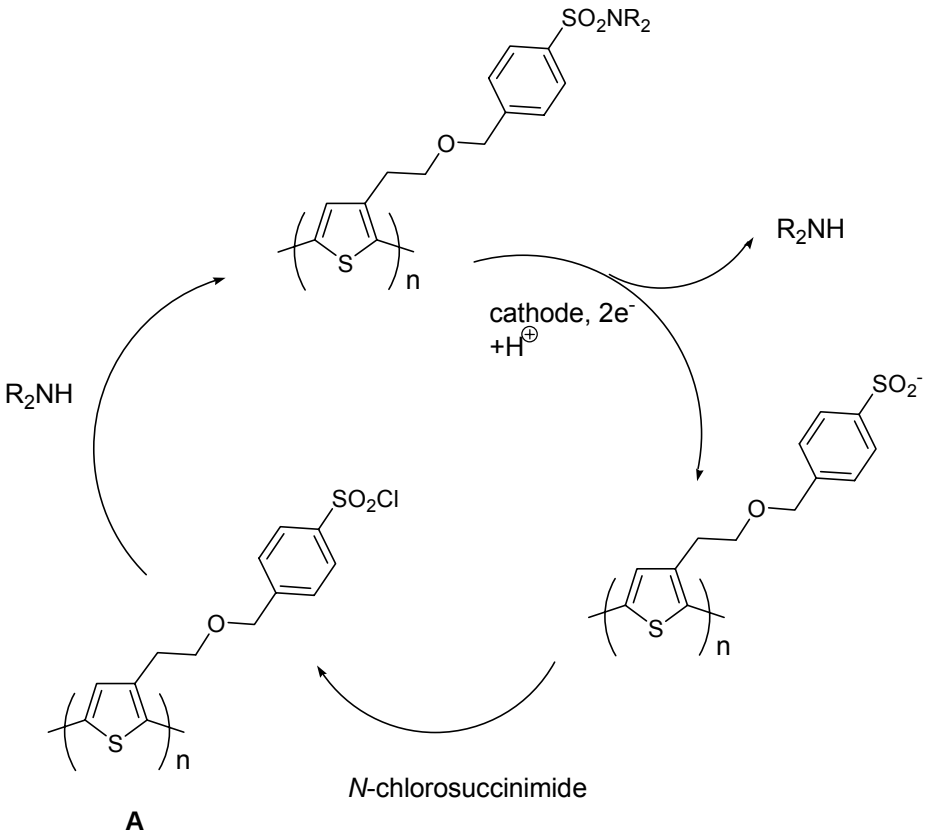


Figure 6. Cleavable and regenerable protecting group on a conducting support

After establishing the above methodology, Pilard *et al*. described the synthesis of a polyamine precursor at a modified cathode surface.[30] The conducting polymer support **A** then was subjected to three chemical modifications which demonstrated that the polythiophene matrix appears to be similar to that of the Merrifield resin (Figure 7). The target molecule **B** obtained in good yield was released from the solid support by cathodic S-N bond scission. No polythiophene denaturation was observed during the chemical process and the conclusion is that this polythiophene modified approach can be a good alternative to usual reactions implying polystyrene beads although this process is not applicable for preparative scale synthesis.

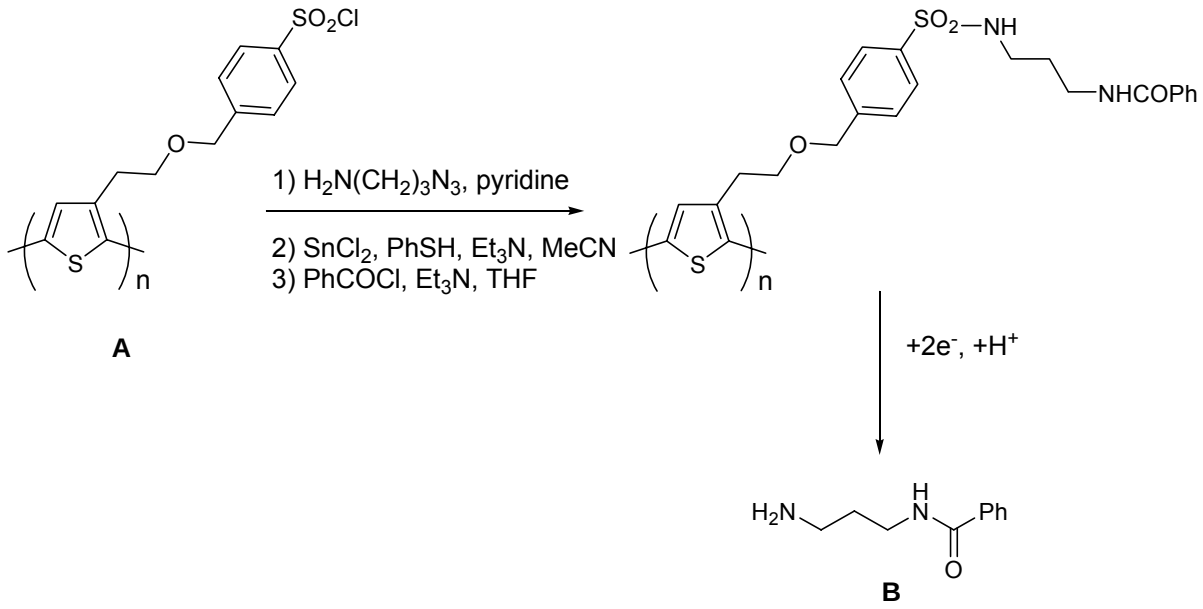
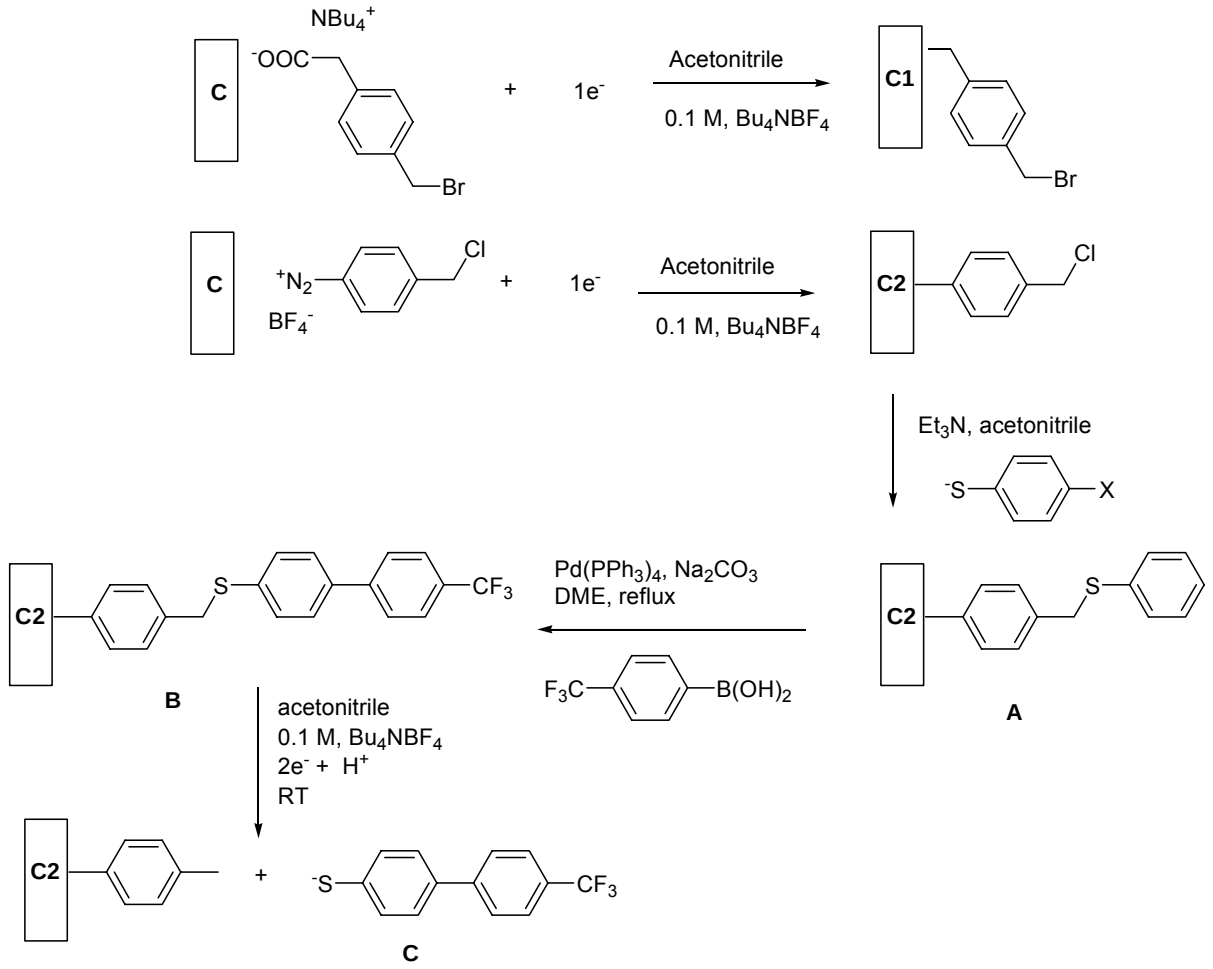


Figure 7. Synthesis of polyamine with electrochemically generated polythiophene support

Recently Pinson *et al.*[31] described the possibility to prepare carbon-based analogues of the Merrifield resin by electrochemical reduction of diazonium salts or oxidation of aryl acetates on high specific surface area carbon felts. These modified felts can undergo further reactions: nucleophilic substitution, Suzuki reaction, and finally reductive electrochemical cleavage, taking advantage of the conductivity of the carbon felt. This provides a simple example of the possible use of electrochemistry in combinatorial synthesis. These carbon felts can find a large variety of applications including ion exchange materials, catalysts, or supports for combinatorial chemistry. This support is robust and insensitive to the solvent and there is no swelling problem as with styrene resin and the conductivity of carbon allows the use of electrochemical reactions. The modified carbon felts **C1** and **C2** were prepared by attaching the 4-chloro- or bromomethylphenyl group to the carbon felt through electrochemical reduction of the tetrafluoroborate of 4-chloromethylbenzenediazonium or by electrochemical oxidation of 4-bromophenylacetate tetramethylammonium (Scheme 13). The halogen atom was substituted by an aromatic thiolate to give the sulfide **A**, which after Suzuki coupling produced **B** and finally the electrochemical cleavage of **B** gave the biphenyl **C** in 32% yield.



Scheme 13. Surface modified carbon felts for combinatorial purpose

For the nucleophilic substitution the yields were satisfactory, but the surface reactions were much slower than in solution. Each step for characterization of the modified carbon felts was done by elemental analysis, scanning electron microscopy and IR spectroscopy. This surface modified carbon electrodes needs further modification as the reactions are much slower and the yields by Suzuki rections are poor as well as analysis through elemental analysis and IR are not reliable enough. Although this process needs further optimization, these modified felts could be used for solid phase synthesis in near future.

Recently Yoshida *et al*.[32] described a “cation pool” method for direct oxidative carbon-carbon bond formation using low temperature electrolysis which is a new approach for conventional and combinatorial organic synthesis. This method involves generation and accumulation of highly reactive carbocations by low temperature electrolysis. In the next step, the carbocations thus produced are allowed to react with various nucleophiles which lead to combinatorial synthesis (Figure 8). Carbocations have been generally considered to be relatively unstable and transient species. But the “cation pool” method enables the easy

accumulation of carbocations in conventional reaction media such as dichloromethane. The electrochemical oxidation method for the generation of carbocations is carried out at low temperature such as -70°C in order to avoid decomposition of carbocations.

By choosing an appropriate solvent and a supporting electrolyte, however, the electrolysis at such low temperature can be accomplished to generate and accumulate carbocations. A divided cell having a sintered glass separator is used in order to avoid the electrochemical reduction of anodically generated carbocations. Tetrabutylammonium tetrafluoroborate is usually used as supporting electrolyte, and dichloromethane is suitable as a solvent because of its low viscosity at low temperature. TfOH (trifluoromethanesulfonic acid) is added in the cathodic chamber to facilitate the reduction of protons in the cathodic process.

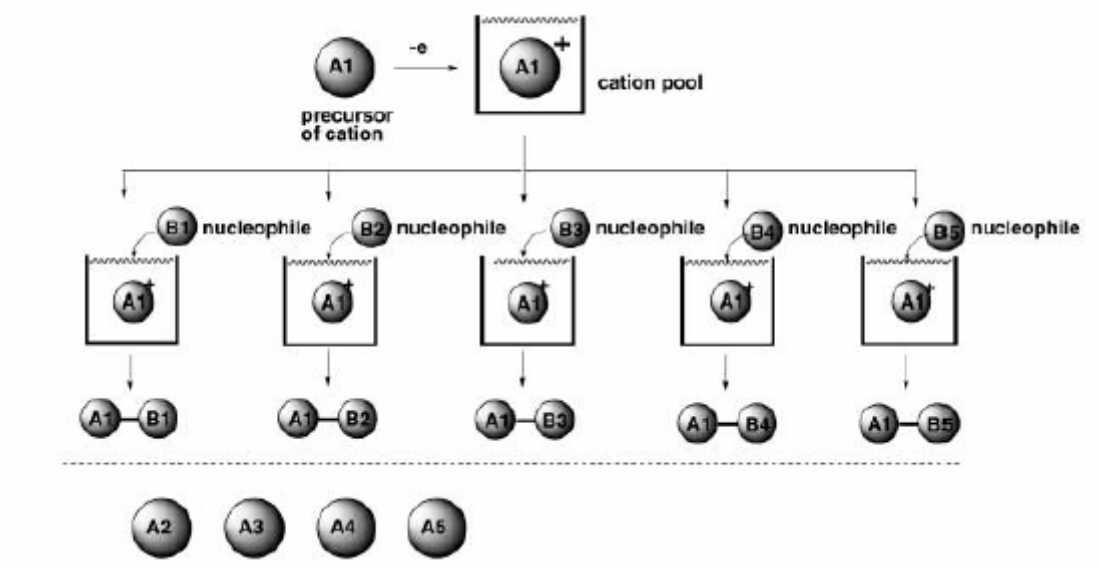
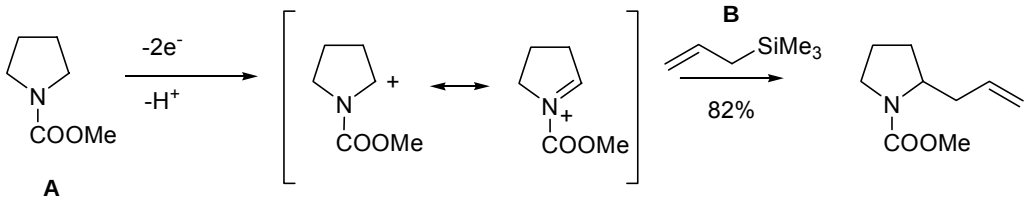


Figure 8. Parallel combinatorial synthesis based upon the “cation pool” method (picture taken from reference[32])

Yoshida and co-workers prepared several carbocation pools, for example for alkoxycarbenium ions, *N*-acyliminium ions and also they have described reduction of a cation pool where the desired products after reactions with several nucleophiles were obtained in good yields.[32]

For the carbamates, the cation pools were generated by low temperature electrolysis (-72°C) and their reactions with carbon nucleophiles such as allylsilanes, enol silyl ethers, and enol acetates gave the desired products in excellent yields (Scheme 14).



Scheme 14. The oxidative carbon-carbon bond formation of *N*-(Methoxycarbonyl)pyrrolidine (**A**) with allyltrimethylsilane (**B**)

The applicability of the “cation pool” method depends upon the stability of the cation that is accumulated. This problem can be overcome by the “cation flow” method. In the “cation flow” method, carbocations are generated in a microflow electrochemical system. Short residence times and efficient temperature control of the microflow system are advantageous for this process. In the “cation flow” system, a carbocation is generated continuously by low temperature electrolysis by using an electrochemical microflow reactor.[32] The generation of the cation can be monitored by an FTIR spectrometer. Thus, the cationic intermediate generated by low-temperature electrolysis is immediately transferred to a vessel, in which a nucleophilic reaction takes place to give the final coupling product. This is a useful method for the synthesis of nitrogen-containing organic molecules.

The “cation flow” method enables the continuous sequential combinatorial synthesis by simple flow switching as shown in Figure 9.[33] In the first step, the “cation flow” generated from **A1** is allowed to react with nucleophile **B1**. Then, the “cation flow” is allowed to react with nucleophile **B2**. In the third step, the “cation flow” is allowed to react with nucleophile **B3**. Then, the precursor of the cation is switched to **A2**, and the “cation flow” generated from **A2** is allowed to react with nucleophiles **B1**, **B2**, and **B3** sequentially. Then, the precursor of the cation is switched to **A3**, and the “cation flow” generated from **A3** is allowed to react with nucleophiles **B1**, **B2**, and **B3** sequentially. Although parallel syntheses enjoy versatile applications in combinatorial chemistry, the present continuous sequential method opens up a new intriguing aspect of combinatorial synthesis.

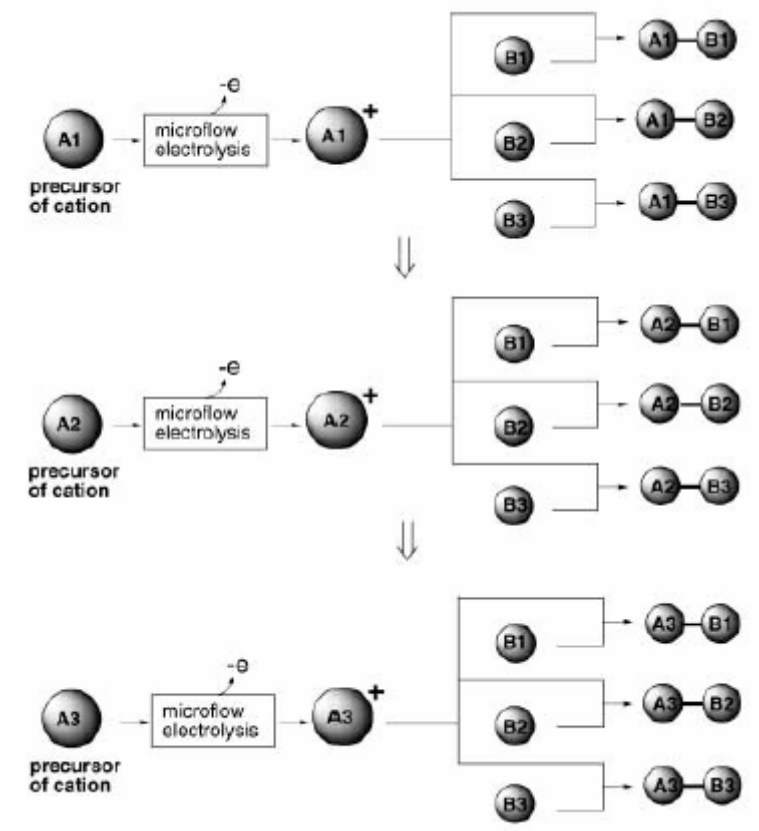
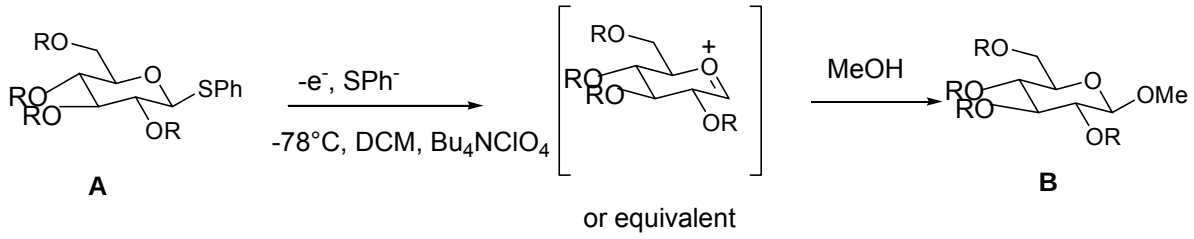


Figure 9. Continuous sequential combinatorial synthesis using the "cation flow" system (picture taken from reference[32])

Recently, a surprising and interesting reaction of these "cation pool" approaches was observed by Yoshida and co-workers where they found that alkoxycarbenium ions have been generated and accumulated as "cation pools" by the low-temperature electrochemical oxidation of α-phenylthioethers.[34] Although they were unsuccessful to prepare glycosyl cations, they have established a one-pot method for electrochemical glycosylation, which involves anodic oxidation of thioglycosides to generate glycosyl cations equivalents followed by their reactions with glycosyl acceptors. They have carried out an electrochemical oxidation of glycoside **A** in Bu_4NClO_4/CH_2Cl_2 at -78°C and subsequently added methanol which gave rise to the formation of **B** in 77% yield (one pot procedure, Scheme 15).

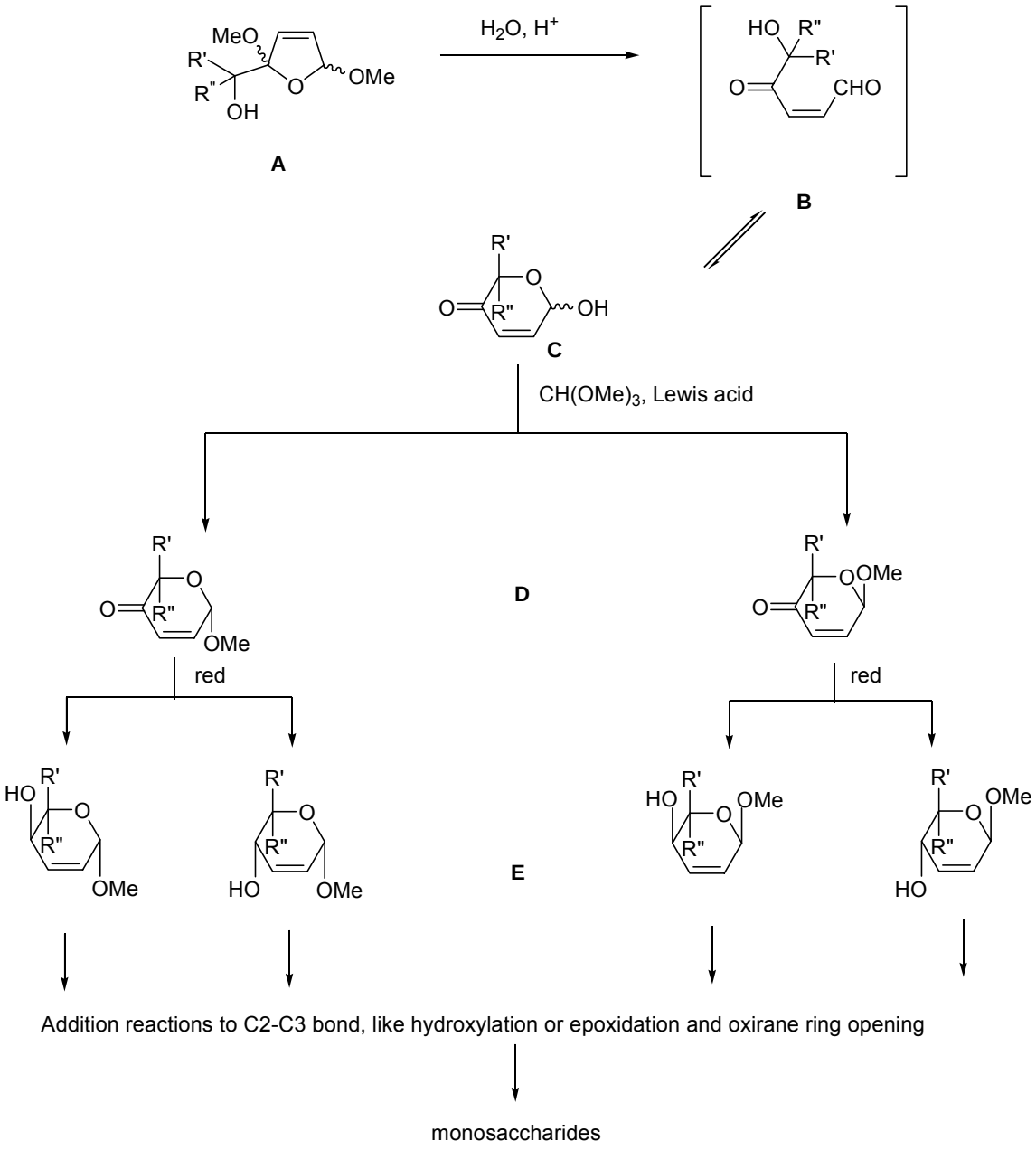


Scheme 15. Electrochemical glycosylation reaction

The cation pool and cation flow methods described above open up a new aspect of chemistry based on carbocations which have been considered to be difficult to achieve in normal reaction media. In summary, combinatorial chemistry and parallel synthesis can benefit greatly by electrochemistry which includes unusual sub-classes of small molecules available by electrosynthesis and providing mild electrochemical alternatives for chemical transformations. Electrochemical reactions are a powerful tool for transforming and assembling organic molecules. Therefore the applications of electroorganic synthesis have been extended at least for solution phase techniques applied to parallel synthesis and combinatorial chemistry. Electrosynthesis remains an area of tremendous potential whose definition has not been established yet but may become a valuable tool in the combinatorial field in the near future.

3.1.5 Achmatowicz rearrangement

In 1971 Achmatowicz and co-workers described the transformation of furans to sugar derivatives, i.e. the route of obtaining monosaccharides from simple furans compounds.[35] The principle of this method is presented in Scheme 16. A mixture of *cis* and *trans* isomers of the 2,5-dimethoxy-2,5-dihydrofuryl carbinol derivative (**A**) was hydrolysed by mild acid to cleave the acetal bonds and the resulting dicarbonyl compound (**B**, not isolated) underwent immediate cyclization to 2,3-dideoxy-DL-alk-2-enopyran-4-ulose (**C**) (mixture of anomers, if R' ≠ R"). Compound **C** was methylated with methyl orthoformate in the presence of Lewis acid catalyst, yielding methyl glycosides (**D**). The reduction of the ketone group in compound **D** with metal hydrides led to sterioisomeric methyl 2,3-dideoxy-DL-alk-2-enopyranosides (**E**). Individual steps of the synthesis showed high or satisfactory yields.



Scheme 16. Achmatowicz rearrangement

This oxidative rearrangement of furyl carbinols to pyranones is now in the literature known as Achmatowicz rearrangement. Two aspects of this synthesis (Scheme 16) are noteworthy. Firstly, compounds with the pyranose ring were formed at an early stage in the synthesis, and all steps leading to asymmetric carbon atoms were performed at this ring. Since the stereochemistries of six membered rings are well known, the predictions of the reaction course, as well as the determination of the configuration and conformation of the resulting products are relatively simple. Secondly, the synthesis has the advantage that no more than two stereoisomeric compounds are formed at any stage; usually these can be separated by chromatography. Consequently, the final products can be obtained as pure diastereoisomers.

This method for total synthesis of monosaccharides seems to provide a convenient route for a number of classes of sugar compounds.

Different groups have applied this method for the synthesis of diastereomeric monosaccharide mimetics. Glycosides are very interesting compounds for further diversification, by which different biologically active compounds can be prepared. The hydroxyl-3-pyranones **R** are very interesting structures with differentiated functionality to allow the facile introduction of other functional groups and/or alkyl residues by reaction with the appropriate nucleophiles and electrophiles (Figure 10).

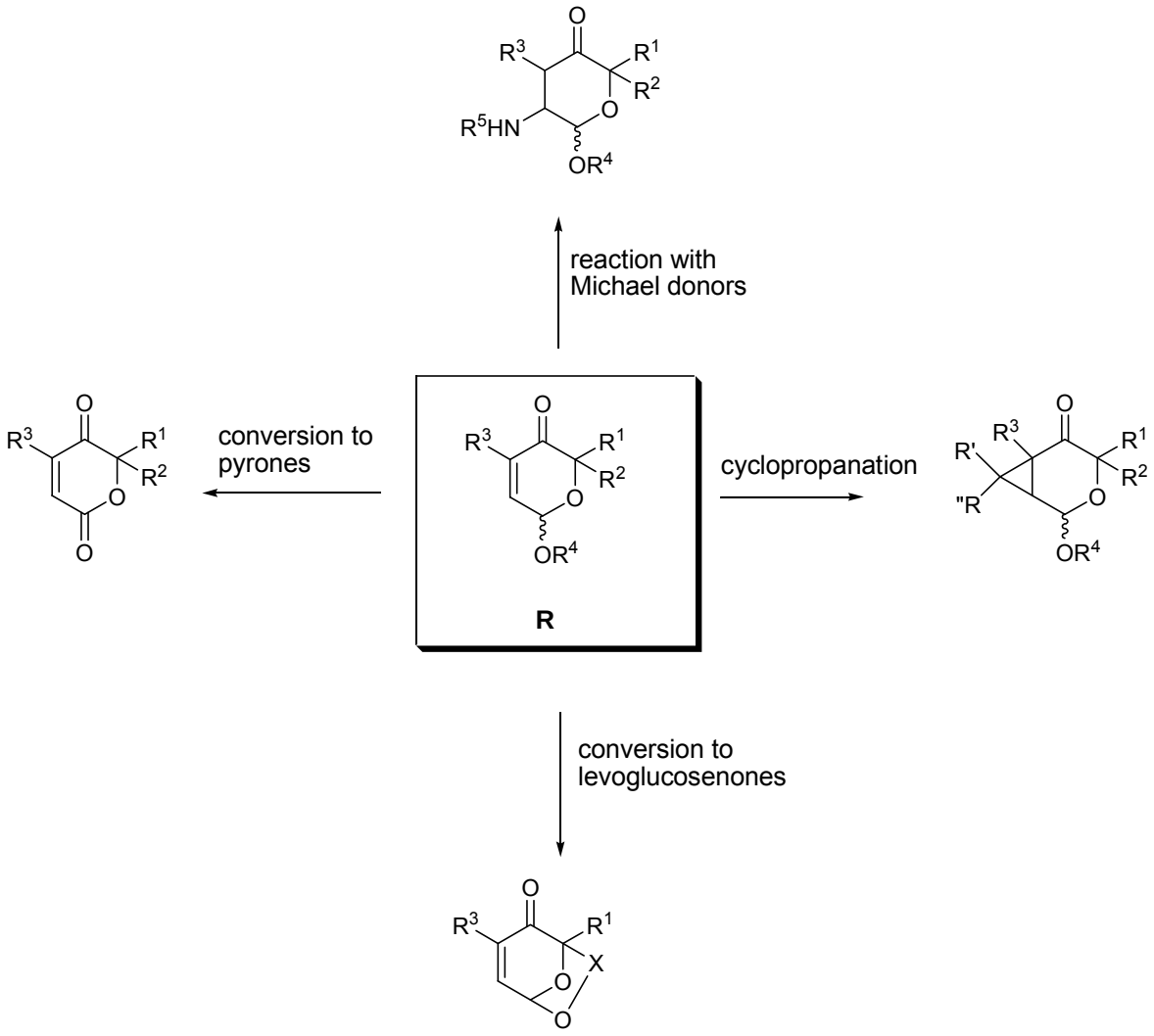
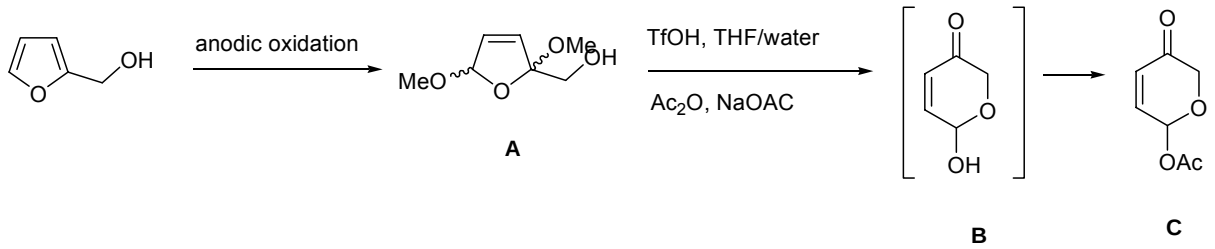


Figure 10. Diversification of Achmatowicz rearrangement product

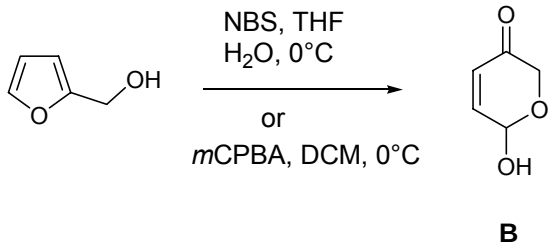
An alternation of the above method involves addition of catalytic amount of trifluoromethane sulfonic acid to the furan intermediate **A**, (Scheme 17) described by Weeks *et al*.[36] This alternation removes the need for the laborius aqueous extraction as the reaction is carried out in wet THF. A further advantage of this route is that the highly unstable hydroxy pyranone

B is never isolated as the reaction is carried out in the presence of acetic anhydride and sodium acetate, which yields the required acetoxy pyranone **C** in 70% yield from furyl alcohol (Scheme 17).



Scheme 17. Oxidative rearrangement of furyl carbinols to acetoxy pyranones via trifluoromethane sulfonic acid

Perron *et al*. described oxidative rearrangement methods for the formation of hydroxy pyranones derivatives **B** directly from furyl carbinols by using *N*-bromosuccinimide in the presence of water at 0°C.[37] Although the yield of the reaction was poor in comparison to the two acid catalyzed reactions, the NBS method is simple and it requires only one step (Scheme 18). Alternatively, Laliberte *et al.*[38] described the preparation of the hydroxy pyranone **B** via a *m*CPBA mediated ring expansion from furyl carbinols, a by-product from this reaction is benzoic acid, the removal of which is problemetic.

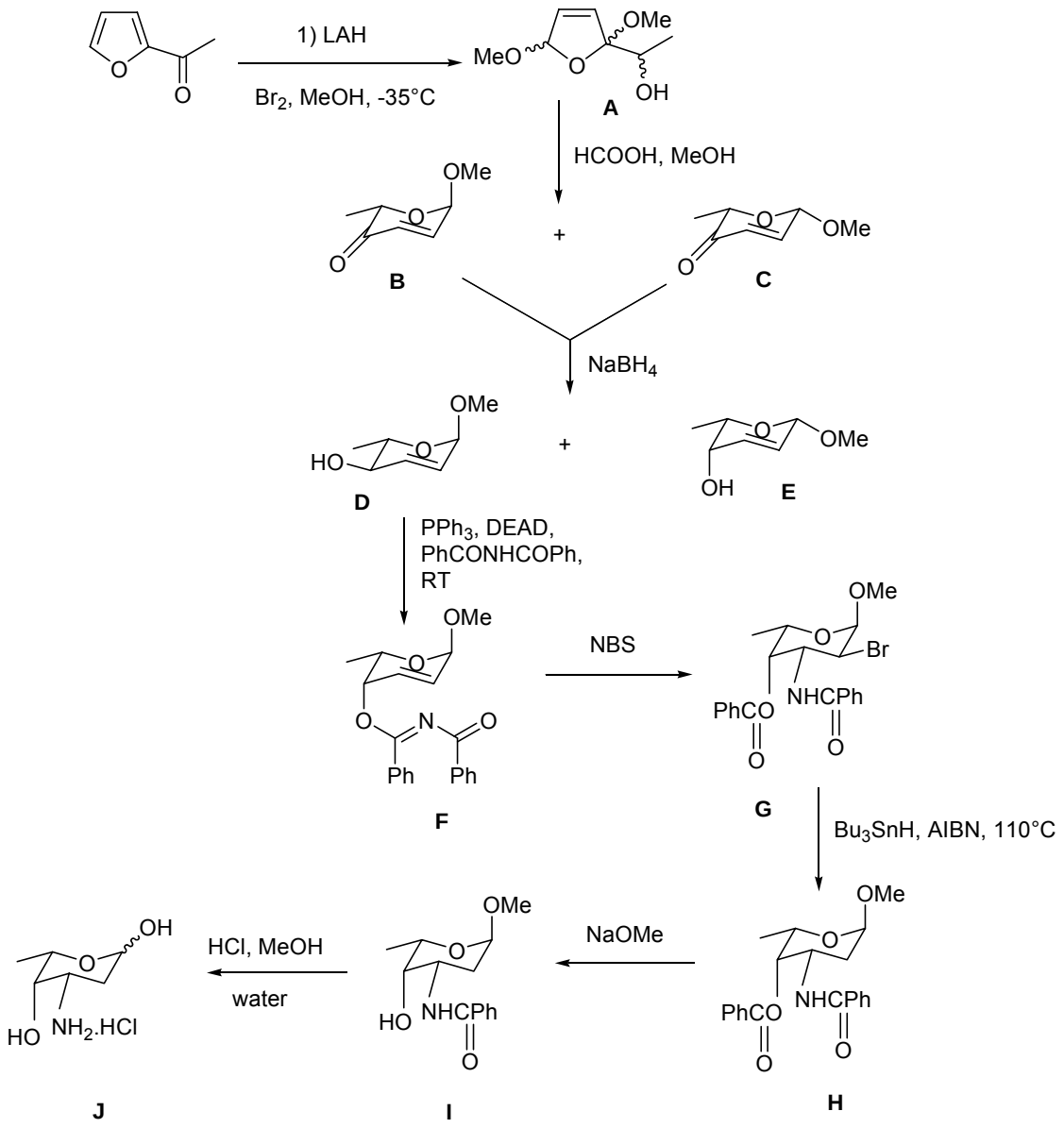


Scheme 18. Oxidative rearrangement of furyl carbinols to hydroxy pyranone **B**

This polymorphic structure **B** is very interesting for the medicinal chemists due to its pharmacological activity. For many natural product syntheses analogues of **B** have been used as starting materials.

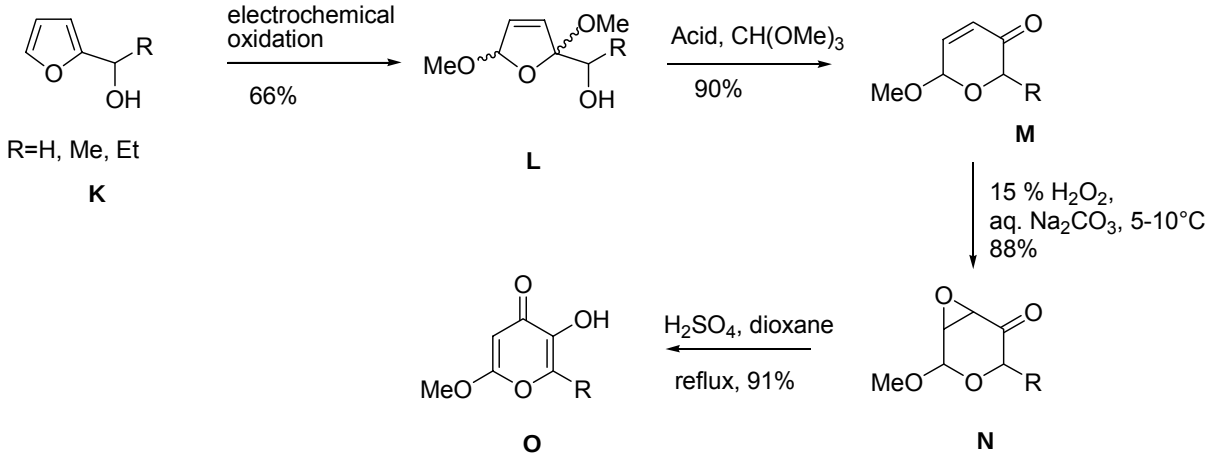
Sammes *et al.* described the synthesis of L-daunosamine and related amino sugars via Achmatowicz rearrangement.[39] L-daunosamine is the sugar component of the anthracycline antibiotics daunomycin and adriamycin, which also exhibits a broad spectrum of activity on solid tumours and soft-tissue sarcomas. According to them reduction of 2-acetylfuran followed by methoxylation gave the corresponding dimethoxydihydrofuran **A**. **A** was treated

with acid under strictly anhydrous conditions to produce pyranuloses **B** and **C** in a 3:1 (α:β) anomer ratio and an overall yield of 83%, which were separated by column chromatography. The major pyranulose product **B** was reduced using sodium borohydride to give the epimeric allylic alcohols **D** and **E** in a 13:1 ratio. They have converted the alcohol **D** in to the imidate **F** under modified Mitsunobu reaction conditions in 86% yield. The imidate **F** was then converted to the bromo amide ester **G** in 91% yield by treatment with 3 equiv of NBS in chloroform-ethanol. The bromo amide ester **G** was treated with Bu_3SnH to give the amide ester **H** in 96% yield. Base solvolysis of the amide ester **H** gave the amido alcohol **I** in 94% yield. Acid hydrolysis of the amide **I** gave DL-daunosamine hydrochloride (**J**) in 45% yield (Scheme 19).



Scheme 19. Synthesis of daunosamine via Achmatowicz rearrangement

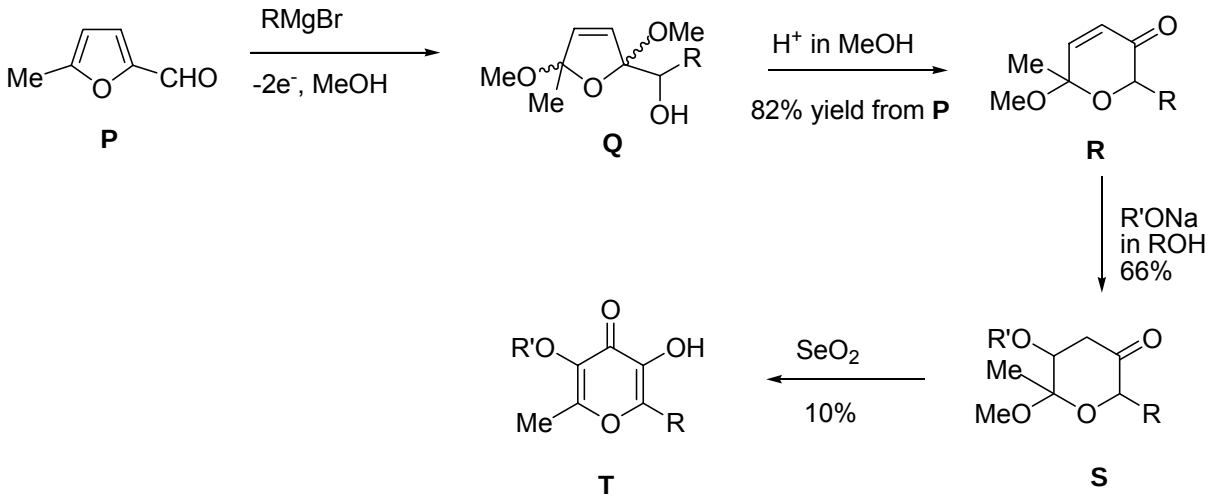
Torii *et al*.[40] described a convenient way for the preparation of maltol (**O**) and its related compounds (Scheme 20) which have been of great interest as the flavoring additives in foods.[41] They described the formation of (**O**) via Achmatowicz rearrangement starting form furfuryl alcohol **K**.



Scheme 20. Preparation of maltol via Achmatowicz rearrangement

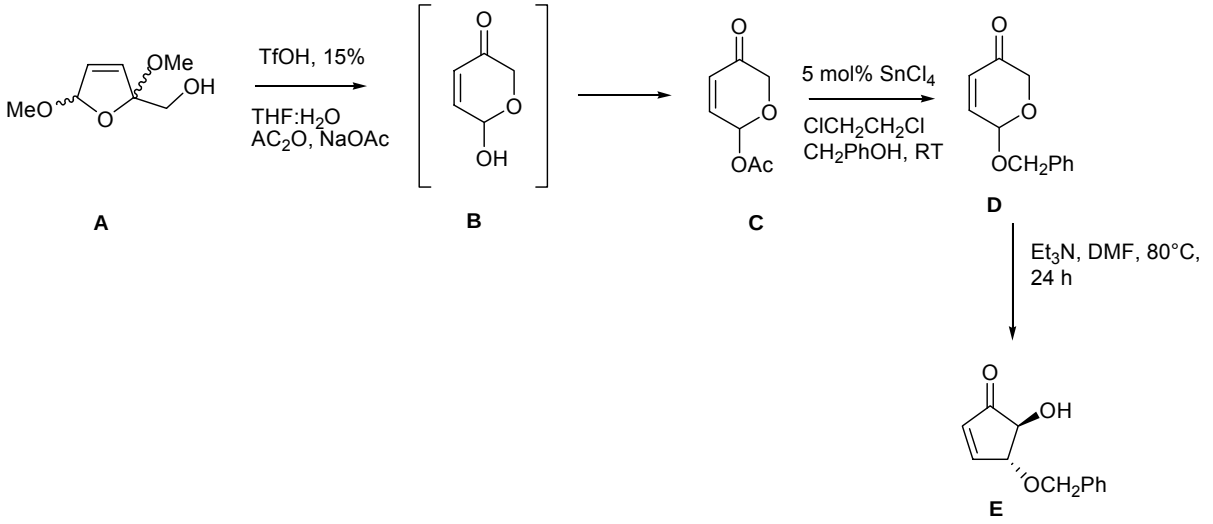
The preparation of **L** was carried out by electrochemical oxidation and the resulting dimethoxylated compound **L** was treated with acid. Subsequent refluxing with methyl orthoformate gave the acetal **M** in 90% yield. Addition of 2 equivalents of 15% H_2O_2 to a two-phase solution containing **M** in diethyl ether and aqueous 5% sodium carbonate at 5-10°C provided the epoxy ketone **N** in 88% yield. Heating of **N** in dioxane in presence of H_2SO_4 afforded maltol (**O**) in 91% yield.

Matshumura *et al*.[42] described a facile synthesis of allixin and its related compounds via Achmatowicz rearrangement. Allixin (**T**), 3-hydroxy-5-methoxy-6-methyl-2-pentyl-4*H*-pyran-4-one, belongs to the class of phytoalexins. Their route is characterized by its low number of steps (5 steps) (Scheme 21). Although the yields at the last step were not excellent, this method makes it possible to prepare a variety of compounds.



Scheme 21. Preparation of allixin via Achmatowicz rearrangement

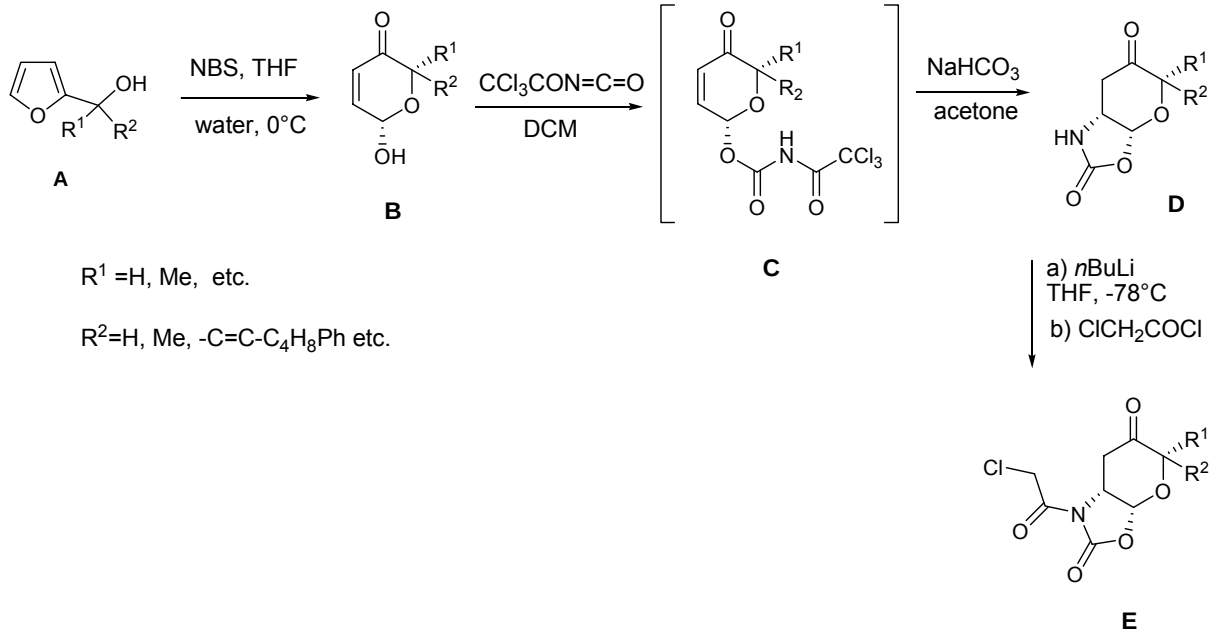
Caddick *et al*. described a facile synthesis of functionalized cyclopentenones via Achmatowicz rearrangement (Scheme 22).[43] Acetate **C** (prepared by a method already described in Scheme 17) was converted to its corresponding benzyl derivative **D** in 82% yield by using catalytic Lewis acid conditions. The isomerisation of pyranone **D** to the corresponding cyclepentenone **E** was done in presence of 5 equiv of triethylamine in hot DMF over a 24 h period which led to **E** in 78% yield.



Scheme 22. Synthesis of functionalized cyclopentenones via Achmatowicz rearrangement

Although this method for the isomerisation of C-2 substituted pyranone has some limitations the potential of the resulting cyclopentenones **E** in natural product synthesis has been demonstrated.

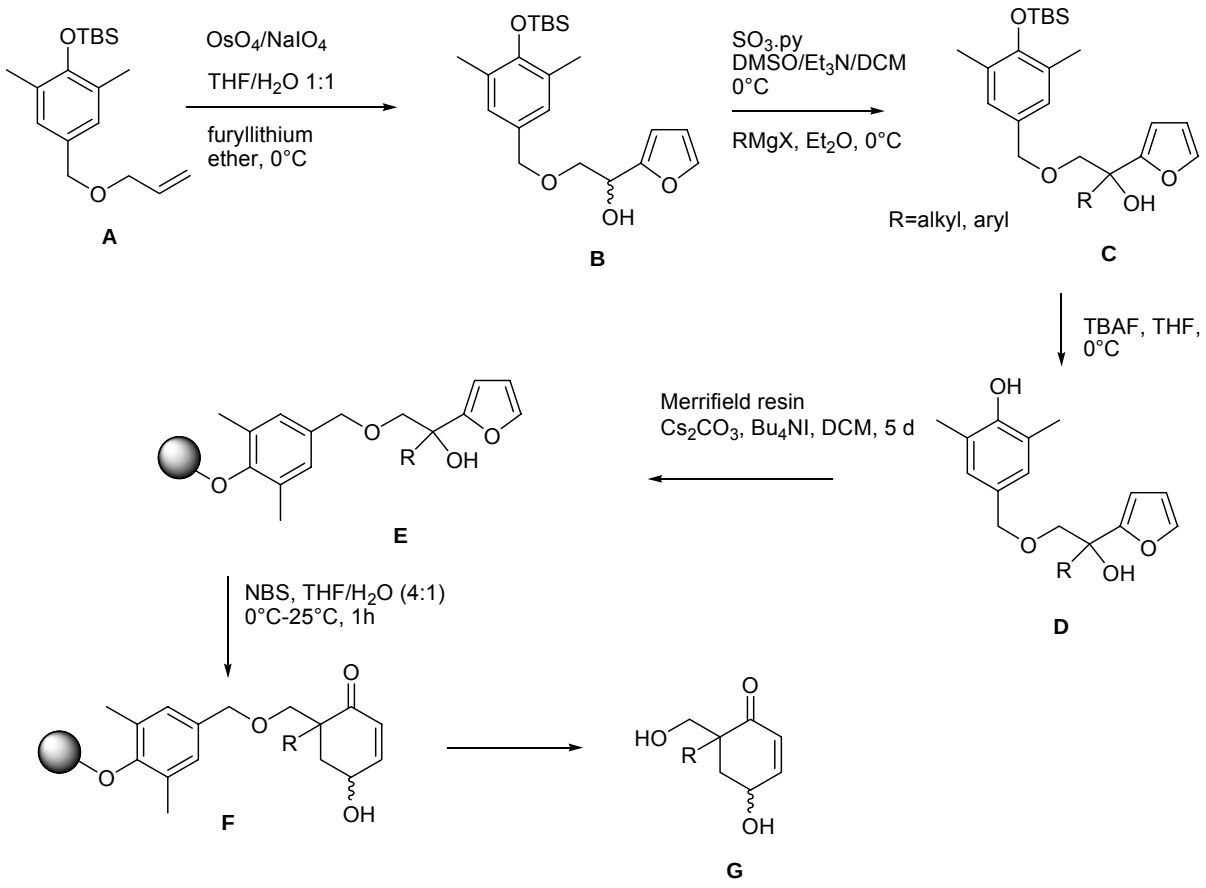
Perron-Sierra *et al*.[44] described the synthesis of the novel bicyclic oxazolone derivatives **E** via Achmatowicz rearrangement which are known as anti-angiogenic agents. According to them the oxidation-rearrangement of the 2-furyl carbinol (**A**) was done with *N*-bromosuccinimide in aqueous media to get the thermodynamically favored isomer **B** almost exclusively. The carbamoylation of pyranone **B** was performed with trichloroacetylisocyanate to produce the corresponding carbamoylated intermediate **C** which was cyclized upon basic treatment to give the bicyclic ring system **D** as a mixture of isomers (16:1). This bicyclic system was then acetylated to afford compound **E** in excellent yields (80-100%) (Scheme 23). These compounds demonstrated potent antiangiogenic activity.



Scheme 23. Synthesis of oxazolone derivatives via Achmatowicz rearrangement

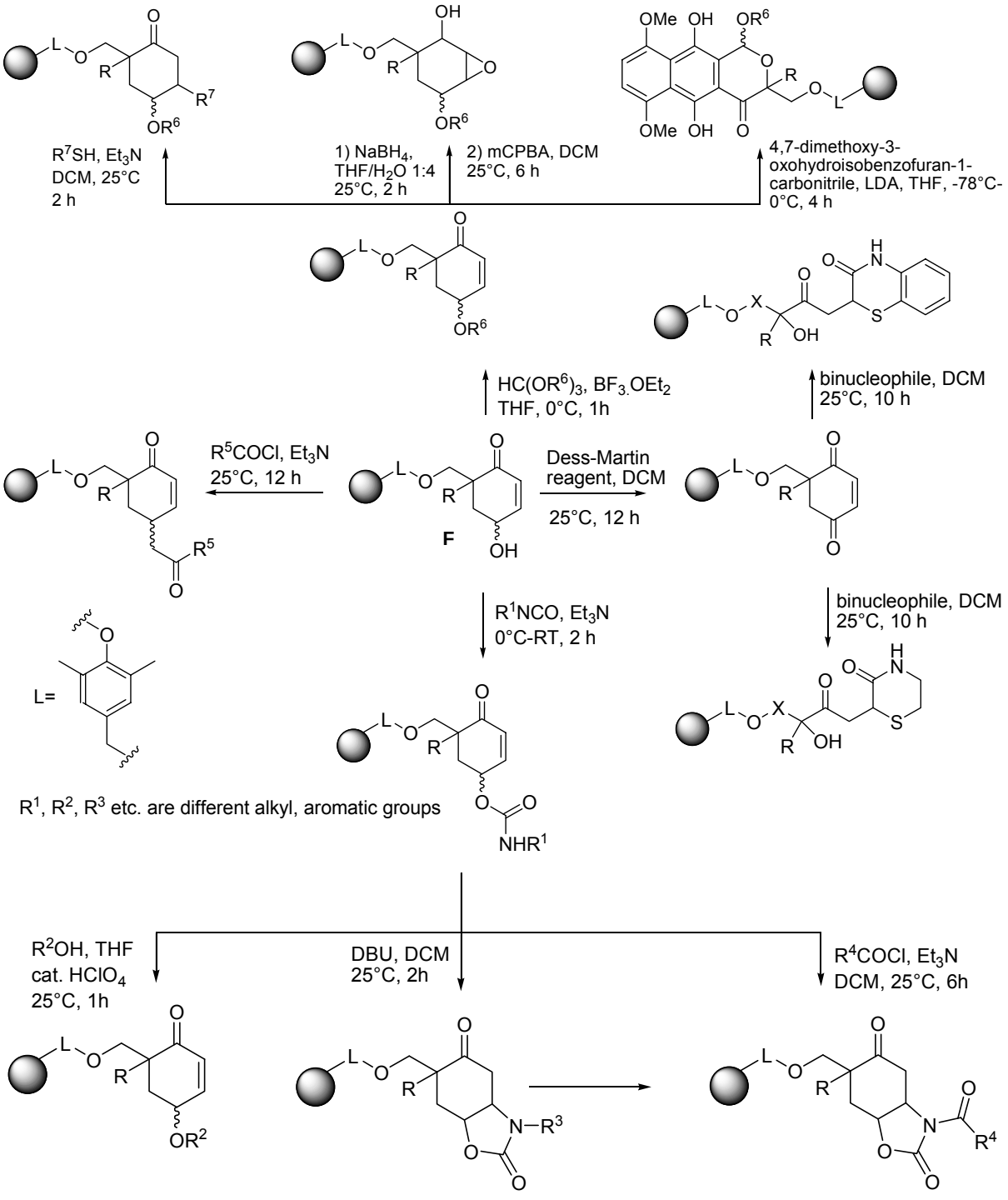
Diversity oriented synthesis (DOS) aims to achieve the efficient synthesis of small molecules having many molecular skeletons starting from a common core structure. Recently Couladouros *et al*. described a combinatorial synthesis of Achmatowicz rearrangement product **F** and its derivatives on solid phase.[45] For the effective use of this molecule in combinatorial chemistry they have identified a suitable linker to attach the pyranone core to the resin (Scheme 24). They have used a oxidatively cleavable aromatic ether which can tolerate basic and mildly acidic or oxidative conditions and can be cleaved rapidly upon treatment with DDQ or TFA. For the loading procedure the respective furyl alcohol was coupled with the linker and then loaded on Merrifield resin by Cs_2CO_3. Thus furyl alcohol **B** was prepared by conversion of allyl ether **A** to the corresponding aldehyde, followed by addition of furyl lithium. This alcohol, after oxidation and subsequent derivatization with Grignard reagents, was transformed into tertiary alcohol **C**, which after desilylation, was

loaded on the resin to afford supported furyl alcohol **E**, which was oxidized to the corresponding *2H*-pyran-3(*6H*)-ones **F** in high yields. Then **F** was cleaved efficiently from the resin to form **G** in high yields (65-95%).



Scheme 24. Achmatowicz rearrangement on solid phase

For the practical demonstration of the use of **F** as key intermediates with great potential for diversification they carried out a significant number of modifications and transformations. With these transformations they produced a library of carbamates, oxazolediones, lactones, heterocycles such as thiazinones, benzothiazinones, diazepinones, etc. These compounds are known to show anticoccidial, antimicrobial, antifungal activities. Some other reactions like $NaBH_4$ reduction, epoxide formation etc. were used by them to prepare other interesting scaffolds (Scheme 25).

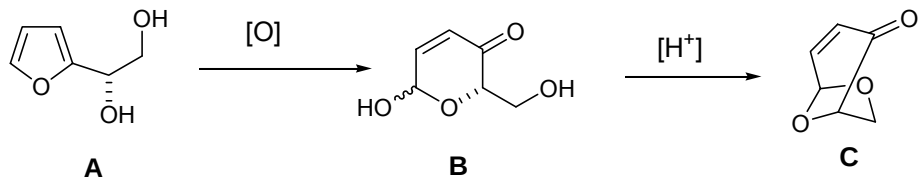


Scheme 25. Diversification of Achmatowicz rearrangement product

The above scheme, nicely demonstrates that the Achmatowicz rearranged product **F** serves as a core structure for a directed library leading to well defined classes of compounds through structural modifications on solid phase.

Schreiber *et al*. described a diversity oriented synthesis of a different Achmatowicz rearranged product.[46] Their aim was to transform the relatively simple substrate **A** into a

more complex product **C** (Scheme 26) which exhibits a bicyclic ketal skeleton with potential for further diversification.



Scheme 26. Achmatowicz reaction in the context of diversity-oriented synthesis

Key to their approach was the transformation of substrates having so called σ-elements in starting materials to furnish products having different skeletons using common reaction conditions.[45] This logic was used to develop the synthetic plan shown in Figure 11, where they took the common furaldehyde substrate **X**, which is transformed into three different furan products (**M**, **N**, **O**) having three different σ-elements. A common set of oxidative and acidic reaction conditions is used to transform substrates **M**, **N**, **O** into three products having distinct molecular skeleton, a bicyclic ketal **R**, a cyclic hemiketal **S** and a *trans*-enedione **T**.

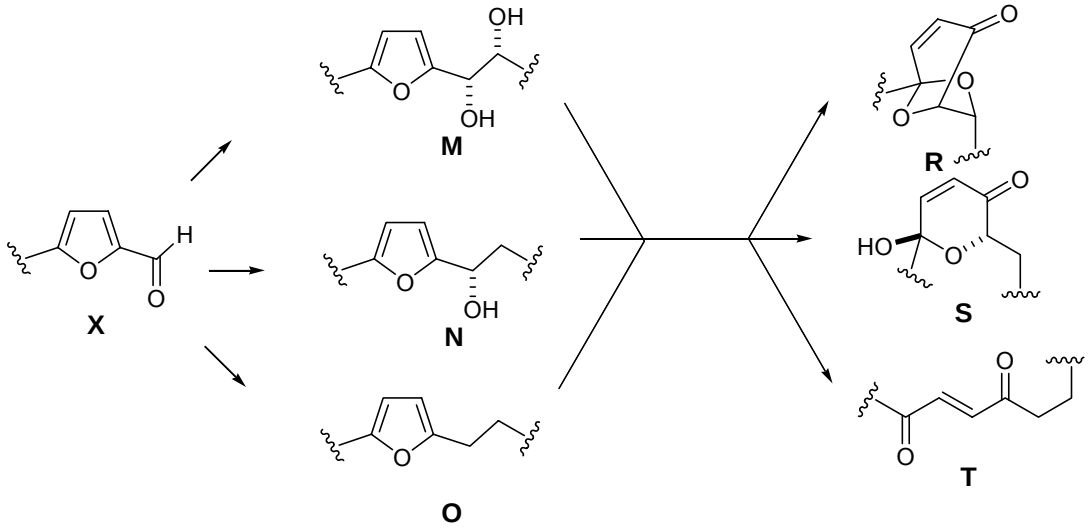
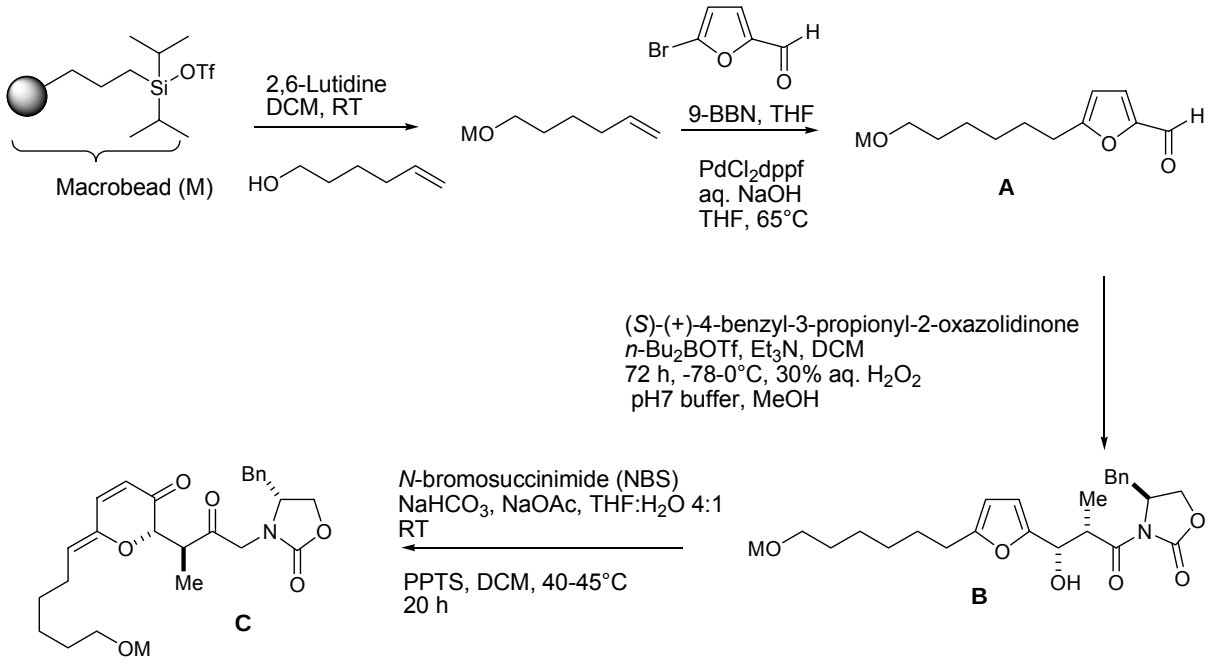


Figure 11. Synthetic plan for a skeletal diversity-generating process

To test the feasibility of this plan they performed solid phase syntheses of three substrates (**M**, **N**, **O**). A two step solid phase process was carried out to produce model compound **A** (Scheme 27). Commercially available 5-hexen-1-ol was loaded onto 500-560 *μ*m polystyrene-based "macrobeads" using 2,6-lutidine in DCM at room temperature. Hydroboration of the terminal olefin with 9-BBN followed by $PdCl_2$(dppf)-mediated Suzuki coupling with commercially available 5-bromo-2-furaldehyde led to the desired macrobead-bound furaldehyde **A** with high loading (0.679 mmol/g) and purity (>85% by LCMS). Evans

aldol reaction with **A** gave α-hydroxy furan **B** in 95% yield, which underwent an initial oxidative ring expansion in presence of NBS, $NaHCO_3$ and NaOAc in THF:water 4:1 at room temperature to the cyclic hemiketal followed by an acid-mediated dehydration to yield the alkylidene-pyran-3-one **C** (86% purity) as a single geometric isomer.



Scheme 27. Diastereoselective Achmatowicz rearrangement on solid phase

They have expanded the above approach to generate skeletal diversity combinatorially with different substituted furan molecules to produce a library of **C**.

From the work described above it can be concluded that pyranone structures, achieved by Achmatowicz rearrangement, present an unique molecular scaffold which can be subjected to further diversification leading to many classes of biologically interesting molecules.

3.2 Parallel multistep synthesis of *N*-substituted pyrrole derivatives using dendritic polyglycerol as a high-loading support

3.2.1 Indroduction

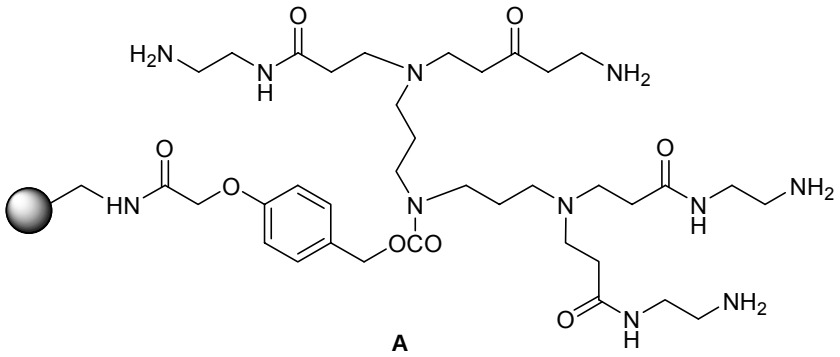
Over the last decade polymeric supports have been recognized as a useful tool in organic synthesis. Solid phase synthesis on modified polystyrene microbeads, which was originally introduced by Merrifield, still remains the major focus in this area. Although highly successful, solid phase synthesis exhibits a number of problems, for example the limited swelling behavior of the polymeric beads in many organic solvents, i.e. protic solvents, the heterogeneous reaction conditions and the low concentration of functional groups (typically $\leq$1.5 mmol substrate per gram polymeric support) for which some of these polymeric supports are of limited use for preparative organic synthesis and catalysis. Therefore, high loading polymeric supports which allow simple characterization of the polymer-bound compounds by standard analytical techniques such as NMR, IR, UV, and SEC would be highly desirable for organic chemists. Fast and convenient characterization on the polymeric support is an important precondition for multistep reactions. Dendritic polymers offer these advantages: similar to solid-phase supports, soluble polymeric supports can be separated from low molecular weight compounds after each reaction step by, for example, ultrafiltration, dialysis, preparative size exclusion chromatography (SEC), or precipitation. Although many multistep organic syntheses have been performed with this dendritic supports, electrochemical reactions have not been investigated yet. The mild approach of electrochemical reactions which often guarantee high selectivity encouraged us to apply this method on dendritic supports for the parallel multistep synthesis of *N*-substituted pyrroles via indirect anodic oxidation of furan derivatives.

3.2.2 Dendrimers and hyperbranched soluble polymers as high loading supports and their application in organic synthesis

There are two major classes of polymeric supports used in combinatorial chemistry: solid phase polymeric supports and soluble polymeric supports, which are further classified by their polymer topology. The conventional solid phase supports have some limitations due to the heterogeneous nature of reactions and the low loading of the functional groups. In addition, organic reactions on polystyrene microbeads require the use of expensive linker system. In order to obtain reasonable quantities of final products, substantial substrate loadings (>1.5 mmol/g) are required, which are difficult to achieve for most linker systems on polystyrene microbeads.[47] Therefore, the scale-up of solid-phase reactions usually requires

additional solution-phase synthesis in order to obtain mmol quantities of compound. Another problem of polystyrene macro beads is the poor swelling in highly polar solvents. In many cases, modification of the unpolar surface with PEG chains has been done to increase the solution phase character of the reaction[48] as a result the loading capacity of the resulted grafted resin, such as TentaGel decreases.[49]

In order to increase the loading capacity of polystyrene microbeads dendritic groups can be attached to every functional group. Such hybrids have been reported by several groups.[50] **A** is such a hybrid polymer (Figure 12).



A

loading=2.8 mmol/g

Figure 12. Polystyrene dendrimer hybrid resin

However, the progress in combinatorial synthesis requires new high-loading resins. Soluble polymeric supports have been proposed since the early seventities as an alternative to solid phase supports.[51] The advantages of soluble polymeric supports are their high reactivity in solution due to the homogeneous conditions and their potential for high loading capacities. Soluble polymers can be used orthogonally in one chemical reaction vessel-with solid-phase supports and can be separated easily.[52]

The most widely used soluble polymeric support in organic synthesis is monomethylated polyethylene glycol (typically MPEG 5000), which is a linear polymer, soluble in many organic solvents and easily precipitated in non polar solvents.[49] But it contains only one reactive functionality and hence exhibits a poor loading capacity. However it is chemically stable and has good reactivity in homogeneous phase. Figure 13 is representing such a linear soluble polymeric support, which has been used for the synthesis of β-lactams.[53]

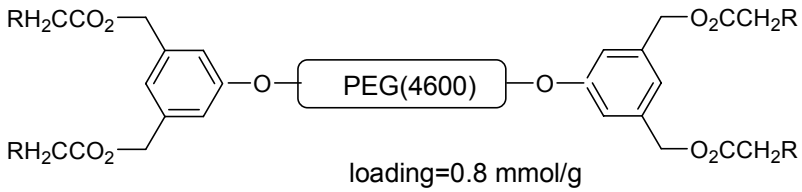


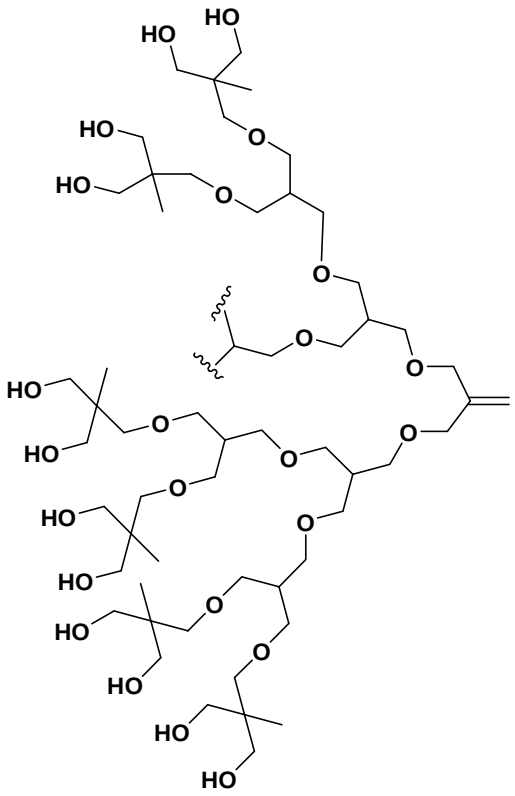
Figure 13. Linear PEG-supports with functional groups only at the terminal positions

In general, linear polymeric supports have potentially high loading capacities, however, their polymer characteristics, such as solubility and chemical stability as well as their material properties in some cases are problematic for broad application in organic synthesis. The disadvantages of linear polymers i.e. limited solubility in many organic solvents, gel formation, and problematic thermal behavior in some cases can be overcome by the use of branched polymeric structure, which has some tree like branching and they are called perfect dendrimers.[54] These macromolecules are soluble in many organc solvents and possess a maximum capacity of functional groups in their periphery. Despite their high price and low chemical stability polyamidoamine (a perfect dendrimer) has been used as a high loading support for the synthesis of indoles by Kim and co-workers.[55]

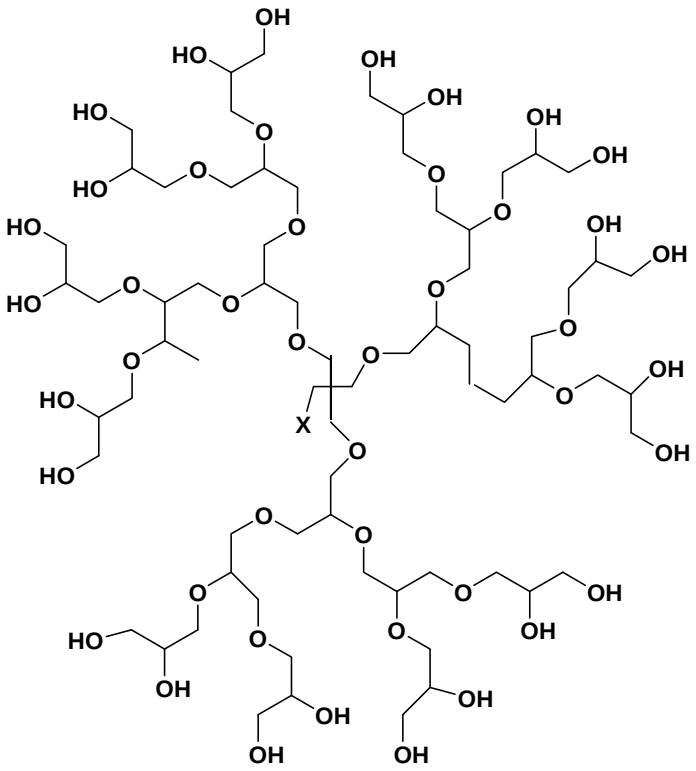
In contrast to dendrimers, hyperbranched polymers are easily available in one reaction step. They contain dendritic, linear and terminal monomer units in their skeleton and hence can be considered as intermediates between linear polymers (degree of branching DB: 0%) and dendrimers (DB: 100%) with an approximate DB between 40 and 60%.[56] The potential loading capacity of these hyperbranched polymers is similarly high as for dendrimers (5 - 14 mmol/g) and some hyperbranched polymers are even commercially available.[57] However, the use of these commercial materials as supports for organic synthesis, is limited due to the chemical stability of the respective polymer backbone (e.g. polyamines, polyesters) and the relatively broad molecular weight distributions (typically >2).

An interesting class of high-loading polymeric supports is dendritic aliphatic polyethers as highly branched analogues of PEG. Aliphatic polyether dendrimers containing terminal 1,3-diol **A** and 1,2-diol units **B** have recently been prepared by Haag *et al*. in a seven- and six-step synthesis, respectively (Figure 14).[58] They are chemically stable, soluble in many organic solvents, show good accessibility and reactivity of the functional groups and possess a high concentration of OH-groups. However, the general drawback of any dendrimer is the tedious multistep preparation of higher generations (molecular weight exceeding 1500 g/mol), which is the lower limit for dialysis and ultrafiltration procedures. For this reason, perfectly branched dendrimers have mainly been used as supports for valuable transition metal catalysts with ligands attached to the core.[59] Another problem of high-generation

dendrimers appears to be steric hindrance and site-site interaction at the outer functional shell.



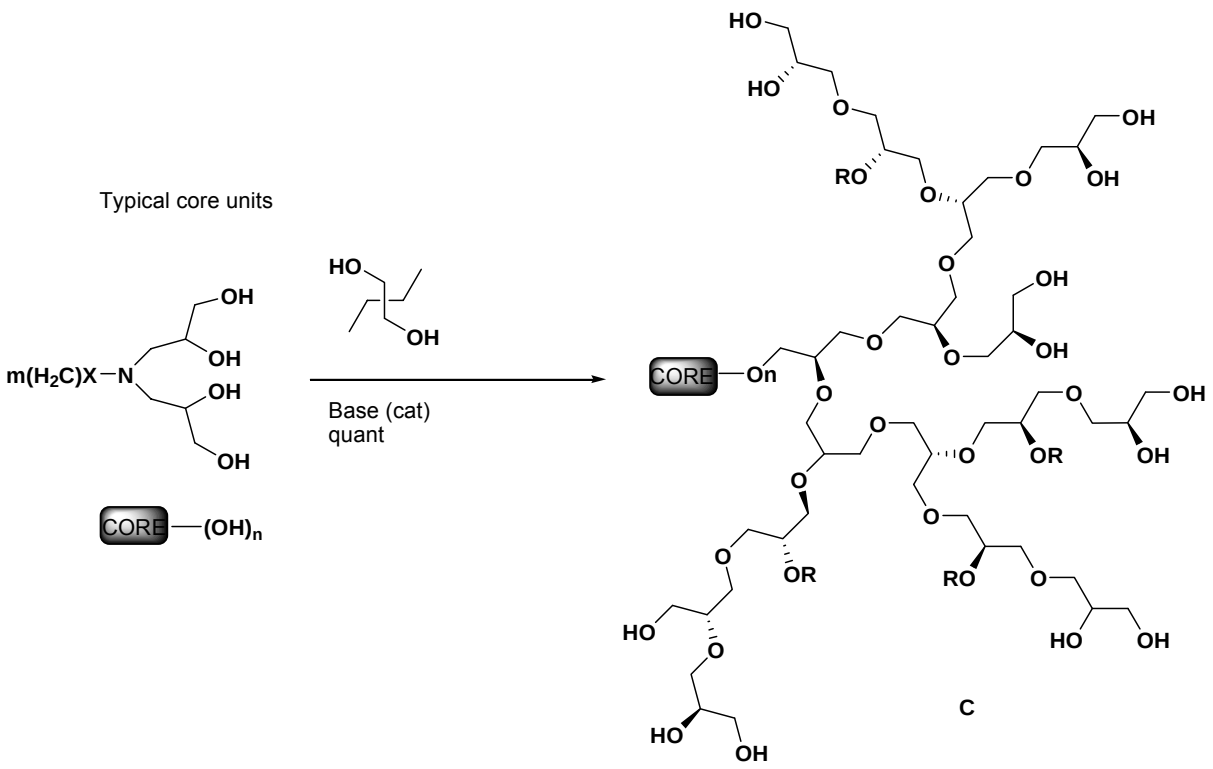
A loading = 5.6 mmol diol g^{-1}



B loading = 7.1 mmol/g

Figure 14. Dendritic supports based on aliphatic polyether (X=core functionality)

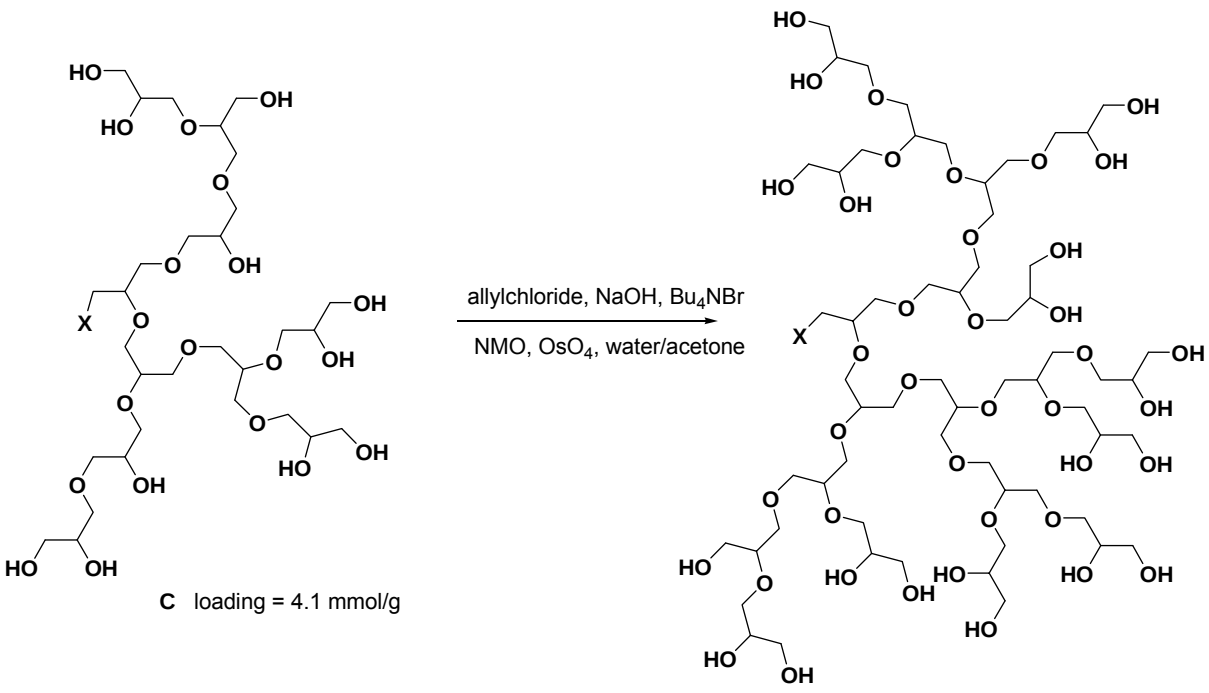
Recently, Haag and co-workers[60] developed the synthesis of well-defined hyperbranched polyglycerol **C**, by using both racemic and enantiomerically pure glycidol monomers (Scheme 28). These polyether polyols are conveniently prepared in a one-step synthesis on a multi-gram scale and possess molecular weights (M_n) up to 30 000 g/mol. Due to the anionic polymerization mechanism (ring-opening multibranching polymerization) quantitative polymer yields are obtained and the molecular weight is controlled by the monomer/initiator ratio. The dendrimer-like structure of the hyperbranched polyglycerol **C** is characterized by exactly one core unit with multiple hydroxyl groups randomly incorporated as linear (OH groups) and terminal groups (1,2-diols). The total density of functional groups in polymer **C** is 13.5 mmol OH per g polymer, of which approximately 60% (8.2 mmol OH per g) are terminal 1,2-diols.[49]



Scheme 28. Synthesis of achiral and chiral hyperbranched polyglycerols **C** (R=H). For simplification only a small fragment of the hyperbranched structure is represented. Exclusively diol-functionalized polyglycerols **C** (R=Me, Et, allyl, Bn) can be prepared by selective synthetic modification.[61] A functional core unit (X=alkene, NH_2, SH) can also be introduced.

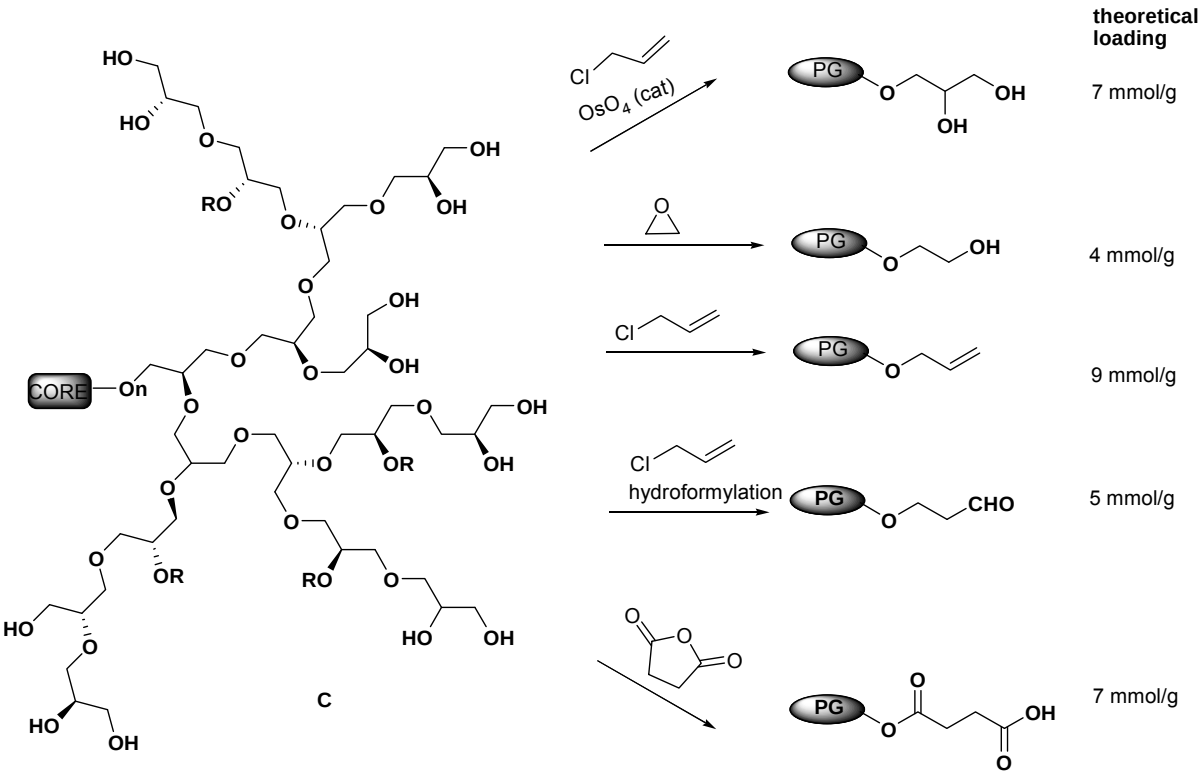
The complete derivatization of the terminal diols in polyglycerol **C** (R=H), with for example acetals, leaves about 40% of the OH groups unaffected (Scheme 28).[45] These remaining OH groups might limit the scope of this new polymeric support for some synthetic applications. For the preparation of a chemically inert polyether support **C** these residual OH groups can be selectively alkylated (R=Me, Et, Allyl, Bn) by using phase transfer conditions to obtain dendritic polymers with exclusively diol linkers.[49]

In order to further increase the loading capacity of the polyglycerol support Haag and co-workers converted the linear glycerol units into terminal 1,2-diols. For this purpose the hyperbranched polyglycerols **C** (R=H) can be transformed into perfectly branched structures, designated “pseudodendrimers” **D** (Scheme 29) by applying one dendrimer synthesis step (allylation and dihydroxylation) subsequent to the preparation of the hyperbranched polymer **C**.[49]



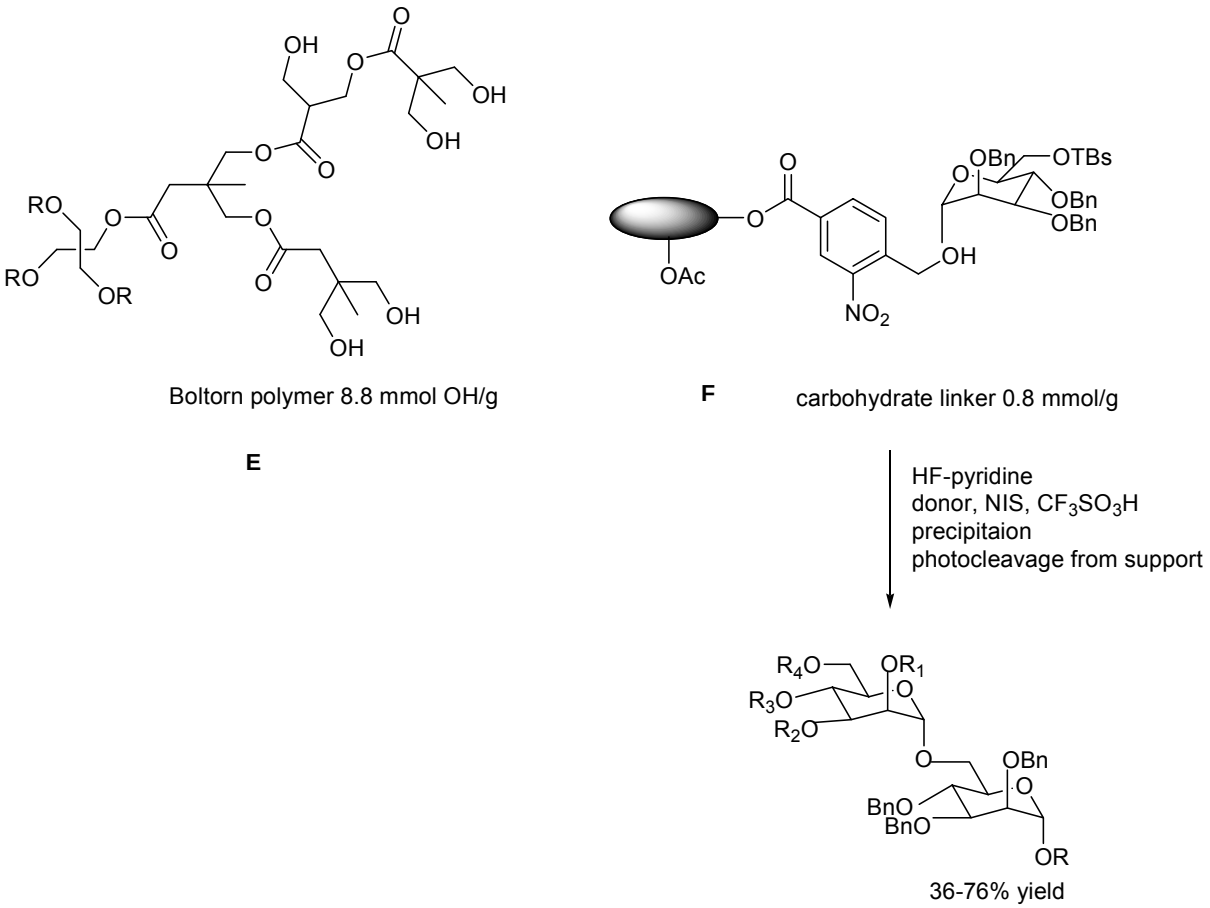
Scheme 29. Synthesis of pseudo-dendritic polyglycerol **D** from the readily available hyperbranched polyglycerol **C**, (**X**=functional core unit)

This strategy increases the capacity of the terminal 1,2-diol units from 4.1 mmol/g for the hyperbranched polymer **C** to 7.1 mmol/g for the pseudodendritic structure **D** and preserves all advantages of the polyether scaffold. For a more general application of polyglycerol **C** in organic synthesis and in order to increase the scope of possible reactions on this support, the conversion of the hydroxyl groups into various other linker functionalities by postsynthetic transformations has been explored by Haag *et al*.[62] (Scheme 30).



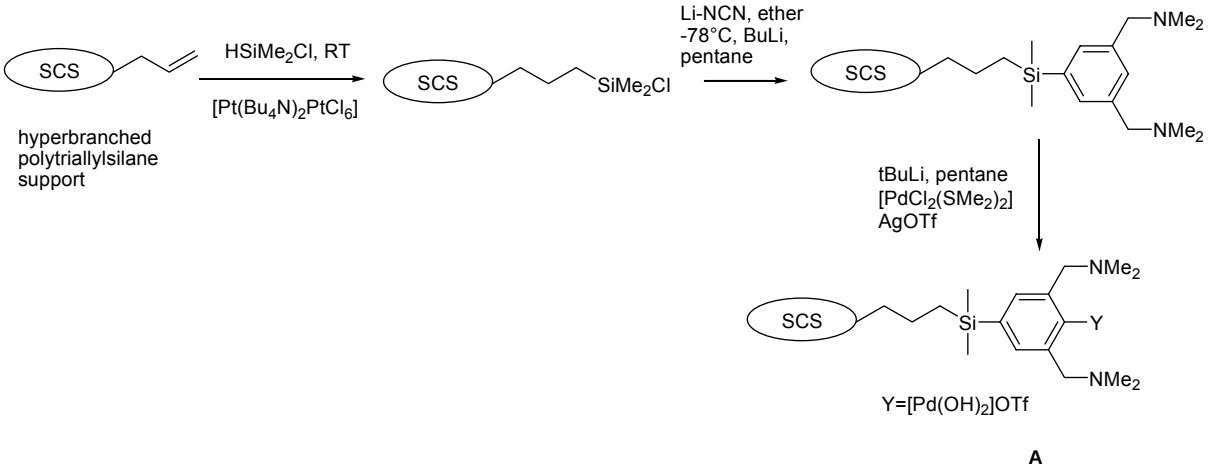
Scheme 30. Synthesis of multifunctional polyglycerols as high-loading supports for organic synthesis with various reactive linkers groups.

Recently, hyperbranched polymers have been introduced as soluble supports in organic synthesis.[63] A hyperbranched polyester support **E** containing 1,3-diols as terminal units was used for the synthesis of disaccharides (Scheme 31) by Parquette *et al*.[63a] They designed a photolabile *o*-nitrobenzylalcohol linker **F** on which a mannosyl acceptor is coupled. Theoretically, these polyesters have a relative high loading capacity (8.8 mmol OH per g) but the experimentally achieved loading with monosaccharides attached to the photo-labile linker **F** was reduced due to the weight of the linker functionality (0.8 mmol/g). For better compatibility, the remaining OH functionalities were converted into acetates. The general use of this hyperbranched polymer **E** as a support is limited due to the chemical sensitivity of the polyester backbone. In addition, these commercially available polyesters have rather low molecular weights (M_n.1500 - 2000).



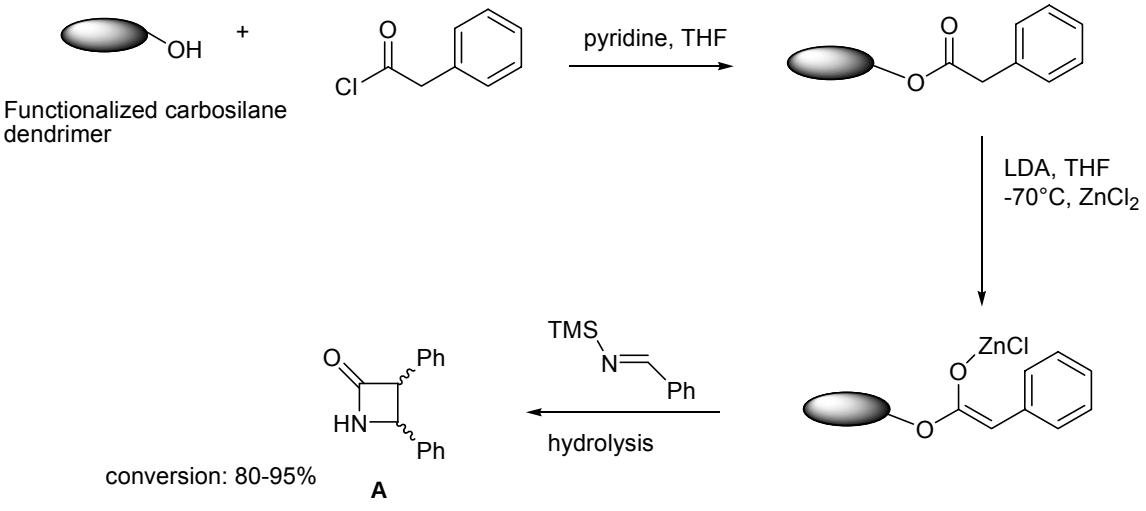
Scheme 31. The use of hyperbranched polyesters **E** and (R = other polymer branches) **F** as homogeneous supports for the synthesis of disaccharides.

Recently van Koten and co-workers established a novel methodology to prepare macromolecular-multisite catalysts obtained by grafting diaminoaryl palladium(II) complexes onto a hyperbranched-polytriallylsilane support.[63f] The Pd(II) centers in the soluble macromolecular catalyst **A** function as independent catalytic sites in a standard aldol condensation reaction and the activity is high. This is the first example of the use of hyperbranched polymers as soluble macromolecular supports for homogeneous catalysis. The catalyst support properties of the hyperbranched polymers are very similar to those of analogous dendrimers, and purification of the intermediates by means of dialysis revealed that **A** is suitable for continuous membrane application (Scheme 32).



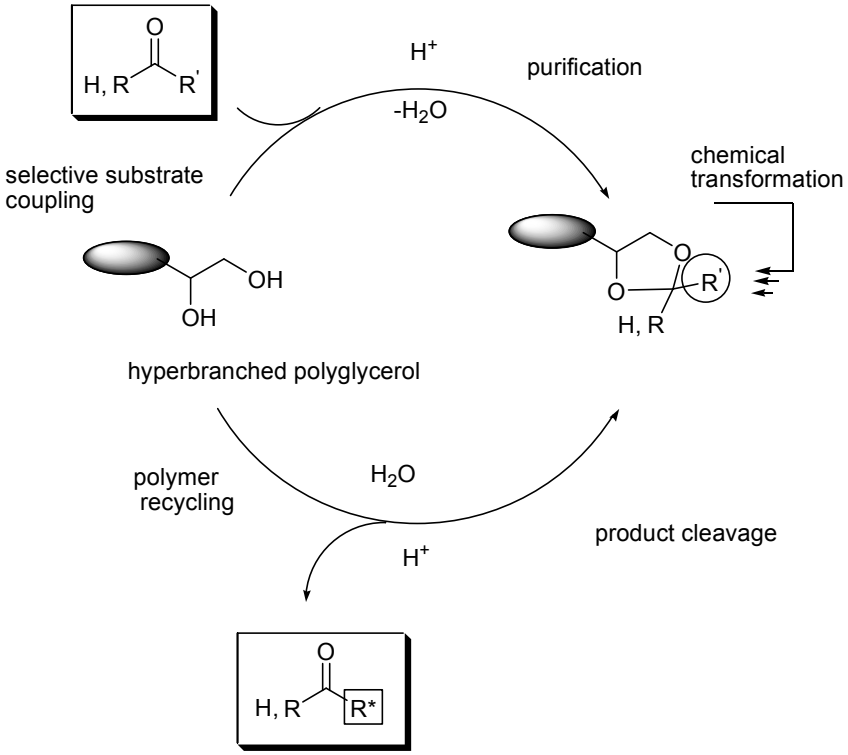
Scheme 32. Synthesis of a hyperbranched-polytriallylsilane supported Pd(II) catalyst

Van Koten *et al*. used functionalized carbosilane dendritic species as soluble supports for the synthesis of *β*-lactams.[61e] To demonstrate the applicability of the support in organic synthesis, the authors immobilized (*p*-bromophenyl)acetic acid which was then transformed into the corresponding biaryl by means of the Suzuki cross-coupling reaction with *p*-methylphenylboronic acid. Quantitative NaOH cleavage of the ester linkage yielded the released biaryl, of which no purity was mentioned.[63e] The different carbosilane dendrimer supports were used for the synthesis of *β*-lactam (**A**) (Scheme 33). The ester functionalized dendrimers were converted to the corresponding zinc enolates followed by a condensation reaction with an imine to a *β*-lactam in excellent yield and purity. Furthermore, it was demonstrated that a small combinatorial library of *β*-lactams could be prepared starting from a carbosilane dendrimer functionalized with different ester moieties. These results show that carbosilane dendrimers can be applied as soluble substrate carriers for the generation of low molecular weight organic molecules.



Scheme 33. *β*-Lactam formation on a dendritic carbosilane support

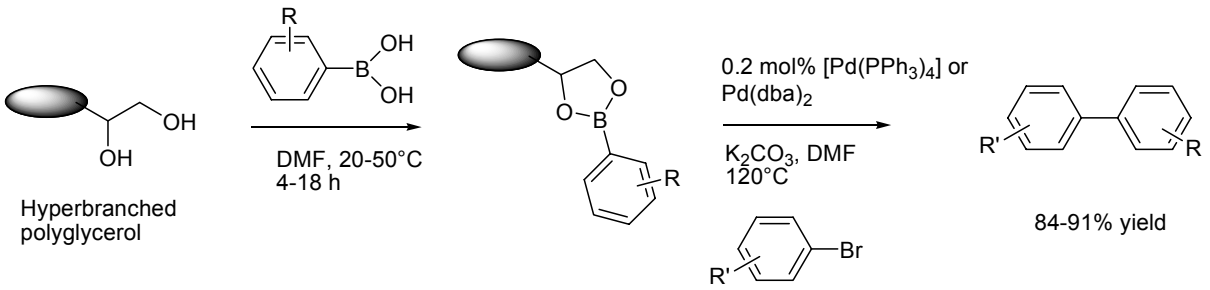
Haag and co-workers used a polyglycerol support which has a high loading capacity (13.5 mmol/g) and contains two kinds of functionalities: linear monohydroxy and terminal dihydroxy groups, which can be modified and serve as a linker as described above for the immobilization of diverse organic compounds. They have reported that it is possible to attach carbonyl compounds directly to polyglycerol via acetal formation and split them off again after one or several modifications (Scheme 34).[63b] Transformations carried out on this support included the synthesis of amino ketones from supported chloroketone as well as biarylaldehydes after Suzuki cross-coupling reactions of supported bromo-benzaldehydes. Polyglycerol is found to be soluble in many polar organic solvents and its aliphatic polyether skeleton is highly stable against a wide range of reaction conditions. Simple separation techniques like dialysis, ultrafiltration, precipitation and liquid-liquid extraction were investigated for this support.[64]



Scheme 34. Immobilization, modification, and release of a carbonyl compound employing a polyglycerol support

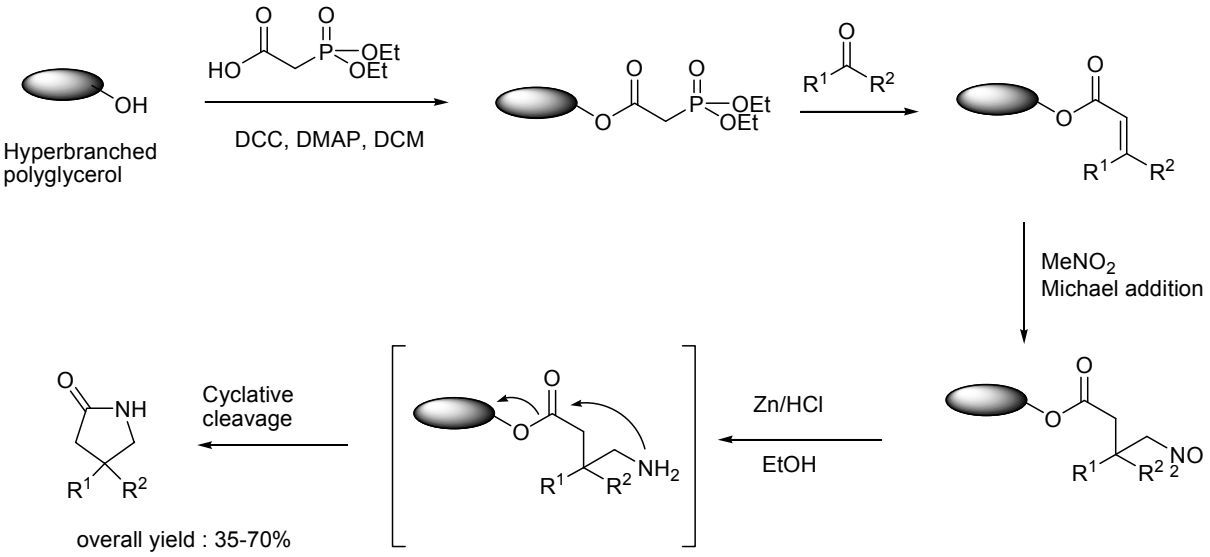
Recently, Haag and coworkers described the use of a soluble high-loading polyglycerol support for functionalized boronic acids without further linker design.[63c] The quantitatively formed polyglycerol boronic esters were subsequently employed in homogeneous Suzuki cross-coupling reactions to give high yields (84-91%) of functional biaryls with minimal

amounts of the Pd catalyst (0.2 mol %). In situ precipitation and ultrafiltration were used as simple and effective purification protocols (Scheme 35).



Scheme 35. Polyglycerol as a highloading support of boronic acids for Suzuki coupling

Multistep syntheses of drug candidates were also performed on this polyglycerol supports by Haag and co-workers.[63d] They have established a general route to GABA lactam analogues on this high-loading support. These biologically interesting compounds (anticonvulsive drugs) have been synthesized in three steps commencing from a polyglycerol supported (diethylphosphono)acetic acid and a carbonyl compound (Scheme 36). The key features of this parallel approach are the cyclative cleavage and simple separation techniques (i.e., dialysis).



Scheme 36. General synthetic route to GABA lactam analogues using hyperbranched polyglycerol support

From all these reactions described above it can be concluded that the polyglycerol supports are compatible with many reaction conditions including organometallic reagents and allow the simple purification using membrane techniques. Dendritic polymeric supports are among the most promising candidates for new high-loading supports in organic synthesis and

catalysis. The high loading capacity and possibility of characterization by standard analytical techniques (including NMR) of soluble dendritic polymers make them attractive candidates for multistep parallel synthesis as well as for homogeneous catalysis. However, none of these soluble dendritic polymers are perfect, some are chemically more robust than polyesters or polyamines and still investigations are going on to make them perfect in terms of stability. But the width of successful synthetic and catalytic applications with these soluble dendritic supports shows their large potential for the near future.

3.2.3 Separation of polyglycerol supports from low molecular weight compounds

It is generally believed that soluble polymeric supports are difficult to separate from the reaction mixture. However, this disregards their advantages (for example, homogeneous reaction conditions, standard analytical techniques, and high-loading capacities in some cases). Several separation techniques (ultrafiltration, dialysis, SEC, precipitation, and phase separation) have been reported for soluble polymeric supports.[63] All these techniques are applicable for the separation of polyglycerol supports from low molecular weight compounds. Nevertheless, it appears that only dialysis and ultrafiltration are useful for the separation of polyglycerol derivatives on a large scale (0.5-3 g). Since these separation techniques up to now were not used in combinatorial synthesis, Haag and co-workers have developed a parallel dialysis unit. Currently, this apparatus (Figure 15) can purify up to 12 samples (ca. 1-5 mmol of compound) simultaneously.[63b] It can be operated in many organic solvents, e.g., chloroform, MeOH, THF, and toluene if a solvent-resistant membrane is used. To the precision of ^{1}H NMR spectroscopy (98%), they could not detect any crosscontamination when using the parallel dialysis apparatus (Figure 15). Typical separation times are 12-36 h, depending on the amount of low molecular weight impurities. In this way, dendritic polyglycerol can be separated from low-molecular-weight impurities in multistep reactions. A fundamental advantage of this technique is the separation of large quantities (up to 10 mmol of substrate) in multiparallel approaches.[63b] Therefore, this process is attractive for the preparation of smaller libraries (10-100 compounds) on a relatively large scale.

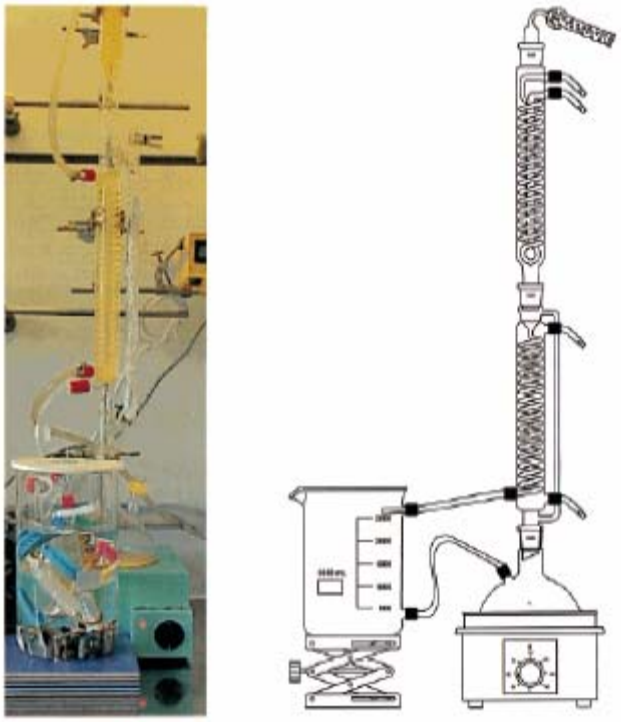


Figure 15. Parallel dialysis apparatus as a new separation tool for soluble polymeric supports (picture taken from reference[63b])

The limitations of this technique are the relatively long separation times (typically 12 - 36 h) and in some cases incompatibility with membrane materials, for example, for the separation of highly reactive or ionic compounds (inorganic salts). Dialysis is also unsuitable for the final cleavage step of a multistep polymer-supported synthesis because the cleaved low-molecular-weight compound would be diluted into a large amount of solvent when diffusing through the membrane. In this case, ultrafiltration can be used.[49]

A very efficient membrane separation technique for soluble macromolecules is ultrafiltration (UF), which was originally introduced by Bayer and co-workers for the automated synthesis of peptides in solution.[65] Like dialysis, it can be employed for the separation of low-molecular-weight compounds from soluble polymeric supports. Membrane materials (organic and inorganic) with high chemical stability and compatibility to most organic solvents are now commercially available.[66] In contrast to dialysis, much shorter separation times (ca. 1 - 3 h) can be achieved with UF because of the application of pressure (3 - 30 bar). It is necessary to use stirred UF cells or continuous flow systems for efficient separations to avoid clogging of the membrane which is costly.[64] Nevertheless, ultrafiltration has been used for the separation of polymeric supports during multistep syntheses as well as for the separation of products after the final cleavage step.[61b]

Phase separation is another simple and fast method for the separation of unpolar compounds from polyglycerol after final cleavage of the products and has been used previously in parallel synthesis by Janda and co-workers.[67] This method is suitable for the separation of organic molecules from water-soluble polymers, is based on liquid - liquid-phase separation between an organic phase (which contains the cleaved organic product) and an aqueous phase (containing the water soluble polymer).

Also, removal of the soluble polymeric support after the final cleavage step by a small silica cartridge is possible with polyglycerol supports.[68] There are other several efficient techniques for separation, which include precipitation or purification through in situ polymerization.[52]

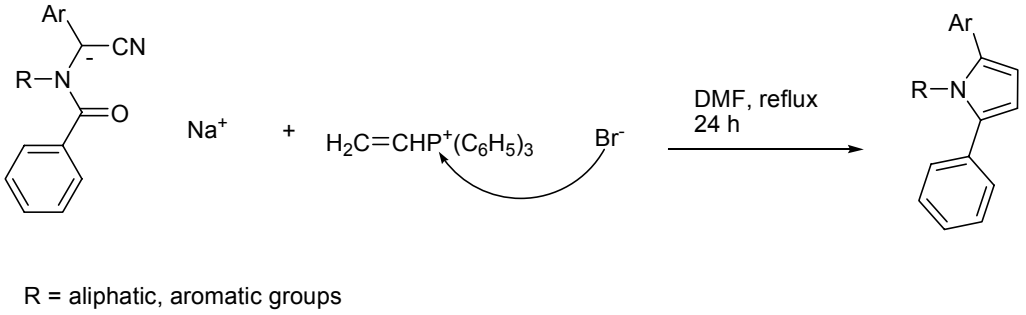
All these separation techniques are alternatives for the traditional methods, such as cristallization, distillation, and column chromatography. However, none of them are fully satisfactory and the application of these techniques to solution-phase synthesis depends on the physiochemical properties of each individual polymer. In addition, these techniques are sensitive to the change of functional groups on the polymeric support during the synthesis. Therefore, the use of soluble polymeric supports in combinatorial synthesis requires the careful selection of the appropriate separation technique.

3.2.5 Recent developments for *N*-substituted pyrrole synthesis in solution

Pyrroles are an important class of heterocyclic compounds whose representatives show a variety of biological activities.[69] Therefore, many methods for the synthesis of *N*-substituted pyrroles have been described in the literature.[70] One of the most commonly used method is the condensation of primary amines with 2,5-dimethoxytetrahydrofuran which was invented by Clauson-Kaas *et al.* in 1950.[9] Although the method of Clauson-Kaas gave excellent yields for different substituted pyrroles, this method is not applicable to compounds which are heat and acid sensitive. In 1982, Chan *et al*. reported the facile synthesis of *N*-substituted pyrroles with almost quantitative yield by the reaction of 1,4-dichloro-1,4-dimethoxybutane (**A**) with primary amine and amide in presence of the weakly basic ion exchange resin Amberlyst (Scheme 37).[71]

Scheme 37. Preparation of *N*-substituted pyrroles in presence of amberlyst

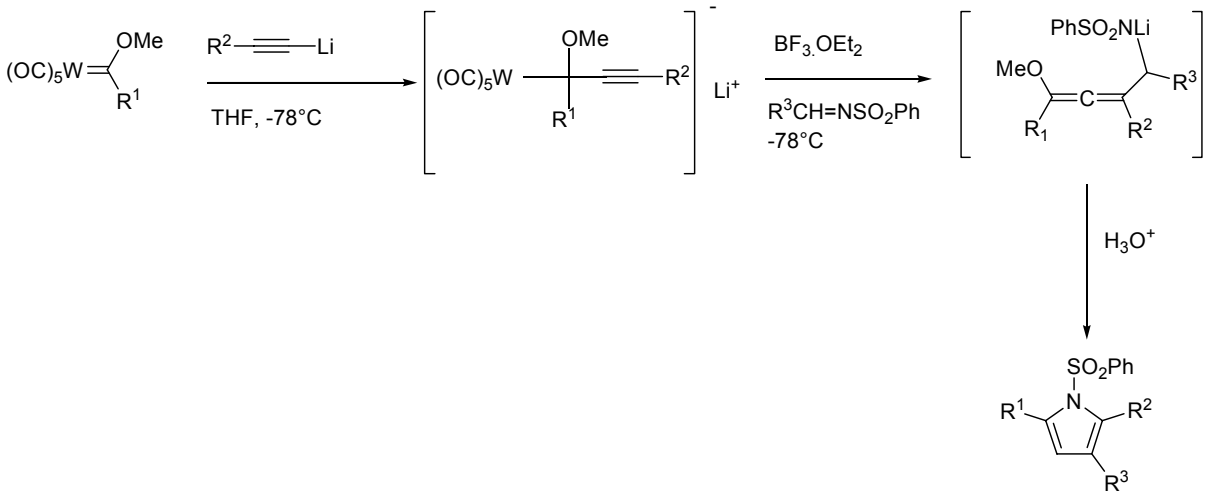
In 1981 Cooney *et al*. reported the synthesis of 1,2,5-trisubstituted pyrroles by intramolecular condensation of a Wittig type reagent with a carbonyl group of a tertiary amide in 50-100% yield (Scheme 38).[72] Although the Paal-Knorr synthesis of 1,2,5-trisubstituted pyrroles from 1,4-diketones and primary amines is classical and widely used, this method allows the preparation of some pyrrole derivatives which cannot be obtained by Paal-Knorr synthesis.



R = aliphatic, aromatic groups

Scheme 38. Preparation of *N*-substituted pyrroles via intramolecular Wittig reaction

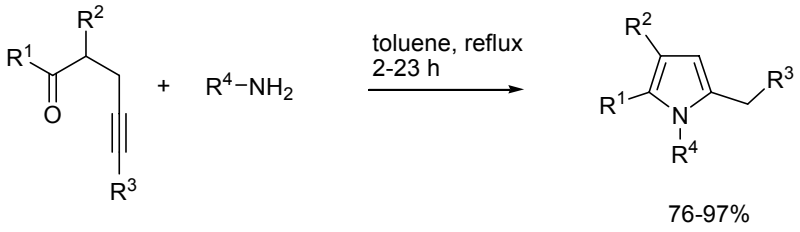
Pyrroles can also be prepared form transition metal intermediates. Iwasawa *et al*. described that a new type of propargyl metallic species can be generated by the addition reaction of alkynyllithium to Fischer-type carbene complexes and these species can be employed for several useful carbon-carbon bond forming reaction such as *N*-substituted pyrrole formation (Scheme 39) in 64-85% yields.[73]



Scheme 39. Preparation of *N*-substituted pyrroles via transition metal intermediates

They have treated the propargyl metallic intermediates with aldehydes, imines and carbondioxide to produce respectively furans, pyrroles and butenolides cotaining various substituents in good yields.

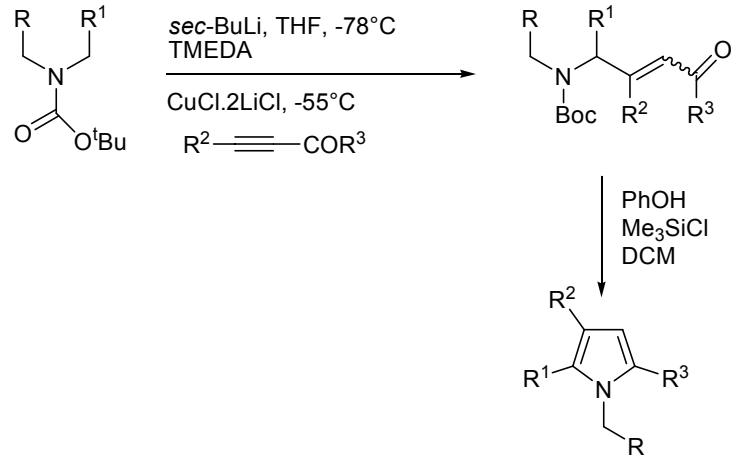
In 1998, Arcadi and co-workers established a new approach for the synthesis of functionalized furans and pyrroles, which can be found in many naturally occuring compounds, through annulation reactions of 4-pentynones.[74] This is a new synthetic strategy for the construction of heterocyclic rings involving alkyne derivatives and the functionalised pyrroles were obtained in good yields (Scheme 40).



Scheme 40. Preparation of *N*-substituted pyrroles via recation with pentynones

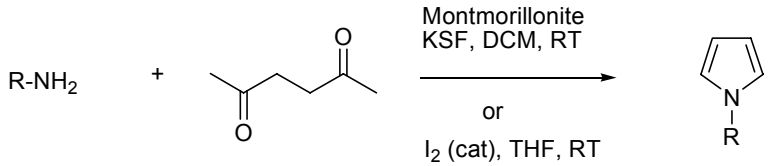
Dieter *et al*.[75] described a facile synthesis via 1,4-conjugate addition reactions to construct the carbon skeleton of pyrrole framework followed by cyclization reactions. By this way they have prepared pyrroles with a wide range of substitution patterns. According to them, α-aminoalkylcuprates prepared from CuCl.2LiCl and 1 equiv of an α-lithiocarbamate undergo conjugate addition reactions to α,β-alkynyl ketones in moderate to good yields, affording *E:Z* mixtures of α,β-enones. Treatment of this conjugate adducts with PhOH/TMSCl in DCM

effected carbamate deprotection and cyclization to afford a flexible two-step synthesis of substituted pyrroles in good yields (Scheme 41).



Scheme 41. Preparation of *N*-substituted pyrroles via conjugate addition reaction

Recenty, Banik *et al*. described two simple syntheses of substituted pyrroles with excellent yields using iodine-catalyzed and montmorillonite KSF-clay-induced modified Paal-Knorr methods.[76] If one of the reactants is a liquid, the reaction proceeds quite well without solvent. This method gives pyrroles with less nucleophilic multicyclic aromatic amines at room temperature (Scheme 42).



Scheme 42. Preparation of *N*-substituted pyrroles via two simple methods

A clay mediated[77] organic reaction and microwave irradiation method[78] have been used for construction of pyrroles under Paal-Knorr conditions. These techniques clearly extend the scope of this reaction, but success with less nucleophilic aromatic amines has not been reported. The method described by Banik and co-workers are much superior to Lewis acid-mediated synthesis of pyrrole in terms of product yield. No extra energy source, such as microwave irradiation or ultrasound is needed for the success of the reactions. Most importantly, these methods have been shown to be versatile pyrrole synthesis procedures, even with less nucleophilic multicyclic aromatic amines.

All these methods described above are general for most kinds of primary amino compounds and have great potential for future applications due to the pharmacological importance of pyrrole moiety.

4 Results and disscussion

4.1 Electroorganic synthesis on solid phase

4.1.1 Principle of indirect anodic oxidation on solid phase

The electrochemical formation and regeneration of redox agents for organic syntheses (indirect electrolysis) widens the potential of electrochemistry. New types of redox catalysts can be formed in-situ and can be regenerated after reaction with the substrates. A great deal of progress has recently been made in the application of organic electron transfer agents, since compounds have been found that are sufficiently stable in both the reduced as well as the oxidized state. Electroorganic synthesis using polymeric supports has not been explored yet.

It has been calculated that for most resins used in SPOS more than 95% of the substrate molecules are buried within the interior of the resin bead,[4] thus a direct electron transfer between the electrode and the substrate molecule is not feasible. However if a redox catalyst (**1** and **2**) is used as a mediator, the electron transfer step at the electrode and the redox reaction with the substrate can be separated (Figure 16). This principle of “indirect electrolysis” has already found wide application in solution-phase electroorganic synthesis, where it offers significant experimental advantages over a direct electrode contact, such as, reduced over potentials or higher selectivity.[79]

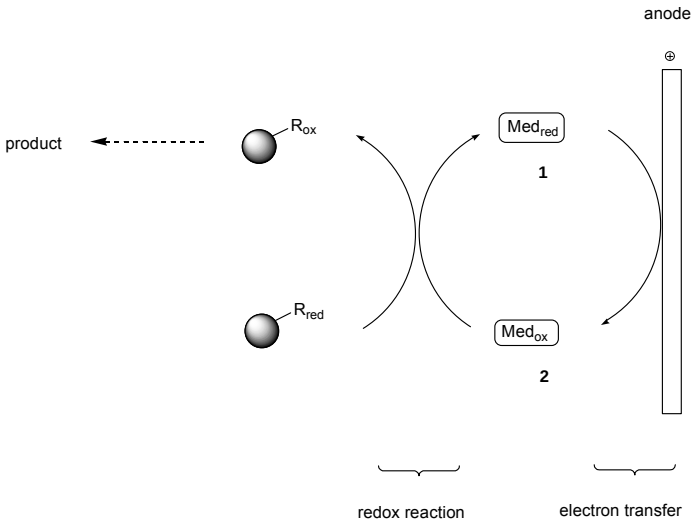
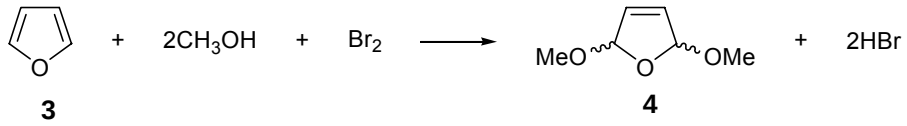


Figure 16. Principle of redox-catalyst-mediated electroorganic synthesis on solid phase

As a model reaction the 2,5-dimethoxylation of furans[9] was chosen. This electrolysis process is mediated by Br^- ions and is performed widely in organic synthesis and even applied on an industrial scale.[80] The products formed are versatile starting materials for further derivatization.[81]

When furan (**3**) is treated with a methanolic solution of bromine or chlorine it adds two methoxy groups whereby 2,5-dimethoxy-2,5-dihydro furan (**4**) and two moles of hydrogen halide are formed (Scheme 43)

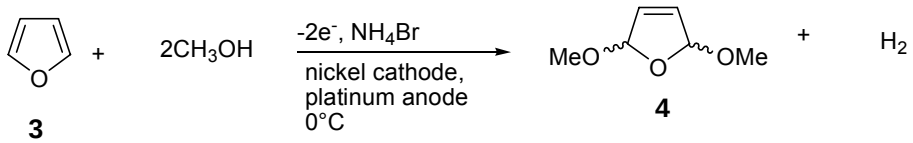


3 **4**

Scheme 43. Methoxylation of furan in presence of bromine

Since dimethoxy-dihydrofuran is sensitive to acids, the reaction is carried out in the presence of sodium carbonate.[82] Several disadvantages are inherent in this chemical method. These include the use of large quantities of bromine and the resultant contamination of the product with halogen-containing impurities which eventually cause decomposition of the acid sensitive acetals. Moreover, the chemical method affords very poor yields of product for furans substituted with electron-withdrawing substituents.[83]

Clauson-Kaas *et al.* developed a methoxylation method,[9] which is simpler and cheaper than the one described above, and which gives a halogen free product in higher yield and can be used on an industrial scale.[84] Furan (**3**) is mixed with a methanolic solution of ammonium bromide and the mixture electrolyzed. At the cathode, hydrogen and ammonia, at the anode bromine are formed. The bromine reacts immediately with furan and after nucleophilic substitution with methanol the dimethoxy-dihydrofuran **4** and hydrogen bromide are formed. The hydrogen bromide and the ammonia from the cathode then regenerate the ammoniumbromide which serves as supporting electrolyte as well as a source of the mediator (Scheme 44).



3 **4**

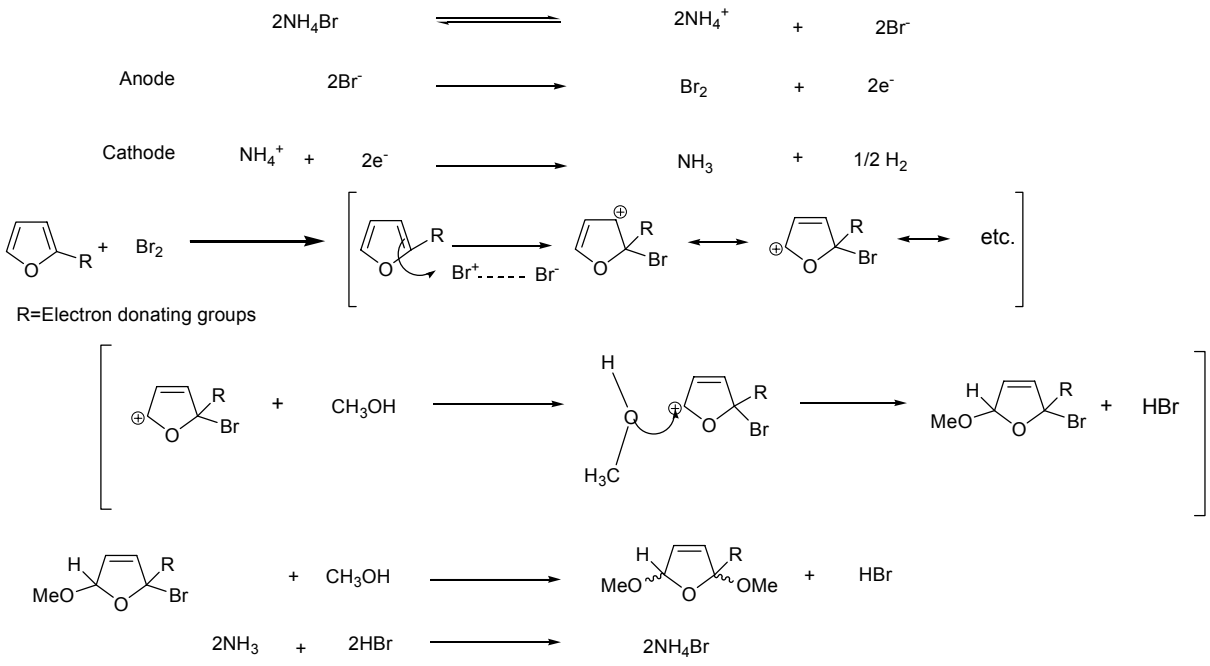
Scheme 44. Methoxylation of furan by an electrochemical process

The yield of dimethoxy-dihydrofuran is 73% and the current yield is 86% as described by Clauson-Kaas *et al*.

4.1.2 Mechanism of the redox reaction

The electrolysis is carried out in methanol and its reaction path depends on the structure of the starting compound and on the supporting electrolyte. Bromide ion, both from the electrolyte and hydrogen bromide evolved in this process, is oxidized to bromonium and recycled in the methoxylation reaction. With ammonium bromide as the supporting electrolyte there is no marked difference in yields on varying the anode material, suggesting that the electrochemical process involves solely discharge of halide ion.[85]

The very frequently used ammonium bromide is suitable only for methoxylation of those furan derivatives which carry electrondonating substituents; a primary oxidation of the bromide ion (Scheme 45) and the addition of bromine to the diene system are assumed.



Scheme 45. Reactions on electrodes

In this indirect anodic oxidation bromide ion (Br^-/Br^+) plays the role of the mediator which is generated from the supporting electrolyte. The reduced form of the mediator (Br^-) is oxidized by a heterogeneous electron transfer to the anode (Figure 17) at a lower potential ($E°_{Br^-/Br^+}$=+1.09 V) than that of the furan. In this way the oxidized form of the mediator (Br^+) results

which in a homogeneous reaction oxidizes the furan to the dimethoxy dihydrofuran and Br^-, resulted in this reaction, is reoxidized in the following cycle to Br^+.

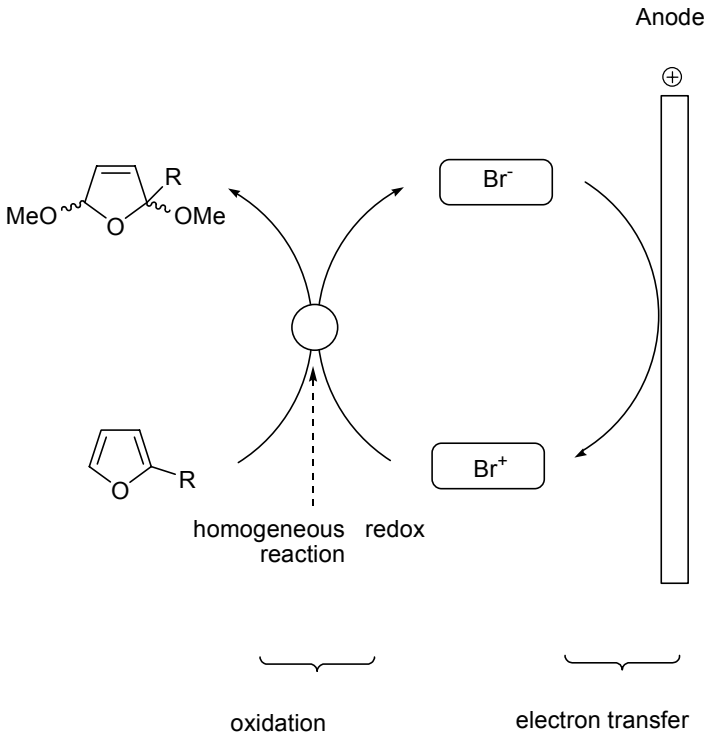
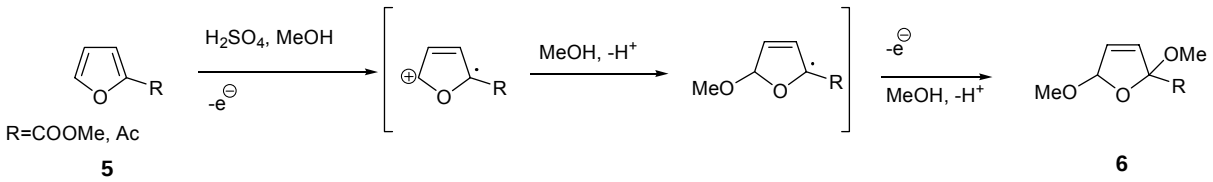


Figure 17. Principle of Br^+/Br^- mediated dimethoxylation of furan

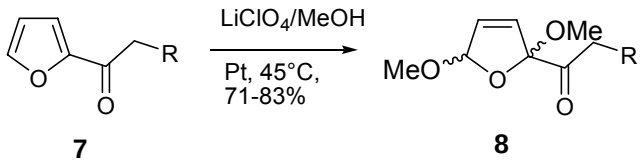
Under certain circumstances a second reaction route appears to be operative, since other nonhalide electrolytes provide the same products although often in poorer yield. For these nonhalide electrolytes, especially in basic media, the anode material is important. At a platinum anode the yields of 2,5-dihydro-2,5-dimethoxyfuran with various electrolytes decrease in the order $NH_4Br >> BF_3 > H_2SO_4 > NaNO_3$, NH_4NO_3.[86]

For electronwithdrawing substituted furans **5**, no product is furnished when NH_4Br is used as a supporting electrolyte and H_2SO_4 must be used instead.[87] The oxidation starts by an electron transfer from the furan to the anode (direct anodic oxidation). Suggestions have been made that the reaction scheme may involve discharge of methanol to methoxy radicals which undergo 1,4 addition to the furan ring (Scheme 46). A mechanism involving the reaction of cation radical with solvent, followed by reoxidation and solvolysis to the final 2,5-dihydro-2,5-dimethoxyfuran **6**, appears justifiable.[88]



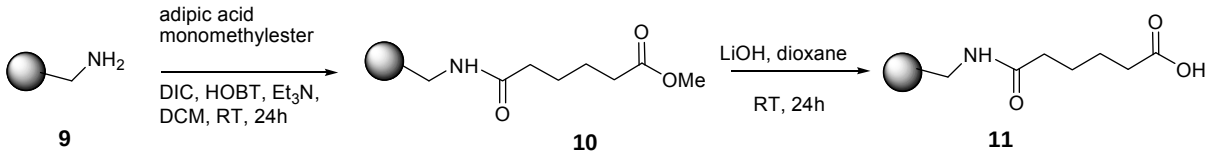
Scheme 46. Anodic oxidation of electron poor furans in presence of sulphuric acid

Thus the successful methoxylation of electron poor furans may require H_2SO_4 as an electrolyte to extend the useful anodic limit of the solvent to the point at which the furan may be discharged. Electrochemical oxidation of electron poor furans **7** can be carried out in methanol containing lithium perchlorate as a supporting electrolyte (Scheme 47) but it requires costly platinum electrodes.



Scheme 47. Electrochemical oxidation of electron poor furans with platinum electrodes

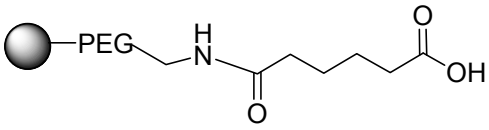
4.1.3. Linker for the solid phase reaction



Scheme 48. Procedure for the preparation of aminomethylated polystyrene resin supported adipic acid

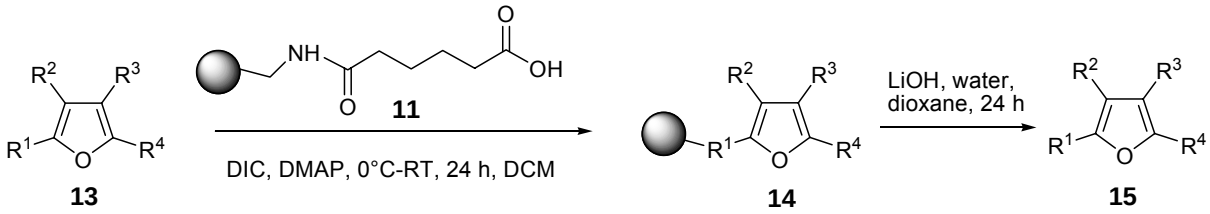
As the expected products are known to be acid sensitive, the carboxy-terminated linker **11** (Scheme 48) was chosen to enable cleavage of the reaction products from the resin under basic conditions[89] Aminomethylated polystyrene resin (Novabiochem, 200-400 mesh, loading 1.13 mmol/g) (**9**) was functionalized with adipic acid monomethyl ester by a standard esterification procedure in presence of DIC and DMAP to prepare **10**. The ester was converted to the acid by basic saponification (1% LiOH/H_2O (20 mL)) to form **11**. Analysis of the coupling efficiency by means of the Kaiser test[90] which detects the remaining free amino groups revealed that essentially no underivatized amino groups had remained. The similar

reaction sequence was followed to prepare aminomethylated tentagel resin supported adipic acid **12**.



12

Attachment of furan derivatives on aminomethylated polystyrene resin supported adipic acid was carried out following a standard esterification procedure[91] in presence of DIC as a coupling agent and DMAP as a catalyst (Scheme 49).



Scheme 49. Attachment of furan derivatives on aminomethylated polystyrene resin supported adipic acid

The following substrates (Table 1) were chosen for esterification. To validate the success of this reaction the solid supported products were cleaved by saponification and the purity of the cleaved product was determined by GC-MS.

Entry	R^1	R^2	R^3	R^4	Purity after cleavage (determined by GC-MS
1	$(CH_2)_3OH$	H	H	H	99%
2	$(CH_2)OH$	H	H	CH_3	99%
3	$CH(CH_3)OH$	H	H	H	95%
4	$CH_2NHCO(CH_2)_5OH$	H	H	H	98%
5	CH_3	$CH(CH_3)OH$	H	CH_3	99%
6	$CH(OTBDMS)(CH_2)_4OH$	H	H	H	98%
7	CH_2OH	H	H	H	99%
8	$CO(CH_2)_4OH$	H	H	H	99%
9	CH_2OH	H	H	CH_2NMe_2	99%
10	$CH(OH)(CH_2)_{10}CH_3$	H	H	H	95%
11	H	H	CH_2OH	H	99%

Table 1. Furan derivatives attached to aminomethylated polystyrene resin supported adipic acid

For the cleavage of the furan derivatives from the solid support these conditions were tried:

1) THF/water (20/1), NaOH (5 equiv.)

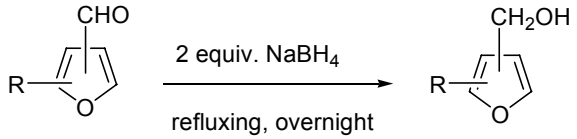
2) MeOH/water (20/1), NaOH (5 equiv.)

3) dioxane/water (20/1), LiOH (5 equiv.)

Best purity was achieved by dioxane/water (20/1), LiOH (5 equiv.) and the cleavage described above for Table 1 was carried out under this condition.

4.1.4 Preparation of the furan substrates for indirect anodic oxidation

The hydroxy alkyl furans were prepared starting from the corresponding aldehyde derivatives by reduction with sodium borohydride (Table 2) as it is a mild reagent and the work up of the reaction is very easy.



Scheme 50. Sodium borohydride reduction to prepare hydroxyl alkyl furan

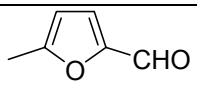
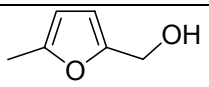
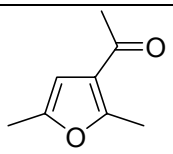
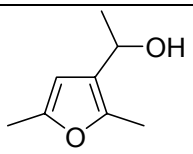
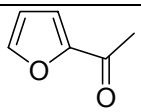
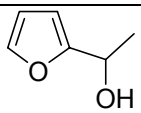
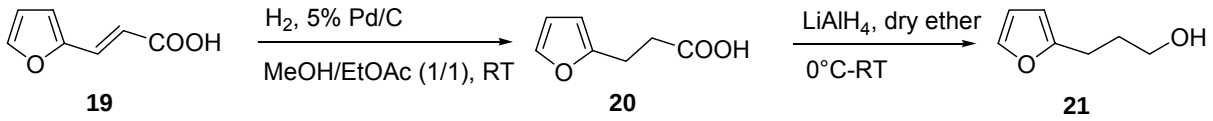
Reactant	Product	Solvent	Yield
	 **16**	Isopropanol	86%
	 **17**	Methanol	80%
	 **18**	Methanol	80%

Table 2. Furan derivatives prepared via sodium borohydride reduction

2-Furanpropionic acid (**20**) was prepared by hydrogenation of the corresponding commercially available furylacrylic acid **19** following the procedure reported by Robertson *et*

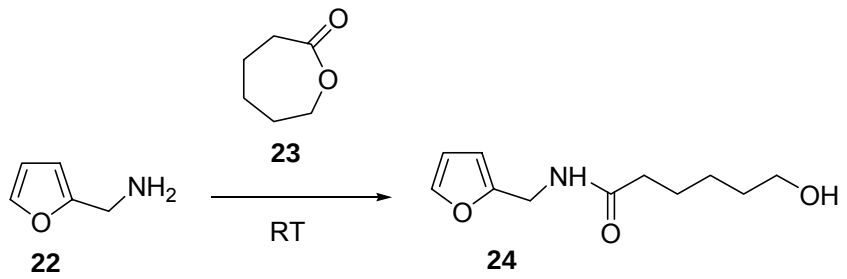
al.[92] However, for optimal yields the reaction conditions had to be slightly changed. Instead of methanol a 1/1 mixture of MeOH/EtOAc was used as solvent in order to prevent overreduction of the furan ring. These hydrogenation conditions furnished the corresponding acid **20** in 57% yield (Scheme 51). The reaction was carefully monitored by TLC otherwise overreduced product will form. **20** should be stored in the dark at -18°C to prevent decomposition.

The reduction of 2-furanpropionic acid (**20**) was performed with lithium aluminium hydride (**21**, yield 67%) in dry ether following the procedure reported by Harmata *et al.*[93]



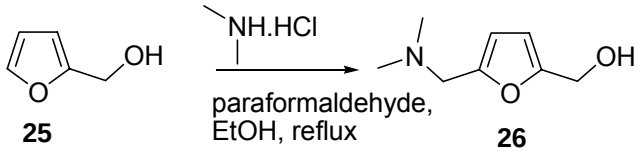
Scheme 51. Preparation of 2-furanpropanol

N-((2-furyl)methyl)-6-hydroxyhexanamide (**24**) was prepared by treatment of commercially available furfuryl amine (**22**) with an excess of 6-caprolactone (**23**) in absence of base at room temperature (Scheme 52).[94] Purification by column chromatography gave 90% yellow solid product **24**.



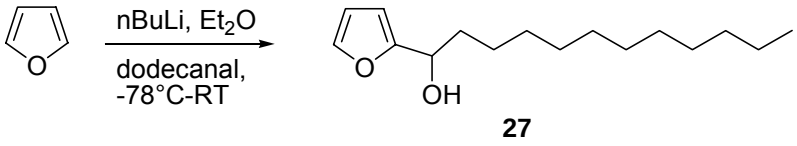
Scheme 52. Preparation of *N*-((2-furyl)methyl)-6-hydroxyhexanamide

A Mannich condensation of furfuryl alcohol (**25**) with dimethylamine hydrochloride and paraformaldehyde produced 5-dimethylaminomethylfurfuryl alcohol (**26**) (Scheme 53)[95] in 33% yield.



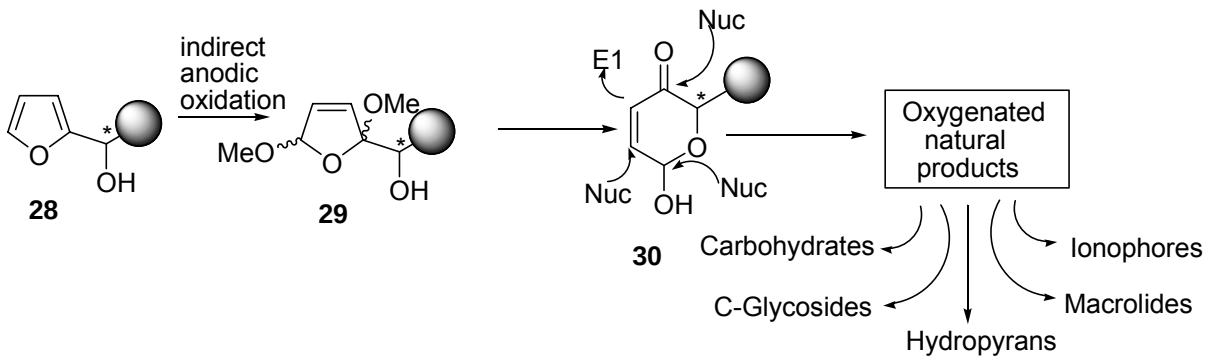
Scheme 53. Preparation of 5-dimethylaminomethylfurfuryl alcohol

To prepare **27**, furan was treated with butyllithium solution at -78°C under argon atmosphere in dry ether. α-Undecyl-2-furan-methanol (**27**) was prepared by the addition of the so prepared furan lithium to dodecanal[96] (Scheme 54). Purification by column chromatography gave the title compound (**27**, 92%) as yellow oil.



Scheme 54. Preparation of α-undecyl-2-furan-methanol

In order to demonstrate the utility of the electroorganic solid phase method and that it can be easily implemented in a multistep solid-phase synthesis sequence, more complex substrates were investigated. For that reason chiral furyl carbinols (**28**) were synthesized which after indirect anodic oxidation when treated with concentrated sulfuric acid gave hydroxy-3-pyranones **30** (Scheme 55). These key intermediates are admirably endowed with differentiated functionality to allow the facile introduction of other functional groups and/or alkyl residues by reaction with the appropriate nucleophiles and electrophiles as shown.



Scheme 55. Implemention of electroorganic solid phase method in a multistep solid phase synthesis

To evaluate this line of diversification 1-(furan-2)hexane-1,6-diol (**33**) was synthesized (Scheme 56). When furan lithium (prepared by in situ) was treated with 6-caprolactone, 1-(furan-2-yl)-6-hydroxyhexan-1-one (**31**) should be formed as nucleophilic additions to medium and large macrolactones generally result in opening of the ring due to the high reactivity of the tetrahedral intermediates obtained from the initial addition (Figure 18).[16, 97] But in the event a mixture of 1-(furan-2-yl)-6-hydroxyhexan-1-one (**31**) and 2-(furan-2-yl)oxepan-2-ol (**32**) (in 1.7/1 ratio) were obtained in this reaction (Scheme 56). The similar type of reaction was reported by David Crich *et al*.[98] where they have got only the hemiketal type of product.

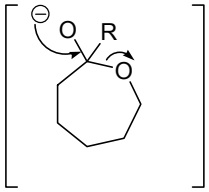
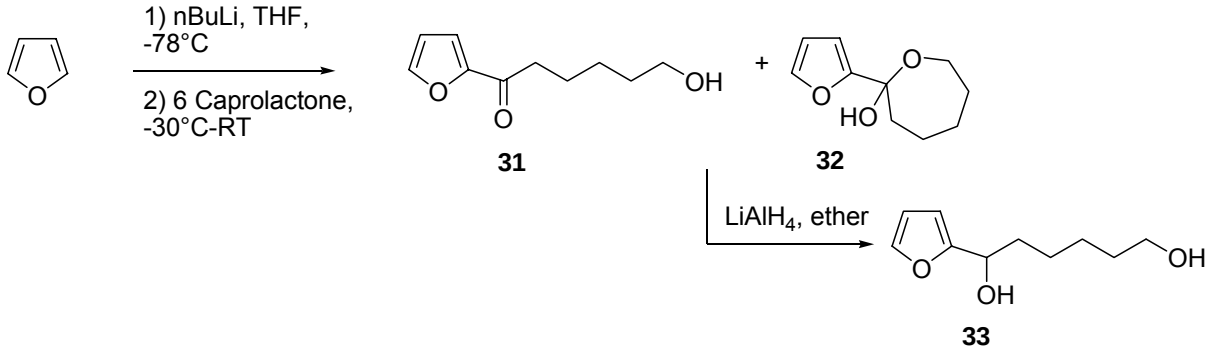
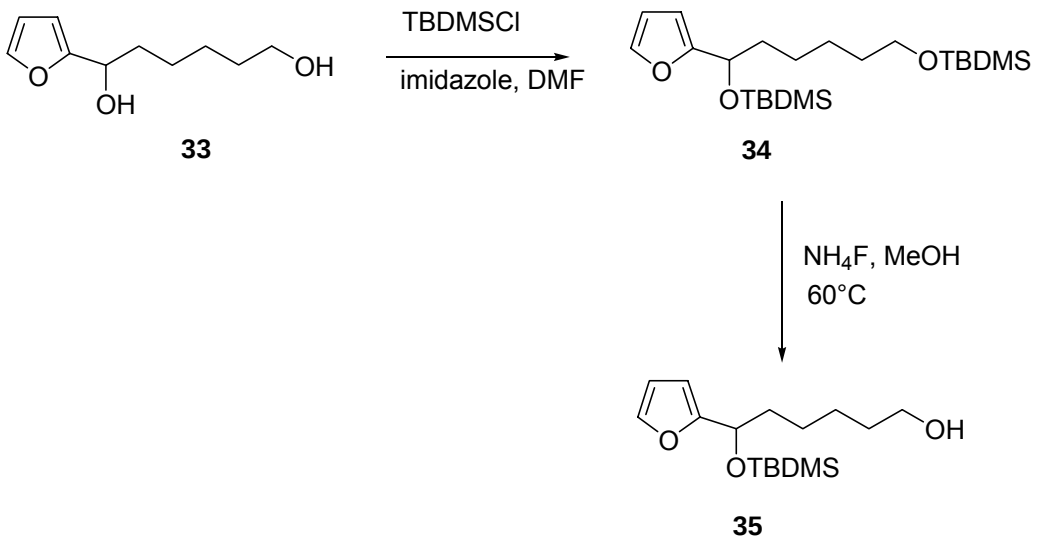


Figure 18



Scheme 56. Preparation of 1-(furan-2-yl)hexane-1,6-diol

The reaction mixture did not require purification as both **31** and **32** were reduced by lithium-aluminiumhydride to give the desired diol **33** in 60% overall yield. As it was assumed to be difficult to attach selectively the primary hydroxyl group with aminomethylated polystyrene resin supported adipic acid, both hydroxyl groups of **33** were first protected with TBDMSCl and then the primary hydroxyl group was selectively deprotected. After attachment to the polystyrene resin, the protected secondary hydroxyl group was deprotected with TBAF on solid phase. The protection of the hydroxyl groups by TBDMSCl was performed following standard procedures using an excess (2.5 equiv) of TBDMSCl (Scheme 57).[99] Purification by column chromatography gave the diprotected alcohol **34** in 81% yield.



Scheme 57. Protection and deprotection of hydroxyl groups of 1-(furan-2-yl)hexane-1,6-diol

Generally treatment of any silyl ethers with excess ammonium fluoride in methanol at 60°C effected cleavage to alcohols within 5 hours.[100] Deprotection at ambient temperature required 1-2 days. NH_4F/MeOH is an economical alternative to TBAF/THF. Methanol is a low boiling solvent that is easy to remove and has good solvating properties for silyl ethers as well as the polar ammonium fluoride. Ammonium fluoride could be expected to function as an effective silyl cleavage agent since its weakly acidic ammonium ion might participate in hydrogen bonding to the ether oxygen during nucleophilic attack on silicon by the fluoride counter anion (Figure 19).

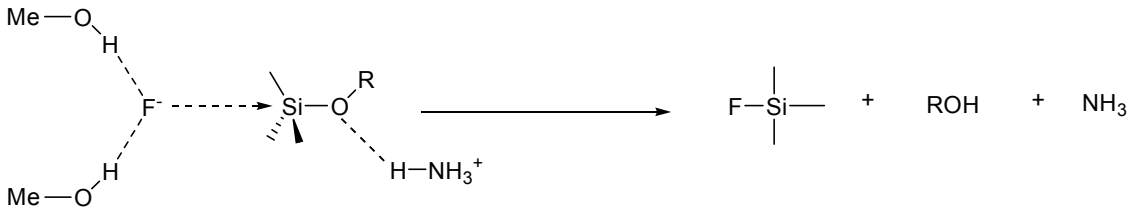
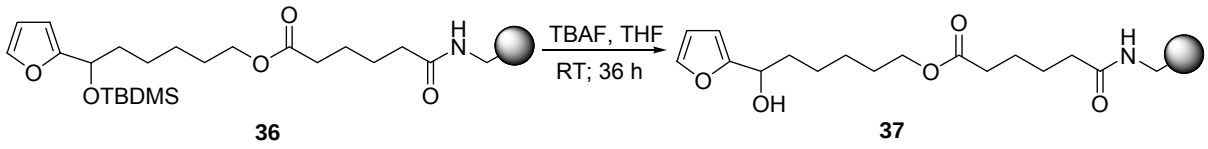


Figure 19. Hydrogen bonding of ammonium ion to the ether oxygen during nucleophilic attack on silicon by the fluoride

This reaction was carried out in dry methanol and in presence of an excess of ammonium fluoride (6 equiv). The reaction had to be monitored carefully because along with the monoprotected product the diol was also forming. After complete consumption of the diprotected product the desired monoprotected product, **35** was isolated in 54% yield after purification by column chromatography (Scheme 57). This monoprotected product was attached to polystyrene resin by the standard esterification procedure as described above.

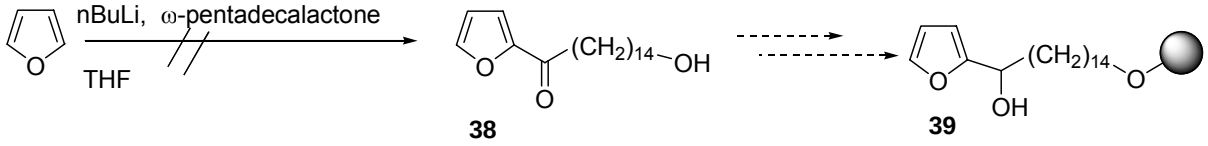
The deprotection of the secondary hydroxy group was done following the method of Wunberg *et al*. in dry THF and in presence of an excess TBAF (5 equiv) (Scheme 58).[101] The deprotection was confirmed by cleaving the substrate from the resin in presence of LiOH in dioxane/water mixture (20/1) at room temperature. The purity of the cleaved product (1-(furan-2-yl)hexane-1,6-diol) (**33**) was > 98% (determined by GC-MS).



36 **37**

Scheme 58. Deprotection of secondary hydroxy group on solid phase

It was described above that the nucleophilic addition of 2-furyl lithium to medium and large macrolactones generally results in opening of the ring forming acyl furans. On that basis a macrolactone (ω-pentadecalactone) was selected for the synthesis of furyl carbinol derivatives. The reaction was carried out in dry THF at -78°C under Ar atmosphere (Scheme 59). The reaction sequence was similar to the one previously described.

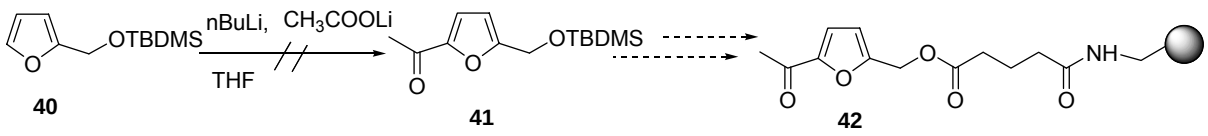


38 **39**

Scheme 59. Attempts to prepare 1-(furan-2-yl)-15-hydroxypentadecan-1-one by lithiation.

However the reaction did not work as expected and after addition of the white crystalline lactone the whole reaction mixture turned to a brown solid. After quenching with saturated ammonium chloride solution the brown solid was dissolved and after extraction with ethyl acetate the crude product was analysed by GC-MS and NMR. From these spectra it was clear that the required product **38** was not formed and the macrolactone was reisolated.

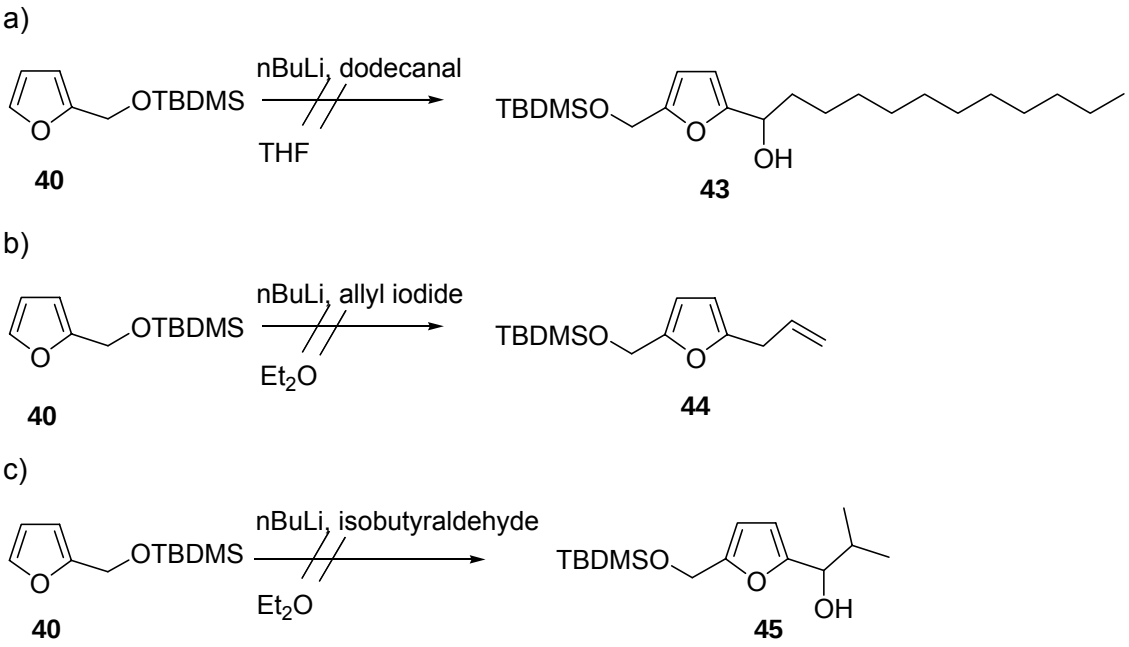
The 2-furanyl ketone moiety is found in a number of natural products,[102] as precursors to alcohols able to provide useful rearranged structures,[103] and in various chemicals of medicinal and agricultural interest.[104] Their access is generally considered as not very easy.[105] Diverse preparative routes, involving a Friedel-Crafts acylation of the furan ring,[106] oxidation of the corresponding alcohols, and several organometallic reactions, have been described.



Scheme 60. Attempts to prepare 2-furanyl ketone moiety by lithiation

((Furan-2-yl)methoxy)(*tert*-butyl)dimethylsilane (**40**) was prepared by standard procedure from commercially available 2-furylalcohol. Attempts were made to use the procedure of Wender *et al*.[107] in the direct *in situ* preparation of 5-[(*tert*-butyl)dimethylsilyloxymethyl]-furan-2-lithium (Scheme 60) and condensation with lithium acetate at -78°C. The reaction was carried out in dry THF at -78°C - 0°C and under Ar atmosphere. After quenching with saturated ammonium chloride solution the resulting bright yellow reaction mixture was extracted with ethylacetate. The combined organic layers were concentrated under reduced pressure and analysed by GC-MS and NMR. From the analysis of the GC-MS and NMR spectra it was clear that the desired product **41** was not formed and only the starting material was detected.

To evaluate the possibility to prepare other furyl carbinol derivatives by lithiation of **40**, the reactions depicted below were performed in Ar atmosphere and at -78°C with dry THF or ether (Scheme 61). But none of them were successful. The reaction with dodecanal has been tried also in presence of dry ether. Unfortunately no reaction occurred. The problem of this transformation could not be identified. But it might be that the TBDMS group was hampering the lithiation.



Scheme 61. Attempts to prepare furyl carbinols

4.1.5 Electrochemical reactions of model substrates in solution

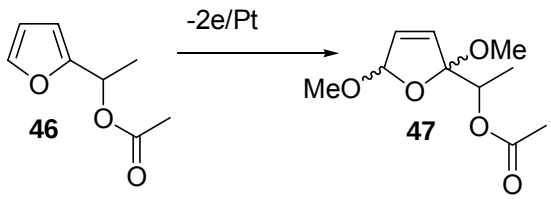
Prior to the synthesis on solid phase some model electrochemical reactions were carried out in solution to characterize the expected reaction products, define the nature of the conducting salt and check different electrolysis conditions latter to be used under solid phase conditions.

As an inexpensive electrolysis apparatus an undivided beaker-type cell (Figure 20, commerical Metrohm titration vessels and lids were adapted in the local machine shop) was equipped with two carbon electrodes (area of the electrodes immersed in the electrolytic solution-2.7 cm^2, distance between the two electrodes-0.5 cm).

Figure 20. Electrolysis apparatus

The cell was then immersed into a cooling bath thermostated at 0°C. For the electrolysis a current density of 0.015 A/cm^2 was applied. The power was supplied by an EA-PS-2032-025 instrument by which the current required for the electrolysis was fixed to 0.04 A and a electronic Coulomb-meter was used to calculate automatically the total electricity consumed for electrolysis.

For all electrochemical experiments galvanostatic conditions were used (constant current method). In the literature the advantage of controlled current density was convincingly documented for methoxylation of 1-(2-furyl)ethylacetate (**46**) which was carried out with a platinum electrode in methanolic media with $(C_2H_5)_4NClO_4$ as supporting electrolyte and yields almost quantitatively the corresponding 2,5-dimethoxy-2,5-dihydro derivative **47** (Scheme 62).



Scheme 62. Anodic oxidation by galvanostatic condition

As far as the same methoxylation is carried out at controlled potential of the anode, so with increasing conversion, i.e. with decreasing concentration of the substrate, the current gradually decreases until it approaches zero toward the end of the electrolysis. In this way

the duration of the electrolysis is prolonged and the working electrode may be passivated, e.g. by its surface being covered by polymers.

In the galvanostatic method, the current was kept constant throughout the reaction and hence the total electricity (F/mol) can easily be calculated by the equation:

Relative amount of electricity (F/mol) = (3600 x Ah)/(96500 x M)

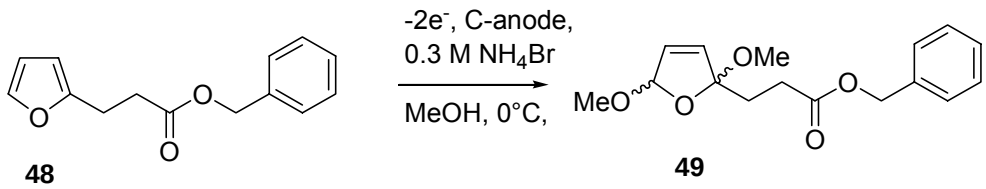
Where Ah = Ampere hour for the reaction measured by a Coulomb-meter
1Ah = 3600 C, C = Coulombs
M = Mole (substrate).

The amount of electricity needed corresponds to the quantity of the reagents in the chemical reaction. The theoretical amount of the electricity can be calculated on the basis of numbers of electrons which are required to promote the reaction. The unit usually used is Faraday per mole (F/mol). Since the electricity needed corresponds to a reagent the yield is often calculated on two different bases. Namely, one is the usual chemical (material) yield and the other is the current yield (or current efficiency), calculated on the basis of the amount of electricity used from the equation

Current yield (%) = (E/T) x 100

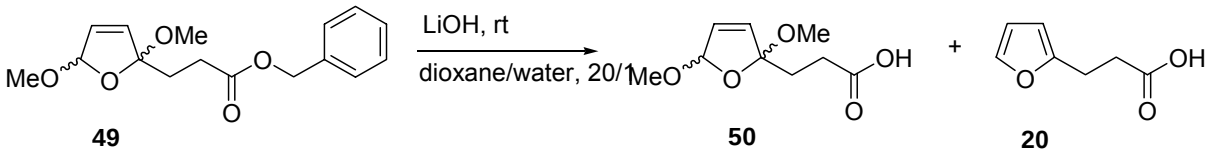
Where E = Amount of the electricity (F/mol) used to complete the reaction and T = theoretical amount of the electricity (F/mol) needed to complete the reaction. In electroorganic synthesis an excess amount of electricity is often required to achieve the synthesis with a satisfying material yield. For the methoxylation of furan 2 electrons are involved, therefore T = 2 F/mol.

For the solution phase experiments benzyl 3-(furan-2-yl)propanoate (**48**) was chosen as a first model substrate as the ester linkage should behave similarly like the linker and substrate linkage on solid support and both of them could be cleaved by an appropriate base. **48** was prepared by the standard esterification method using DIC and DMAP as catalyst. The elctrolysis was carried out at 0°C and a 0.3 M solution of ammonium bromide in MeOH was used as a supporting electrolyte and redox catalyst. A current density of 0.015 A/cm^2 was applied for the electrolysis, and the total amount of electricity needed for the reaction was 3 F/mol. After extraction with ethyl acetate the compound **49** was isolated as an isomeric mixture in 95% yield (Scheme 63).



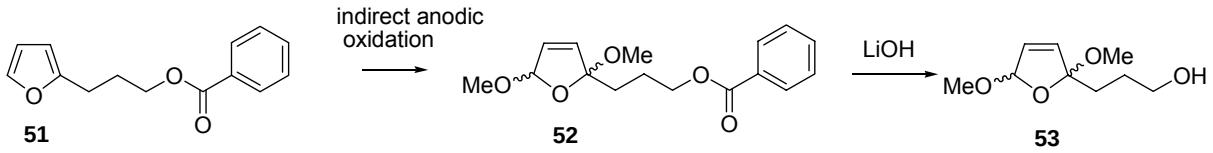
Scheme 63. Electrochemical preparation of benzyl 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanoate

In the solid phase synthesis the final product has to be cleaved off the resin by base. To evaluate the basic cleavage of the electrochemically prepared 2,5-dihydro-2,5-dimethoxyfuran product, the model compound benzyl 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanoate (**49**) was hydrolysed by LiOH (Scheme 64). The reaction was carried out in dioxane/water (20/1) at room temperature. After stirring for 12 h, water was added to the reaction mixture and the aqueous layer was washed with ethyl acetate to remove the benzyl alcohol. As the acid was in salt form in the aqueous layer, the aqueous layers were collected and treated with a buffer solution (pH=4, acetic acid/sodium acetate) in order to recover the acid. Then the aqueous layer was extracted with ethyl acetate and the organic layer was analyesd with GC-MS and NMR. From the analysis of the spectra it can be concluded that the organic layer was a mixture of 2-furanpropionic (**20**) and the 2,5-dihydro-2,5-dimethoxyfuran derivative **50**. The 2-furanpropionic was formed during protonation with the buffer as the desired 2,5-dihydro-2,5-dimethoxyfuran derivative **50** is very acid sensitive.



Scheme 64. Attempt to cleave the ester bond

Due to the instability of the 2,5-dihydro-2,5-dimethoxyfurans towards acids 3-(furan-2-yl)propyl benzoate (**51**) was chosen as the new model substrate so that after cleavage 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanol (**53**) will be isolated without requiring treatment with acid (Scheme 65).



Scheme 65. Electrochemical preparation of 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propyl benzoate

The model substrate 3-(furan-2-yl)propyl benzoate (**51**) was prepared by standard esterification method with 2-furanpropanol in presence of DIC as coupling reagent and DMAP as catalyst.

4.1.6 The quest for conducting salts and solvents for solid phase electroorganic synthesis

For the solid phase anodic oxidation of polystyrene resin supported 2-furanpropanol, methanol could not be used as a solvent because of the poor swelling of polystyrene resin in such a polar solvent. For that reason the swelling property of the polystyrene resin was checked in THF:MeOH (2:5), THF:MeOH (10:1), THF:MeOH (5:1), THF:MeOH (1:1), dioxane:MeOH (1:1). Dioxane:MeOH (1:1) was identified as the solvent mixture exhibiting the desired property.

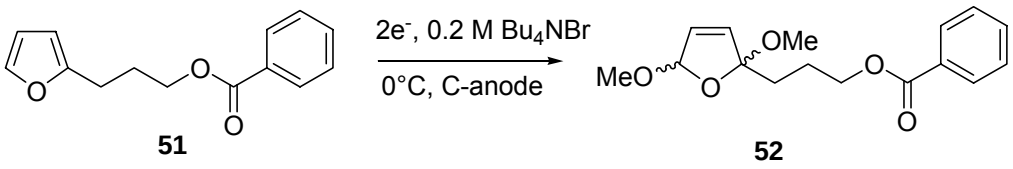
As ammonium bromide was not properly soluble in dioxane:MeOH (1:1). A suitable conducting salt was needed which should be properly soluble in this solvent and will provide bromide ions to mediate the electron transfer from the furan to the anode. Bromide containing ammonium salts such as trioctylamine hydrobromide and tetrabutylammonium bromide were evaluated serving as conducting salt.

Trioctylamine hydrobromide was prepared from commercially available trioctyl amine and hydrobromic acid. The experiment was carried out with the cell described above with two carbon electrodes. The cell was charged with 3-(furan-2-yl)propyl benzoate (**51**) and 40 mL 0.2 M trioctylamine hydrobromide in dioxane/MeOH (1/1) at 0°C. For the electrolysis a current density of 0.015 A/cm^2 was applied. The reaction was monitored by GC-MS, but even after 0.2581 Ah (8 F/mol, four times of the theoretical amount of electricity) electricity were consumed, no product was formed and the starting material was recovered. Instead of using dioxane/MeOH as solvent the same reaction was carried out in MeOH only, but the product **52** was not formed and the starting material was recovered. The failures of these reactions can be explained due to the inability of trioctylamine hydrobromide to mediate the anodic

oxidation. The indirect anodic oxidation was then tried with tetrabutylammonium bromide as conducting salt.

The experimental set up was to the one described above. The electrolysis was carried out in a 0.2 M tetrabutylammonium bromide solution in dioxane/MeOH (20/20 mL) at 0°C. For the electrolysis a current density of 0.015 A/cm^2 was applied. The reaction was monitored by GC-MS and after 0.1650 Ah (3 F/mol, which was required for the complete conversion of the starting material) electricity was consumed, the required 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propyl benzoate (**52**) was isolated as isomeric mixtures by extraction.

Although the swelling property of the substituted polystyrene resin was best in dioxane/MeOH among the solvents tested above, a second solvent screen was performed for the elctrolysis process. In each case the electrolysis was carried out in a 0.2 M tetrabutyl ammonium bromide solution in 40 mL solvent at 0°C. The current density was also fixed at 0.015 A/cm^2 (Scheme 66). The results of these experiments are summarized in Table 3.



51 **52**

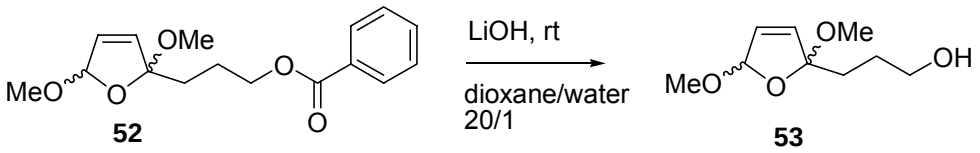
Scheme 66. Electrochemical preparation of 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propyl benzoate

Entry	Solvent	Electricity [F/mol]	Isolated yield [%]
1	THF:MeOH 2:5	4	90
2	THF:MeOH 10:1	8	0
3	THF:MeOH 5:1	8	0
4	dioxane:MeOH 1:1	3	90
5	THF:MeOH 1:1	3	90

Table 3. Anodic oxidations in different solvents

In case of entry 2 and 3 only the starting material was recovered, even after 8 F/mol electricity were consumed as the corresponding 2,5-dihydro-2,5-dimethoxyfuran **52** was not observed. It could be that the amount of methanol was not sufficient for the dimethoxylation. Although 4 and 5 produced similar results, the superior swelling property of polystyrene resin in 4 led to the identification of Bu_4NBr in MeOH/dioxane (1/1) as an ideal electrolyte.

3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propyl benzoate (**52**) prepared by the above mentioned procedure was cleaved by LiOH (1 equiv) in presence of dioxane/water (20/1) at room temperature and the corresponding alcohol **53** was isolated in 90% yield (Scheme 67).



Scheme 67. Cleavage of 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propyl benzoate by LiOH

The cleavage had also been carried out in THF/water (20/1) and MeOH/water (20/1) mixtures using NaOH (1 equiv) as base. The best purity was achieved by using dioxane/water (20/1) as solvent and LiOH (1 equiv) as base.

Other model reactions (Table 4) were carried out in dioxane/MeOH (1/1) using 0.2 M tetrabutylammonium bromide as the conducting salt and excellent yields were achieved with a current density 0.015 A/cm^2. GC-MS was used to monitor the reactions as well as to determine the purity of the final product. Substrate **57** was prepared by standard Grignard reaction of 1-(furan-2-yl)-6-hydroxyhexan-1-one (**31**) with commercilally available ethyl magnesium chloride in dry THF under argon at 0°C followed by esterification with benzoic acid in presence of DIC and DMAP.[108]

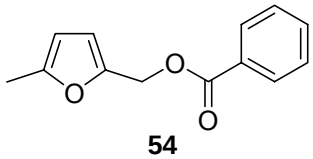
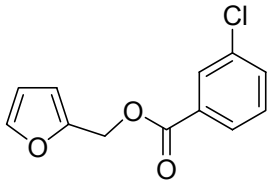
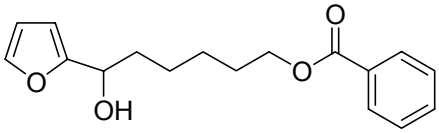
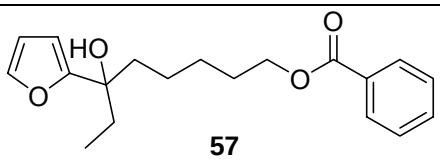
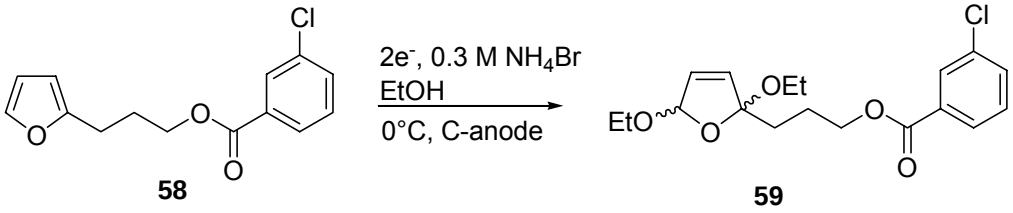
Entry	Substrate	Electricity [F/mol]	Purity	Isolated yield
1	 **54**	4	95%	90%
2	 **55**	3	95%	90%
3	 **56**	16	90%	78%
4	 **57**	16	90%	88%

Table 4. Electrochemical model reactions in solution

Substituting MeOH for EtOH in the electrolyte for the electrolysis of 3-(furan-2-yl)propyl 3-chlorobenzoate (**58**) furnished the corresponding diethoxylated dihydrofuran **59** in 78% (3 F/mol) (Scheme 68).



58 **59**

Scheme 68. Indirect anodic ethoxylation

4.1.7 Study of different parameters of the electroorganic oxidation on solid phase

For the indirect anodic oxidation on solid phase, polystyrene supported 2-furanpropanol **60** was chosen as a test sbstrate (Figure 21) to optimize the reaction conditions to achieve the best yield and the best purity.

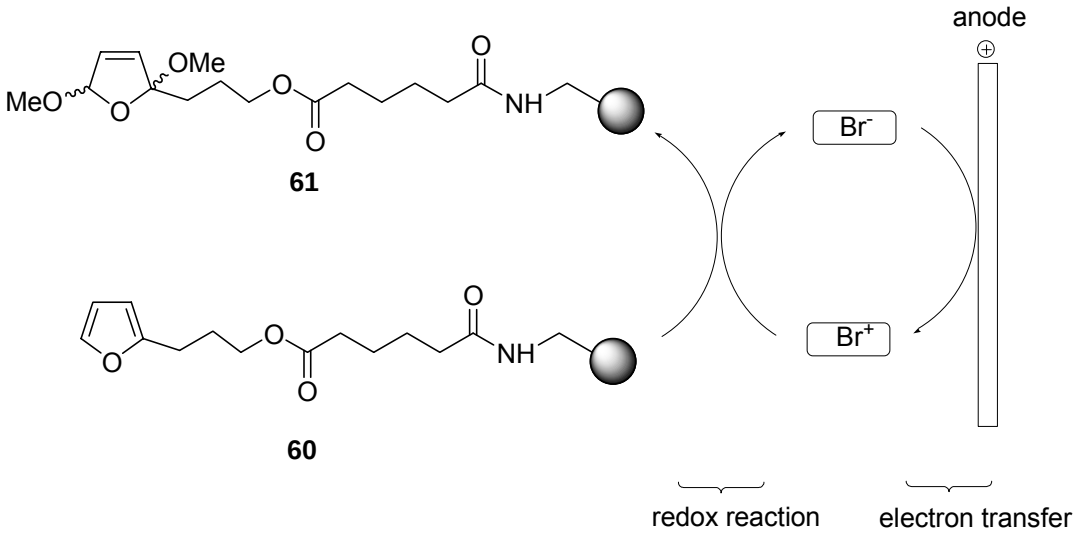
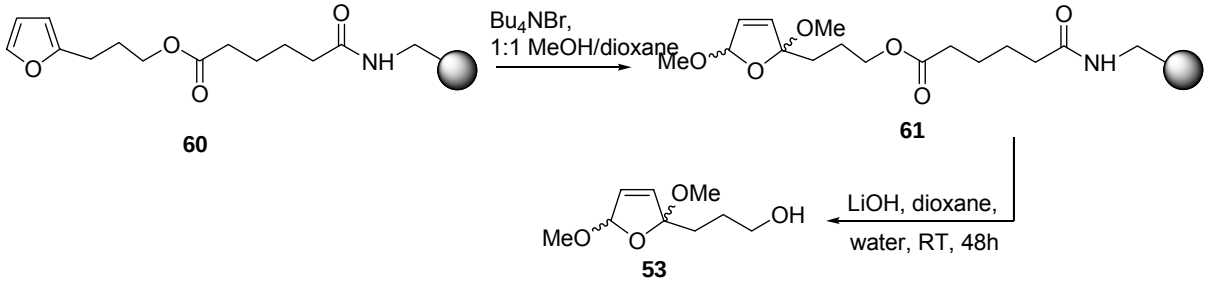


Figure 21. Br^+/Br^- mediated dimethoxylation of solid supported 2-furanppropanol

To establish the methodology of indirect anodic oxidation on solid phase the following reactions were performed with varying several parameters. The results obtained are summarized in Table 5. 2-Furanpropanol (**21**) was attached via esterification to aminomethylated polystyrene resin supported adipic acid. Resin bound substrate **60** was subjected to the electrolysis conditions (Scheme 69) used in solution. Cleavage of the electrolysis product **61** by LiOH (5 equiv) in dioxane/water (20/1) furnished the corresponding 2,5-dimethoxydihydrofuran **53**.



Scheme 69. Anodic oxidation on solid phase

The cell was charged with 0.09 g resin **60** (0.08 mmol) and 40 mL 0.2 M tetrabutylammonium bromide in dioxane/MeOH (1/1) and the yield was calculated after cleavge by LiOH (5 equiv) in dioxane/water (20/1) to furnish the corresponding 2,5-dimethoxydihydro furan **53** as a *cis/trans* mixture.

Entry	Electrode distance (cm)	Current density (A/cm^2)	Electricity (F/mol)	Temperature (°C)	Isolated yield	GC-MS purity (%)
1	0.5	0.015	40	0	57	97
2	0.5	0.015	40	RT	52	89
3	1.6	0.015	40	0	Not isolated	19 (not complete conversion)
4	0.5	0.015	20	0	Not isolated	42 (not complete conversion)
5	0.5	0.015	120	0	27	46
6	0.5	0.30	40	0	49	84

Table 5 Variation of reactions parameters in the electroorganic oxidation on solid phase

From Table 5 it can be concluded that the best conditions for the solid phase electroorganic oxidation are

1) Temperature = 0°C,

2) Electrode distance = 0.5 cm,

3) For complete conversion 40 F/mol electricity is required.

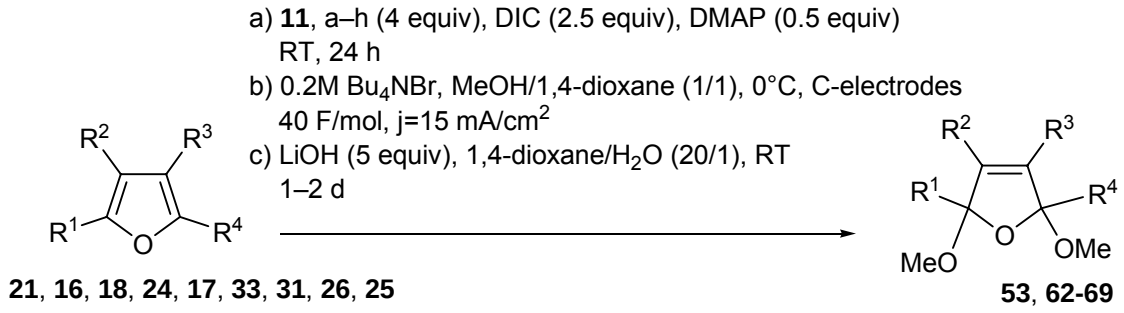
4) For complete conversion and best yield, best current density is 0.015 A/cm^2

In order to study the influence of electrolyte concentration on the electrochemical formation of 3-(2,5-dihydro-2,5-dimethoxyfuran2-yl)propanol (**53**) different reactions were carried out and the results are summarized in Table 6. The cell was charged with 0.09 g resin **60** (0.08 mmol) and 40 mL 0.X M tetrabutylammonium bromide (X=0.02 M, 0.2 M, 0.3 M) in dioxane/MeOH (1/1), and the other conditions were the best conditions concluded from the above experiments. The best yield was achieved with 0.2 M tetrabutylammonium bromide solution in dioxane/MeOH (1/1).

Run	Bu_4NBr	Electricity	Yield
1	0.02 M	60 F/mol	47%
2	0. 2 M	40 F/mol	57%
3	0.4 M	40 F/mol	55%

Table 6. Influence of electrolyte concentration

Having identified the optimal reaction conditions the scope of this reaction (**Scheme 22**) was explored with substrates **21**, **16**, **18**, **24**, **17**, **33**, **31**, **26**, **25** (Scheme 70, Table 7). Apparently uninfluenced by the substitution pattern the dimethoxylated 2,5-dihydrofurans were formed in high yields (50–63% over three steps) and excellent purities starting from mono-, di-, and trisubstituted furans (Table 7, entries 1–3 and 5). The electrochemical solid phase transformation tolerates various functional groups (alkyl, OH, ester, amide). No reaction took place with electron-poor furan **31** and 5-(dimethylaminomethyl)furfurylalcohol (**26**) (Table 7, entries 7,8), whose unreactive behavior was known from earlier work in solution. Substituting MeOH for EtOH in the electrolyte for the electrolysis of substrate **21** furnished the corresponding diethoxylated dihydrofuran **70** in 53% (>98% purity). For furan **25** the dimethoxylated 2,5-dihydrofuran **69** was isolated in 19% yield and with 95 % purity, (determined by ^1H NMR spectroscopy and GC/MS). The poor yield was due to the high volatility of the product.



21, **16**, **18**, **24**, **17**, **33**, **31**, **26**, **25**

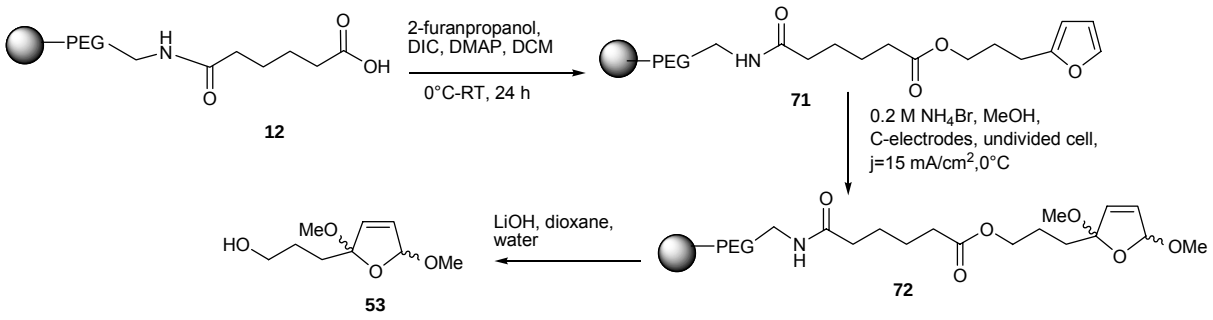
53, **62-69**

Scheme 70. Anodic oxidation on solid phase with different substituted furans

Entry	Furans	R^1	R^2	R^3	R^4	yield [%]	purity [%]
1	**21**	$-(CH_2)_3OH$	-H	-H	-H	57	97
2	**16**	$-CH_2OH$	-H	-H	$-CH_3$	63	97
3	**18**	$-CH(CH_3)OH$	-H	-H	-H	50	95
4	**24**	$CH_2NHCO(CH_2)_5OH$	-H	-H	-H	53	95
5	**17**	$-CH_3$	$CH(CH_3)OH$	-H	$-CH_3$	63	95
6	**33**	$-CH(OH)(CH_2)_4OH$	-H	-H	-H	53	97
7	**31**	$-CO(CH_2)_4OH$	-H	-H	-H	0	-
8	**26**	$-CH_2OH$	-H	-H	CH_2NMe_2	0	-
9	**25**	$-CH_2OH$	-H	-H	-H	19	95

Table 7. Scope and limitations of the electroorganic 2,5-dimethoxylation of furans on solid phase.

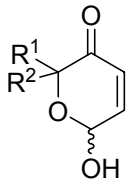
Although for reason of cost and loading efficiency cross-linked polystyrene (PS) resins still are the most widely used support in SPOS, but this reaction on solid phase was established also using tentagel resin as a solid support. As methanol is ideal for swelling of tentagel resin the electrolysis can even be carried out in 0.2 M ammonium bromide solution in methanol, which corresponds to the original electrolyte used by Clauson-Kaas[7] for the solution phase electrolysis. The electrolysis was carried out galvanostatically consuming 50 F/mol electricity. The solid supported reaction product was cleaved by LiOH in dioxane/water (20/1) mixture to furnish 3-(2,5-dihydro-2,5-dimethoxy-2)propanol (**53**) as a *cis/trans* mixture in 55% yield and >95% purity (determined by ^{1}H NMR spectroscopy and GC/MS) as a yellow oil (*cis/trans* mixture) (Scheme 71).



Scheme 71. Indirect anodic oxidation with tentagel supported furan

4.1.8 Achmatowicz rearrangement

To demonstrate the utility of the electroorganic solid phase method and that it can be easily implemented in a multistep solid-phase synthesis, a challenging multistep synthesis on solid phase was attempted. The target chosen was the highly functionalized product **73**, which can serve as a scaffold for further derivatization[45]



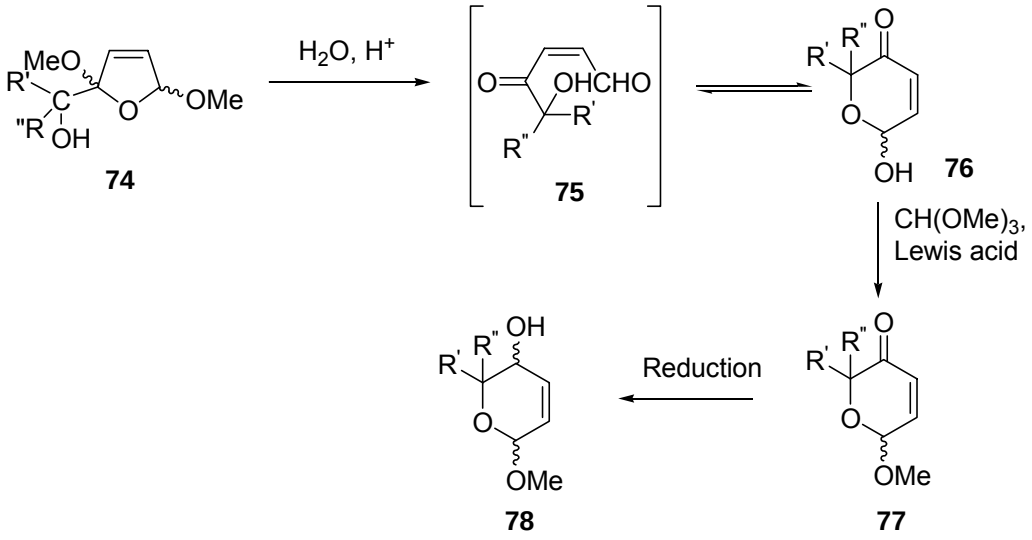
73

Recent developments of polymer supported chemistry have been driven by interest in the assembly of libraries of molecular diverse compounds for combinatorial chemistry.[109] Excellent examples of sophisticated directed libraries have been reported, including pharmacophoric scaffolds,[110] and even natural products with highly complex architectures.[111] This field is very interesting due to suitably functionalized druglike[112] structures having specific architecture and rigidity, and their short synthetic pathways comprising reliable, clean, and high-yielding reactions, as well as an overall "diversification strategy" resulting ideally in "libraries of libraries"[113] of scaffolds. Libraries are mainly formed with a number of derivatives with the same central structure of a core molecule. Several versatile molecules that were key intermediates used by traditional medicinal chemists, for example, Corey's lactone, the Wieland-Miescher ketone, and the Prelog-Djerassi lactone, could lead to a variety of pharmacophoric frameworks. These starting materials are small molecules equipped with many reactive sites and functionalities, which can undergo both skeletal rearrangements and functional group interconversions. The use of such a polymorphic compound as the goal of a library would be of great advantage since: many known synthetic key intermediates lead to medicinally important scaffolds which possess high potential for

both structural and functional diversification and their chemical transformations and modifications in solution are well documented.

2*H*-pyran-3(6*H*)-one **73** and its derivatives exhibit significant biological activities. Such compounds have also acted as templates for the synthesis of monosaccharides and glycosides. In addition, they undergo skeletal rearrangements to yield a wide range of structures ranging from polyhydroxylated chains and benzodiazepines to butenolides and anthraquinones.

Achmatowicz *et al*. reported[35] a route for obtaining monosaccharides from simple furan compounds (Scheme 72) (see also 3.1.5 and Scheme 16).

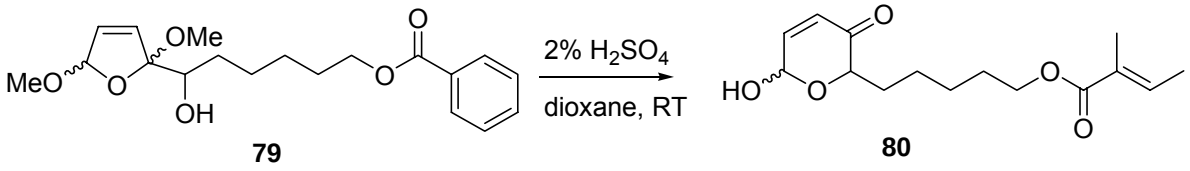


Scheme 72. Achmatowicz rearrangement

Before applying the above Scheme on solid phase, some model reactions were carried out in solution. Chiral furyl carbinol, 6-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)-6-hydroxyhexyl benzoate (**79**) was prepared by electrolysis of 6-(furan-2-yl)-6-hydroxyhexylbenzoate (**56**) following the standard electrolysis condition in solution as described above.

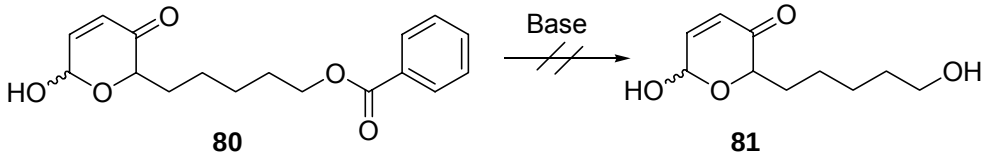
For the rearrangement a solution of 6-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)-6-hydroxyhexyl benzoate) (**79**) in dioxane was treated with 2% H_2SO_4 (v/v) at rt (Scheme 73) as described by Caddic *et al*.[41] The reaction mixture was quenched with solid $NaHCO_3$ and extraction with ethyl acetate gave compound **80** as a mixture of stereoisomers in 80% yield. This hydroxypyranone derivative **80** exhibits low stability in aqueous solution at ambient temperatures but can be stored at reduced temperature without significant decomposition. The work up procedure for this reaction was laborious and problematic. The reaction

conditions required an aqueous solution of sulfuric acid, which had to be removed in vacuo at the end of the reaction maintaining a water bath temperature below 30°C.



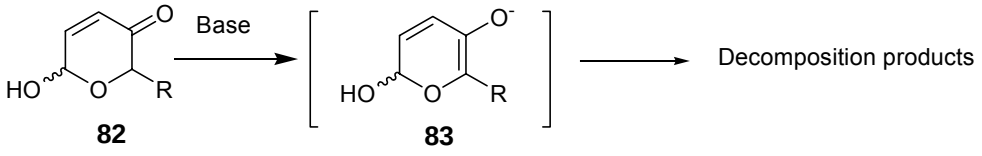
Scheme 73. Achmatowicz rearrangement on model substrate in solution

As the main aim was to cleave the rearranged product (6-hydroxy-2-(5-hydroxypentyl)-*2H*-pyran-3(*6H*)-one)} (**81**) from solid phase, the hydrolysis of **80** was tried in presence of base (Scheme 74).



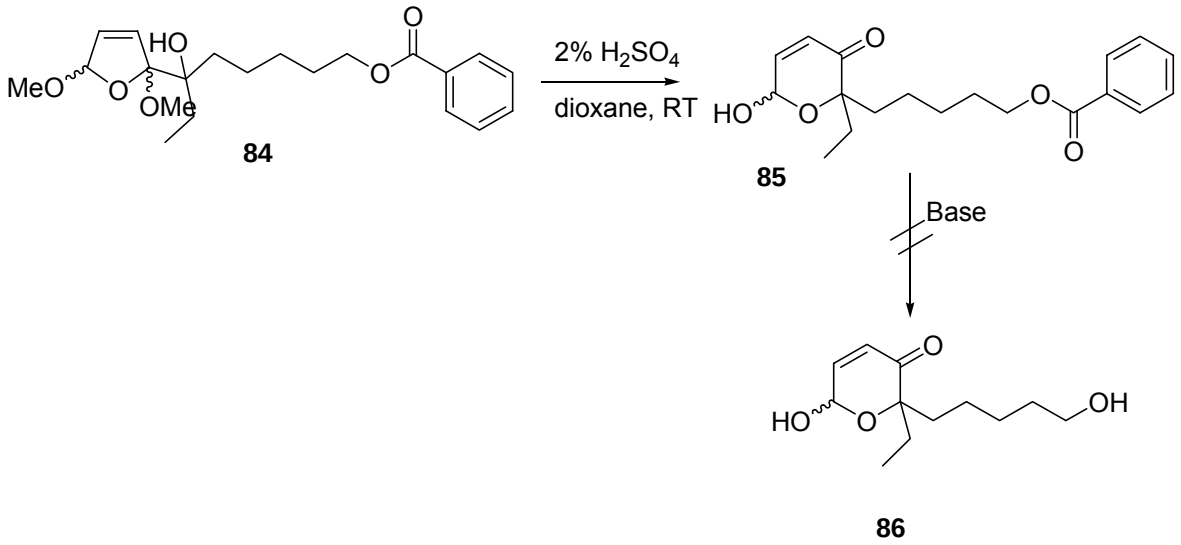
Scheme 74. Cleavage of model Achmatowicz rearranged product by base

The reactions were performed with different bases, for example LiOH in dioxane/water (20/1), NaOH in dioxane/water (20/1), KOH in dioxane/water (20/1), NaOMe in dry methanol, K_2CO_3 in methanol/THF mixture. But none of them were successful. In all cases benzoic acid was isolated (methyl benzoate for the cleavage with NaOMe) along with some decomposition products. Actually, there is literature precedence that hydroxypyranone derivatives **82** undergo rapid decomposition under basic conditions (Scheme 75).[114]



Scheme. 75. Decomposition of hydroxypyranone in presence of base

In order to avoid this type of decomposition the above rearrangement sequence was performed with 6-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)-6-hydroxyoctyl benzoate (**84**) (Scheme 76), Because after rearrangement no enolizable proton will exist in position 2 of the pyranone derivative.

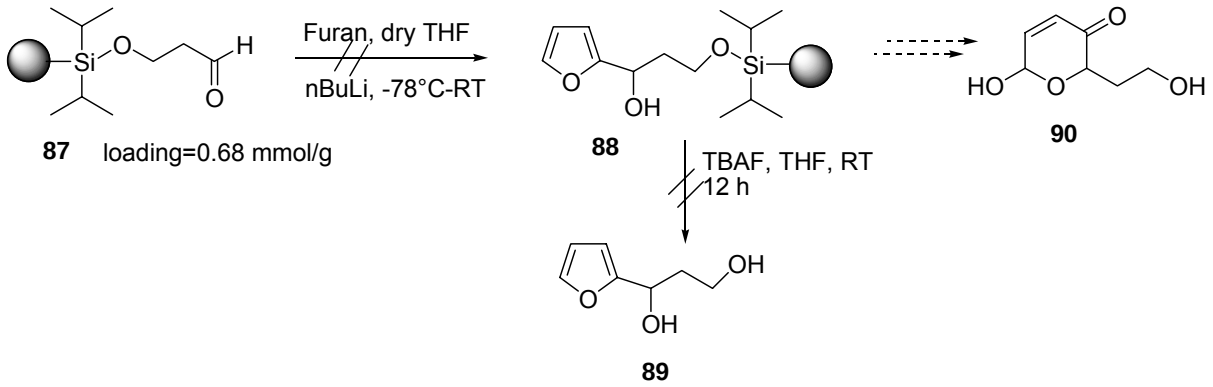


84 **85** **86**

Scheme 76. Model Achmatowicz rearrangement with different substrate

Although the rearrangement in presence of 2% H_2SO_4 (v/v) at room temperature gave the 5-(2-ethyl-3,6-dihydro-6-hydroxy-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (**85**) in 77% yield, the subsequent cleavage was unsuccessfull in presence of base. Again, only decomposition was observed.

For the cleavage of 6-hydroxy-2-(5-hydroxypentyl)-2*H*-pyran-3(*6H*)-one (**81**) from solid support base could not be used as the product was unstable in basic condition. Therefore, an acid labile linker **87** was chosen in which hydroxy propanaldehyde was attached to polystyrene support via a disopropyl silyl ether linkage (Scheme 77). Silyl ethers are inert towards strong bases, oxidants[115] (ozone, Dess-Martin periodinate, sulfur trioxide-pyridine complex) and weak acids (e.g. 1 mol/L HCOOH in DCM), but can be selectively cleaved by treatment with HF in pyridine or with TBAF. Silyl ether attachment has been successfully used for the solid phase synthesis of oligosaccharides.[116]



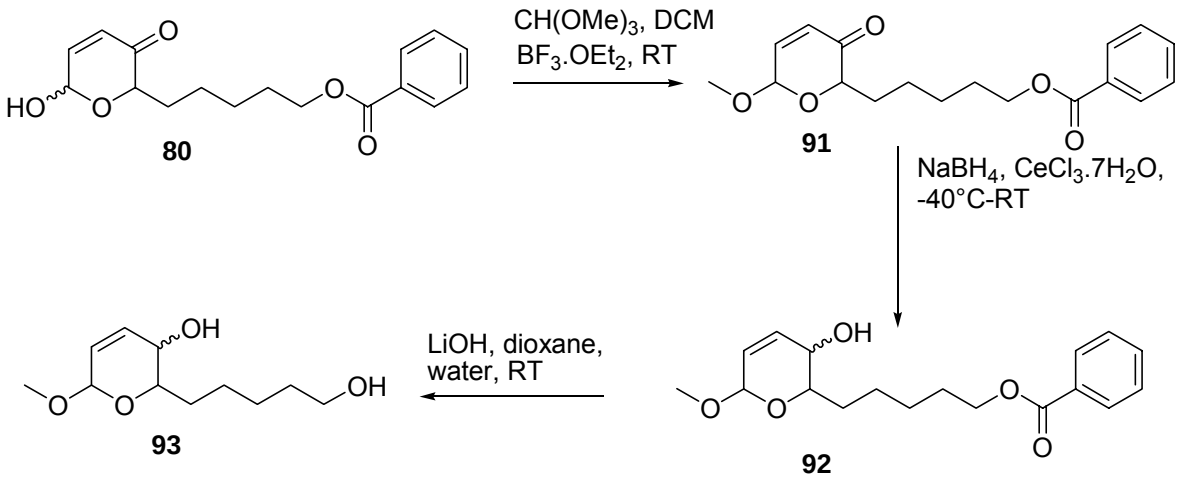
87 loading=0.68 mmol/g **88** **89** **90**

Scheme 77. Addition of lithiated furan using a silyl linker

The reaction was carried out in dry THF under argon atmosphere. The lithiation of furan was carried out at -78°C for 2 h, and then the furyl lithium solution was added to the solution of silylated polystyrene resin attached aldehyde **87** in dry THF at -78°C and stirred for 3 h. After stirring the solution overnight at room temperature the resulted blood red solution was quenched with MeOH and water. After washing with DMF, DMF/water, THF, MeOH, the brown beads were analysed by IR. No peak of aldehyde was observed in the IR spectra. The resin was then cleaved with TBAF (5 equiv.) in dry THF. But after cleavage the required diol **89** was not found. Only some decomposition products were found.

The same reaction was tried following a similar procedure as described by Ganesan *et al.*[117]. In which a furan was attached on solid support and the electrophile was an aldehyde. Following their procedure the lithiation was carried out in dry THF at -30°C under Ar atmosphere. After stirring the reaction mixture for 4 h at -30°C the furyl lithium solution was added slowly to the solution of aldehyde attached to silylated polystyrene resin **87** in dry THF at -30°C. The reaction was allowed to slowly warm up to room temperature (30 min) and stirring continued. Methanol (2 mL) was added and the resin filtered and washed with water, methanol and THF. But after cleavage with TBAF the required diol **89** was not found. Only some decomposition products were found. Somehow the electrophillic attack did not take place on solid phase because the resin could not swell properly at -78°C.

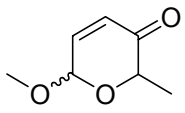
As the isolation of 6-hydroxy-2-(5-hydroxypentyl)-*2H*-pyran-3(*6H*)-one (**81**) was impossible so further modifications on solid phase were necessary to produce a more stable intermediate (Scheme 78).



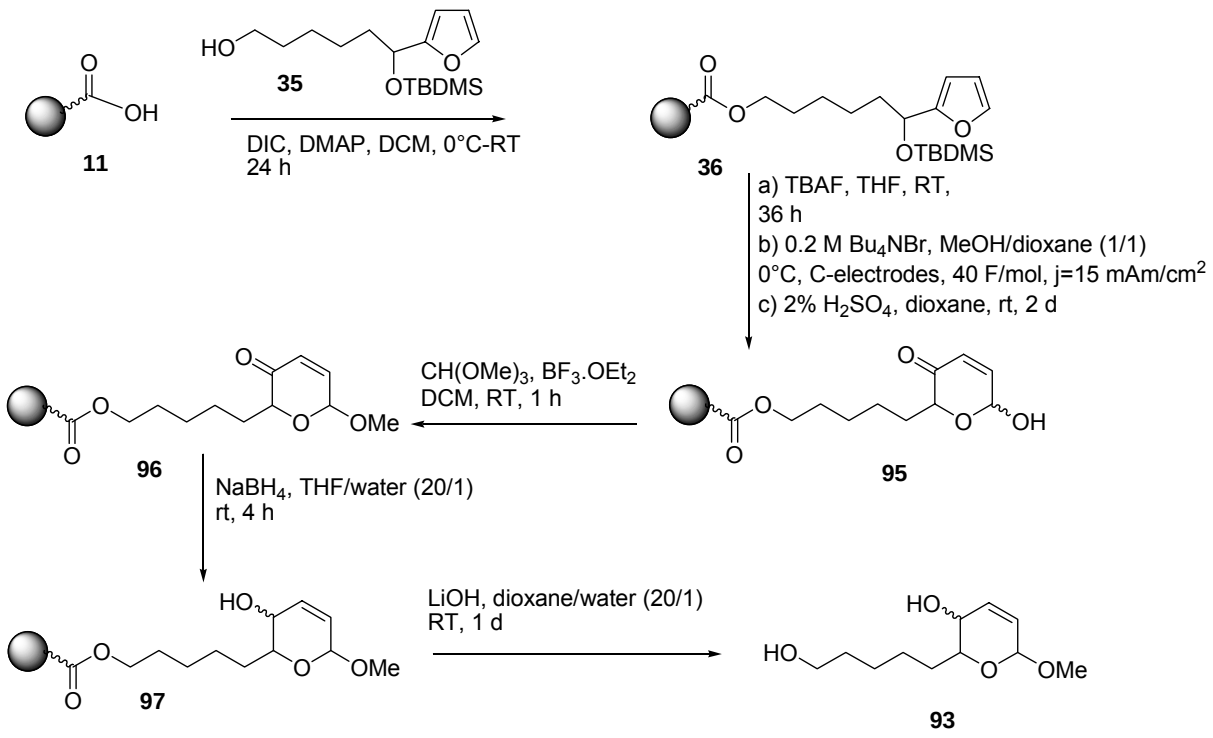
Scheme 78. Modification of the Achmatowicz rearranged product in solution

As there was good evidence[118] for an increased stability of **93** in presence of strong base e.g. KOH, the above scheme was thought to be successful. As described by Hodgson *et al*.[116] the previously prepared rearranged product 5-(3,6-dihydro-6-hydroxy-3-oxo-2*H* pyran-2-yl)pentyl benzoate **80** was treated with $CH(OMe)_3$ and $BF_3.OEt_2$ in dry dichloromethane. The reaction mixture was stirred for 2 h. But after quenching with $NaHCO_3$ solution and extraction with DCM the required product **91** was not formed. Analysis of the crude reaction mixture by NMR and GC-MS revealed a mixture of different products and in the NMR no peak was found in the alkene region. The reason could be that the double bond of the pyranone ring **80** might react with $CH(OMe)_3$ as the reaction was stirred for 2 h which led to decomposition.

For that reason the same reaction was carried out again by the similar procedure and it was monitored by thin layer chromatography. It had been observed that the reaction was finished within 5 minutes. After quenching with $NaHCO_3$ and extraction with DCM the desired product **91** was isolated as an isomeric mixture in 90% yield. For the reduction of the keto group of **91**, the reduction was carried out by a similar procedure as described by Sammes *et al*.[119] for similar type of pyranosids (**94**). According to them a solution of 5-(3,6-dihydro-6-methoxy-3-oxo-2*H* pyran-2-yl)pentyl benzoate (**91**) in THF was added slowly to a stirred solution of sodium borohydride in water at 0°C. After stirring it for 30 min at 0°C, neutralisation with dilute acetic acid, the product was extracted with ether and analysed by NMR. But only traces of product (**92**) along with lots of decomposition products were found. The reaction was performed again following the procedure of Hodgson *et al*.[116] Following their procedure the reaction was carried out in presence of cerium trichloride heptahydrate in absolute ethanol and at –40 °C. After purification by silicagel chromatography 96% of the required product **92** was isolated as an isomeric mixture. Cleavage of the reduced product by LiOH in dioxane/water mixture at room temperature followed by purification through silicagel chromatography gave 90% of **93** as an isomeric mixture.



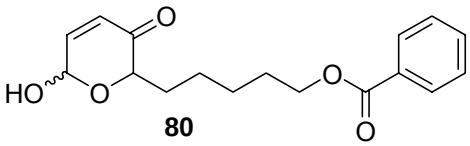
94



Scheme 79. Solid phase synthesis of the Achmatowicz rearranged product

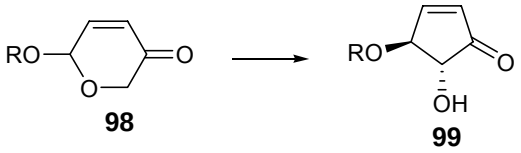
The above reaction sequence was carried out on solid phase (Scheme 79). The monosilyl-protected diol was attached to aminomethylated polystyrene supported adipic acid **11** using the standard esterification method. After deprotection with TBAF, α-hydroxyfuran **37** was electrolyzed as described above. The resulting α-hydroxy-2,5-dialkoxy-dihydrofuran **66** rearranged upon addition of aq. H_2SO_4 in 1,4-dioxane to the 6-hydroxy-2,3-dihydro-6H-pyran-3-one **95**. $BF_3 \cdot Et_2O$ mediated acetalization with $HC(OMe)_3$ was carried out for 1 h at room temperature as described by Couladouros *et al.*[45]. 1,2-reduction with $NaBH_4$ was done in THF/water (20/1) at room temperature and cleavage by saponification delivered the desired product **93** which was isolated in 33% yield (over seven steps on solid phase). The reaction sequence detailed above clearly demonstrates that in contrast to previous attempts using modified electrodes[28,30,31] this indirect approach is suitable for multistep syntheses on the solid phase which can lead to libraries of diversified compounds or natural products.

As the hydroxypyranones **73** are well suited as starting materials for the preparation of a variety of biologically important molecules,[120] it was chosen for diversity oriented synthesis. An important feature of hydroxypyranones is that they are admirably endowed with differentiated functionality suitable for further elaboration by reaction with selected nucleophiles and electrophiles. For that purpose different model reactions were tried in solution with hydroxypyranone **80** towards the goal of using the Achmatowicz reaction in the context of combinatorial synthesis on solid phase.



80

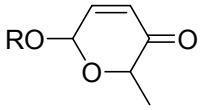
Attempts were made to synthesize functionalized cyclopentenones via rearrangement of pyranones. Despite the fact that numerous methods are available for the synthesis of cyclopentane derivatives very few of them offer simple reaction conditions. A novel ring contraction of 6-alkoxy-2,3-dihydro-6H-pyran-3-ones **98** provides a short and efficient access to highly functionalized cyclopentenones **99** [121] (Scheme 80).



98 **99**

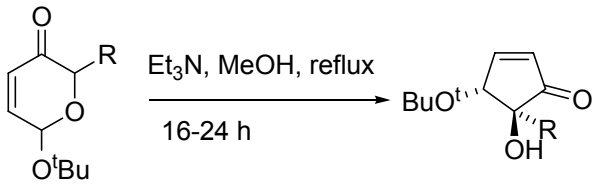
Scheme 80. Cyclopentenones via rearrangement of pyranones

Kolb *et al*.[121] reported the isomerisation reaction of pyranones to a cyclopentenone using a palladium catalysed procedure in presence of a buffer. Although they did not find the desired cyclopentenone derivative with their optimized conditions from C-2 substituted pyranone **100**. Therefore, this was not a practical way for cyclopentenone formation from substrate **80** which is already a C-2 substituted pyranone.



R=Me, Et **100**

Caddick *et al*. described a modified procedure, which could be carried out in preparative scale without the requirement of metal catalysts using only an amine base.[43] They have described the base mediated isomerisation of C-2 substituted pyranones **101** to form substituted functionalized cyclopentenones **102** (Scheme 81). They found that simply changing the solvent from DMF to MeOH gave the isomerisation products in moderate to good yield.

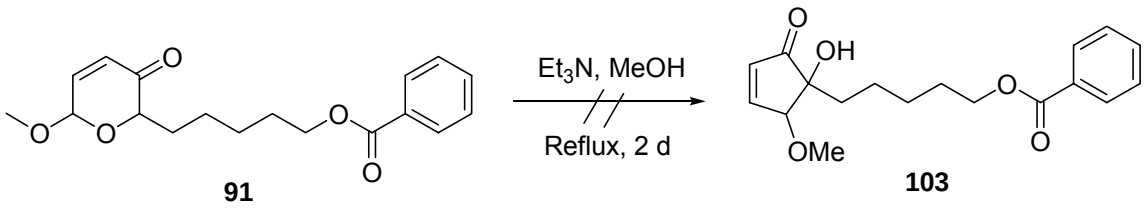


R=Me, Et, Ph. **101**

37-60% **102**

Scheme 37. Substituted cyclopentenones via rearrangement of C-2 substituted pyranones

Following the above procedure 5-(3,6-dihydro-6-methoxy-3-oxo-2*H* pyran-2-yl)pentyl benzoate (**91**) was treated with Et_3N (5 equiv) in methanol (Scheme. 82) and the reaction mixture was refluxed for 2 days.

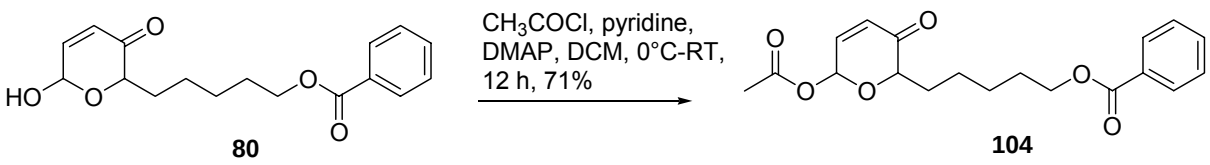


91 **103**

Scheme. 82. Attempts to prepare cyclepentenones via rearrangement of pyranones in solution

The desired cyclopentenone **103** was not formed after working up the reaction mixture by extraction with ethyl acetate. From analysis of the NMR of the crude product only starting material was detected. The same reaction was performed in DMF instead of methanol, but the desired product was not found.

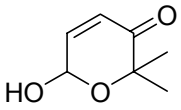
Activation of the hemiacetal hydroxyl functionality was achieved through the formation of the acetoxypyranone with acetic anhydride and sodium acetate affording the acetate in 60-70% yield.[43] According to this procedure **80** was treated with acetic anhydride (4 equiv) and sodium acetate (4 equiv.) in THF (Scheme. 83). But even after 2 days the reaction was not complete and only traces of product **104** were detected along with reactant **80** which was in major portion. Clive *et al*. reported pivaloylation of pyranosidulose in presence of pyridine and DMAP in DCM.[122] Following this procedure **80** was treated with acetyl chloride (2.5 equiv), pyridine and DMAP in dry DCM at 0°C. Overnight stirring at room temperature followed by extraction furnished the acetylated product **104** in 71% yield (Scheme 83).



80 **104**

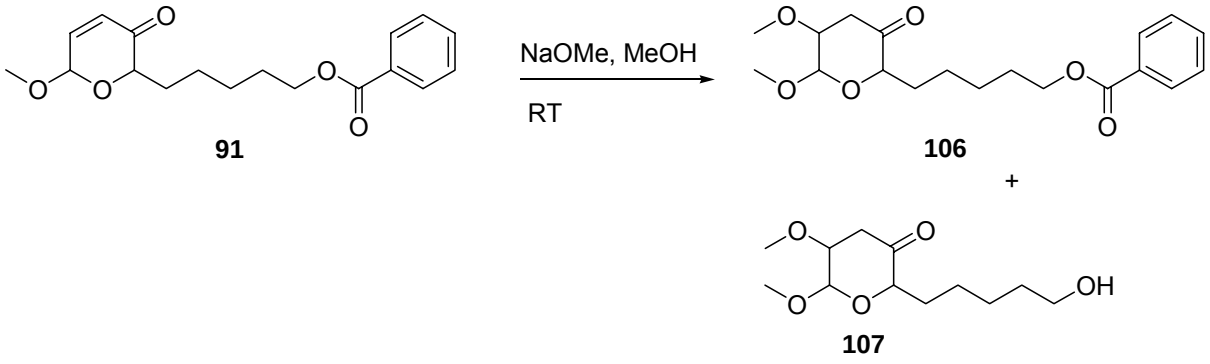
Scheme 83. Attempts to prepare 5-(3,6-dihydro-6-acetoxy-3-oxo-2*H*-pyran-2-yl)pentyl benzoate

The *2H*-pyran-3(*6H*)-ones of the general formula **105**, are widely used as starting materials for the synthesis of a variety of compounds[123] including several sugar and amino sugar derivatives.[124] For example, 1,4-addition of a nucleophile to the Michael acceptor moiety of **105**, gives efficiently 2-aminosugar precursors for the synthesis of antibiotics,[125] anticoccidals.[126]



105

Matsumura *et al.*[42] reported the Michael addition of methoxide anion to a pyranone ring. Following their procedure 5-(3,6-dihydro-6-methoxy-3-oxo-2*H* pyran-2-yl)pentyl benzoate (**91**) was treated with NaOMe/MeOH (1 equiv.) at room temperaute (Scheme 84)

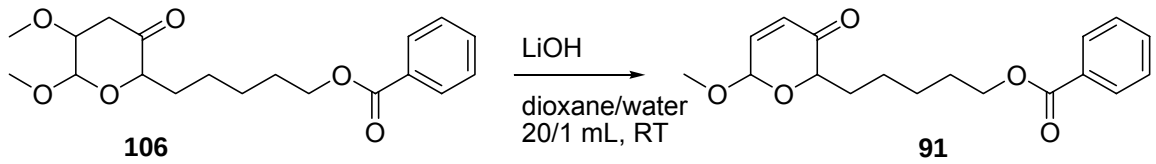


91 **106** + **107**

Scheme. 84. Attempts to prepare 5-(3,6-dihydro-6-acetoxy-3-oxo-2*H* pyran-2-yl)pentyl benzoate

The reaction was carefully monitored by GC-MS. After extraction with ethyl acetate the desired product **106** was observed in 80% purity and only trace amounts of dihydro-2-(5-hydroxypentyl)-5,6-dimethoxy-2*H*-pyran-3(4*H*)-one **107** could be detected. But when the reaction was carried out in presence of excess NaOMe (2.5 equiv) (to get predominantly dihydro-2-(5-hydroxypentyl)-5,6-dimethoxy-2*H*-pyran-3(4*H*)-one) (**107**) only decomposition of **106** and **107** was observed.

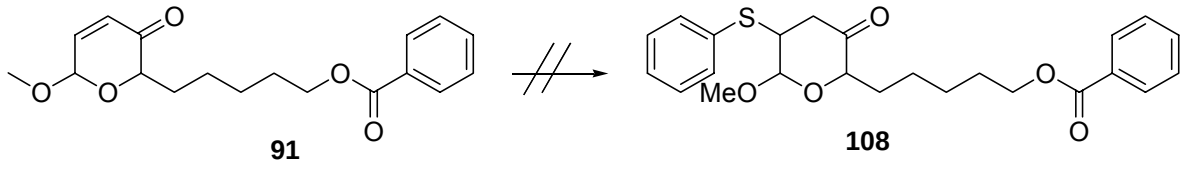
To isolate dihydro-2-(5-hydroxypentyl)-5,6-dimethoxy-2*H*-pyran-3(4*H*)-one (**107**), the Michael addition product 5-(tetrahydro-5,6-dimethoxy-3-oxo-2*H* pyran-2-yl)pentyl benzoate **(106)** was treated with LiOH (1 equiv.) in dioxane/water mixture at room temperature (Scheme 85). But instead of cleavage of the ester linkage retro Michael addition occured and the starting material (**91**) was detected by GC-MS. Only decomposition was observed when an excess amount of base was used. As this Michael addition behaved so capricious even in solution and it required careful monitoring of the reaction by GC-MS, it was considered to be impractical for a solid phase reaction sequence.



106 **91**

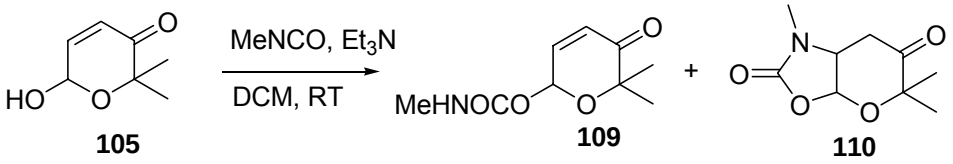
Scheme 85. Attempts to cleave 5-(tetrahydro-5,6-dimethoxy-3-oxo-2*H* pyran-2-yl)pentyl benzoate by base

Groot *et al*. reported the conversion of α,β -unsaturated ketones into β-(phenyl-thio)ketones.[127] According to them a fast addition of thiophenol was observed when sodium thiophenolate in THF was used. Following their procedure a solution of 5-(3,6-dihydro-6-methoxy-3-oxo-2*H* pyran-2-yl)pentyl benzoate (**91**)in dry THF was added to a solution of sodium thiophenolate (2 equiv) in THF and the mixture was stirred at room temperature, but after strring for one day the desired product **108** was not formed. Haroutounian *et al*. reported the stereoselective Michael addition of thiophenols to dihydropyridone system in a polar solvent (MeOH) in order o stabilize the enolate anion, using a large excess of nucleophile [128]. Moreover, a slightly alkaline pH environment prevented the possibility of a retro-Michael reaction to occur. Following their procedure the pH of a methanolic solution of thiophenol (3 equiv) was adjusted to 8 by addition of triethylamine and a methanolic solution of **91** (Scheme 86) was added, and the reaction mixture was stirred at room temperature and monitored by TLC. But even after one day no product was found and the starting material was discovered by GC-MS.



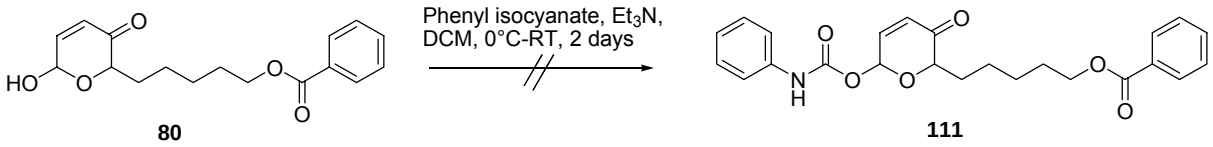
Scheme 86. Attempts to prepare 5-(tetrahydro-6-dimethoxy-3-oxo-5-(phenylthio)-2*H*-pyran-2-yl)pentyl benzoate by Michael addition

Georgiadis *et al*. described the carbamate formation between a pyranone and methyl isocyanate and triethylamine in DCM at room temperature.[129] They observed, that when *2H*-pyran-3(*6H*)-one **105** was treated with methyl isocyanate and triethylamine in DCM at room temperature, a minor by-product (5*H*-pyrano-[3,2-d]oxazole-2,6-dione) **110** formed along with the carbamate **109**. This was the intramolecular Michael adiition product which may be considered as a protected 2-aminosugar precursor (Scheme 87).



Scheme 87. Formation of carbamate from Achmatowicz rearrangement product

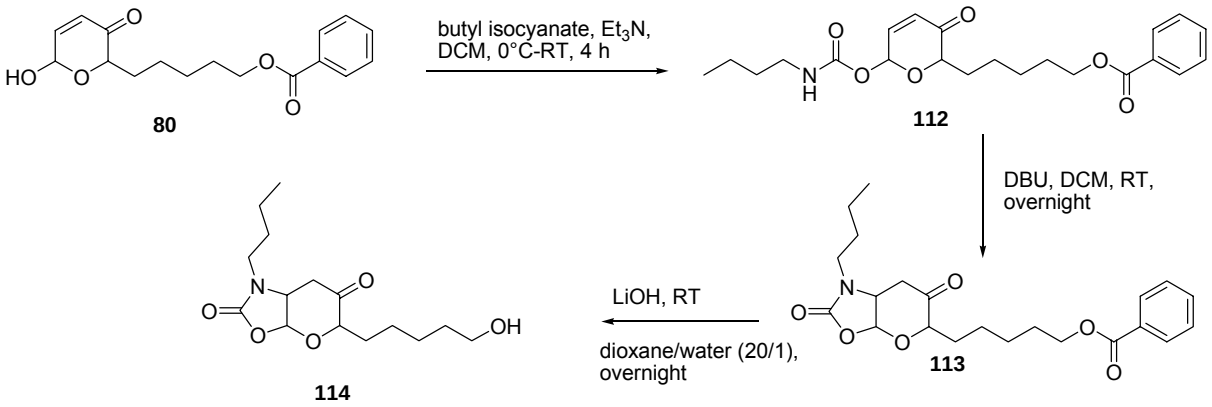
They found that when the carbamate **109** was treated with sodium bicarbonate in acetone/water solution at room temperature, it was converted to the bicyclic product **110** almost quantitatively. Along these lines Couladouros *et al*. described that under alkaline conditions (DBU) these carbamates quantitatively converted into pharmacophoric oxazolidinones **110**.[45] Following the procedure of Georgiadis *et al*. **80** was treated with phenyl isocyanate (1.5 equiv) and triethylamine in dry DCM at 0°C under argon atmosphere and allowed to warm at room temperature (Scheme 88).



Scheme 88. Attempts to prepare carbamate with phenyl isocyanate

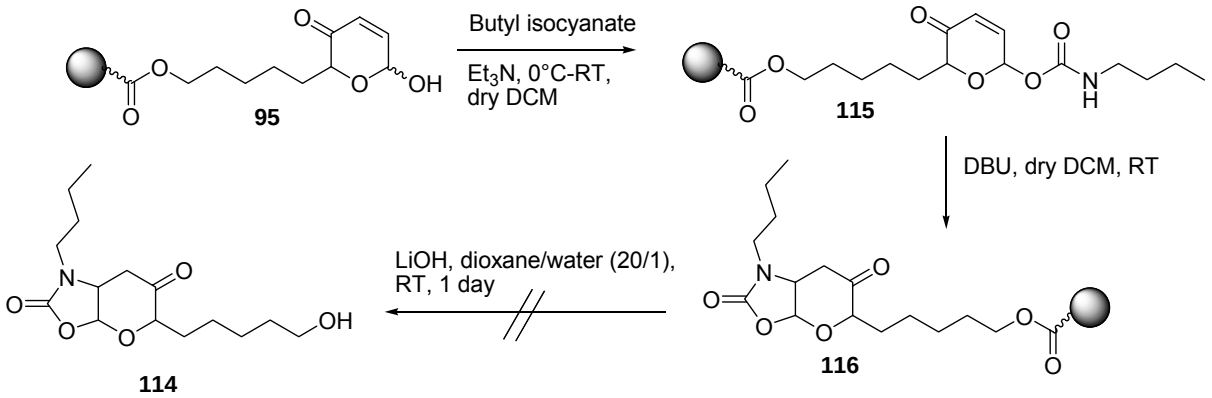
But even after two days, and refluxing, the desired product **111** was not found and the starting material was detected by GC-MS.

A similar reaction was performed with butyl isocyanate (1.5 equiv) in dry DCM and triethylamine (0.5 equiv) at 0°C under argon atmosphere and allowed to warm to room temperature (Scheme 89) for 4 h. Finally, purification by silica gel chromatography gave the corresponding butyl carbamate **112** in 60% yield. Following the procedure of Couladouros *et al*., **112** was treated with DBU (2 equiv) in dry DCM at room temperature. After stirring overnight 5-(1-butylhexahydro-2,6-dioxo-1*H*-pyrano[3,2-*d*]oxazol-5-yl)pentyl benzoate (**113**) was isolated in 80% yield. **113** was cleaved by LiOH in dioxane/water mixture at room temperature and 1-butyl-dihydro-5-(5-hydroxypentyl)-1*H*-pyrano[3,2-*d*]oxazol-2,6(3a*H*,*5H*)-dione (**114**) was isolated in 88% yield.



Scheme 89. Preparation of 1-butyl-dihydro-5-(5-hydroxypentyl)-1*H*-pyrano[3,2-*d*]oxazol-2,6(3a*H*,*5H*)-dione

To prepare 1-butyl-dihydro-5-(5-hydroxypentyl)-1*H*-pyrano[3,2-*d*]oxazol-2,6(3a*H*,*5H*)-dione (**114**) on solid phase, similar reaction conditions were carried out on solid phase (Scheme 90, Table 8).



Scheme 90. Attempts to prepare carbamate and Michael addition product on solid phase

After cleavage the crude product was analysed by NMR and GC-MS. The analysis of the spectra revealed that in all cases decomposition of the product has occured.

Entry	Conditions	Results
1	a) 10 equiv butylisocyanate, 12 equiv. Et_3N, dry DCM, 0°C-RT, 6 h. b) 12 equiv DBU, dry DCM, RT, overnight.	No product
2	a) 15 equiv butylisocyanate, 18 equiv. Et_3N, dry DCM, 0°C-RT, 10 h. b) 15 equiv DBU, dry DCM, RT, overnight.	No product
3	a) 15 equiv butylisocyanate, 18 equiv. Et_3N, dry DCM, 0°C-RT, overnight. b) 15 equiv DBU, dry DCM, RT, 2 d	No product
4	a) 15 equiv butylisocyanate, 18 equiv. Et_3N, dry DCM, 0°C, overnight. b) 15 equiv DBU, dry DCM, RT, 2 d	No product

Table 8. Attempts to prepare 1-butyl-dihydro-5-(5-hydroxypentyl)-1*H*-pyrano[3,2-*d*]oxazol-2,6(3a*H*,*5H*)-dione on solid phase

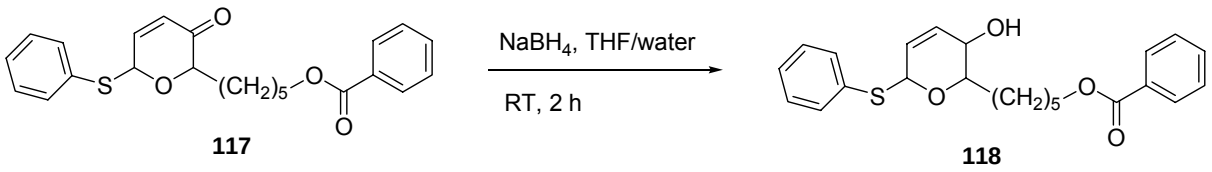
Silva *et al*. reported the substitution of an anomeric acetyl group with a thiophenol moiety using boron trifluoride etherate as catalyst in dry dichloromethane.[130] It was believed that for the transformation of the hydroxyl group of **80** to a thiophenyl group similar reaction conditions could be applicable. Following their procedure 5-(3,6-dihydro-6-hydroxy-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (**80**) was treated with PhSH (1.64 mmol) and BF_3 OEt_2 (0.82 mmol) in dry DCM at 0°C (Scheme 91). After stirring for 2 h at 0°C the desired product **117** was isolated in 68% yield.

80 **117**

Scheme 91. Preparation of 5-(3,6-dihydro-6-phenylthio-3-oxo-2*H* pyran-2-yl)pentyl benzoate

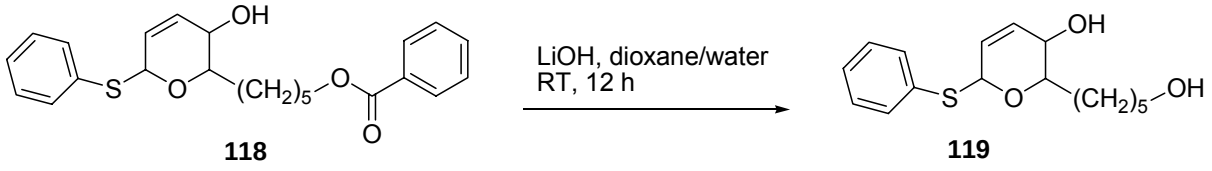
As 5-(3,6-dihydro-6-phenylthio-3-oxo-2*H* pyran-2-yl)pentyl benzoate (**117**) was unstable in basic media, it was necessary to reduce the keto group before performing the basic

cleavage. The reduction was carried out in a THF/water mixture with sodium borohydride at room temperature for 2 h (Scheme 92). After purification the corresponding alcohol **118** was isolated in 74% yield.



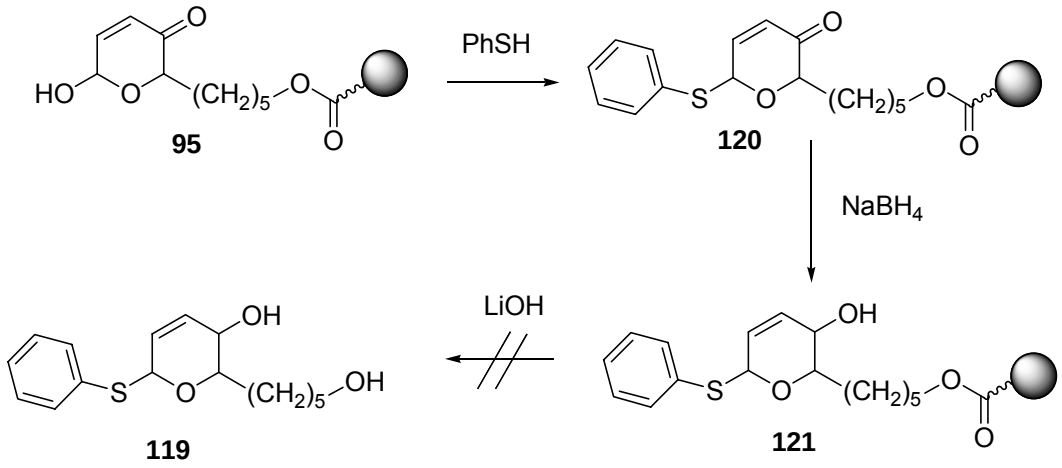
Scheme 92. Preparation of 5-(3,6-dihydro-6-phenylthio-3-hydroxy-2*H* pyran-2-yl)pentyl benzoate

5-(3,6-dihydro-6-phenylthio-3-hydroxy-2*H*-pyran-2-yl)pentyl benzoate (**118**) was cleaved by LiOH in dioxane/water mixture at room temperature (Scheme 93) and 3,6-dihydro-2-(5-hydroxypentyl)-6-phenylthio-2*H*-pyran-3-ol (**119**) was isolated in 90% yield (Scheme 93).



Scheme 93. Cleavage of the ester linkage of 5-(3,6-dihydro-6-phenylthio-3-hydroxy-2*H* pyran-2-yl)pentyl benzoate

To prepare 3,6-dihydro-2-(5-hydroxypentyl)-6-phenylthio-2*H*-pyran-3-ol (**119**) on solid phase, the similar reaction conditions were tried on solid phase (Scheme 94, Table 9). For all cases after cleavage with LiOH, PhSH was detected along with some decomposition products (analysed by NMR and GC-MS). From these results it can be concluded that this base labile linker is not suitable for further diversification following this route.



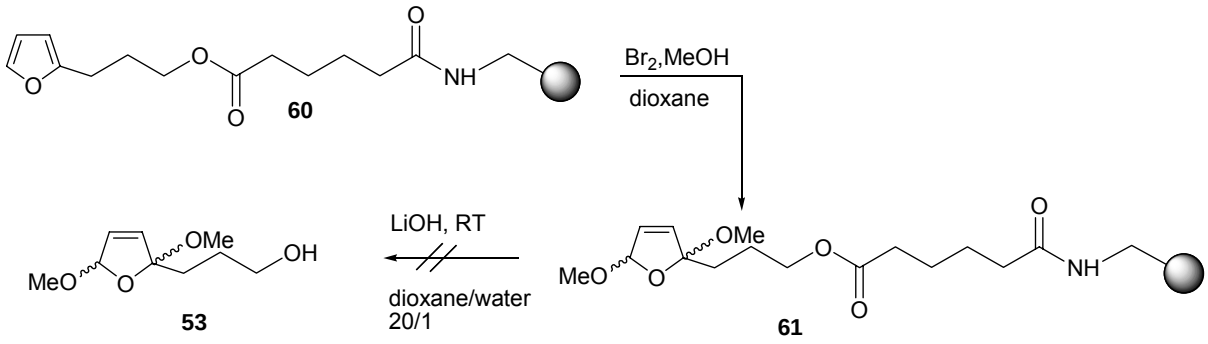
Scheme 94. Attempts to prepare thiophenol via substitution on solid phase

Entry	Conditions	Results
1	a) 3 equiv PhSH, 1 equiv. $BF_3.OEt_2$, dry DCM, 0°C, 3 h. b) 3 equiv $NaBH_4$, THF/water, RT, 3 h.	No product
2	a) 3 equiv PhSH, 1 equiv. $BF_3.OEt_2$, dry DCM, 0°C-RT, overnight. b) 4 equiv $NaBH_4$, THF/water, RT, overnight.	No product
3	a) 3 equiv PhSH, 1 equiv. $BF_3.OEt_2$, dry DCM, under Ar atmosphere, 0°C-RT, 24 h b) 4 equiv $NaBH_4$, THF/water, RT, 24 h.	No product

Table 9. Attempts to prepare 3,6-dihydro-2-(5-hydroxypentyl)-6-phenylthio-2*H*-pyran-3-ol on solid phase

4.1.9 Comparison between electrochemical oxidation and non-electrochemical oxidation on solid phase

Experiments were carried out to compare the results of electrochemical oxidation with non-electrochemical oxidation. Polystyrene resin supported 2-furanpropanol **60** was treated with Br_2 in dioxane/MeOH mixture (Scheme 95). The resin **61** was washed with DCM (4x20 mL), THF (4x20 mL), DCM (2x20 mL). The ester cleavage was carried out in dioxane/water (20/1) with LiOH at room temperature.



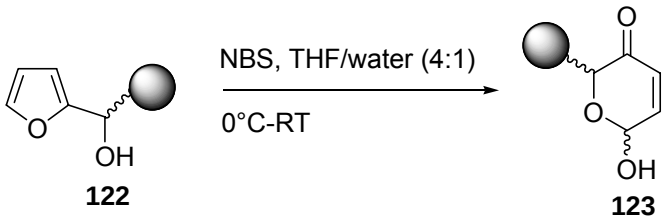
Scheme 95. Attempted solid phase oxidation of furan with Br_2 and MeOH

The following reaction conditions were tried for the furan oxidation with Br_2/MeOH. In no case 3-(2,5-dihydro-2,5-dimethoxy-2)propanol (**53**) could be isolated. Only some decomposed products were observed.

1) 1 equiv Br_2, MeOH/dioxane (20/20 mL), -30°C-0°C, 1 h.	No Product
2) 1 equiv Br_2, MeOH/dioxane (20/20 mL), -30°C-0°C, 3 h.	No Product
3) 1 equiv Br_2, MeOH/dioxane (20/20 mL), -30°C-0°C, 0.5 h.	No Product
4) 2 equiv Br_2, MeOH/dioxane (20/20 mL), -30°C-0°C, 1 h	No Product
5) 2 equiv Br_2, MeOH/dioxane (20/20 mL), rt, 1 h	No Product
6) 2 equiv Br_2, MeOH/dioxane (20/20 mL), 0°C-rt, 12 h	No Product
7) 1 equiv Br_2, MeOH/THF (20/20 mL), -30°C-0°C, 1 h.	No Product

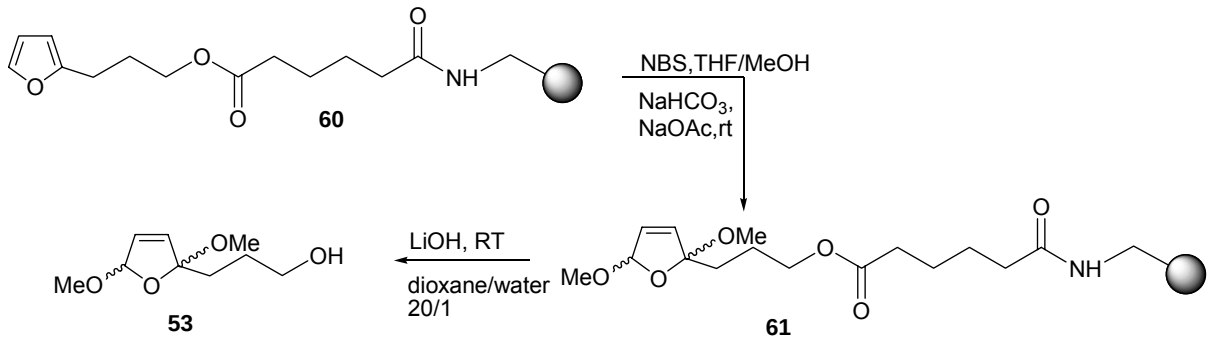
Table 10. Attempts for solid phase oxidation of furan with Br_2 and MeOH

Couladouros *et al*. reported the oxidation of solid supported furyl alcohols **122** to *2H*pyran-3(*6H*)-ones **123** by NBS (N-bromo succinimide) in THF/water (4/1) (Scheme 96).[45]



Scheme 96. NBS oxidation of furyl alcohol on solid phase

Following their procedure polystyrene resin supported 2-furanpropanol was treated with NBS (2 equiv) in THF/water/MeOH (10/1/10) instead of using THF/water (4:1) as a solvent but after cleavage with LiOH in dioxane/water (20/1) the required 3-(2,5-dihydro-2,5-dimethoxy-2)propanol (**53**) was isolated only in 2% GC yield. S. L. Schreiber *et al*. reported the oxidation of solid supported furyl alcohol with NBS, $NaHCO_3$ and NaOAc in THF/water (1:1) at room temperature for 1 h to form the solid supported *2H*-pyran-3(*6H*)-ones **123**.[46] Following their procedure polystyrene resin supported 2-furanpropanol **60** was treated with NBS (30 equiv) $NaHCO_3$ (103 equiv) and NaOAc (50 equiv) in THF/MeOH (1:1) at room temeperature for 1 h and after cleavage with LiOH in dioxane/water (20/1) the required 3-(2,5-dihydro-2,5-dimethoxy-2)propanol (**53**) was isolated in 30% yield (Scheme 97).



Scheme 97. Solid phase oxidation of furan with NBS in MeOH

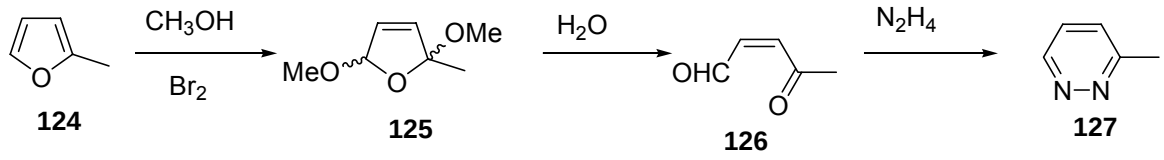
From these above experiments it can be concluded that for the chosen substrates and linker system the electrochemical solid phase method provides the best results.

4.1.10 Synthesis of pyridazines via electrochemical oxidation of furans on solid phase

Recent developments of polymer-supported chemistry have been driven by interest in the assembly of libraries of molecular diverse compounds for their use in various screening protocols.[131] The development of reliable procedures that address issues concerning the synthesis of *N*-bearing aromatic heterocycles would be an important contribution to the field.

The Pyridazine ring systems have been recognized as versatile pharmacophores in medicinal chemistry and its derivatives show a wide range of biological actions.[132] Curiously, only a few studies on the SPOS of pyridazine derivatives have been described,[133] and therefore the development of convenient, versatile and efficient solid phase routes to access chemical libraries of these compounds is highly desirable.

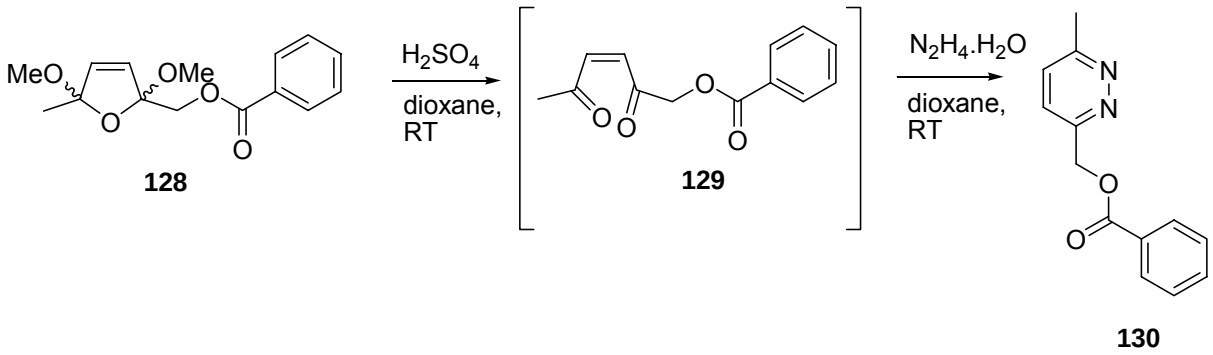
Clauson-Kaas *et al*. reported the oxidation of 2-methylfuran (**124**), which after acid hydrolysis yielded unsaturated 1,4-dicarbonyl compounds (**126**) and finally by addition of hydrazine to the dicarbonyl compound formed 3-methylpyridazine (**127**) (Scheme 98).[134]



Scheme 98. Formation of pyridazine from furan

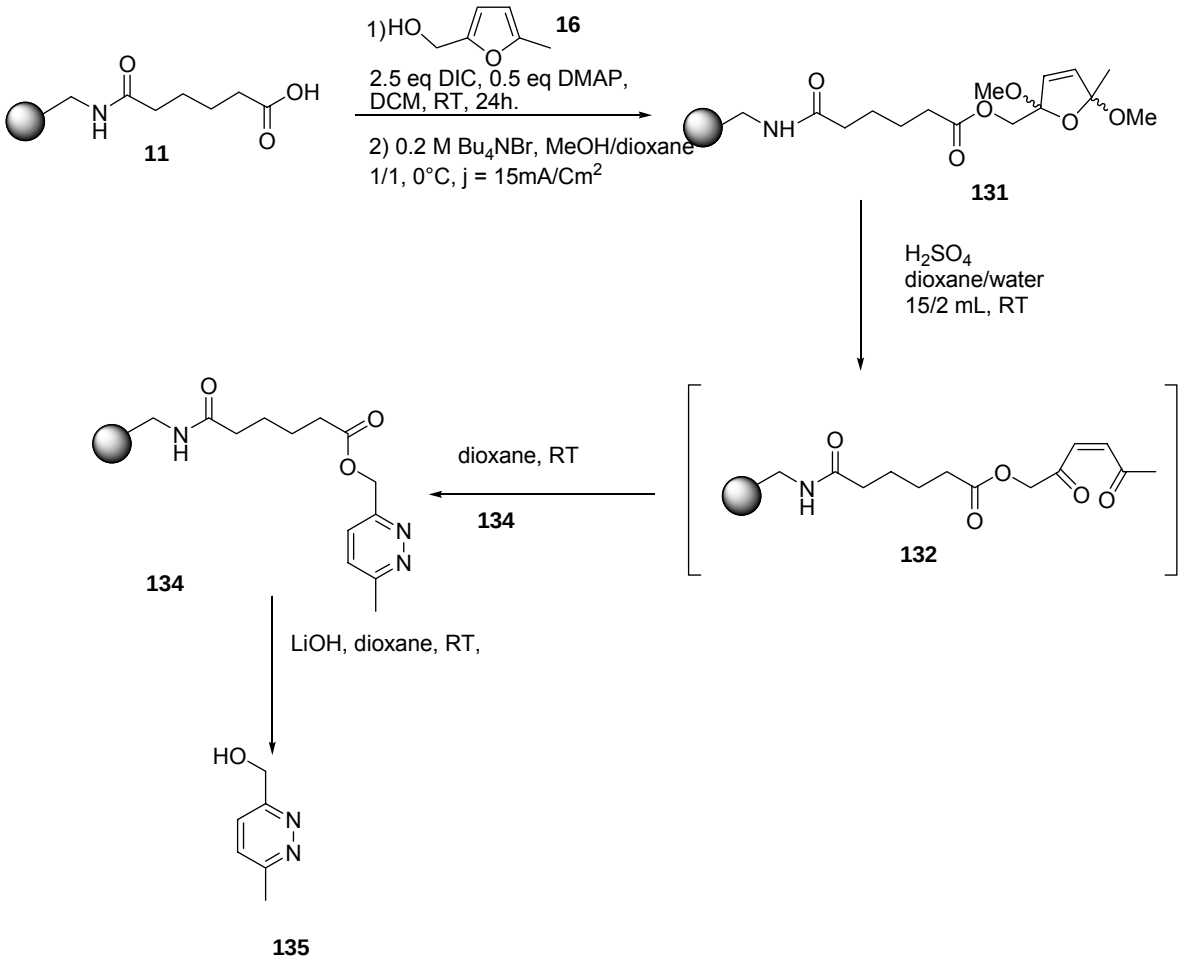
To demonstrate the synthetic potential of the 2,5-dimethoxylation of furans, solid phase synthesis of pyridazine derivatives was chosen.

Before performing the reactions on solid phase, some model reactions were carried out in solution. (2,5-Dihydro-2,5-dimethoxy-5-methylfuran-2-yl) methyl benzoate (**128**) was used as a model substrate. After its convenient preparation by indirect anodic oxidation it was treated with aq. H_2SO_4 (0.6 equiv) at room temperature in dioxane. After complete hydrolysis (monitored by TLC) 1 equiv hydrazine hydrate (**134**) was added to the reaction mixture and after 15 min stirring (6-methylpyridazin-3-yl)methyl benzoate (70%) (**130**) was isolated and purified by column chromatography in 70% yield (Scheme 99).



Scheme 99. Pyridazine formation in solution

Once the reaction sequence was established in solution, several reactions were carried out to optimize the reaction conditions on solid phase (Scheme 100). The results and conditions of these reactions are summarized in Table 11. The resin **131** was prepared by the standard electrochemical method described above.

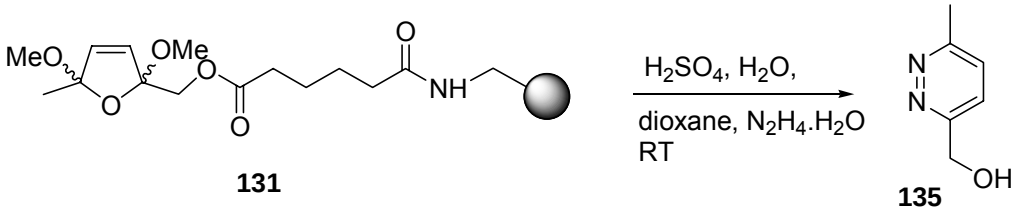


Scheme 100. Preparation of 6-methyl-3-pyridazinmethanol

Entry	Conditions	Results (GC-MS)
A)	1) Aq. H_2SO_4 (0.08 equiv), dioxane/water (15/2) mL, RT, 10 min 2) $N_2H_4.H_2O$ (1 equiv), 30 min 3) LiOH (5 equiv), dioxane/water (20/1) mL, RT, overnight	**62**, 20% purity of **135** (analysed by GC-MS)
B)	1) Aq. H_2SO_4 (1.5 equiv), dioxane/water (15/2) mL, RT, 30 min 2) $N_2H_4.H_2O$ (12 equiv), overnight 3) LiOH (5 equiv), dioxane/water (20/1) mL, RT, overnight	40% purity of **135** (analysed by GC-MS)
C)	1) Aq. H_2SO_4 (1.5 equiv), dioxane/water (15/2) mL, RT, 15 min 2) $N_2H_4.H_2O$ (12 equiv), overnight 3) LiOH (5 equiv), dioxane/water (20/1) mL, RT, overnight	30% purity of **135** (analysed by GC-MS)

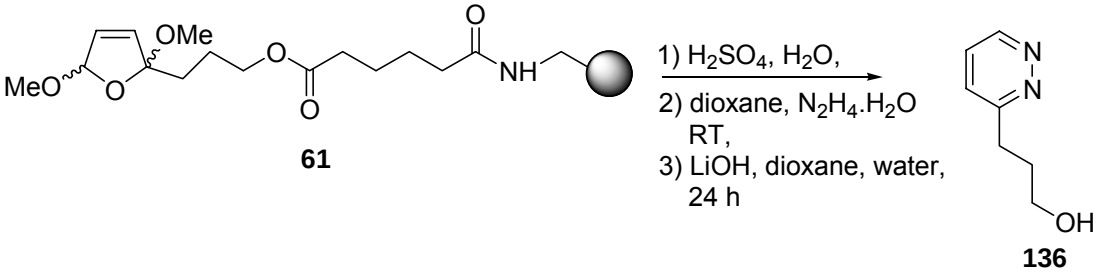
Table 11 Attempts for solid phase preparation of 6-methyl-3-pyridazinmethanol

The yields of the cleaved 6-methyl-3-pyridazinmethanol (**135**) were always poor in these above experiments. For that reason cleavage of the ester linkage via hydrazinolysis was considered. So the hydrolysis of **131** was carried out in presence of aq. sulphuric acid (2 equiv) in dioxane for 20 min. Finally 30 equiv of hydrazine were added and the mixture was shaken for 15 min. This concomitant hydrozinolysis furnished **135** in very good yield and excellent purity (60% yield, >95 % purity) (Scheme 101).



Scheme. 101 Preparation of 6-methyl-3-pyridazinmethanol by direct cleavage of ester bond with hydrazine

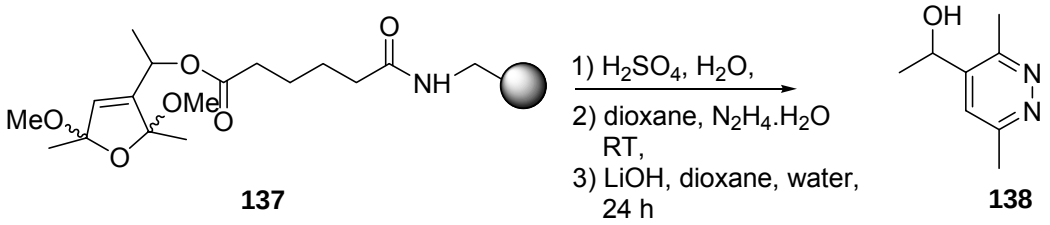
On the basis of this encouraging result, several other pyridazine derivatives were prepared. Resin **61** was treated with aq. H_2SO_4 (2 equiv) in dioxane for 30 min. After filtering the resin, hydrazine hydrate (30 equiv) was added to the resin suspension in dioxane. But in this case no product was found even after shaking the resin with hydrazine for overnight. So a basic cleavage (LiOH, in dioxane/water mixture) was needed for isolation of the desired product (Scheme 102). Finally **136** was isolated by silica gel chromatography in good yield (55%).



61 **136**

Scheme 102. Preparation of 3-pyridazinpropanol

α-Methyl-4-(3,6-dimethylpyridazine)methanol (**138**) was prepared (60%) by a similar procedure as described for **136** (Scheme 103)**.**



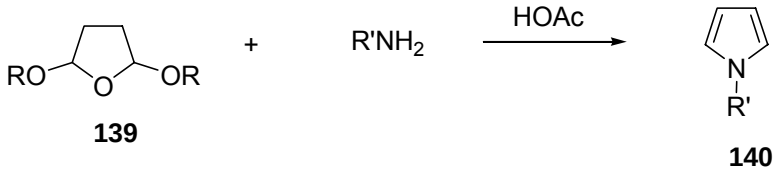
137 **138**

Scheme 103. Preparation of α-methyl-4-(3,6-dimethylpyridazine)methanol

In summary, this sequence represents a new solid phase route to 1,2 pyridazine which compares very well to alternative solid phase approaches of this class of heterocycles.

4.1.11 Attempts to preparation of 1,3-disubstituted pyrroles

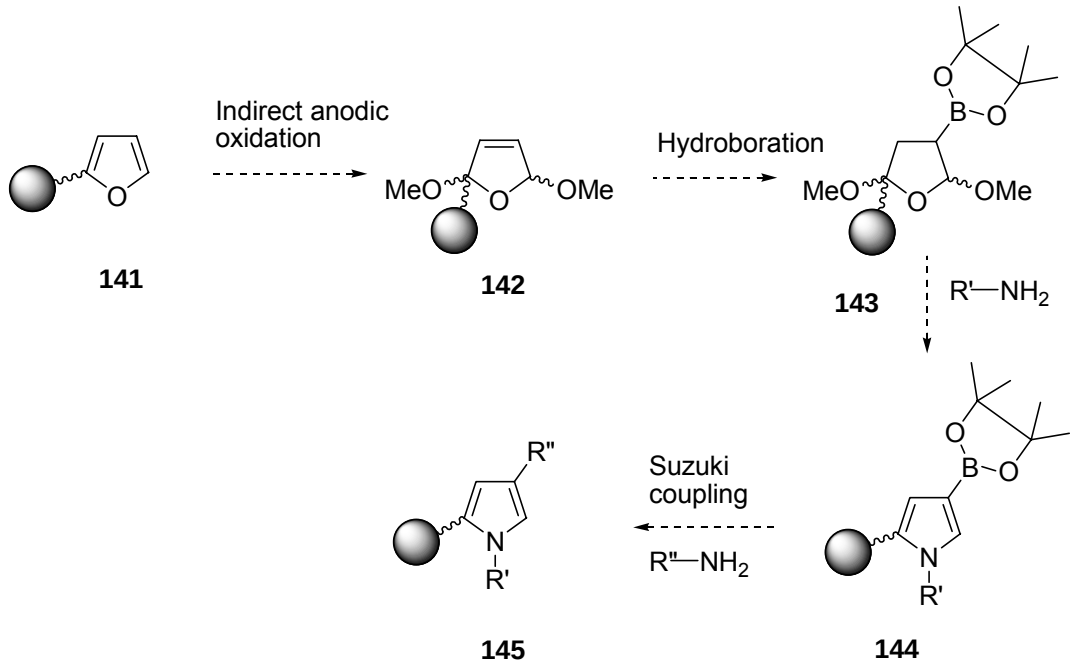
In 1952 Clauson-Kaas and Tyle described an excellent general method for the preparation of *N*-substituted pyrroles **140** through reaction of 2,5-dialkoxytetrahydrofurans **139** with primary amines (Scheme 104).[135]



139 **140**

Scheme 104. Preparation of *N*-substituted pyrroles from 2,5-dialkoxytetrahydrofurans

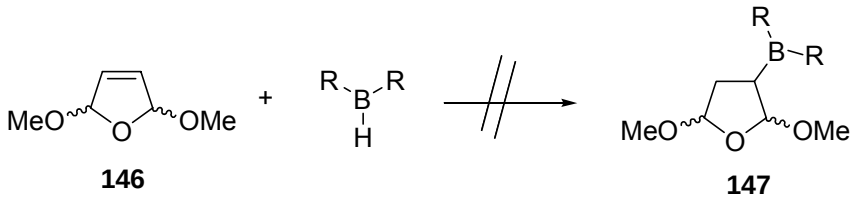
As the preliminary work of solid phase electrochemistry was successful to prepare 2,5-dihydro-2,5-dimethoxyfuran in good yield, the following plan was envisioned to prepare 1,3-disubstituted pyrroles on solid phase (Scheme 105). Organoboron compounds play a pivotal role in modern organic chemistry because of their functional versatility[136] and their implications in asymmetric synthesis.[137] For that reason hydroboration and subsequent Suzuki coupling were chosen for this synthesis.



141 **142** **143** **144** **145**

Scheme 105. Preparation of 1,3-disubstituted pyrrole from 2,5-dialkoxytetrahydrofurans

In the above scheme, the hydroboration reaction was the crucial step for which no literature precedent existed even in solution phase. Some model hydroboration reactions were performed with commercially available 2,5-dimethoxy-2,5-dihydrofuran (**146**) (Scheme 106). For the above model reaction different hydroborating reagents were used along with varying conditions.

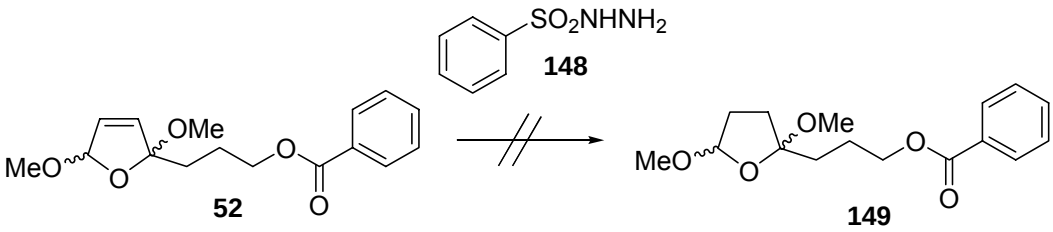


Scheme 106. Hydroboration on 2,5-dialkoxytetrahydrofurans

Neither 9-BBN (9-borabicyclo[3.3.1]nonaness) nor catecholborane, catecholborane with 2% Wilkinson's catalyst, pinacolborane, borane (BH_3), ($BH_3.Me_2S$) provided successful results. The reactions were performed with differents solvents e.g. THF, toluene etc. but the desired product **147** was not found. Most of the time decomposition was observed as the starting 2,5-dimethoxy-2,5-dihydrofuran (**146**) is sensitive to Lewis acids. Failure of this hydroboration prompted us to use an alternative method to prepare 2,5-dialkoxytetrahydrofurans. One of the alternative method was to reduce the olefin bond of 2,5-dimethoxy-2,5-dihydrofuran.

Although an increasing number of reactions has been adapted to solid phase synthesis, the most prominent method still not successfully applied to solid phase organic synthesis is the hydrogenation reaction, since it require the reaction between two heterogeneous entities. Diimide reductions of olefins using sulfonylhydrazides is a well known process[138] and Lacombe *et al*. reported the use of diimide for the reduction of resin-bound olefinic substrate. According to them, the diimide, prepared from sulfonylhydrazide, was found to efficiently reduce the olefinic substrates[139]. Typically, the reaction proceeds in over 90% yield to afford the reduction product cleanly after cleavage from Wang resin.

Before performing the reduction on solid phase some model reactions were carried out in solution using 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propyl benzoate (**52**) as the starting olefin (Scheme 107). As described by Lacombe *et al*. the above reaction was carried out in DMF under argon atmosphere with 5 equiv_benzenesulfonylhydrazide (**148**). The reaction mixture was heated to 50°C (Lacombe et al. reported the hydrogenation at 100°C, which could lead to decomposition of **52**. But even after one day the desired product **149** was not found. From the analysis of spectra (GC-MS and NMR) the starting material and some decomposition products were detected.



Scheme 107. Reduction of 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propyl benzoate with benzenesulfonylhydrazide

The reduction was also performed in presence of potassium azadicarboxylate (KOOCN=NCOOK) in MeOH under argon atmosphere at room temperature as described by Denmark *et al*.[140] A mixture of acetic acid and pyridine were used to maintain the pH of the reaction mixture as the starting material (**52**) is acid sensitive. Unfortunately the desired reduced product was not formed even after one day. The reaction did not proceed at all and (**52**) was recovered.

The failure of this reduction even in solution phase revealed the sensitivity of the 2,5-dimethoxy-2,5-dihydrofuran towards many reagents. For that reason the strategy was changed and the synthesis of *N*-substituted pyrroles was attempted with high loading soluble polymeric supports as these can overcome some of the problems associated with solid phase supports, such as heterogeneous reactions like hydrogenation. The syntheses of *N*-substituted pyrroles with high-loading polymeric supports are described in the second part of this thesis.

4.2 Parallel multistep synthesis of *N*-substituted pyrrole derivatives using dendritic polyglycerol as a high-loading support

4.2.1 Dendritic polyglycerol supports

In the past few years, soluble high-loading polymers and dendrimers have been introduced by several groups in combinatorial chemistry. Solid-phase synthesis exhibits a number of problems due to the heterogeneous nature of the reaction and the low concentration of the accessible functional groups. In contrast to solid-phase supports, soluble polymeric supports have high loading capacities.[47] Soluble polymeric supports enable to use homogeneous reaction conditions and also standard analytical techniques (TLC, IR, NMR, MALDI-TOF, etc.) can be applied which is useful for a multistep process. One drawback of soluble polymeric supports is the fact that there is no generally applicable separation technique in contrast to solid phase supports, where filtration is method of choice. However, a variety of simple separation methods exists, such as conventional precipitation, liquid–liquid extraction, and filtration over silica-gel, or techniques which separate by molecular size such as dialysis, ultrafiltration, and size exclusion chromatography (SEC).[62]

Some of the most commonly used linear soluble polymeric supports have the disadvantage of either very low loading capacity (e.g., monomethylated poly(ethylene glycol), 5000 g mol^{-1} (MPEG 5000), 0.2 mmol g^{-1}, only one reactive group per polymer molecule) or problematic polymer characteristics, such as solubility and chemical stability (e.g., poly(vinyl alcohol) (PVA), 22.7 mmol g^{-1}, reactive group on every monomer unit).[49]

In some cases, these advantages can be overcome by the use of branched polymer architectures.[47] These macromolecules are soluble in many organic solvents (depending on their shell functionalities) and possess a maximum capacity of easily accessible functional groups in their periphery. Dendrimers as supports for organic synthesis, mainly catalysis, have been frequently used.[141] However, the general drawback of any dendrimer is the tedious and expensive multistep preparation of higher generations.[63] Another problem of high-generation dendrimers is steric hindrance and site–site interaction at the outer functional shell. These problems might be overcome by using randomly branched polymer structures as supports.[49] In contrast to dendrimers, hyperbranched polymers are easily available in one reaction step in large quantities.[142] They contain dendritic, linear and terminal monomeric units and can be considered as intermediates between linear polymers and dendrimers with an approximate degree of branching between 50 and 75%.[47] Hyperbranched polymers in contrast to dendrimers, are polydisperse and the reactive sites will be distributed throughout

the molecule. The potential loading capacity of hyperbranched polymers is similarly high as for dendrimers (5-14 mmol g^{-1}) and thus allows for parallel synthesis on the millimole scale.[61]

In this pyrrole synthesis hyperbranched polyglycerol **150** was used as a high loading polymer support (Figure 22). The immobilization was performed using the 'built-in' terminal 1,2-diols and therefore no additional linker was necessary. This soluble aliphatic polyether support has high loading capacity (13.5 mmol OH g^{-1}). Haag *et al*. developed a convenient method to prepare this polymer on a kilogram scale. It is soluble in most organic solvents (depending on the OH-group functionalization) and the polyether skeleton is stable under a wide range of reaction conditions. Haag *et al*. reported on the use of hyperbranced polyglycerol **X** as a high loading polymer support for carbonyl compounds[63b] or boronic acids for polymer supported Suzuki-reactions[63c] and for the parallel multistep synthesis of GABA lactam analogues.[62d]

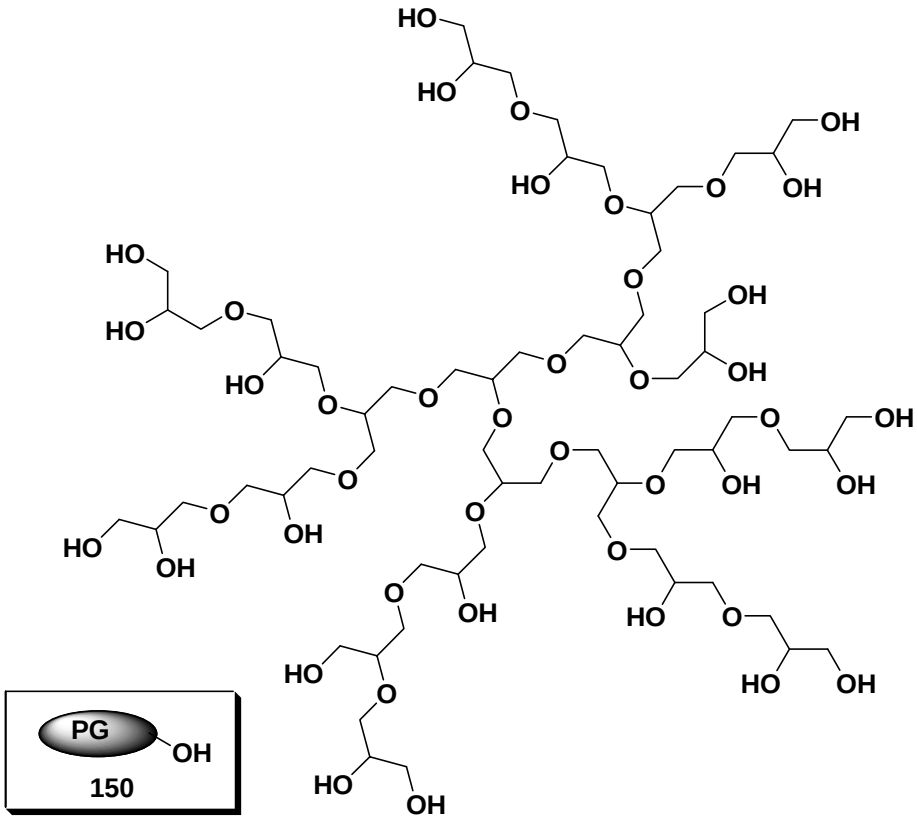
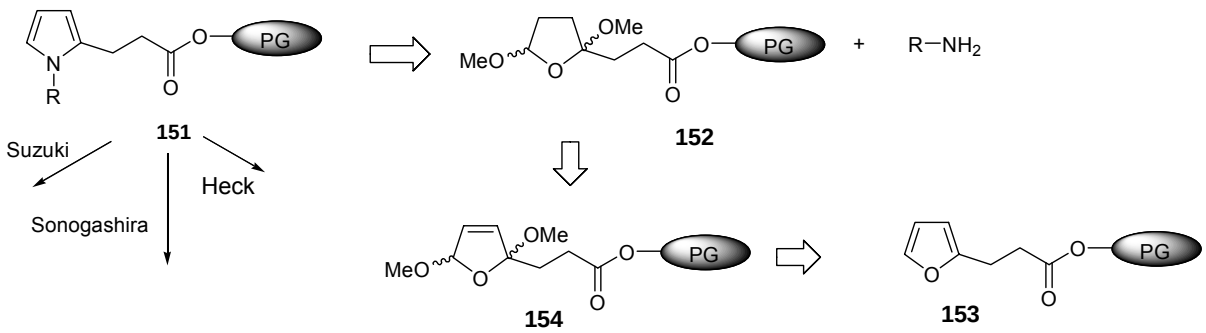


Figure 22. Dendritic polyglycerol support. The depicted polymer structure represents only one possible isomer and a small part of the polyglycerol (M_n=8000 g mol^{-1})

In this chapter the use of polyglycerol **150** as a high-loading dendritic support for the multistep synthesis of *N*-substituted pyrrole propanoic acid derivatives **151** is described (Scheme 108). The retrosynthetic analysis showed the requirement of 2,5-dimethoxytetrahydrofurans **152** as the key intermediate which can be formed by indirect electrolytic methoxylation of the corresponding furan derivatives **153** and subsequent catalytic reduction of the resulting 2,5-dimethoxy-2,5-dihydrofurans **154**. After the reaction of 2,5-dimethoxytetrahydrofurans with primary amine as described by Clauson-Kaas and Tyle[134] and further diversification by palladium catalysed reaction, the desired pyrroles **151** could be released from the polymeric support by saponification.



Scheme 108. Retrosynthetic approach for *N*-substituted pyrrole propanoic acid derivatives and further diversification by palladium catalyzed coupling reaction

These pyrrole derivatives are interesting drug like structures (Figure 23). For example AG3433 (**155**) is a potent inhibitor of matrix metalloproteases (MMPs) currently undergoing preclinical evaluation.[143] **155** was found to have good selectivity, a good metabolic profile as well as good oral bioavailability. Recently Kozikowski and co-workers identified compound **156**, as a potent and selective norepinephrine reuptake inhibitor. The aim was to develop a parallel approach for these *N*-substituted pyrrole derivatives for biological evaluation

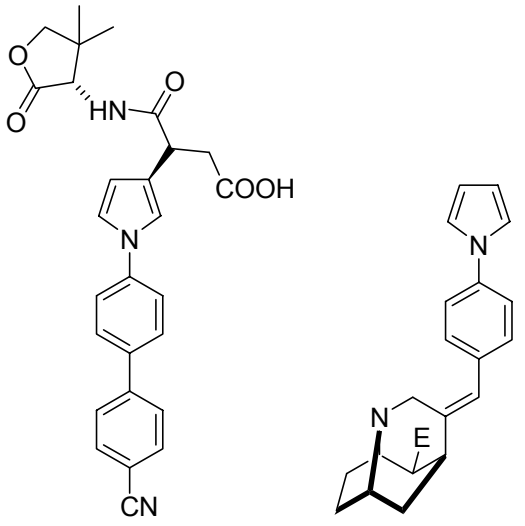
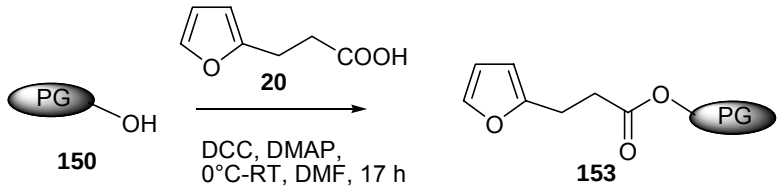


Figure 23. Some biologically active pyrrole moiety

4.2.2 Indirect anodic oxidation with dendritic polyglycerol as high loading support

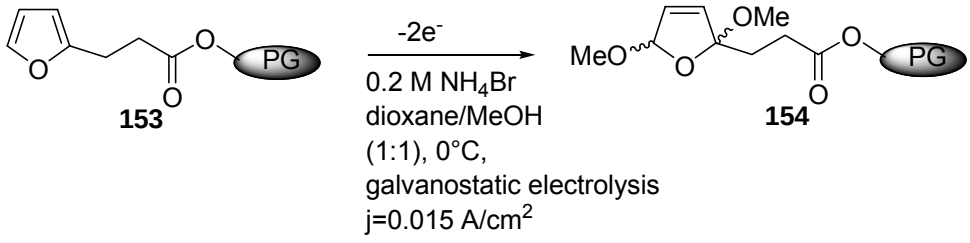
In the previous chapter a practical method for electroorganic synthesis with polymeric supports, which is applicable for library synthesis has been described. It was believed that the indirect electroorganic approach can also be applied with the soluble polymeric supports.

The indirect anodic oxidation was carried out with dendritic polyglycerol supported 2-furanpropanoic acid (**20**). **20** was attached to polyglycerol **150** via esterification using dicyclohexyl carbodiimide (DCC)/*N,N*-dimethylaminopyridine (DMAP) coupling (Scheme 109).[63d] The reaction was carried out in dry DMF and the formed urea can be removed by filtration and subsequent dialysis. The 2-furanpropionic acid polyglycerylester (**153**) was obtained in good conversion and yield (63% conversion and 72% yield, the yield is based on the ratio of obtained mass to expected mass according to the conversion introduced by Haag *et al*.[62d]).



Scheme 109. Immobilization of 2-furanpropanoic acid on the polyglycerol support **150** via DCC-coupling

For the electrochemical reaction the experimental set up was similar to those as described in the previous chapter. An undivided beaker-type cell (commerical Metrohm titration vessels and lids were adapted in the local machine shop) was equipped with two carbon electrodes (area of the electrodes immersed in the electrolytic solution: 2.7 cm^2, distance between the two electrodes: 0.5 cm). Due to the high loading of 2-furanpropionic acid polyglycerylester (**153**) (6.50 mmol/g), it was hardly soluble in methanol. Therefore a mixture of dioxane/MeOH (1:1) was used as the solvent for the electrolysis. The only unknown factor in this reaction was the required amount of electricity for complete conversion. The reaction conditions which were tried for optimization of the electrolysis step are summarized in Table 12.



Scheme 110. Indirect electrolysis with high-loading polyglycerol support

Entry	Electrode distance [cm]	Current density [A/cm^2]	Electricity [F/mol]	Temperature [°C]	Conversion (by NMR) **C** (%)
1	0.5	0.015	4	0	0
2	0.5	0.015	3	0	100
3	0.5	0.015	2	0	70

Tableb 12. Attempted electrolysis conditions using high-loading polyglycerol support

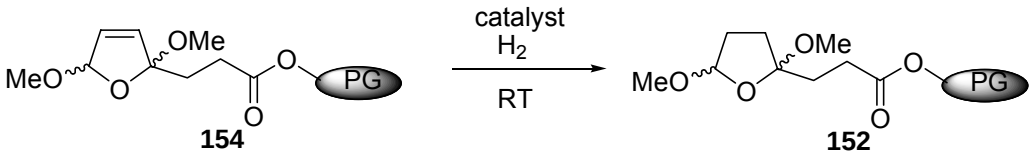
In case of entry 1 the reaction mixture was analyzed by NMR, but the desired product **154** was not found. To analyse the product, the reaction mixture was saponified by LiOH to split off from the polymeric support and from the NMR it was clear that the furan ring was opened due to overoxidation as described by Tori *et al*.[17] For entry 3, after analysis by NMR, both starting material and products were found. Entry 2 gave best the results and after working up the reaction through filtration the desired 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanoic acid polyglyceryl ester (**154**) was furnished in quantitative conversion and 80% (isomeric mixtures) yield without requiring further purification.

Compared to our previous indirect electrochemical method on solid phase the use of a soluble polymeric support resulted in an increase in both chemical and current yield. On solid phase a large amount of electricity was always needed to achieve complete conversion causing poor current yield.

4.2.3 Hydrogenation with soluble polymeric support

The key step in retrosynthetic analysis for the formation of *N*-substituted pyrroles, was the reduction of the olefin moiety of the electrochemically generated 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanoic acid polyglyceryl ester (**154**). Miyakoshi *et al*. described the catalytic hydrogenation of 2-alkanoyl-2,5-dimethoxy-2,5-dihydrofurans over palladium on charcoal in ethyl acetate at room temperature for 6 h to afford 2-alkanoyltetrahydrofurans in 79-95% yields.[144]

For the optimization of the hydrogenation two catalysts were tried (5% Pd on activated carbon and 5% Pt on activated carbon, Table 13). All these reactions were carried out with 0.46 g of **154** in 50 mL solvent at room temperature (Scheme 111).



Scheme 111. Hydrogenation of 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanoic acid polyglyceryl ester

Entry	Catalyst (5% metal on activated C)	Amount of the catalyst [g]	Solvent	Reaction time [h]	Conversion (from NMR)
1	Pd	0.2	MeOH	12	ca. 50%
2	Pd	0.4	MeOH	24	ca. 80%
3	Pd	0.4	MeOH/EtOAc (1:1)	24	ca. 80%
4	Pt	0.25	MeOH	24	100%
5	Pt	0.12	MeOH	24	ca. 90%

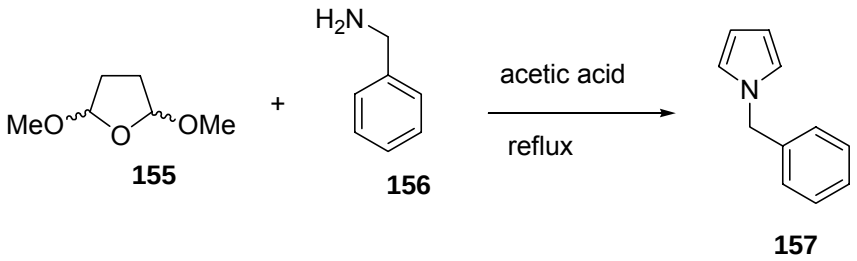
Table 13. Optimization of hydrogenation of 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanoic acid polyglyceryl ester

The conditions listed in entry 4 led to quantitative conversion and the desired (tetrahydro-2,5-dimethoxyfuran-2-yl)propanoic acid polyglyceryl ester (**152**) was isolated as an isomeric mixture in 77% yield without requiring further purification.

4.2.4 *N*-substituted pyrrole formation with high-loading dendritic polyglycerol support

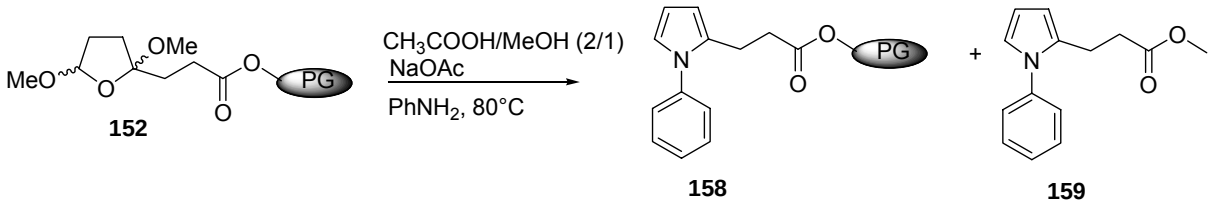
After getting the key intermediate **152** in hand the pyrrole formation could be attempted. In 1952 Clauson-Kaas and coworkers employed a variety of simple aliphatic and aromatic primary amines together with 2,5-dialkoxytetrahydrofurans to obtain the corresponding *N*-substituted pyrroles in good yield[134]. This general reaction appeared to invite wider exploitation since it enables the simple, direct replacement of sufficiently basic $–NH_2$ by the 1-pyrrolyl group. Usually, this reaction is accomplished by using acetic acid as both the catalyst and the solvent. The employment of other acids has hardly been reported for this purpose.[145] In a model reaction benzyl amine (**156**) was treated with 2,5-dialkoxytetrahydrofuran (**155**) in refluxing acetic acid, but the corresponding pyrrole **157** was obtained in only 20% yield (Scheme 112). This low yield was apparently due to the lability of

the pyrrole moiety under these acidic conditions. In 1995 Jefford and coworkers described a procedure where they added sodium acetate to acetic acid.[146] They have used a solution of amine, **155**, and sodium acetate (each 1:1:1 mol ratio) in 100 mL acetic acid and heated the reaction mixture at 80°C for 30 min. Following their procedure *N*-benzyl pyrrole (**157**) was isolated in 80% yield.



Scheme 112. Synthesis of *N*-benzyl pyrrole

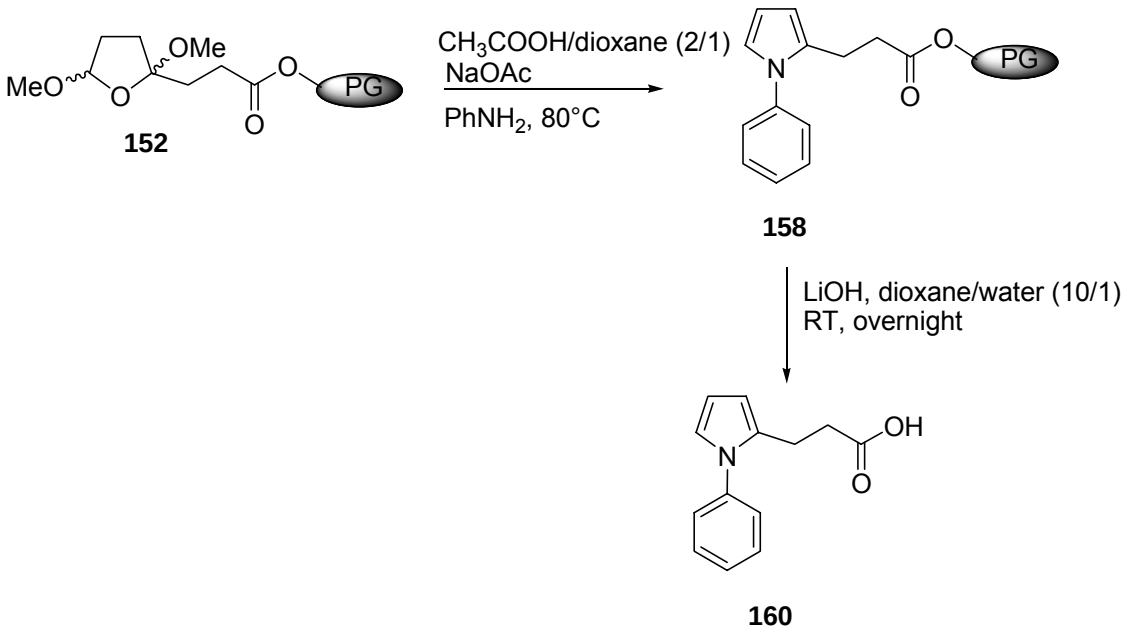
Having identified convenient conditions for a model substrate, a solution of 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanoic acid polyglyceryl ester (**152**) (1 equiv) in methanol was treated with aniline (2 equiv) in acetic acid/NaOAc (1 equiv NaOAc) mixture at 80°C (Scheme 113). After strring the reaction mixture for 2 h the crude mixture was purified by dialysis in methanol. But during dialysis, **159** was detected along with aniline in the solution outside the dialysis tube as was revealed by NMR. Therefore, it can be concluded that either during dialysis or during the condensation reaction **159** was forming due to transesterification with methanol.



Scheme 113. Condensation with aniline in presence of acetic acid/methanol (2/1)

As a significant proportion of the desired product was lost by this way the condensation was carried out in presence of acetic acid/dioxane (2/1) at 80°C for 2 h (Scheme 114). After evaporation of the solvent the crude reaction mixture was dialysed in chloroform for 24 h and the desired product **158** was isolated in 55% yield and the conversion determined as quantitative. The cleavage of the ester linkage was done very efficiently by saponification in presence of LiOH in dioxane/water (10/1) mixture at room temperature for overnight. After acidification of the reaction mixture with hydrochloric acid and subsequent extraction with

ethyl acetate, the desired pyrrole **160** was isolated in 55% yield after purification by column chromatography.



Scheme 114. Preparation of 3-(1-(4-biphenyl)-1*H*-pyrrol-2-yl)propanoic acid

With these optimized reaction conditions in hand several condensations reactions between **152** with different primary amines were carried out. In each case the conversion of the condensation was quantitative (Table 14).

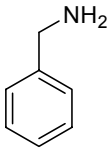
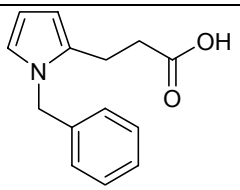
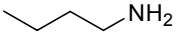
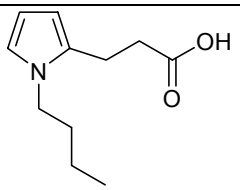
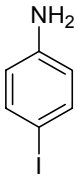
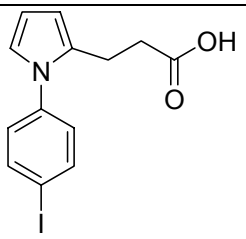
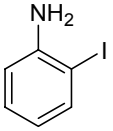
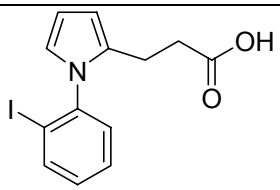
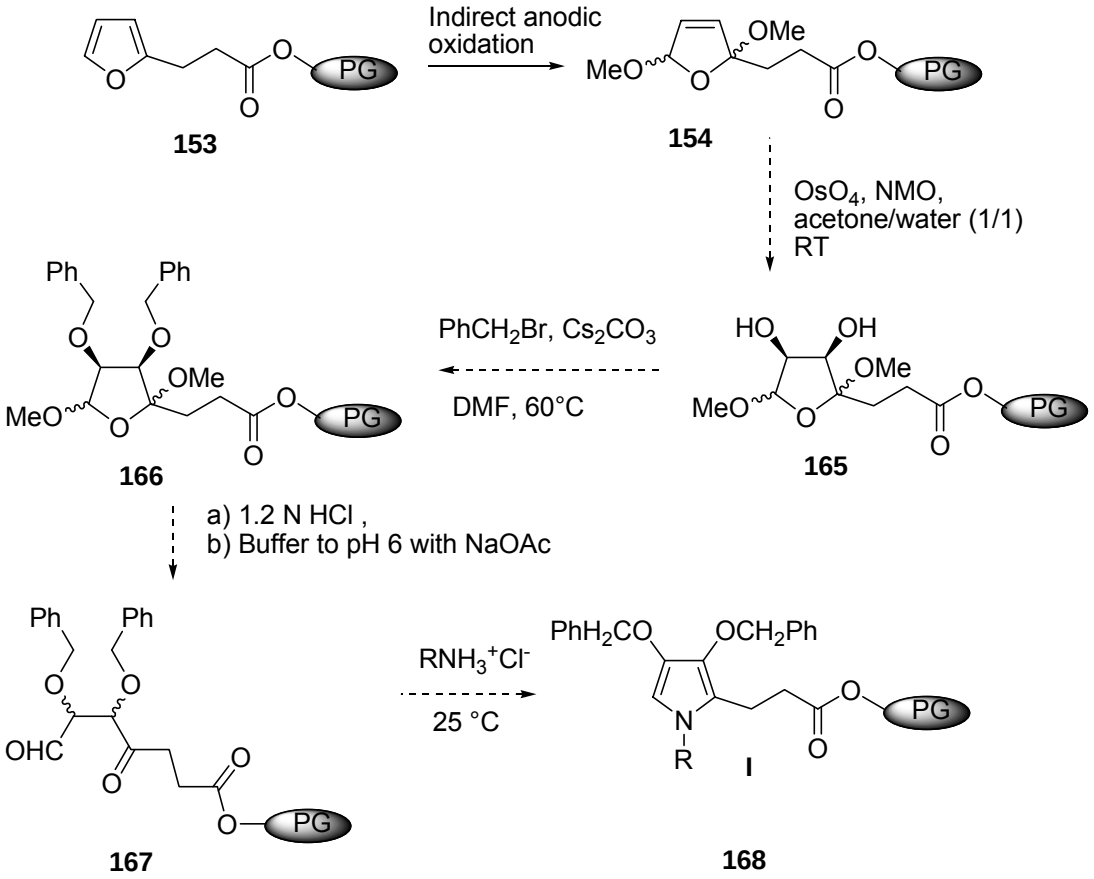
Entry	Amine	Cleaved product	Time [h]	Overall isolated yield [%]
1		 **161**	2	52
2		 **162**	2	50
3		 **163**	2	65
4		 **164**	2	65

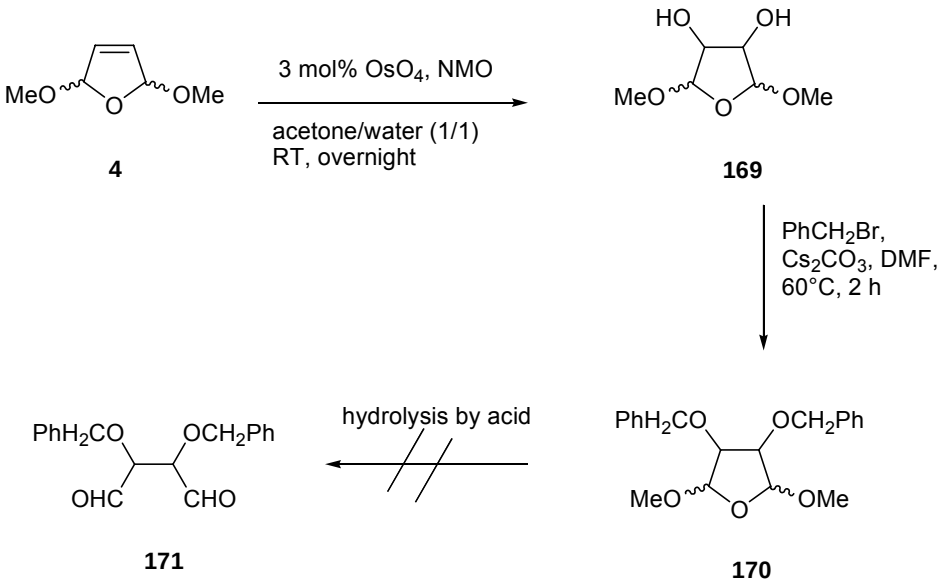
Table 14. Preparation of different pyrrole derivatives by condensation with amine

This result encouraged us to investigate further diversification on this *N*-substituted pyrrole moiety as well as exploring a short and efficient synthesis of 3,4-dialkoxypyrroles which are suitable precursors for porphyrins synthesis. Dialkoxy pyrroles are electrochemically oxidized to highly conducting polypyrroles linked uniformly in 2,5 position.[147] Merz *et al*.[148] described a convenient synthesis of *N*-substituted 3,4-dialkoxypyrroles from 2,5-dimethoxy-2,5-dihydrofuran. Following their scheme, high-loading polyglycerol supported 3,4-dialkoxypyrrole **168** synthesis was attempted (Scheme 115).



Scheme 115. 3,4-dialkoxypyrrole synthesis with high-loading dendritic polyglycerol support

Before implementing the above scheme on soluble polymeric support, some model reactions in solution phase were performed. Commercial 2,5-dimethoxy-2,5-dihydrofuran (**4**) was chosen as a standard model substrate. Although the dihydroxylation of **4** with $KMnO_4$ is known,[149] the goal was to use the high-loading dendritic polyglycerol as support. Haag *et al* described the synthesis of dendritic polyglycerol by dihydroxylation with osmium tetroxide and *N*-methylmorpholine-*N*-oxide.[150] Following their procedure the dihydroxylation was carried out at room temperature in acetone/water (1/1) mixture using 3 mol% osmium tetroxide and finally purified by silica gel chromatography to furnish **169** in 50% yield as a mixture of isomers (Scheme 116).

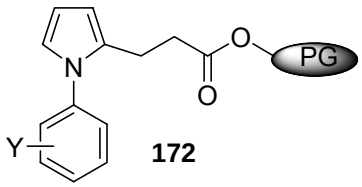


Scheme 116. Attempted synthesis of 3,4-dialkoxypyrrole in solution

Dueno *et al*. described a cesium promoted *O*-alkylation of alcohols as an efficient method for ether synthesis.[151] Following their procedure the *O*-benzylation was performed in DMF at 60°C using cesium carbonate as a base. The desired product **170** was isolated by purification through column chromatography as an isomeric mixture in 80% yield. Unexpectedly the key step, namely the hydrolysis of **170** in presence of acid turned out to be the most difficult step within this reaction sequence. Merz *et al*.[100] described hydrolysis of **170** in a mixture of CF_3COOH and water within 50 to 90 min. Following their procedure hydrolysis of **170** was carried out but unfortunately the hydrolysis did not occur even after 3 h and subsequent heating led to several decomposition products analyzed by TLC and GC-MS. The hydrolysis was also tried with 2N hydrochloric acid which led again to decomposition. As this hydrolysis was so capricious even in solution and it was always necessary to monitor the reaction by TLC and needed subsequent buffering (which could be very difficult with soluble polymeric support) it was considered to be impractical for a soluble polymeric reaction sequence. Therefore, a different line of diversification was attempted, which turned out to be successful.

4.2.5 Suzuki cross-coupling using polyglycerol supports

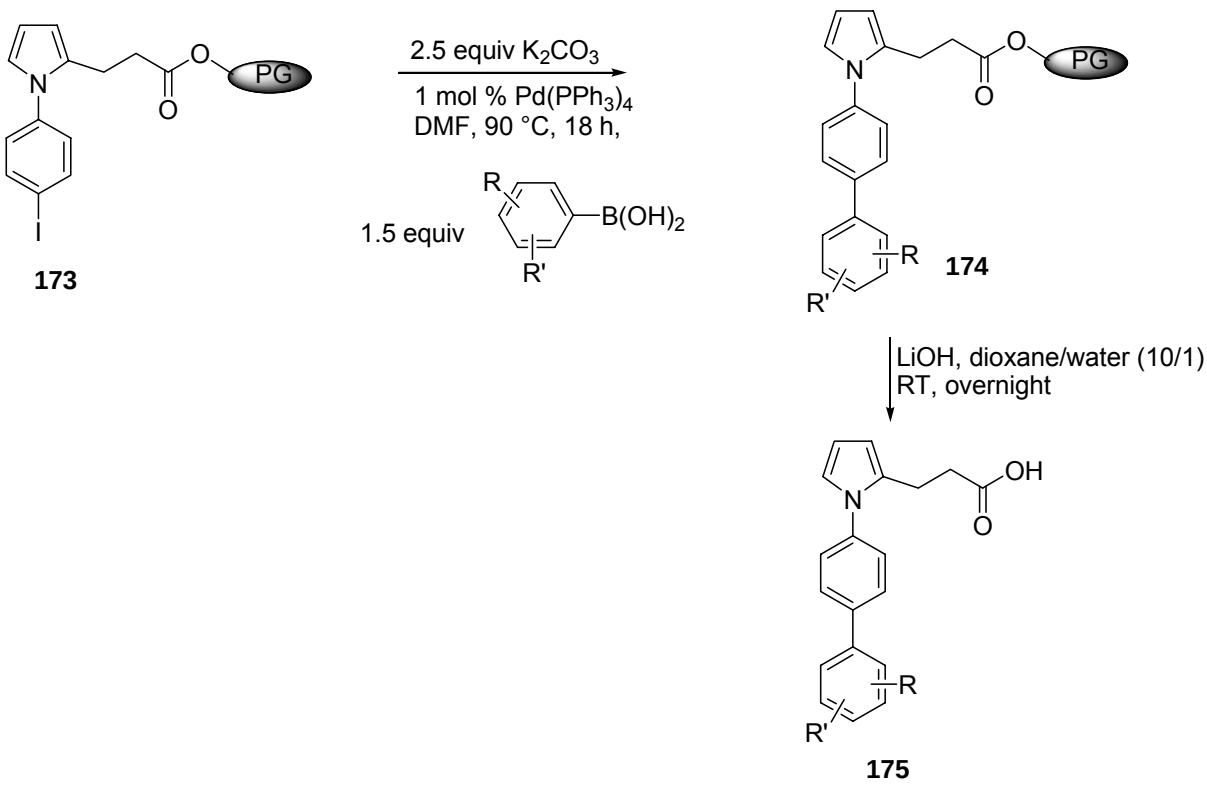
If the pyrrole **172** is suitably substituted with other functional groups, it opens a way for further diversification by preparing other interesting pyrrole containing structures.



172

As an appropriate stating material polyglycerol-supported pyrrole **173** was identified and diversified using several Pd catalyzed reactions exploiting the aryl iodide moiety. For palladium catalyzed reactions insoluble polymers of several kinds have been examined as possible supports and in many cases offered significant advantages over conventional solution phase routes.[152] However, this solid phase approach requires a great deal of development time. Furthermore, it is always difficult following reactions and characterizing products still attached to the polymer beads by routine analytical methodologies (e.g. ^{1}H, ^{13}C-NMR, IR, etc.).

Suzuki cross-coupling reactions have been investigated by several groups on solid phase supports.[153] A limiting factor on solid phase is the large amount of palladium catalyst (typically 5-20 mol %) required for these heterogeneous reactions. For soluble polymers, only recently, a perfect silane dendrimer has been used for this reaction which allows a homogeneous catalysis conditions.[63e] However, in this case a total of 250 mol % of palladium catalyst was used. Recently Haag and coworkers[63c] described a Suzuki coupling of polyglycerol-supported *p*-bromo benzacetal with phenyl boronic acid and it appears that very low catalyst concentrations (0.2-0.5 mol %) are sufficient to produce the polymer supported coupling product in high yield. They have used tetrabutylammonium bromide as a phase transfer catalyst. Following their procedure a solution of 3-(1-(4-iodophenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester (**173**) was treated with different boronic acids and K_2CO_3 in DMF under argon atmosphere and the reaction mixture was heated to 90°C for 18 h (Scheme 117). It was found that a low catalyst concentration ($Pd(PPh_3)_4$, 1 mol %) was sufficient for complete conversion as well as simplified the work up protocol and reduced costs. In addition, no additional phase transfer catalyst was needed. The results for different boronic acids are summarized in Table 15. In all cases the conversions were quantitative (determined from the ^{1}H NMR spectra). The catalyst was removed by simple filtration and easy purification of all products could be achieved via dialysis in chloroform. The final Suzuki coupled product **175** was cleaved off the polyglycerol supports by saponification as described above and isolated afer purification by column chromatography in good overall yields (60-62%).



Scheme 117. Suzuki coupling with polyglycerol support

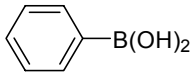
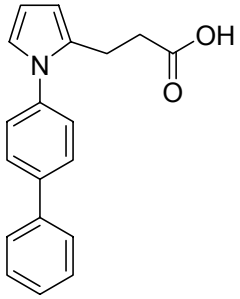
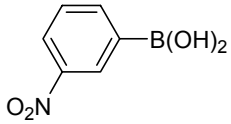
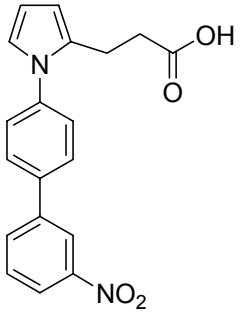
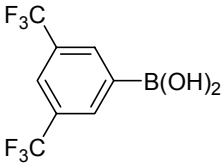
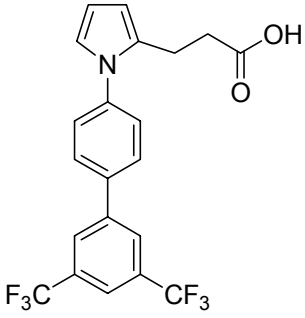
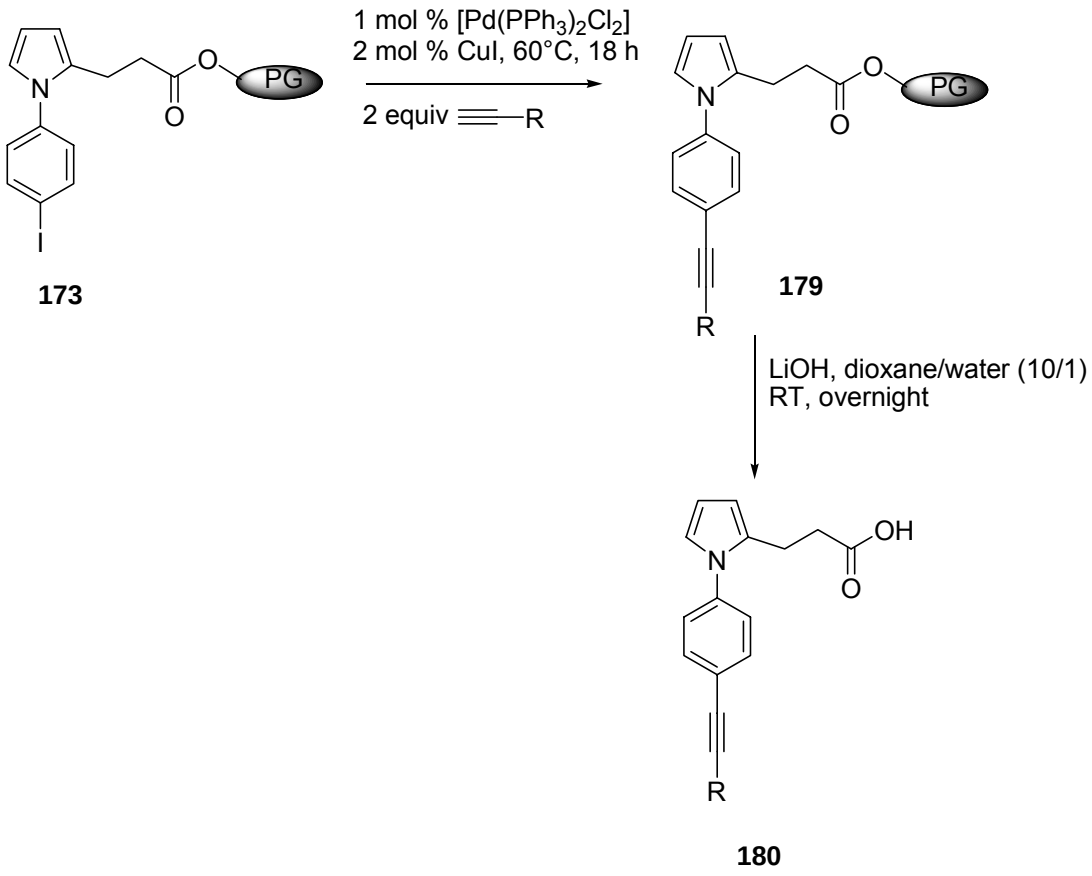
Entry	Boronic acid	Cleaved product	Yield (%)
1		 **176**	60
2		 **177**	60
3		 **178**	62

Table 15. Suzuki coupling with polyglycerol support

4.2.6 Sonogashira coupling reaction using polyglycerol supports

The Sonogashira coupling reaction of terminal alkynes with halides provides a powerful method for synthesizing conjugated alkynes, an important class of molecules that have found application in diverse areas ranging from natural product chemistry to materials science.[154] The Sonogashira reaction (condensation of aryl halides with terminal alkynes in the presence of Cu(I) and Pd(0) catalysts) has been used quite often for the preparation of polymer-supported aryl acetylenes[155] Due to the low loading capacities of these polymeric supports (typically <1.5 mmol/g) the resulting heterogeneous reaction conditions require large amount of catalyst. Waldmann *et al*. described Sonogashira reaction of soluble polymer-supported (POE-6000) aryl iodide where they have used 10 mol % of catalyst $[Pd(PPh_3)_2Cl_2]$.[156]

But with polyglycerol **150**, due to its soluble nature only 1 mol % catalyst was sufficient for quantitative transformation. The coupling of **173** with different terminal acetylene was carried out with 1 mol % catalyst [$Pd(PPh_3)_2Cl_2$] and 2 mol % CuI in dioxane/Et_3N (2/1) mixture under argon atmosphere at 60°C for 18 h (Scheme 118). Simple purification by dialysis and subsequent cleavage by saponification furnished the coupled products **180** in good yields (60-65%) and quantitative conversions (Table 16).



Scheme 118. Sonogashira coupling with polyglycerol support

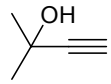
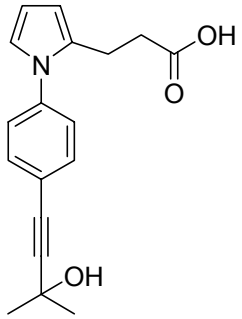
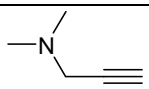
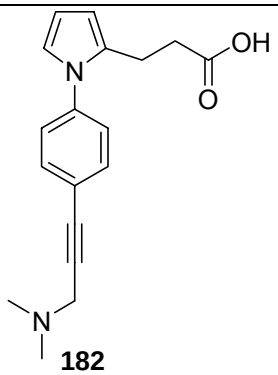
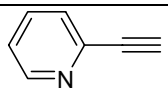
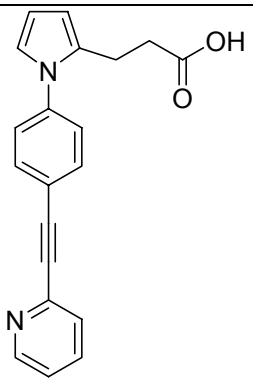
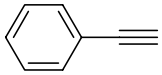
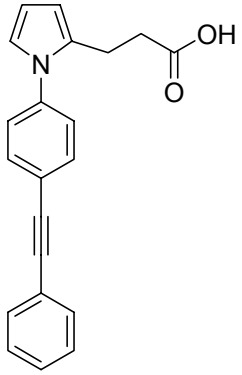
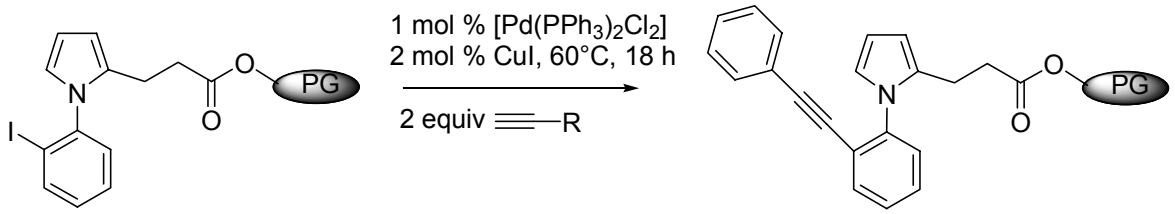
Entry	Alkyne	Cleaved product	Yield (%)
1		 **181**	65
2		 **182**	60
3		 **183**	65
4		 **184**	60

Table 16. Sonogashira coupling with polyglycerol support

For the pyrrole **183** there was an impurity even after purification which was difficult to remove due to the presence of both basic and acid groups in **183**. This Sonogashira coupling was performed also with soluble polymer-supported pyrrole **185** under the same conditions where it contained a 2-iodophenyl moiety, but the resulted coupled product **186** was obtained only in 50% conversion which was not unexpected due to the high steric hindrance in the parent compound (Scheme 119).



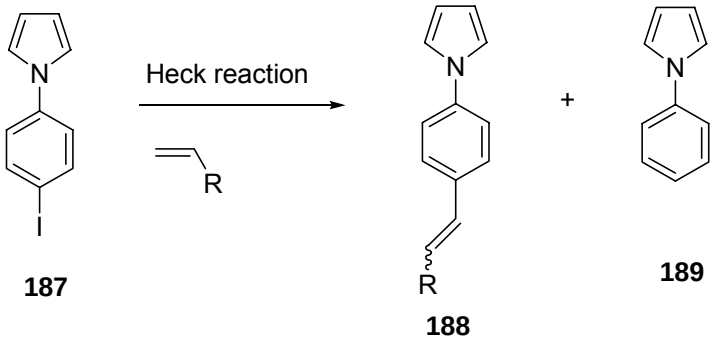
185 **186**

50% conversion

Scheme 119. Sonogashira coupling in *ortho* position

4.2.7 Heck reaction with soluble polymeric support

The palladium catalysed reaction of organic halides with alkenes[157] (Heck reaction) has now become a well established synthetically important method for the formation of carbon-carbon bonds, as is testified by their widespread application in organic synthesis of natural products during the last decade.[158] However, for these *N*-substituted pyrroles the Heck reaction was found to be the most difficult Pd-catalyzed reaction. Several reactions were performed in solution with substrate **187** to identify optimal conditions (Scheme 120) but none of them were fully satisfactory.



187 **188** **189**

Scheme 120. Model Heck reaction in solution

The conditions of all the attempted reactions are summarized in Table 17. In each case the reaction was carried out under argon atmosphere with dry solvent and monitored by GC-MS and the conversion was calculated by GC-MS.

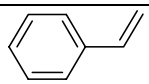
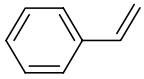
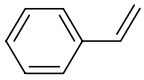
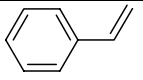
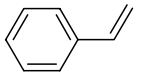
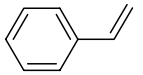
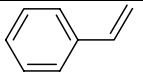
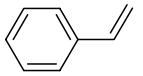
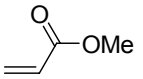
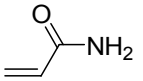
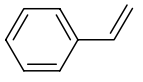
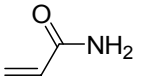
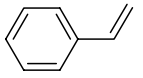
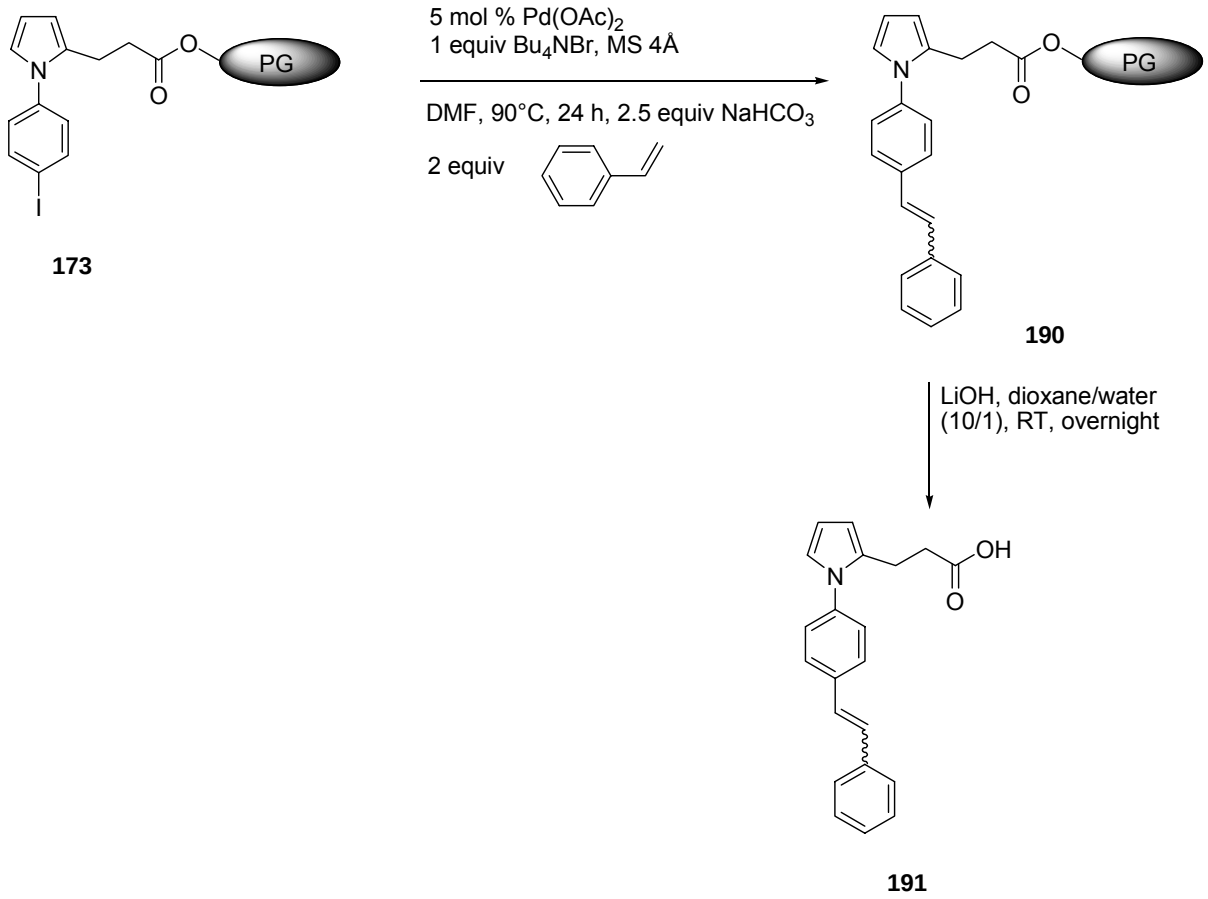
Entry	T (°C)	t (h)	Solvent	Catalyst	Base	Alkene	Result **187**/**188**/**189** (% GC-MS)
1	100	4 h	DMF	5 mol % $[Pd(PPh_3)_2Cl_2]$	Et_3N		0/40/60
2	100	4 h	DMF	5 mol % $Pd(OAc)_2$/10 mol % PPh_3	Et_3N		0/40/60
3	100	6 h	DMF	5 mol % $Pd(PPh_3)_4$	Et_3N		0/60/50
4	120	12 h	DMF	5 mol % $Pd(PPh_3)_4$	K_2CO_3		80/20/0
5	120	2 h	DMF	5 mol % $Pd(PPh_3)_4$	CH_3COOK		0/50/50
6	90	2 h	DMF	5 mol % $Pd(OAc)_2$/1 equiv Bu_4NBr	K_2CO_3		0/90/10
7	100	2 h	DMF	5 mol % $Pd(OAc)_2$/1 equiv Bu_4NBr	CH_3COOK		50/50/0
8	100	2 h	DMF	5 mol % $Pd(OAc)_2$/1 equiv Bu_4NBr	Ag_2CO_3		40/60/0
9	90	2 h	DMF	5 mol % $Pd(OAc)_2$/1 equiv Bu_4NBr	K_2CO_3		0/60/50
10	90	2 h	DMF	5 mol % $Pd(OAc)_2$/1 equiv Bu_4NBr	K_2CO_3		0/50/50
11	90	2 h	DMF	5 mol % $Pd(OAc)_2$/1 equiv Bu_4NBr/4Å molecular sieve	$NaHCO_3$		0/90/10
12	90	2 h	DMF	5 mol % $Pd(OAc)_2$/1 equiv Bu_4NBr/4Å molecular sieve	$NaHCO_3$		0/70/30
13	120	6 h	toluene	5 mol % $Pd_2(dba)_3$/10 mol % PPh_3	Ag_2CO_3		20/20/60

Table 17. Attempted Heck reaction in solution

The time indicated in Table 17 is the time after which the best conversion was achieved and each reaction was carried out for 24 h after which no further improvement of conversion was observed. From these above tried conditions entry 5 and entry 11 gave the best results with styrene. Entry 11 was performed following the reaction sequence described by Jeffery *et al*.

Following the reaction sequence of Jeffery *et al*.[159] $NaHCO_3$, tetrabutyl ammonium bromide and DMF was treated with 4Å molecular sieves under argon atmosphere. After stirring at room temperature for 15 min, a solution of soluble polymer-supported pyrrole **173** in DMF was added to that reaction mixture along with styrene. The reaction mixture was stirred for 24 h at 90°C after addition of 5 mol% $Pd(OAc)_2$ and the polymer supported crude product was purified by dialysis in chloroform. Even after dialysis for 24 h, the reaction mixture still contained some black particles and therefore the NMR of the crude reaction mixture was not clear. After subsequent cleavage by saponification the desired Heck coupled product **191** was isolated in 60 % yield (Scheme 121).



Scheme 121. Heck reaction with soluble polymeric support

From these above results dendritic polyglycerol **150** appears to be a very promising and versatile soluble polymer in liquid phase synthesis as excellent conversions as well as yield

can be achieved by these supports. The elecrolysis step was efficiently carried out with higher current yield. Therefore, it can be concluded that multistep synthesis via electrochemical step using dendritic polyglycerol supports is possible which can be a useful tool in combinatorial chemistry.

5. Summary and outlook

5.1 Summary

In this thesis it was demonstrated that electroorganic synthesis on solid phase can be achieved using conventional soild supports. To establish the method, 2,5-dimethoxylation of furans was cosen as a model reaction. As in most resins used in solid phase organic synthesis more than 95% of the substrate molecules are buried within the interior of the resin bead, a direct electron transfer between the electrode and the substrate molecules is not feasible. Therefore, a redox catalyst is used as a mediator, to separate the electron transfer step at the electrode and the redox reaction with the substrate. In solution phase electrochemistry this indirect electrolysis method often reduces the overpotential and gives products in high selectivities. For the electrolysis of furan bromonium ion acts as a mediator which is generated from ammonium bromide used as supporting electrolyte (Figure 24).

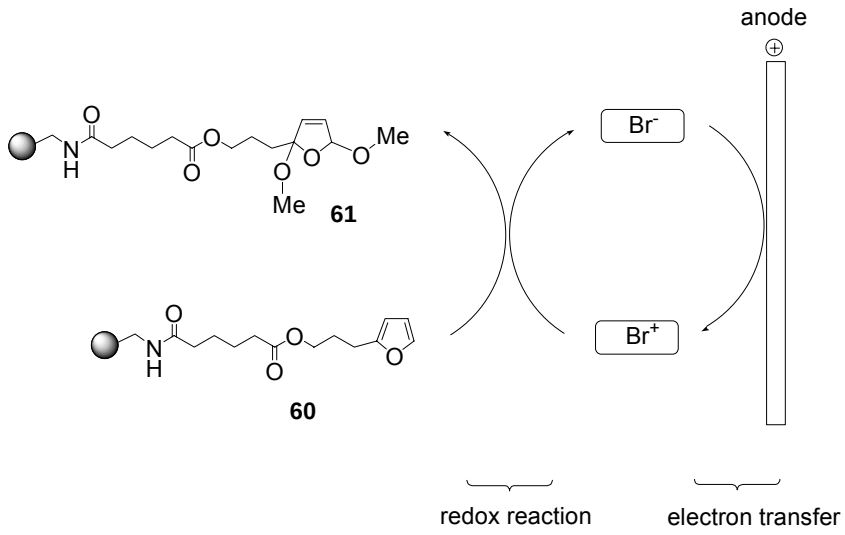
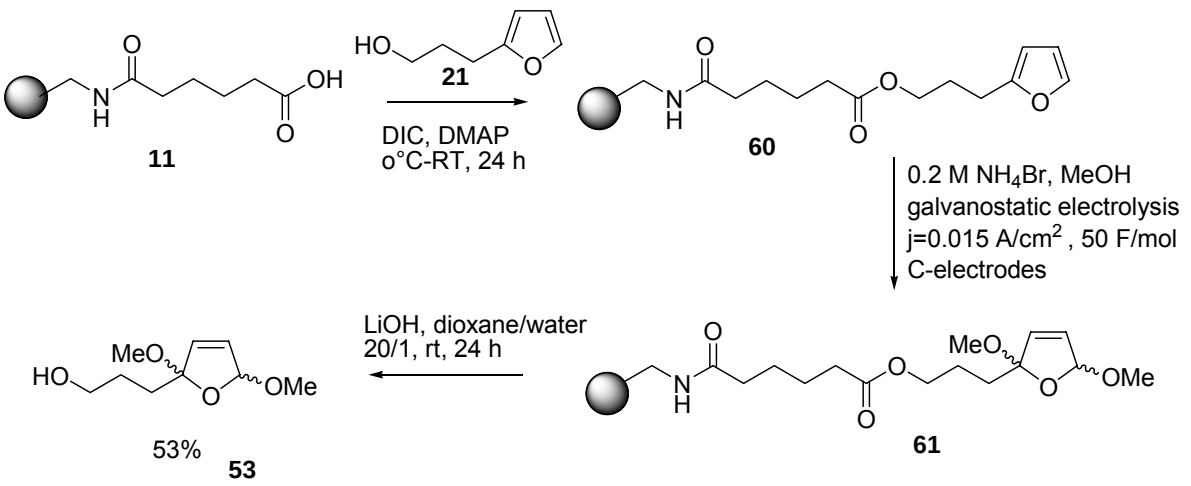


Figure 24. Principle of Br^+/Br^- mediated dimethoxylation of solid supported furan

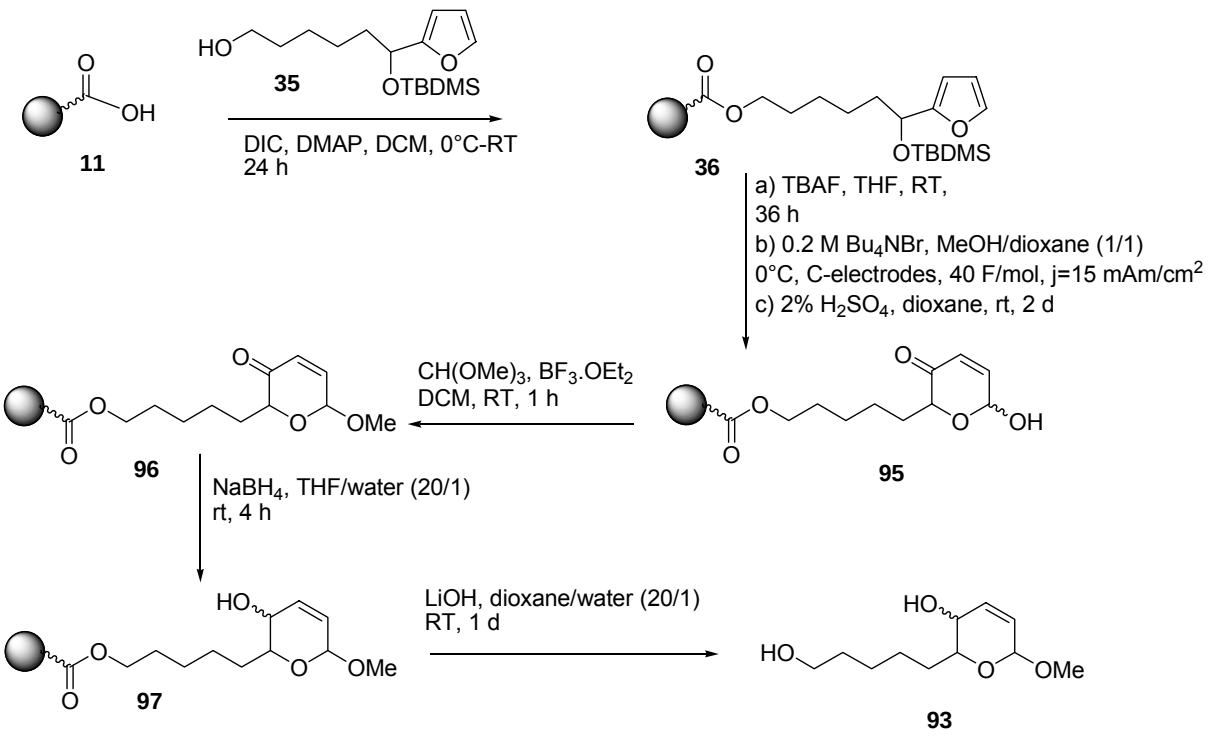
As the expected reaction products **53** are known to be acid sensitive a carboxy-terminated linker **11** was chosen to enable cleavage of the reaction products from the resin under basic conditions. Furylalcohols **21** were attached using common esterification methods (DIC) to resin **11** (Scheme 122). Resin-bound substrate **60** was subjected to the standard electrolysis conditions used in solution. Cleavage of electrolysis product **61** furnished 2,5-dimethoxydihydrofurans **53** as a *cis/trans* mixture in good yields (50-60%) and >95% purity (determined by 1H NMR spectroscopy and GC/MS).



Scheme 122. Electrochemical oxidation of 2-furanpropanol on solid phase

Having identified the optimal reaction conditions the scope of this reaction was explored with different substituted furans. Apparently uninfluenced by the substitution pattern the dimethoxylated 2,5-dihydrofurans were formed in high yields (50–63% over three steps) and excellent purities starting from mono-, di-, and trisubstituted furans. The electrochemical solid phase transformation tolerates various functional groups (alkyl, OH, ester, amide). No reaction took place with electron-poor furans and 5-(dimethylaminomethyl)furfurylalcohol whose unreactive behavior was known from earlier work in solution. Substituting MeOH for EtOH in the electrolyte for the electrolysis of substrate **60** furnished the corresponding diethoxylated dihydrofuran in similar yields.

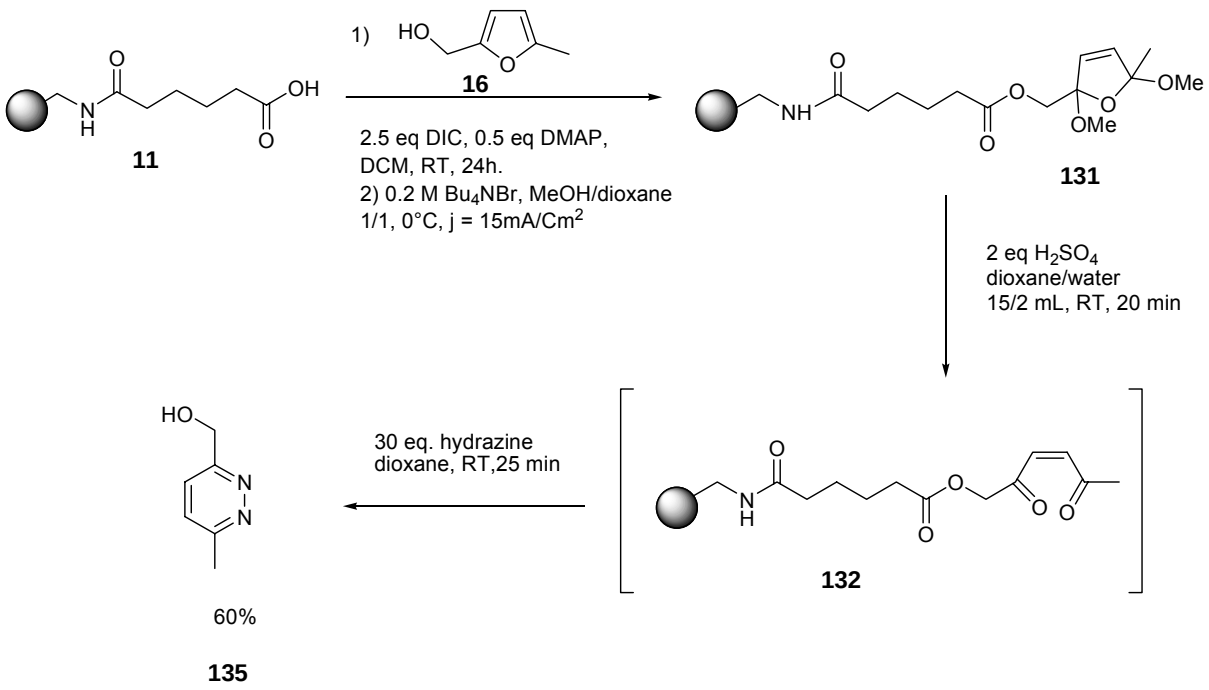
To demonstrate the utility of the electroorganic solid phase method and that it can be easily implemented in a multistep solid-phase synthesis, more demanding examples were investigated. The target chosen was the highly functionalized product **93**, which can serve as a scaffold for further derivatization (Scheme 123). The monosilyl-protected diol was attached to PS-beads **11** using a standard esterification method. After deprotection with TBAF α-hydroxyfuran was electrolyzed as described above. The resulting α-hydroxy-2,5-dialkoxydihydrofuran rearranged upon addition of aq. H_2SO_4 in 1,4-dioxane to the 6-hydroxy-2,3-dihydro-6H-pyran-3-on **95**. After $BF_3{\cdot}Et_2O$ mediated acetalization with $HC(OMe)_3$,1,2-reduction with $NaBH_4$, and cleavage by saponification the desired product **93** was isolated in 33% yield (over seven steps on solid phase). The reaction sequence detailed above clearly demonstrates that this indirect approach is suitable for multistep syntheses on the solid phase which can lead to libraries of diversified compounds or natural products.



Scheme 123. Implemention of electroorganic solid phase synthesis for multistep solid phase synthesis

However, further diversification on scaffold **95** was disappointing, although high quality diversification on **95** was achieved in solution phase which indicates the limitations of the linker chosen for solid phase chemistry.

The products formed by indirect anodic oxidations of furans, are versatile starting materials for further derivatization. In particular the latent carbonyl type reactivity of 2,5-dialkoxydihydrofurans motivated us to use the electrochemically generated reaction products in the synthesis of pyridazine heterocycles, which show a wide range of biological activities. After electroorganic oxidation of the substrate **16** the ketal moiety of the intermediate **131** were hydrolysed with acid to deliver unstable dicarbonyl compound which after subsequent reaction with an excess of hydrazine hydrate and concomitant hydrazinolysis furnished 4-methyl-pyridazine-1-carbinol (**135**) in good yield and excellent purity (60% yield, >95 % purity) (Scheme 124). This sequence represents a new solid phase route to 1,2-pyridazines which compares very well to alternative solid phase approaches of this class of heterocycles.



Scheme 124. Pyridazine formation on solid phase

In conclusion the above presented practical method for electroorganic synthesis with polymeric supports is suitable for library synthesis.

The conventional solid phase approach exhibits a number of problems due to the heterogeneous nature of reactions and the low concentration of functional groups (typically ≤1.5 mmol substrate per g polymer). Recenty dendritic high-loading soluble polymeric supports have been introduced into multistep parallel synthesis which feature homogeneous reaction conditions and enable the application of standard analytical techniques (TLC, IR, NMR, etc). After establishing the electroorganic synthetic method on solid phase it was believed that this method can be applied to dendritic soluble polymeric supports as well. A small library of dendritic soluble polymer supported *N*-substituted pyrroles which are interesting drug like structures was synthesized in a multistep way by using anodic oxidation of furan as the key step. Hyperbranched polyglycerol **150** (Figure 25) was used as a high loading polymer support. The immobilization was performed using the 'built-in' terminal 1,2-diols and therefore no additional linker was necessary. This soluble aliphatic polyether support has high loading capacity (13.5 mmol OH g^{-1}), soluble in most organic solvents (depending on the OH-group functionalization) and the polyether skeleton is stable under a wide range of reaction conditions.

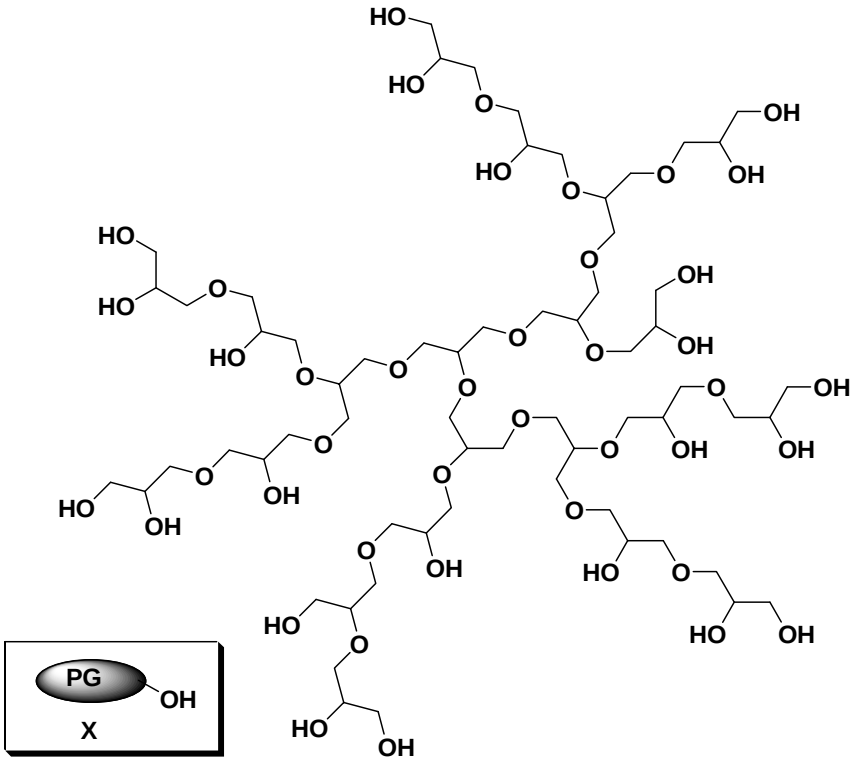
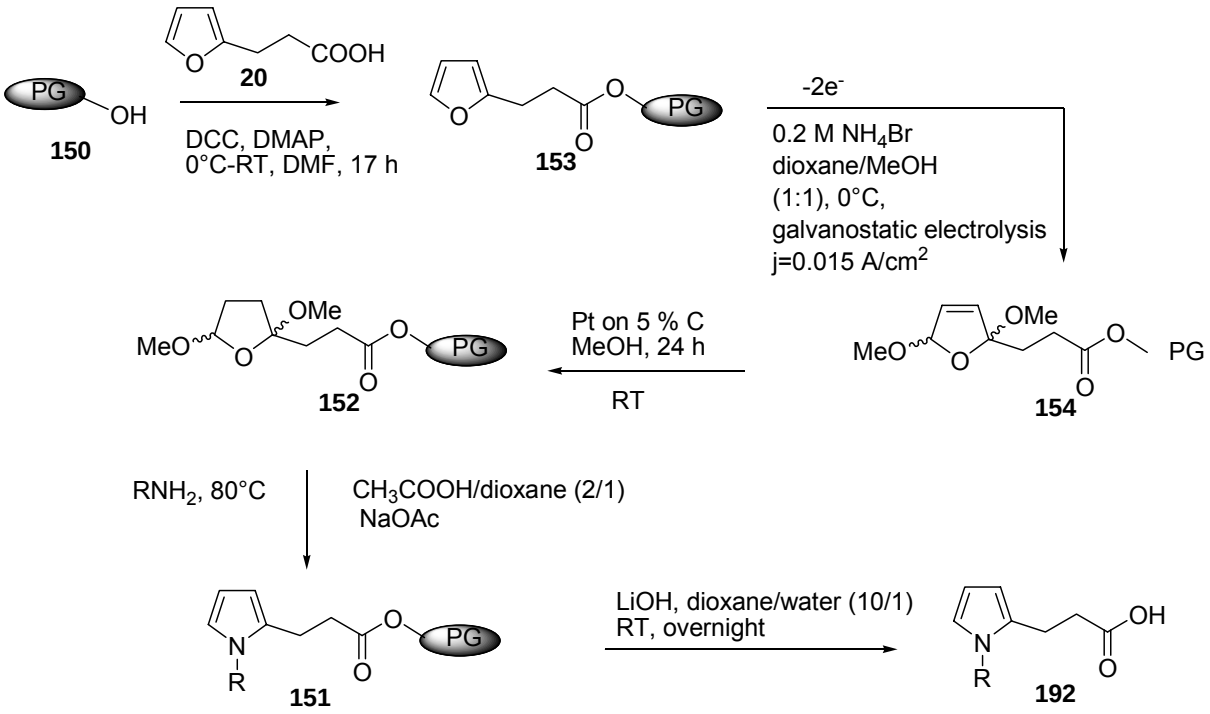


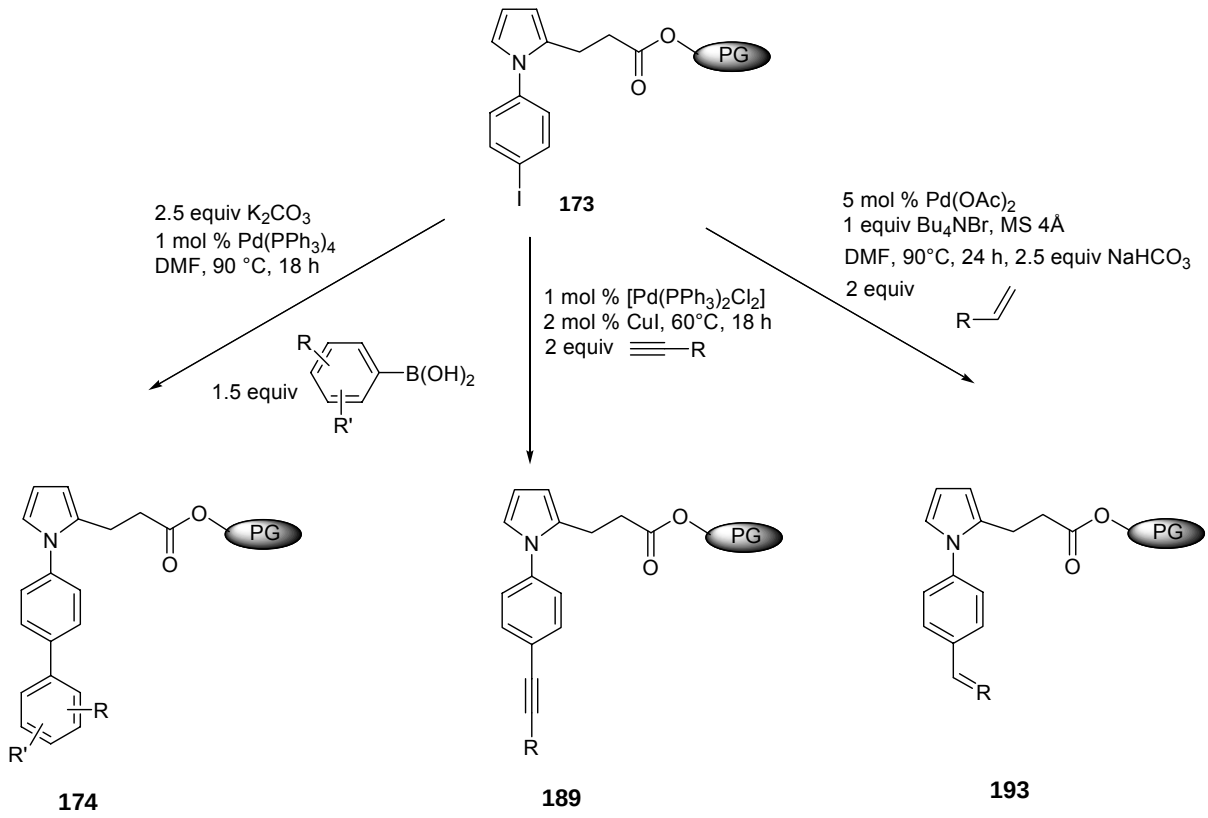
Figure 25. Dendritic polyglycerol support

2-Furanpropionic acid (**20**) was immobilized on the polyglycerol support via esterification using DCC/DMAP coupling in dry DMF (Scheme 125). The resulting ester **153** was isolated after dialysis in good conversion and yield (63% conversion and 72% yield). **153** was then electrolysed galvanostatically using 0.2 M ammonium bromide as supporting electrolyte in a dioxane/MeOH (1/1). After consumig 3 F/mol electricity the desired product **154** was isolated in quantitative conversion and 80% yield as an isomeric mixture without requiring purification by dialysis. The reduction of the olefin bond of **154** was carried out in methanol with 5% Pt overnight which gave the desired **152** in quantitative conversion and 77% yield. The polymer supported dimethoxytetrahydrofuran **152** was then hydrolysed in presence of acetic acid/dioxane (2/1) at 80°C and after condensation with different primary amines it gave the *N*-substituted pyrroles **151** in quantitative conversion. All the polymer supported pyrroles were purified by dialysis. Finally the polyglycerol supported pyrroles were split off very efficiently via saponification by LiOH which gave the corresponding acids **192** in good yields (50-65%) after purification by silicagel chromatography. A small library of *N*-substituted pyrroles was prepared by this way.



Scheme 125. Multistep *N*-substituted pyrroles synthesis on soluble polymeric supports via electrochemical reactions

The potential of this approach for further diversification was demonstrated using palladium catalyzed reactions on soluble polymeric supports with substrate **173** (Scheme 126).



Scheme 126. Diversification via palladium catalyzed reaction

A small library of palladium catalyzed coupled *N*-substituted pyrroles was synthesized in very good yields (60-65%) and quantitative conversions. Although palladium catalyzed reactions on solid phase approach are already established, often a large amount of expensive catalyst is required. But for polyglycerol **150**, due to its soluble nature, only 1-5 mol% Pd catalyst was sufficient for complete conversion for Suzuki and Sonogashira couplings. From all these above reactions it can be concluded that electroorganic synthesis can be applied in an efficient way for multistep synthesis both on solid and soluble polymeric supports which should be exploited in combinatorial synthesis in the near future.

5.2 Outlook

Every new synthetic methodology has to compete with the current benchmark. Therefore the reactions must be easily accessible in large quantitites, be chemically and mechanically mild, purification should be easy by standard laboratory techniques. In addition, the new reactions should also allow mmol-scale synthesis. For electrochemical reactions on polymeric supports all these criteria can be satisfied. Applications of electrochemistry on solid phase further simplify the purification process. On the other hand, soluble polymeric supports are giving the possibility of higher current yield, which is an important criterion in electrochemistry. Some further electrochemical reactions can be applied on polymeric supports. For example, an

effective and mild electrocatalytic procedure by electrochemically generated homogeneous electron transfer agent tris(p-tolyl)-amine could be applied for the removal of 1,3-dithiane protecting groups on solid phase which also serves as a linker (Figure 25).

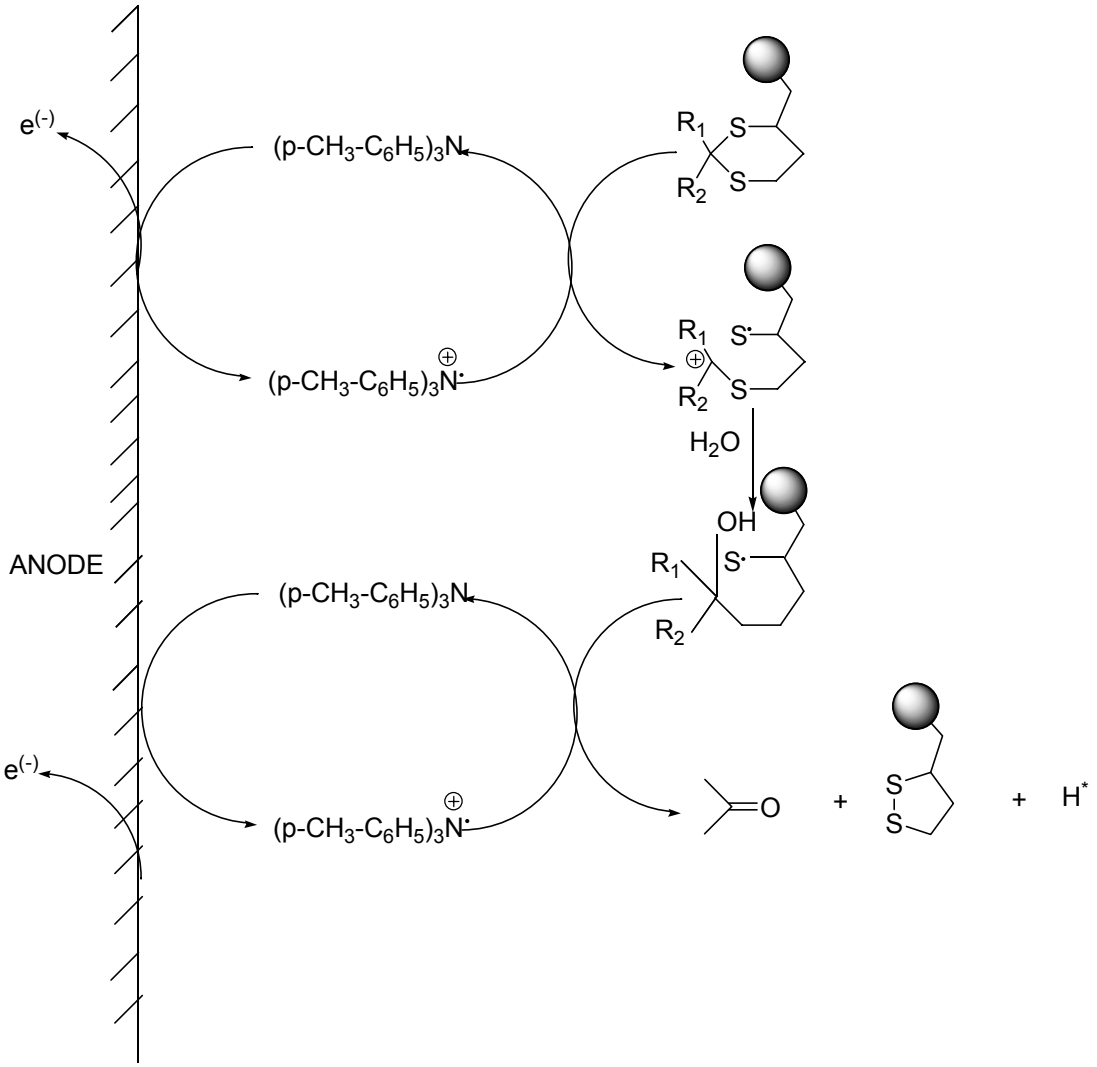
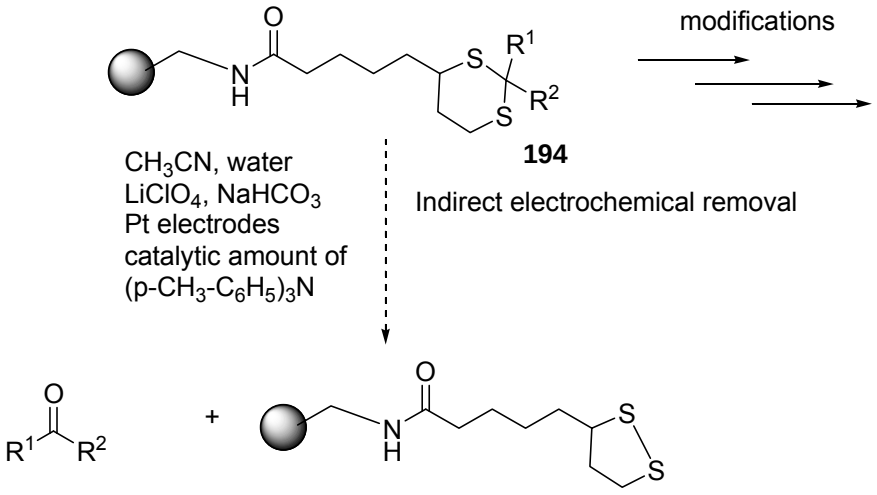


Figure 25. Electrochemical removal of dithiane protecting group or linker on solid phase

Along with the electrochemical cleavage some further diversifications can be done with solid support bound product **194** (Scheme 127) and it will also allow combinatorial synthesis.



Scheme 127. Combinatorial approach via electrochemical cleavage

Whether or not a new electrochemical reaction with polymeric supports is suitable for general application in organic synthesis can only be determined by its application in diversified library synthesis in a multiparallel fashion. Electrochemical methods have been introduced in the field of combinatorial chemistry in solution phase. Electrochemical methods on polymeric supports have been described only recently. The results from above described experiments are sufficiently encouraging in terms of yields, purities and costs, thust it can be expected that successful applications of polymer supported electrochemical synthesis will be carried out in the near future for combinatorial synthesis purpose.

6 Experimental Section

6.1 Materials, instruments and general methods for purification and analyses

Reagents:

The reagents were purchased from Acros Chimica, Advanced Chemtech, Aldrich, Avocado, Fluka, J.T Baker, Merck, Novabiochem, Riedel de Haen, Roth, or Sigma. All solvents, when not purchased with necessary purity or dryness were distilled using standard methods. Dry THF and dry Et_2O were purchased from Aldrich.

Dichloromethane	Reflux and distillation over P_2O_5 and then over CaH_2
Diethylether	Reflux and distillation over sodium
Methanol	Reflux and distillation over magnesium
Tetrahydrofuran	Reflux and distillation over sodium/potassium

Silica gel flash liquid chromatography:

Purifications were performed using silica gel from J.T. Baker or Merck (particle size 40-60 µm) under approximately 0.5 bar pressure.

Thin layer chromatography (TLC):

TLC was carried out on Merck precoated silica gel plates (60F-254) using ultraviolet light irradiation 254 nm or the following solutions as developing agents:
Staining solution A: 25 g molybdatophosphoric acid and 10 g cerium (IV) sulfate in 60 mL concentrated sulfuric acid and 940 mL water.
Staining solution B: 12 g molybdatophosphoric acid in 250 mL ethanol.
Proportions of the solutions used to monitor different reactions and the R_f values are described in the experimental sections.

Infrared spectroscopy:

IR spectra were measured on Bruker Vector 22 with a diffuse reflectance head A527 from Spectra Tech. The following notations indicate the intensity of the absorption bands: s=strong, m=middle, w=weak, br=broad absorption band.

Mass spectroscopy (HRMS):

Mass spectra were recorded by using electron impact ionization (EI), fast atom bombardment (FAB) techniques. High resolution mass spectra (HRMS, 70 eV EI and FAB) were measured on a Jeol SX 102A spectrometer. The matrix used for FAB was 3-nitrobenzylalcohol (3-NBA).

Nuclear magnetic resonance spectroscopy:

^{1}H and ^{13}C-NMR spectra were recorded using a Varian Mercury 400 spectrometer (400 MHz (^{1}H) and 100.6 MHz (^{13}C)). Chemical shifts are expressed in part per million (ppm) from internal tetramethylsilane standard. Coupling constants (*J)* are given in Hertz (Hz) and the following notations indicate the multiplicity of the signals: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt=doublet of a triplet, q=quartet, quin=quintet, m (multiplet), br (broad signal).

Gas chromatography-mass spectrometry (GC-MS):

Spectra were obtained from a Hewlett Packard 6890 GC system coupled to a Hewlett Packard 5973 Mass Selective Detector. A HP 5TA capillary column (0.33 µm x 25 m x 0.2 mm) and helium flow rate of 2 mL/min were used.

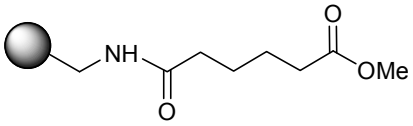
Method A (DB_50_S): temperature gradient: 0 min (50°C) → 4 min (80°C) → 6 min (300°C) → 14 min (300°C).

Method B (RP50): temperature gradient: 0 min (50°C) → 5 min (100°C) → 15 min (300°C) → 20 min (300°C).

6.2 Electroorganic synthesis on solid phase

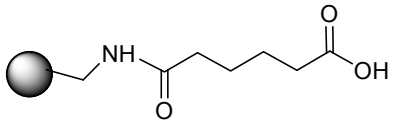
6.2.1 Experimental section for chapter 4.1.3

Procedure for the formation of aminomethylated polystyrene resin supported adipic acid monomethyl ester (10)



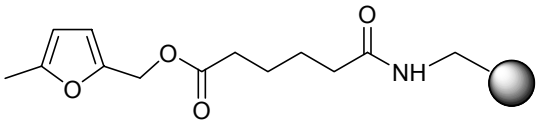
To 4.00 g (4.52 mmol) Aminomethylated polystyrene resin (Novabiochem, 200-400 mesh, loading 1.13 mmol/g) in a 100 mL round bottomed flask were added 50 mL dry drichloromethane and the resin was allowed to swell for 5 min. Then 1.93 mL (13.6 mmol) monomethyladipate, 2.09 mL (13.6 mmol) DIC, 1.82 g (13.6 mmol) HOBT, and 1.88 mL (13.6 mmol) triethylamine were added respectively to the resin suspension. The reaction mixture was shaken for 24h. Then the resin was filtered and washed with DCM (4x30 mL), THF (4x30 mL), DMF (2x30 mL), THF/MeOH (20/20 mL), THF/cyclohexane (20/20 mL), DCM (2x30 mL). The resin was dried in vacuo for 24 h.

Procedure for the preparation of aminomethylated polystyrene resain supported adipic acid (11)



In a fritted funnel reactor aminomethylated polystyrene resin supported adipic acid monomethyl ester (prepared in the previous experiment) was swelled in 40 mL dioxane and 1% LiOH/H_2O (20 mL) was added to the resin. The mixture was shaken for 24 h. 32 % HCl (1 mL) was added to adjust the pH to 3 and the mixture was shaken for another 2 hours. The resin was filtered and washed with THF (4x30 mL), THF/1 N HCl (10/10 mL), THF/water (10/10 mL), DCM/MeOH (20/20 mL), DCM/cyclohexane (20/20 mL), DCM (2x30 mL). After washing the resin was dried in vacuo for 24 h.

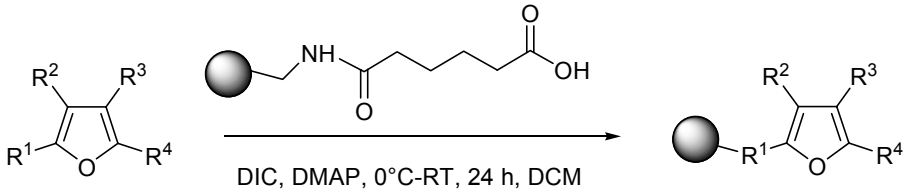
Procedure for the formation of aminomethylated polystyrene resin supported 5-methyl furfuryl alcohol (14)



In a 100 mL round bottomed flask 0.51 g aminomethylated polystyrene resin supported adipic acid (0.49 mmoL) was swelled in 30 mL dry dichloromethane. At 0 °C 0.03 g (0.24 mmol) DMAP, 0.22 g (2.0 mmol) 5-methyl furfuryl alcohol, and 0.19 mL (1.2 mmol) DIC were added respectively and the reaction mixture was shaken for 24 h at room temperature. The resin was filtered and washed with DCM (4x20mL), THF (4x20 mL), DMF (2x20 mL),

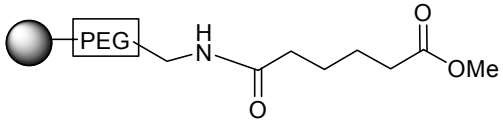
DMF/water [2x(10/10 mL)], DCM/MeOH [2x(10/10 mL)] and DCM (4x20 mL). After washing the resin was dried in vacuo for 24 h.

The procedures and washing protocols for the formation of other aminomethylated polystyrene resin supported furan derivatives are similar as described above.



Entry	R^1	R^2	R^3	R^4
1	$(CH_2)_3OH$	H	H	H
2	$(CH_2)OH$	H	H	CH_3
3	$CH(CH_3)OH$	H	H	H
4	$CH_2NHCO(CH_2)_5OH$	H	H	H
5	CH_3	$CH(CH_3)OH$	H	CH_3
6	$CH(OTBDMS)(CH_2)_4OH$	H	H	H
7	CH_2OH	H	H	H
8	$CO(CH_2)_4OH$	H	H	H
9	CH_2OH	H	H	CH_2NMe_2
10	$CH(OH)(CH_2)10CH_3$	H	H	H
11	H	H	CH_2OH	H

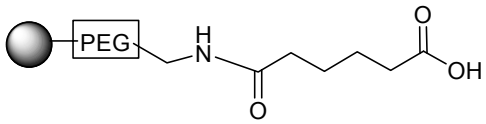
Formation of aminomethylated tentagel resin supported adipic acid monomethyl ester



To 3.15 g (0.85 mmol) of aminomethylated tentagel resin (Novasyn, loading 0.27 mmol/g) in a 100 mL round bottomed flask were added 50 mL dry drichloromethane and the resin was allowed to swell for 5 min. Then 0.36 mL (2.55 mmol) monomethyladipate, 0.39 mL (2.55 mmol) DIC, 0.39 g (2.55 mmol) HOBT, and 0.35 mL (2.55 mmol) triethylamine were added respectively to the resin suspension. The reaction mixture was shaken for 24h. Then the resin was filtered and washed with DCM (4x30 mL), THF (4x30 mL), DMF (2x30 mL),

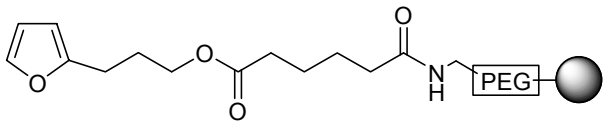
THF/MeOH (20/20 mL), THF/cyclohexane (20/20 mL), DCM (2x30 mL). The resin was dried in vacuo for 24 h.

Formation of aminomethylated tentagel resin supported adipic acid (12)



In a fritted funnel reactor resin aminomethylated tentagel resin supported adipic acid monomethyl ester (prepared in the previous experiment) was swelled in 40 mL dioxane and 1% $LiOH/H_2O$ (20 mL) was added to the resin. The mixture was shaken for 24 h. 32 % HCl (1 mL) was added to adjust the pH to 3 and the mixture was shaken for another 2 hours. The resin was filtered and washed with THF (4x30 mL), THF/1 N HCl (10/10 mL), THF/water (10/10 mL), DCM/MeOH (20/20 mL), DCM/cyclohexane (20/20 mL), DCM (2x30 mL). After washing the resin was dried in vacuo for 24 h.

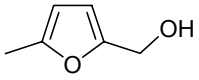
Formation of aminomethylated tentagel resin supported 2-furanpropanol (71)



In a 100 mL round bottomed flask 2.15 g resin supported adipic acid (0.82 mmoL) was swelled in 30 mL dry dichloromethane. At 0 °C 0.05 g (0.41 mmol) DMAP, 0.41 g (3.28 mmol) 2-furanpropanol, and 0.31 mL (2.1 mmol) DIC were added respectively and the reaction mixture was shaken for 24 h at room temperature. The resin was filtered and washed with DCM (4x20mL), THF (4x20 mL), DMF (2x20 mL), DMF/water [2x(10/10 mL)], DCM/MeOH [2x(10/10 mL)] and DCM (4x20 mL). After washing the resin was dried in a vacuo for 24 h.

6.2.2 Experimental section for chapter 4.1.4

5-Methyl furfuryl alcohol (16)



5.00 g (45.4 mmol) of 5-methylfurfural were added slowly at room temperature to a solution of 3.43 g (90.8 mmol) sodiumborohydride in 40 mL isopropanol. The colour of the reaction mixture was yellow. The mixture was stirred overnight. 5% HCL (10 mL) was added slowly to acidify to pH-4. 30 mL water was added to the reaction mixture and the solution was extracted with ethylacetate (4x50 mL). The combined organic layers were separated and dried over Na_2SO_4. The reaction mixture was concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/ EtOAc 3:1) to give the corresponding alcohol as a yellow oil in 4.18 g (80%).

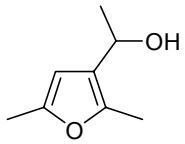
^{1}H NMR (400 MHz, $CDCl_3$) δ=2.00 (brs, 1H, -OH), 2.27 (s, 3H, -CH_3), 4.52 (s, 2H, -CH_2OH), 5.90 (dd, *J*=2.9 Hz, 1.05 Hz, 1H), 6.14 (d, *J*=2.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ=13.7 (-CH_3), 57.6 (-CH_2-), 106.4 (-CH), 108.9 (-CH), 152.5,(-C-), 152.6 (-C-).

GC-MS (RP50): t_R=4.98 min, m/z=112 (100%), 97 (50%), 95 (90%).

R_f 0.3 (cyclohexane/ EtOAc 3:1).

1-(2,5-Dimethylfuran-3-yl)ethanol (17)



A solution of 3-acetyl-2,5-dimethylfuran (5.00 g, 36.2 mmol) in 10 mL methanol was added slowly at 0°C to a solution of sodium borohydride (2.73 g, 72.4 mmol) in 10 mL methanol The resulting brown reaction mixture was refluxed overnight. 5% HCl (10 mL) was added slowly to acidify to pH-4. 30 mL water was added to the reaction mixture and the solution was extracted with ethylacetate (4x50 mL). The combined organic layers were dried over Na_2SO_4. The reaction mixture was concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/ EtOAc 5:1) to give 4.12g (80%) of the corresponding alcohol as a yellow oil.

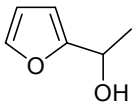
^{1}H NMR (400 MHz, $CDCl_3$) δ=1.39 (dd, *J*=6.3 Hz, 0.9 Hz, 3H, CH_3), 1.75 (bs, -OH), 2.23 (d, *J*=3.1 Hz, 6H, -2CH_3), 4.76 [q, *J*=6.5 Hz, 1H, -CH(Me)-OH], 5.93 (s, 1H, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ=11.8 (-CH_3), 13.6 (-CH_3), 24.0 (-CH_3), 62.8 (-CHOH), 104.3 (-CH), 124.2 (-C-), 145.8 (-C-), 150.0 (-C-).

GC-MS (DB_50_S): t_R=4.27 min, m/z=140 (56%), 125 (75%), 97 (65%), 43 (100%).

R_f 0.25 (cyclohexane/ EtOAc 5:1)

1-(Furan-2-yl)ethanol (18)



A solution of 2-acetylfuran (5.00 g, 45.40 mmol) in 10 mL methanol was added slowly at 0°C to a solution of sodium borohydride (3.83 g, 90.80 mmol) in 10 mL methanol. The resulting brown reaction mixture was refluxed overnight. 5% HCl (10 mL) was added slowly to acidify to pH-4. 30 mL water was added to the reaction mixture and the solution was extracted with ethylacetate (4x50 mL). The organic layer was separated and dried with Na_2SO_4. The reaction mixture was concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/EtOAc 5:1) to give the corresponding alcohol 4.35 g (86%) as a yellow oil.

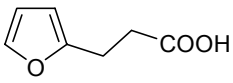
^{1}H NMR (400 MHz, $CDCl_3$) δ=1.45 (d, *J*=6.5 Hz, 3H, -CH_3), 2.06 (bs, -OH), 4.80 [q, *J*=6.5 Hz, 1H, -CH(Me)-OH], 6.14 (td, *J*=3.1 Hz, 0.8 Hz, 1H), 6.24 (dd, *J*=3.1 Hz, 1.8 Hz, 1H), 7.28 (dd, *J*=1.8 Hz, 0.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ=21.4 (CH_3), 64.7 (-CHOH), 105.3 (-CH), 110.3 (-CH), 141.6 (-CH), 157.3 (-C-).

GC-MS (DB_50_S): t_R=3.10 min, m/z=112 (56%), 97 (100%).

R_f 0.25 (cyclohexane/ EtOAc 5:1)

2-Furanpropionic acid (20)



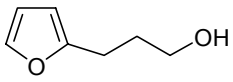
In a three-neck 250 mL flask palladium on activated charcoal [0.3 g, (5% Pd)] was placed and 100 mL ethyl acetate was added to it under Ar at room temperature. 10 g (72.46 mmol) 2-furylacrylic acid was added to the solution followed by addition of 100 mL methanol to the reaction mixture. The solution was flushed five times with Ar using vacuum/Ar cycles. A balloon filled with hydrogen gas was attached to one of the necks of the flask. After putting the flask under vacuum the solution was flushed with hydrogen gas. The reaction mixture was stirred at room temperature for 5 h. The mixture was then filtered through celite under vacuum and the filtrate was concentrated under reduced pressure and purified by sublimation under reduced pressure to afford 5.7 g (57%) of the corresponding acid as a yellowish solid. This compound should be stored in the dark at -18°C to prevent decomposition.

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.70 (t, *J*=6.9 Hz, 2H, -CH_2-COOH), 2.97 (t, *J*=6.9 Hz, 2H, -CH_2), 6.04 (dd, *J*=1.9 Hz, 0.8 Hz, 1H), 6.28 (dd, *J*=3.1 Hz, 1.9 Hz, 1H), 7.31 (dd, *J*=1.9 Hz, 0.8 Hz, 1H), 10.83 (brs, 1H, -COOH).

^{13}C NMR (100 MHz, $CDCl_3$) δ=23.3 (-CH_2), 32.7 (-CH_2COOH), 105.6 (-CH), 110.4 (-CH), 141.5 (-CH), 153.9 (-C-), 179.1 (-COOH).

R_f 0.30 (cyclohexane/ EtOAc 1:1).

2-Furanpropanol (21)



A two-neck 100 mL flask was charged with lithium aluminium hydride (0.67 g, 17.85 mmol) and 10 mL dry ether were added under Ar at 0°C. A solution of 2-furanpropionic acid (2 g, 14.28 mmol) in 10 mL dry ether was added to the lithium aluminium hydride solution over 20 min under Ar at 0°C. The reaction mixture was stirred overnight at room temperature. The mixture was then quenched with 0.67 mL water, 0.67 mL 15% NaOH, and 2.01 mL water. The resulting white reaction mixture was stirred for 1 h. The mixture was filtered under vacuum and the residue was washed with diethyl ether (3x30 mL). The combined filtrates were concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/ EtOAc 1:1) to give 1.20 g (67%) of the corresponding alcohol as a colourless oil.

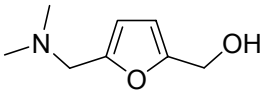
^{1}H NMR (400 MHz, $CDCl_3$) δ=1.88 (m, *J*=6.9 Hz, 2H, -CH_2),1.97 (bs, -OH), 2.72 (t, *J*=7.3 Hz, 2H, -CH_2), 3.66 (t, *J*=6.4 Hz, 2H, -CH_2OH), 6.04 (dd, *J*=3.1 Hz, 0.9 Hz, 1H), 6.28 (dd, *J*=3.1 Hz, 1.8 Hz, 1H), 7.31 (dd, *J*=1.8 Hz, 0.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ=24.5 (-CH_2), 31.1 (CH_2), 62.2 (-CH_2OH), 105.2 (-CH), 110.3 (-CH), 141.1 (-CH), 155.8 (-C-).

GC-MS (RP50): t_R=6.59 min, m/z=126 (50%), 108 (60%), 81 (100%)

R_f 0.20 (cyclohexane/ EtOAc 1:1)

5-Dimethylaminomethylfurfuryl alcohol (26)



To a solution of 2-furanmethanol (5.00 g, 50.9 mmol) in 100 mL ethanol, 4.15 g (50.9 mmol) dimethylamine hydrochloride, 4.29 g (152.8 mmol) paraformaldehyde were added respectively at room temperature and the light yellow reaction mixture was refluxed for 24 h. The resulting brown reaction mixture was concentrated under reduced pressure. The residue was diluted with water (40 mL) and 5 mL 10M NaOH were added to the aqueous solution. The aqueous layer was extracted with ethyl acetate (4x 60 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by silicagel chromatography (EtOAc) to yield 2.616 g (33%) of the title compound as a yellow oil.

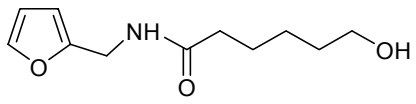
^{1}H NMR (400 MHz, $CDCl_3$) δ=2.18 (s, 6H, -2CH_3), 3.37 (s, 2H, -CH_2N), 4.48 (s, 2H, -CH_2O), 6.08 (d, *J*=3.1 Hz, 1H, -CH), 6.13 (d, *J*=3.1 Hz, 1H, -CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ=44.9 (-CH_3), 55.9 (-CH_2), 57.3 (-CH_2), 107.9 (-CH), 109.6 (-CH), 151.7 (-C-), 154.7 (-C-).

GC-MS (RP50): t_R=7.68 min, m/z=155 (100%), 124 (70%), 111 (100%), 94 (30%), 83 (50%).

R_f 0.30 (EtOAc)

_N_-((Furan-2-yl)methyl)-6-hydroxyhexanamide (24)



6-Caprolactone (40.18 mL, 378.85 mmol) was added slowly to furfuryl amine (4.00 g, 41.2 mmol) over 1 h at room temperature. The reaction mixture was stirred overnight and the excess reagents were removed in vacuo and purified by silicagel chromatography (EtOAc) to give 7.82 g (90%) of the corresponding amide as a yellow solid.

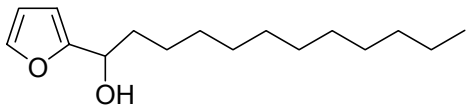
^{1}H NMR (400 MHz, $CDCl_3$) δ=1.42 (m, 2H, -CH_2),1.57 (m, 2H, -CH_2), 1.69 (m, *J*=7.4 Hz, -2H, -CH_2), 2.22 (t, *J*=7.4 Hz, 2H, -CH_2), 3.66 (t, *J*=6.4 Hz, 2H, -CH_2OH), 4.43 (d, J=5.3 Hz, -2H, -CH_2NH), 6.05 (bs, 1H, -NH), 6.22 (dd, *J*=3.1 Hz, 0.8 Hz, 1H), 6.31 (dd, *J*=3.1 Hz, 1.9 Hz, 1H), 7.35 (dd, *J*=1.9 Hz, 0.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ=25.4 (-CH_2-), 25.5 (-CH_2-), 32.4 (-CH_2-), 36.5 (-CH_2-),36.6 (-CH_2-), 62.6 (-CH_2-OH), 107.6 (-CH), 110.6 (-CH), 142.3 (-CH), 151.6 (-C-), 173.1 (-NHCO-).

GC-MS (RP50): t_R=12.44 min, m/z=211 (35%), 139 (20%), 96 (100%), 81 (90%).

R_f 0.25 (EtOAc)

1-(Furan-2-yl)dodecan-1-ol (27)



A dried two-neck 250 mL flask was charged with furan (1.06 mL, 14.68 mmol) and 50 mL dry ether were added slowly to it under Ar at -78°C°. A 1.6 M solution of butyllithium in hexane (9.62 mL, 15.42 mmol) was added to the furan solution under Ar. The colour of the reaction mixture was changing from light pink to bright yellow. The resulting bright yellow reaction mixture was stirred at -30°C for 30 min. Dodecanal (3.56 mL, 16.14 mmol) was added to the reaction mixture over 20 min at 0°C. The resulting turbid reddish yellow reaction mixture was stirred at room temperature for 3 h. Saturated ammonium chloride solution (15 mL) was added to the reaction mixture which turned to a transparent bright yellow solution. Then 40 mL ethyl acetate were added and the solution was extracted with ethyl acetate (4x40 mL).

The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/EtOAc 10:1) to give 2.19 g (92%) of the title compound as a light yellow solid.

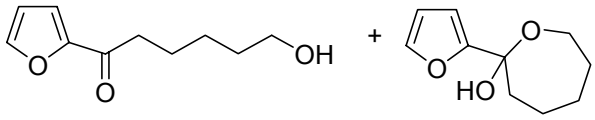
^{1}H NMR (400 MHz, $CDCl_3$) δ=0.86 (t, *J*=6.6 Hz, -CH_3), 1.25 (s, 20H, -$(CH_2)_{10}$), 1.85 (m, 2H, -CH_2), 1.83 (q, *J*=6.8 Hz, 2H), 4.65 (t, *J*=6.8, 1H, -CHOH), 6.22 (td, *J*=3.2 Hz, 0.8 Hz, 1H), 6.32 (dd, *J*=3.2 Hz, 1.9 Hz, 1H), 7.36 (dd, *J*=1.9 Hz, 0.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ=14.3 (CH_3), 22.9 (-CH_2), 25.6 (-CH_2), 29.5 (-CH_2), 29.6 (-CH_2), 29.75 (-CH_2), 29.79 (-CH_2), 29.85 (-CH_2), 29.87 (-CH_2), 32.1 (-CH_2), 35.7 (-CH_2), 68.0 (-CHOH), 105.9 (-CH), 110.3 (-CH), 142.0 (-CH), 157.1 (-C-).

GC-MS (RP50): t_R=1192 min, m/z=252 (35%), 97 (100%).

R_f 0.20 (cyclohexane/ EtOAc 2:1)

1-(Furan-2-yl)-6-hydroxyhexan-1-one (31 and 32)



A dried two-neck 250 mL flask was charged with furan (2.13 mL, 29.36 mmol) and 50 mL of dry ether were added slowly to it under Ar at -78°C°. A 1.6 M solution of butyllithium in hexane (19.19 mL, 30.8 mmol) was added to the furan solution under Ar. The colour of the reaction mixture was changing from light pink to bright yellow. The resulting bright yellow reaction mixture was stirred at -30°C for 30 min. 6-caprolactone (3.11 mL, 29.3 mmol) was added to the reaction mixture over 20 min at 0°C. The resulting turbid reddish yellow reaction mixture was stirred at room temperature for 3 h. Saturated ammonium chloride solution (15 mL) was added to the reaction mixture and which turned to a transparent bright yellow solution. Then 40 mL ethyl acetate were added and the solution was extracted with ethyl acetate (4x40 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and the resulting oily yellow crude product (5.13 g) was used for the next reaction step without further purification.

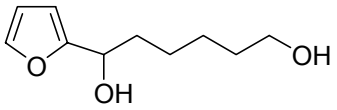
Ratio: major/minor: 1.7/1 (**31**/**32**)

^{1}H NMR (400 MHz, CDCl3) δ=1.32-1.80 (m, CH_2), 2.21 (brs, -OH), 2.30 (t, *J*=7.4 Hz, 2H, -CH_2), 2.83 (t, *J*=7.3 Hz, 2H, -CH_2), 3.57 (t, *J*=6.4 Hz, 2H^{min}), 3.64 (t, *J*=6.5 Hz, 2H^{maj}), 4.04 (m, *J*=6.4 Hz, 2H), 6.23 (dt, *J*=3.3 Hz, 0.9 Hz, 1H^{min}), 6.33 (dd, *J*=3.3 Hz, 1.8 Hz, 1H^{min}), 6.51 (dd, *J*=3.5 Hz, 1.5 Hz, 1H^{maj}), 7.17 (dd, *J*=3.5 Hz, 0.8 Hz, 1H^{maj}), 7.35 (dd, *J*=1.8 Hz, 0.9 Hz, 1H^{min}), 7.56 (dd, *J*=1.5 Hz, 0.8 Hz, 1H^{maj}).

^{13}C NMR (100 MHz, CDCl3) δ=23.4 (-CH_2), 24.1 (CH_2), 24.8 (CH_2), 25.6 (CH_2), 28.5 (CH_2), 32.6 (CH_2), 34.4 (CH_2), 38.5 (CH_2), 38.9 (CH_2), 62.8, 64.3, 106.6, 110.4, 112.3, 117.1, 142.1, 146.4, 153.0, 156.6, 189.8 (-CO).

GC-MS (RP50): t_R=11.50 min, m/z=182 (10%), 123 (20%), 110 (100%), 95 (50%).
t_R=11.00 min, m/z=179 (10%), 115 (100%), 97 (50%), 55 (60%).

1-(Furan-2-yl)hexane-1,6-diol (33)



A dried two-neck 250 mL flask was charged with lithium aluminium hydride (1.87 g, 49.3 mmol) and 50 mL of dry ether was added to it under Ar at 0°C. A solution of the crude product (5.13 g, 27.4 mmol) in 30 mL of dry ether was added over 20 min to the lithium aluminium hydride solution under Ar at 0°C. The reaction mixture was stirred overnight at room temperature. The mixture was then quenched with 1.87 mL of water, 1.87 mL of 15% NaOH, and 5.61 mL of water and the resulting white reaction mixture was stirred for 1 h. The mixture was filtered under vacuum and the residue was washed with diethyl ether (3x50 mL). The combined filtrates were concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/ EtOAc 2:1) to give 3.12 g (60%) of the corresponding alcohol as a yellow oil.

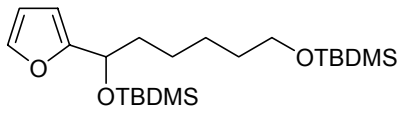
^{1}H NMR (400 MHz, $CDCl_3$) δ=1.37 (m, 4H, -CH_2-CH_2),1.55 (m, *J*=6.8 Hz, 2H), 1.83 (q, *J*=6.8 Hz, 2H), 2.20 (bs, 2H, -OH), 3.59 (t, *J*=6.5 Hz, 2H, -CH_2OH), 4.65 (t, *J*=6.8, 1H, -CHOH), 6.20 (td, *J*=3.2 Hz, 0.8 Hz, 1H), 6.30 (dd, *J*=3.2 Hz, 1.9 Hz, 1H), 7.34 (dd, *J*=1.9 Hz, 0.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ=25.4 (-CH_2), 25.6 (-CH_2), 32.7 (-CH_2), 35.6 (-CH_2), 62.8 (-CH_2OH), 67.7 (-CHOH), 105.9, 110.3 (-CH), 142.0 (-CH), 157.1 (-C-).

GC-MS (RP50): t_R=11.87 min, m/z=184 (20%, 166 (10%), 97 (100%).

R_f 0.20 (cyclohexane/ EtOAc 2:1)

Protection of both hydroxyl groups of 1-(furan-2-yl)hexane-1,6-diol (34)



A two-neck 100 mL flask was charged with 1-(furan-2-yl)hexane-1,6-diol (1.85 g, 10.1 mmol) and 30 mL of dry DMF was added to it under Ar at room temperature. Imidazole (2.39 g, 35.2 mmol) and *tert*-butyldimethylsilyl chloride (4.54 g, 30.5 mmol) were added to the reaction mixture respectively and the reaction mixture was stirred overnight at room temperature. 30 mL of water were added to the reaction mixture and the solution was extracted with diethyl ether (2x40 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by silicagel chromatography (cyclohexane/ EtOAc 50:1) to give the corresponding diprotected alcohol 4.14 g (81%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=-0.06 (s, 3H, -CH_3), 0.04 (s, 9H, -CH_3), 0.87 (m, 18H, t-Bu), 1.33 (m, 4H, -CH_2-CH_2), 1.50 (m, 2H, -CH_2), 1.80 (m, 2H, -CH_2), 3.58 (t, *J*=6.6 Hz, 2H, -CH_2-OTBDMS), 4.66 (t, *J*=7.0 Hz, 1H, -CH-OTBDMS), 6.14 (td, *J*=3.1 Hz, 0.8 Hz, 1H), 6.29 (dd, *J*=3.2 Hz, 1.9 Hz, 1H), 7.34 (dd, *J*=1.8 Hz, 0.8 Hz, 1H).

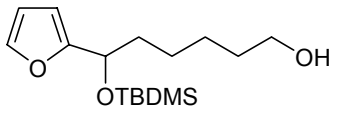
^{13}C NMR (100 MHz, $CDCl_3$) δ=-4.8 (-Si-CH_3), -4.6 (-Si-CH_3), -4.4 (-Si-CH_3), 18.6 (quaternary carbon atom of the t-Bu group), 18.7 (quaternary carbon atom of the t-Bu group), 25.5, 25.9, 26.1, 26.3, 33.1, 37.3, 63.4 (CH_2OH), 68.7 (CH-OTBDMS), 105.6 (-CH), 110.1 (-CH), 141.2 (-CH), 157.5 (-C-).

GC-MS (RP50): t_R=12.74 min, m/z=412 (10%), 355 (30%), 285 (35%), 149 (100%), 107 (70%), 81 (99%).

R_f 0.30 (cyclohexane/ EtOAc 50:1)

HR-MS (EI) of $C_{22}H_{44}O_3Si_2$: Theoretical 412.2829 [M^+], found 412.2820.

Deprotection of the primary hydroxyl group of 1-(furan-2-yl)hexane-1,6-diol (35)



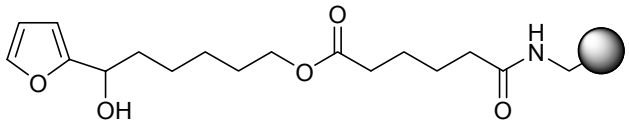
To a solution of the diprotected alcohol (3.35 g, 8.11 mmol) in dry methanol (25 mL), NH_4F (3.42 g, 92.5 mmol) was added to it at once and the resulting reaction mixture was stirred and heated at 60°C. The reaction was monitored by thin-layer chromatography. 20 mL water were added to the reaction mixture and the solution was extracted with ethyl acetate (4x40 mL). The combined organic layers were dried over Na_2SO_4 and the resulting reaction mixture was concentrated under reduced pressure and purified by silicagel chromatography to give 1.32 g (54%) of the corresponding monoprotected alcohol as a colourless oil.

^{1}H NMR (400 MHz, CDCl3) δ=-0.07 (s, 3H, -CH_3), 0.04 (s, 3H, -CH_3), 0.87 (s, 9H, t-Bu), 1.33 (m, 4H, -CH_2-CH_2), 1.55 (m, 2H, -CH_2), 1.80 (m, 2H, -CH_2), 3.60 (t, *J*=6.6 Hz, 2H, -CH_2OH), 4.66 (t, *J*=7.0 Hz, 1H, -CH-OTBDMS), 6.14 (td, *J*=3.1 Hz, 0.8 Hz, 1H), 6.29 (dd, *J*=3.2 Hz, 1.9 Hz, 1H), 7.34 (dd, *J*=1.8 Hz, 0.8 Hz, 1H).

GC-MS (RP50): t_R=11.97 min, m/z=281 (10%), 241 (10%), 223 (30%), 211 (35%), 173 (40%), 149 (40%), 107 (80%), 81 (100%), 75 (80%).

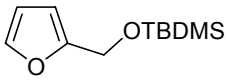
R_f 0.30 (cyclohexane/ EtOAc 4:1)

Deprotection of the secondary hydroxyl group on solid phase (37)



To a mixture of the resin supported mono protected furan (1.12 g, 1.1 mmol) in 20 mL of dry THF at room temperature was added TBAF (5.50 mL, 5.53 mmol) and the reaction mixture was shaken for 36 h at room temperature. Then the resin was filtered and washed with DCM (4x20 mL), THF (4x20 mL), DMF (2x20 mL), DMF/water [2x(10/10 mL)], DCM/MeOH [2x(10/10 mL)], and DCM (4x20 mL). After washing the resin was dried in vacuo for 24 h.

((Furan-2-yl)methoxy)(*tert*-butyl)dimethylsilane (40)



A two-neck 100 mL flask was charged with 2-furylalcohol (5 g, 50.9 mmol) and 50 mL of dry DMF was added to it under Ar at room temperature. Imidazole (6.93 g, 101.8 mmol) and *t*-butyldimethylsilyl chloride (11.5 g, 76.3 mmol) were added to the reaction mixture respectively under Ar at room temperature and the reaction mixture was stirred overnight at room temperature. 30 mL of water were added to the reaction mixture and the solution was extracted with diethyl ether (2x40 mL). The combined organic layers were dried over Na_2SO_4 and the resulting reaction mixture was concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/EtOAc 50:1) to give 9.49 g (87%) of the corresponding protected alcohol as a colourless oil.

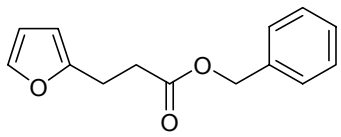
^{1}H NMR (400 MHz, $CDCl_3$) δ=0.08 (s, 6H, -$(CH_3)_2$), 0.91 (m, 9H, t-Bu), 4.65 (s, 2H, -CH_2O), 6.21 (dd, *J*=3.1 Hz, 0.8 Hz, 1H), 6.35 (dd, *J*=3.1 Hz, 1.8 Hz, 1H), 7.35 (t, *J*=1.8 Hz, 0.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ=-4.7 (-CH_3), 18.9 (-C-), 26.4 (-CH_3), 58.6 (-CH_2O), 117.8 (-CH), 110.2 (-CH), 142.5 (-CH), 154.4 (-C-).

R_f 0.3 (cyclohexane/ EtOAc 50:1).

6.2.3 Experimental section for chapter 4.1.5

Benzyl 3-(furan-2-yl)propanoate (48)



To a solution of 2-furylpropionic acid (1.00 g, 7.14 mmol) in 20 mL dry DCM, 0.04 g (0.35 mmol) DMAP, 0.88 mL (8.56 mmol) benzyl alcohol and 1.21 mL (7.85 mmol) DIC were added respectively at 0°C and the light yellow reaction mixture was stirred for 24 h at room temperature. The reaction mixture was filtered through cotton, concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/ EtOAc 20:1) to yield 1.46 g (88%) of the title compound as a yellow oil.

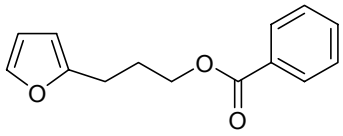
^{1}H NMR (400 MHz, $CDCl_3$) δ=2.75 (t, *J*=7.2 Hz, 2H, -CH_2), 3.00 (t, *J*=7.2 Hz, 2H, -CH_2), 5.15 (s, 2H, -OCH_2), 6.04 (dd, *J*=3.1 Hz, 0.8 Hz, 1H), 6.28 (dd, *J*=3.1 Hz, 1.8 Hz, 1H), 7.31 (dd, *J*=1.8 Hz, 0.8 Hz, 1H), 7.33-7.40 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=23.7 (-CH_2), 32.9 (-CH_2), 66.6 (-OCH_2), 105.6 (-CH, furan ring), 110.4 (-CH, furan ring), 128.46, 128.47, 128.7, 136.1, 141.3 (-CH, furan ring), 154.1 (-C-, furan ring), 172.5 (-CO-).

GC-MS (RP50): t_R=11.36 min, m/z=230 (30%), 139 (100%), 97 (80%), 91 (90%).

R_f 0.3 (cyclohexane/ EtOAc 20:1)

3-(Furan-2-yl)propyl benzoate (51)



To a solution of 2-furanpropanol (0.27 g, 2.17 mmol) in 20 mL dry DCM, 0.01 g (0.09 mmol) DMAP, 0.22 g (1.82 mmol) benzoic acid and 0.31 mL (1.91 mmol) DIC were added respectively at 0°C and the light yellow reaction mixture was stirred for 24 h at room temperature. The reaction mixture was filtered through cotton, concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/ EtOAc 50:1) to give 0.33 g (80%) of 3-(furan-2-yl)propyl benzoate as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.13 (qn, *J*=6.8 Hz, 2H, -CH_2), 2.82 (t, *J*=7.4 Hz, 2H, -CH_2), 4.37 (t, *J*=6.4 Hz, 2H, -CH_2O), 6.04 (dd, *J*=3.1 Hz, 0.8 Hz, 1H), 6.28 (dd, *J*=3.1 Hz, 1.8 Hz, 1H), 7.31 (dd, *J*=1.8 Hz, 0.8 Hz, 1H), 7.42-8.08 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=24.5 (-CH_2), 27.4 (-CH_2), 64.2 (-CH_2O), 105.5 (-CH, furan ring), 110.4 (-CH, furan ring), 128.5, 129.8, 130.5, 131.1, 141.3 (-CH, furan ring), 155.1 (-C-, furan ring), 166.7 (-CO-).

GC-MS (RP50): t_R=11.52 min, m/z=230 (20%), 108 (100%), 77 (50%).

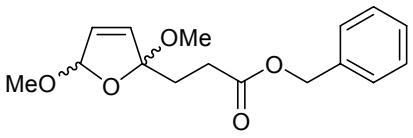
R_f 0.3 (cyclohexane/ EtOAc 50:1)

General procedure for electrochemical anodic oxidation using ammonium bromide as supporting electrolyte

For the experimental setup an undivided beaker-type cell (commerical Metrohm titration vessels and lids were adapted in the local machine shop) was equipped with two carbon

electrodes (area of the electrodes immersed in the electrolytic solution: 2.7 cm^2, distance between the two electrodes: 0.5 cm). The cell was charged with furan substrate (1-4 mmol) and 40 mL 0.3 M ammonium bromide in MeOH. The cell was then immersed into a cooling bath thermostated at 0°C. For the electrolysis a current density of 0.015 A/cm^2 was applied. The power was supplied by an EA-PS-2032-025 instrument by which the current required for the electrolysis was fixed to 0.04 A and a electronic Coulomb-meter was used to calculate automatically the total electricity consumed for the electrolysis. After complete conversion of the starting material, 1 g $NaHCO_3$ was added to the bright yellow solution mixture and the reaction mixture was concentrated under reduced pressure until a yellowish-white solid was formed. Then 20 mL water were added and the solution was extracted with ethyl acetate (4x50 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and finally dried in vacuo to furnish the desired product.

Formation of benzyl 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanoate using ammonium bromide as supporting electrolyte (49)



The experimental setup was as described above for the general electrochemical anodic oxidation. The reaction was carried out with 0.51 g (2.16 mmol) benzyl 3-(furan-2-yl)propanoate. After 0.1715 Ah (3 F/mol, which was required for the complete conversion of the starting material) electricity was consumed the title compound was isolated in 95% yield (0.61 g) as a yellow oil (*cis/trans* mixture) without further purification.

Ratio: major/minor: 3/1

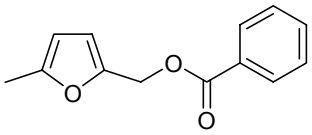
^{1}H NMR (400 MHz, $CDCl_3$) δ=2.15 (m, 2H, -CH_2), 2.40 (m, 2H, -CH_2), 3.08 (s, 3H, -OMe^{min}), 3.16 (s, 3H, -OMe^{maj}), 3.42 (s, 3H, -OMe^{min}), 3.46 (s, 3H, -OMe^{maj}), 5.09 (s, 2H, -OCH_2^{maj}), 5.10 (s, 2H, -OCH_2^{min}), 5.40 (t, *J*=1.1 Hz, 1H, maj), 5.72 (t, *J*=1.2 Hz, 1H, min), 5.81 (dd, *J*=5.9 Hz, 1.2 Hz, 1H, maj), 5.84 (dd, *J*=6.0 Hz, 1.2 Hz, 1H, min), 5.98 (dd, *J*=5.8 Hz, 1.2 Hz, 1H, maj), 6.02 (dd, *J*=5.9 Hz, 1.1 Hz, 1H, min), 7.30-7.40 (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 29.1+29.4 (-CH_2-), 34.1+34.2 (-CH_2-), 49.9+50.5 (-OMe), 55.8+56.4 (-OMe), 66.3+66.4 (-OCH_2), 107.3+108.5, 113.4+114.6, 128.3, 128.40, 128.45, 128.70, 128.74, 131.5+131.7, 132.2+132.9, 136.2+136.3, 173.3+173.5 (-COPh).

GC-MS (RP50): t_R=12.40 min, 12.61 min, 12.86 min, (isomeric mixtures), m/z=260 (30%), 229 (40%), 169 (30%), 154 (60%), 125 (50%), 97 (60%), 91 (100%).

6.2.4 Experimental section for chapter 4.1.6

(5-Methylfuran-2-yl)methyl benzoate (54)



To a solution of 5-methyl furfuryl alcohol (1.0 g, 8.92 mmol) in 20 mL dry DCM, 0.04 g (0.37 mmol) DMAP, 0.91 g (7.44 mmol) benzoic acid and 1.26 mL (8.18 mmol) DIC were added respectively at 0°C and the light yellow reaction mixture was stirred for 24 h at room temperature. The reaction mixture was filtered through cotton, concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/ EtOAc 50:1) to give the title compound in 82% yield (1.51 g) as a yellow oil.

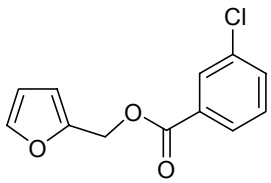
^{1}H NMR (400 MHz, $CDCl_3$) δ=2.30 (s, 3H, -CH_3), 5.25 (s, 2H, -CH_2O), 5.95 (dd, *J*=2.9 Hz, 1.05 Hz, 1H), 6.35 (d, *J*=2.9 Hz, 1H), 7.42-8.08 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=13.7 (-CH_3), 58.9 (-CH_2-), 106.8 (-CH), 112.0 (-CH), 128.5, 129.9, 130.3, 133.2, 147.9,(-C-), 153.4 (-C-),166.5 (-COPh).

GC-MS (RP50): t_R=10.62 min, m/z=216 (50%), 105 (70%), 95 (100%).

R_f 0.3 (cyclohexane/ EtOAc 3:1)

(2-Furanmethyl)-3-chlorobenzoate (55)



To a solution of 2-furanmethanol (2.0 g, 20.38 mmol) in 20 mL dry DCM, 0.1 g (0.84 mmol) DMAP, 2.68 g (16.98 mmol) 3-chloro-benzoic acid and 2.88 mL (18.68 mmol) DIC were

added respectively at 0°C and the light yellow reaction mixture was stirred for 24 h at room temperature. The reaction mixture was filtered through cotton, concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/EtOAc 50:1) to give 3.68 g (92%) of the title compound as a yellow oil.

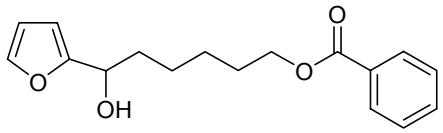
^{1}H NMR (400 MHz, $CDCl_3$) δ=5.36 (s, 2H, -CH_2O), 6.39 (dd, *J*=3.1 Hz, 1.8 Hz, 1H), 6.49 (m, 1H), 7.35 (t, *J*=7.8 Hz, 1H), 7.45 (dd, *J*=1.9 Hz, 0.8 Hz, 1H), 7.50-8.08 (m, 3H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=59.0 (-CH_2), 64.2 (-CH_2O), 110.8 (-CH), 111.2 (-CH), 128.1, 130.0, 131.8, 133.3, 134.7, 143.6 (-CH), 149.4 (-C-), 165.2 (-COPh).

GC-MS (RP50): t_R=11.19 min, m/z=236 (50%), 201 (30%), 139 (60%), 81 (100%).

R_f 0.30 (cyclohexane/ EtOAc 50:1).

6-(Furan-2-yl)-6-hydroxyhexylbenzoate (56)



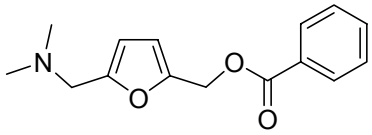
To a solution of 1-(furan-2-yl)hexane-1,6-diol (0.51 g, 2.73 mmol) in 20 mL dry DCM, 0.02 g (0.13 mmol) DMAP, 0.33 g (2.73 mmol) benzoic acid and 0.46 mL (3.00 mmol) DIC were added respectively at 0°C and the light yellow reaction mixture was stirred for 24 h at room temperature. The reaction mixture was filtered through cotton, concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/EtOAc 4:1) to give 0.41 g (52%) of 6-(furan-2-yl)-6-hydroxyhexylbenzoate as a yellow oil.

Ratio: major/minor: 2/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.45 (m, 4H, -CH_2-CH_2),1.75 (qn, *J*=6.8 Hz, 2H), 1.86 (qn, *J*=6.8 Hz, 2H), 2.20 (bs, 1H, -OH), 4.30 (t, *J*=6.6 Hz, 2H, -CH_2O), 4.65 (t, *J*=6.8, 1H, -CHOH), 6.20 (td, *J*=3.2 Hz, 0.8 Hz, 1H), 6.30 (dd, *J*=3.2 Hz, 1.9 Hz, 1H), 7.34 (dd, *J*=1.9 Hz, 0.8 Hz, 1H).7.40-8.05 (m, -5H, -Ph).

R_f 0.30 (cyclohexane/EtOAc 4:1)

(5-((Dimethylamino)methyl)furan-2-yl)methyl benzoate



To a solution of (5-((dimethylamino)methyl)furan-2-yl)methanol (1.00 g, 6.4 mmol) in 20 mL dry DCM, 0.03 g (0.27 mmol) DMAP, 0.65 g (5.3 mmol) benzoic acid and 0.91 mL (5.9 mmol) DIC were added respectively at 0°C and the light yellow reaction mixture was stirred for 24 h at room temperature. The reaction mixture was filtered through cotton, concentrated under reduced pressure and purified by silicagel chromatography (EtOAc/MeOH 1:1) to give 0.67 g (58%) of the title compound as a yellow oil.

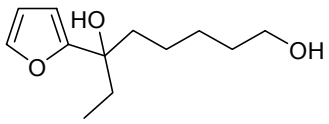
^{1}H NMR (400 MHz, $CDCl_3$) δ=2.26 (s, 6H, -2CH_3), 3.45 (s, 2H, -CH_2N), 5.27 (s, 2H, -CH_2O), 6.18 (d, *J*=3.1 Hz, 1H, -CH), 6.40 (d, *J*=3.1 Hz, 1H, -CH), 7.40-8.05 (m, -5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=45.2 (-CH_3), 56.1 (-CH_2), 58.9 (-CH_2), 109.6 (-CH), 111.6 (-CH), 128.5, 129.9, 130.2, 133.2, 149.3 (-C-), 153.5 (-C-), 166.4 (-COPh).

GC-MS (RP50): t_R=12.11 min, m/z=259 (30%), 215 (50%), 105 (100%).

R_f 0.30 (EtOAc/MeOH 1:1)

6-(Furan-2-yl)octane-1,6-diol



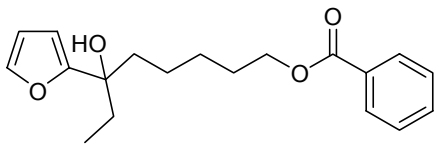
A 2.0 M solution of EtMgCl (9.6 mL, 19.23 mmol) in THF was added slowly over 20 min to a solution of 1-(furan-2-yl)-6-hydroxyhexan-1-one (0.71 g, 3.84 mmol) in 40 mL dry THF under Ar at 0°C. The reaction mixture was stirred for 4 h and allowed to warm to room temperature. The reaction mixture was quenched with 5 mL saturated ammonium chloride solution. After a further 10 min of stirring, the solution was extracted with diethyl ether (4x 20 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/ EtOAc 1:2) to give 0.69 g (83%) of the corresponding alcohol as a yellow oil.

^{1}H NMR (400 MHz, CDCl3) δ=0.85 (t, *J*=7.4 Hz, 1H, -CH_3), 1.32-1.90 (m, 10H, -CH_2), 2.21 (bs, 2H, -OH), 3.60 (t, *J*=6.4 Hz, 2H, -CH_2O), 6.18 (dd, *J*=3.1 Hz, 0.8 Hz, 1H), 6.30 (dd, *J*=3.3 Hz, 1.8 Hz, 1H), 7.33 (dd, *J*=1.8 Hz, 0.8 Hz, 1H).

GC-MS (RP50): t_R=10.26 min, m/z=212 (10%), 193 (50%), 125 (100%).

R_f 0.3 (cyclohexane/EtOAc 1:2).

(6-(Furan-2-yl)-6-hydroxyoctyl)benzoate (57)



To a solution of 6-(furan-2-yl)octane-1,6-diol (0.69 g, 3.25 mmol) in 20 mL dry DCM, 0.02 g (0.16 mmol) DMAP, 0.39 g (3.25 mmol) benzoic acid and 0.55 mL (3.57 mmol) DIC were added respectively at 0°C and the light yellow reaction mixture was stirred for 24 h at room temperature. The reaction mixture was filtered through cotton, concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/EtOAc 2:1) to give 0.87 g (85%) of (6-(furan-2-yl)-6-hydroxyoctyl)lbenzoate as a yellow oil.

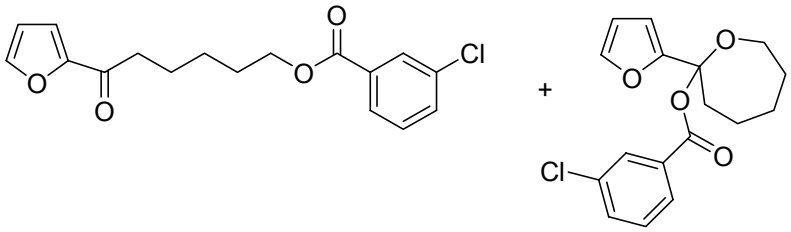
^{1}H NMR (400 MHz, CDCl3) δ=0.85 (t, *J*=7.4 Hz, 1H, -CH_3), 1.32-1.90 (m, 10H, -CH_2), 2.21 (bs, 1H, -OH), 4.25 (t, *J*=6.6 Hz, 2H, -CH_2O), 6.18 (dd, *J*=3.1 Hz, 0.8 Hz, 1H), 6.30 (dd, *J*=3.3 Hz, 1.8 Hz, 1H), 7.33 (dd, *J*=1.8 Hz, 0.8 Hz, 1H) 7.42-8.05 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=8.3 (-CH_3), 23.7 (-CH_2), 26.7 (-CH_2), 29.1 (-CH_2), 32.9 (-CH_2), 39.6 (-CH_2), 65.3 (-CH_2O), 74.9 (-C-OH), 105.5 (-CH), 110.2 (-CH), 128.4, 129.7, 130.6, 132.9, 141.4 (-CH), 158.7 (-C-), 166.7 (-CO).

GC-MS (RP50): t_R=13.95 min, m/z=316 (10%), 125 (50%), 105 (100%), 77 (60%).

R_f 0.30 (cyclohexane/EtOAc 4:1)

6-(Furan-2-yl)-6-oxohexyl 3-chlorobenzoate



To a crude mixture of 1-(furan-2-yl)-6-hydroxyhexan-1-one and 2-(furan-2-yl)oxepan-2-ol (1.00 g, 5.3 mmol) in 20 mL dry DCM, 0.03 g (0.22 mmol) DMAP, 0.69 g (4.4 mmol) 3-chloro-benzoic acid and 0.75 mL (4.86 mmol) DIC were added respectively at 0°C and the light yellow reaction mixture was stirred for 24 h at room temperature. The reaction mixture was filtered through cotton, concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/EtOAc 5:1) to give 1.63 g (94%) of mixture of products as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.32-1.80 (m, CH_2), 2.30 (t, *J*=7.4 Hz, 2H, -CH_2), 2.83 (t, *J*=7.3 Hz, 2H, -CH_2), 4.04 (m, *J*=6.4 Hz, 2H), 4.21 (t, *J*=6.6 Hz, 2H, -CH_2O^{min}), 4.25 (t, *J*=6.6 Hz, 2H, -CH_2O^{maj}), 6.33 (dd, *J*=3.3 Hz, 1.8 Hz, 1H^{min}), 6.51 (dd, *J*=3.5 Hz, 1.5 Hz, 1H^{maj}), 7.17 (dd, *J*=3.5 Hz, 0.8 Hz, 1H^{maj}), 7.35 (dd, *J*=1.8 Hz, 0.9 Hz, 1H^{min}), 7.56 (dd, *J*=1.5 Hz, 0.8 Hz, 1H^{maj}), 7.32-8.05 (m, 8H, -2 Ph ring protons).

GC-MS (RP50): t_R=14.73 min, m/z=320 (20%), 139 (40%), 110 (100%), 95 (60%).
t_R=15.67 min, m/z=231 (100%), 186 (70%), 173 (50%).

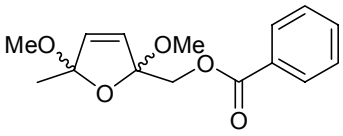
R_f 0.30 (cyclohexane/EtOAc 5:1)

General procedure for electrochemical anodic oxidation using tetrabutylammonium bromide as supporting electrolyte

The experimental setup and work up of the reaction was as described for the above reaction. But in these experiments 40 mL 0.2 M tetrabutylammonium bromide in dioxane/MeOH (1/1) was used as the supporting electrolyte.

For electrochemical anodic oxidation experiments all the desired dimethoxylated furan derivatives were isolated without further purification in good yields and purities.

Formation of (2,5-dihydro-2,5-dimethoxy-5-methylfuran-2-yl)methyl benzoate using tetrabutylammonium bromide as supporting electrolyte (128)



The experimental setup and work up of the reaction were as described above in the general procedure. The reaction was carried out with 0.11 g (0.51 mmol) (5-methylfuran-2-yl)methyl benzoate and after 0.0545 Ah (4 F/mol, which was required for the complete conversion of the starting material) electricity was consumed the title compound was isolated in 90% yield (0.13 g) as a yellow oil (*cis/trans* mixture).

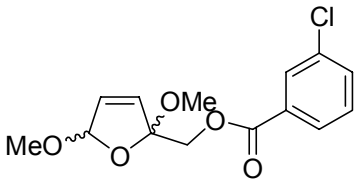
Ratio: major/minor: 2/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.50 (s, 3H, -CH_3^{min}), 1.62 (s, 3H, -CH_3^{maj}), 3.25 (s, 3H, -OMe^{maj}), 3.29 (s, 3H, -OMe^{maj}), 3.34 (s, 3H, -OMe^{min}), 3.38 (s, 3H, -OMe^{min}), 4.30 (d, *J*=11.3 Hz, 1H, -CH_2O^{min}), 4.45 (d, *J*=11.3 Hz, 1H, -CH_2O^{maj}), 4.56 (d, *J*=11.3 Hz, 1H, -CH_2O^{maj}), 4.61 (d, *J*=11.3 Hz, 1H, -CH_2O^{min}),5.97 (d, *J*=5.6 Hz, 1H, min), 6.01 (d, *J*=5.7 Hz, 1H, maj), 6.03 (d, *J*=5.8 Hz, 1H, min), 6.07 (d, *J*=5.8 Hz, 1H, maj), 7.42-8.08 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=23.8+23.9 (-Me), 50.41+50.47+50.54+50.70 (-OMe), 65.8+66.7 (-CH_2O), 110.7, 111.5+111.6, 112.2, 129.8, 129.9, 130.1, 130.3, 133.2+133.3, 135.9, 136.3, 166.1+166.3 (-COPh).

GC-MS (RP50): t_R=11.72 min, 11.75 min, (isomeric mixtures), m/z=263 (30%), 247 (20%), 143 (100%), 125 (50%), 111 (80%), 105 (90%), 77 (50%).

Formation of (2,5-dihydro-2,5-dimethoxyfuran-2-yl)methyl-3-chlorobenzoate using ammonium bromide as supporting electrolyte



The experimental setup and work up of the reaction were as described above in the general procedure. The reaction was carried out with 0.31 g (1.27 mmol) (2-furanmethyl)-3-chlorobenzoate and after 0.0909 Ah (3 F/mol, which was required for the complete conversion of the starting material) electricity were consumed the title compound was isolated in 90% yield (0.15 g) as a yellow oil (*cis/trans* mixture).

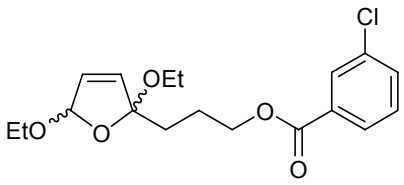
Ratio: major/minor: 1.5/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=3.19 (s, 3H, -OMe^{maj}), 3.26 (s, 3H, -OMe^{min}), 3.42 (s, 3H, -OMe^{maj}), 3.52 (s, 3H, -OMe^{min}), 4.32 (d, *J*=11.3 Hz, 1H, -CH_2O^{min}), 4.37 (d, *J*=11.3 Hz, 1H, -CH_2O^{maj}), 4.52 (d, *J*=11.3 Hz, 1H, -CH_2O^{maj}), 4.56 (d, *J*=11.3 Hz, 1H, -CH_2O^{min}),5.53 (t, *J*=1.1 Hz, 1H, min), 5.78 (t, *J*=1.1 Hz, 1H, maj), 5.97 (t, *J*=1.1 Hz, 1H, min), 5.98 (t, *J*=1.1 Hz, 1H, maj), 6.12 (dd, *J*=5.8 Hz, 0.9 Hz, 1H, min), 6.15 (dd, *J*=5.8 Hz, 0.9 Hz, 1H, maj), 7.33-8.10 (m, 4H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 50.0+50.6 (-OMe), 55.9+56.6 (-OMe), 66.9+67.1 (-CH_2O), 107.6+108.7, 127.9, 128.1, 129.7, 129.9, 129.94, 130.1, 131.3, 131.4, 131.8, 132.0, 132.9, 133.1, 133.35, 133.38, 134.6, 134.8, 164.9+165.1 (-COPh).

GC-MS (RP50): t_R=12.40 min, m/z=297 (3%), 267 (2%), 139 (80%), 129 (100%), 111 (60%), 101 (70%).

Formation of 3-(2,5-dihydro-2,5-diethoxyfuran-2-yl)propyl 3-chlorobenzoate using ammonium bromide as supporting electrolyte (59)



For the experimental setup an undivided beaker-type cell (commerical Metrohm titration vessels and lids were adapted in the local machine shop) was equipped with two carbon electrodes (area of the electrodes immersed in the electrolytic solution: 2.7 cm^2, distance between the two electrodes: 0.5 cm). The cell was charged with 0.54 g (2.04 mmol) 3-(furan-2-yl)propyl 3-chlorobenzoate and 40 mL 0.3 M ammonium bromide in EtOH. The cell was then immersed into a cooling bath thermostated at 0°C. For the electrolysis a current density of 0.015 A/cm^2 was applied. The power was supplied by an EA-PS-2032-025 instrument by which the current required for the electrolysis was fixed to 0.04 A and a electronic Coulomb-meter was used to calculate automatically the total electricity consumed for the electrolysis. After 0.1650 Ah (3 F/mol, which was required for the complete conversion of the starting material) electricity were consumed, 1 g $NaHCO_3$ was added to the bright yellow solution mixture and the reaction mixture was concentrated under reduced pressure until a yellowish-white solid was formed. Then 20 mL water were added and the solution was extracted with

ethyl acetate (4x50 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and finally dried in vacuo to furnish 0.34 g (78%) of 6-(2,5-dihydro-2,5-diethoxyfuran-2-yl)-6-hydroxyhexyl benzoate as a yellow oil (*cis/trans* mixture).

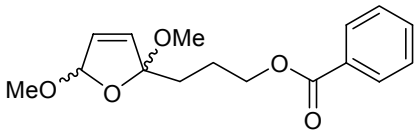
Ratio: major/minor: 1.5/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.15 (m, 3H, -CH_3), 1.23 (m, 3H, -CH_3), 1.75-1.95 (m, 4H, -$(CH_2)_4$), 3.30 (m, 2H, -CH_2-), 3.62 (s, 2H, -CH_2-), 3.84 (s, 2H, -CH_2-), 4.33 (m, 1H, -CH_2O), 5.54 (t, *J*=1.1 Hz, 1H, min), 5.80 (t, *J*=1.1 Hz, 1H, min), 5.91 (dd, *J*=5.9 Hz, 1.1 Hz, 1H, min), 5.94 (dd, *J*=5.9 Hz, 1.3 Hz, 1H, maj), 6.00 (dd, *J*=5.9 Hz, 1.2 Hz, 1H, min), 6.02 (dd, *J*=5.9 Hz, 1.1 Hz, 1H, maj), 7.33-8.02 (m, 4H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 15.53+15.56 (-CH_3), 15.59+15.68, 23.5+23.6 (-CH_2-), 24.8, 25.3, 27.3, 35.9+36.1 (-CH_2-), 57.9, 58.4, 64.7+64.8, 65.6+65.7, 80.6, 95.6, 106.0+106.4, 107.2+108.6, 113.6+114.8, 127.92+127.94, 129.82+129.86+129.88, 131.2, 131.4, 132.2+132.3, 133.0+133.1, 133.5, 133.9, 134.1, 144.4, 159.8, 165.5 (-COPh).

GC-MS (RP50): t_R=13.41 min, 13.48 min, (isomeric mixtures), m/z=308 (3%), 262 (2%), 152 (100%), 139 (60%), 123 (50%), 107 (90%), 96 (50%).

Formation of 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propyl benzoate using tetrabutylammonium bromide as supporting electrolyte (52)



The experimental setup and work up of the reaction was as described above in the general procedure. The reaction was carried out with 0.27 g of (1.20 mmol) 3-(furan-2-yl)propyl benzoate and after 0.1650 Ah (3 F/mol, which was required for the complete conversion of the starting material) electricity was consumed the title compound was isolated in 90% yield (0.24 g) as a yellow oil (*cis/trans* mixture).

Ratio: major/minor: 1.5/1

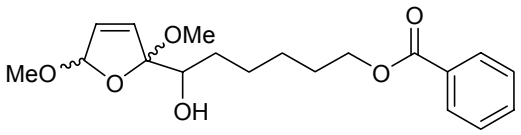
^{1}H NMR (400 MHz, $CDCl_3$) δ=1.80 (m, 2H), 1.92 (m, 2H), 3.11 (s, 3H, -OMe^{min}), 3.19 (s, 3H, -OMe^{maj}), 3.45 (s, 3H, -OMe^{min}), 3.50 (s, 3H, -OMe^{maj}), 4.25 (q, *J*=6.6 Hz, 2H, -CH_2O-), 5.46 (t, *J*=1.1 Hz, 1H, min), 5.73 (t, *J*=1.2 Hz, 1H, maj), 5.89 (dd, *J*=5.9 Hz, 1.2 Hz, 1H, min), 5.91

(dd, *J*=6.0 Hz, 1.2 Hz, 1H, maj), 6.03 (dd, *J*=5.8 Hz, 1.2 Hz, 1H, min), 6.04 (dd, *J*=5.9 Hz, 1.1 Hz, 1H, maj), 7.4-8.10 (m, 5H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 27.2+27.3 (-CH_2-), 35.9-36.3 (-CH_2-), 49.9+50.5 (-OMe), 55.8+56.4 (-OMe), 63.0 (-CH_2O), 107.3+108.5, 114.1+115.2, 131.1+131.3, 133.3+133.8, 166.7+166.8 (-COPh).

GC-MS (RP50): t_R=12.95 min, m/z=291(10%), 260 (20%), 229 (30%), 129 (100%), 105 (80%), 77 (50%)

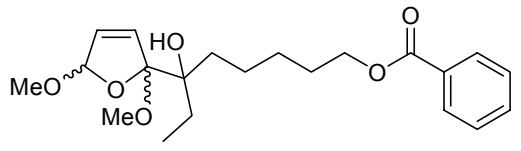
Formation of 6-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)-6-hydroxyhexyl benzoate using tetrabutylammonium bromide as supporting electrolyte (79)



The experimental setup and work up of the reaction were as described above in the general procedure. The reaction was carried out with 0.35 g (1.21 mmol) 6-(furan-2-yl)-6-hydroxyhexylbenzoate and after 0.4719 Ah (16 F/mol, which was required for the complete conversion of the starting material) electricity was consumed the title compound was isolated in 78% yield (0.34 g) as a yellow oil (*cis/trans* mixture).

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.3-1.2 (m, 9H, -$(CH_2)_4$ and 1 hydroxyl group), 3.08 (s, 3H, -OMe^{maj}), 3.09 (s, 3H, -OMe^{min}), 3.14 (s, 3H, -OMe^{min}), 3.16 (s, 3H, -OMe^{maj}), 3.50 (t, *J*= 5.08 Hz 1H, -CH-OH), 4.30 (t, *J*=6.6 Hz, 3H, -CH_2O), 5.37 (t, *J*=1.1 Hz, 1H, maj), 5.42 (t, *J*=1.1 Hz, 1H, min), 5.65 (q, *J*= 1.1 Hz, 1H), 5.85 (dd, *J*= 5.8 Hz, 1.1 Hz, 1H, min), 5.90 (m, 1H, maj), 6.04 (m, 1H, maj), 6.07 (m, 1H, min), 7.40-8.05 (m, 5H, -Ph).

Formation of (6-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)-6-hydroxyoctyl) benzoate using tetrabutylammonium bromide as supporting electrolyte (84)



The experimental set up and work up of the reaction was as described abobe in the general procedure. The reaction was carried out with 0.21 g (0.66 mmol) (6-(2,5-dihydro-2,5-

dimethoxyfuran-2-yl)-6-hydroxyoctyl) benzoate and after 0.2830 Ah (16 F/mol, which was required for the complete conversion of the starting material) electricity had been consumed, 0.22 g (88%) of the title compound were isolated as a yellow oil (*cis/trans* mixture).

Ratio: major/minor: 2/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=0.90 (m, 3H, $-CH_3$), 1.40-1.85 (m, 11H, $-(CH_2)_5$ and 1 hydroxyl group), 3.08 (d, *J*=1.4 Hz, 3H, $-OMe^{min}$), 3.17 (s, 3H, $-OMe^{maj}$), 3.49 (s, 3H, $-OMe^{maj}$), 3.51 (d, *J*=1.4 Hz, 3H, $-OMe^{min}$), 4.30 (t, *J*=6.6 Hz, 3H, $-CH_2O$), 5.42 (q, *J*=0.9 Hz, 1H, maj), 5.67 (q, *J*=0.9 Hz, 1H, min), 5.97 (td, *J*=6.1 Hz, 1.4 Hz, 1H, maj), 6.01 (td, *J*=6.1 Hz, 1.4 Hz, 1H, min), 6.07 (dd, *J*=4.9 Hz, 0.9 Hz, 1H, maj), 6.09 (td, *J*=6.1 Hz, 1.1 Hz, 1H, min), 7.40-8.05 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=8.72+8.76 ($-CH_3$), 9.0+9.1 ($-CH_3$), 23.6 ($-CH_2$), 23.7 ($-CH_2$), 23.8 ($-CH_2$), 24.0 ($-CH_2$), 27.2 ($-CH_2$), 27.3 ($-CH_2$), 27.4 ($-CH_2$), 27.5 ($-CH_2$), 26.7 ($-CH_2$), 29.1 ($-CH_2$), 29.2 ($-CH_2$) 34.0 ($-CH_2$), 34.2 ($-CH_2$), 34.3 ($-CH_2$), 34.9 (CH_2), 50.25+50.28 (-OMe), 50.62+50.63 (-OMe), 56.80+56.81 (-OMe), 56.9+57.0 (-OMe), 65.41+65.44+65.47+65.53 ($-CH_2O$), 76.4 (-C-OH), 77.88+77.89 (-C-OH),107.7 (-CH), 108.50+108.57 (-CH),117.5+117.6 (-CH), 119.7+119.8 (-CH),128.46+128.48+128.49, 129.7, 131.60+131.65, 131.76+131.78, 131.81+131.83, 132.1+132.2, 132.91+132.93, 132.96+132.97, 166.7 (-CO).

GC-MS (RP50): t_R=14.97 min, 15.02 min, (isomeric mixtures), m/z=378 (10%), 129 (100%), 105 (50%), 77 (60%).

6.2.5 Experimental section for chapter 4.1.7

General procedure for electrochemical anodic oxidation using tetrabutylammonium bromide as supporting electrolyte on solid phase

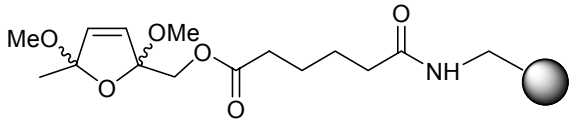
For the experimental setup an undivided beaker-type cell (commerical Metrohm titration vessels and lids were adapted in the local machine shop) was equipped with two carbon electrodes (area of the electrodes immersed in the electrolytic solution: 2.7 cm^2, distance between the two electrodes: 0.5 cm). The cell was charged with aminomethylated polystyrene resin supported furans (0.1-0.5 mmol) and 40 mL 0.2 M tetrabutylammonium bromide in dioxane/MeOH (1/1). The cell was then immersed into a cooling bath thermostated at 0°C. The beads were stirred slowly with the help of a magnetic stirrer. For the electrolysis a current density of 0.015 A/cm^2 was applied. The power was supplied by an EA-PS-2032-025 instrument by which the current required for the electrolysis was fixed to

0.04 A and a electronic Coulomb-meter was used to calculate automatically the total charged consumed for the electrolysis. After 40 F/mol electricity was consumed the slightly yellow suspension was filtered. The resin was washed with DCM (4x20 mL), THF (4x20 mL), DMF (2x20 mL), DMF/water [2x(10/10 mL)], DCM/MeOH [2x(10/10 mL)], and DCM (4x20 mL).

General procedure for the cleavage of 2,5-dihydro-2,5-dimethoxyfuran derivatives from aminomethylated polystyrene resin

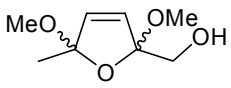
In a fritted funnel resin aminomethylated polystyrene supported 2,5-dihydro-2,5-dimethoxyfuran derivative (0.1-0.5 mmol) was swelled in 20 mL dioxane and then an aqueous LiOH solution (0.5-2.5 mmol in 2 mL water) was added. The suspension was shaken for 24 h at room temperature. The resin was filtered and the filtrate was stored in a flask. Again dioxane and LiOH solution were added to the resin (same quantity as described above) and the suspension was again shaken for another 24 h. The resin was filtered and the filtrate was added to the previous filtrate. The combined filtrates were concentrated under reduced pressure until a yellowish-white solid started to precipitate. Then 5 mL water was added and the solution was extracted with ethyl acetate (4x20 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and finally dried in vacuo to furnish the corresponding alcohol as a yellow oil (*cis/trans* mixture).

Formation of aminomethylated polystyrene resin supported (2,5-dihydro-2,5-dimethoxy-5-methylfuran-2-yl)methanol (131)



The experimental setup of the reaction and washing protocol of the resin were as described in the general procedure. The reaction was carried out with 0.26 g (0.24 mmol) aminomethylated polystyrene resin supported 5-methyl furfuryl alcohol. After 0.2548 Ah (40 F/mol) electricity was consumed the slightly yellow suspension was filtered and after washing the resin was dried in vacuo for 24 h.

Cleavage of (2,5-dihydro-2,5-dimethoxy-5-methylfuran-2-yl)methanol from aminomethylated polystyrene resin (62)



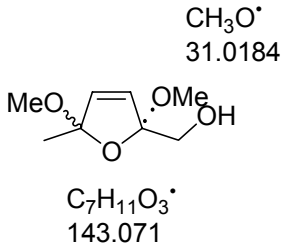
The experimental procedure for the cleavage of aminomethylated polystyrene resin supported (2,5-dihydro-2,5-dimethoxy-5-methylfuran-2-yl)methanol was as described in the general procedure. The reaction was carried out with 0.26 g (0.23 mmol) of resin. Finally 25.2 mg of (2,5-dihydro-2,5-dimethoxy-5-methylfuran-2-yl)methanol (63 % yield, 97 % purity, determined by ^{1}H NMR spectroscopy and GC/MS) was isolated as a yellow oil (*cis/trans* mixture).

Ratio: major/minor: 2/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.46 (s, 3H, -CH_3^{min}), 1.56 (s, 3H, -CH_3^{maj}), 3.17 (s, 3H, -OMe^{maj}), 3.25 (s, 3H, -OMe^{min}), 3.26 (s, 3H, -OMe^{maj}), 3.29 (s, 3H, -OMe^{min}), 3.51-3.76 (m, 2H, -CH_2O), 5.87 (d, *J*=5.6 Hz, 1H, min), 5.88 (d, *J*=5.7 Hz, 1H, maj), 5.99 (d, *J*=5.8 Hz, 1H, maj), 6.03 (d, *J*=5.8 Hz, 1H, maj).

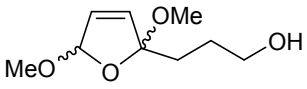
^{13}C NMR (100 MHz, $CDCl_3$) δ=22.2, 22.4 (-Me), 49.0+49.1+49.2+49.5 (-OMe), 64.8+65.0 (-CH_2-OH, maj+min), 109.5+109.7, 110.7, 112.9, 128.5+128.9, 134,7+134.8

GC-MS (RP50): t_R=6.98 min, 7.11 min (isomeric mixtures), m/z=143 (100%), 111 (90%).



FAB inactive.

3-(2,5-Dihydro-2,5-dimethoxy-2-furan)propanol (53)



The experimental setup of the reaction and washing protocol of the resin were as described above in the general procedure. The reaction was carried out with 0.51 g (0.44 mmol) of aminomethylated polystyrene resin supported 2-furanpropanol. After 0.4606 Ah (40 F/mol) electricity was consumed the slightly yellow suspension was filtered, washed and finally the

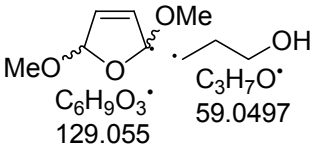
cleavage was carried out with LiOH as described in the general section to afford 43 mg (57% yield, 97 % purity, determined by ^{1}H NMR spectroscopy and GC/MS) of the title compound as a yellow oil (*cis/trans* mixture).

Ratio: major/minor: 1.5/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.56 (m, 2H), 1.82 (m, 2H), 2.3 (s,1H, -OH), 3.09 (s, 3H, -OMe^{min}), 3.17 (s, 3H, -OMe^{maj}), 3.43 (s, 3H, -OMe^{min}), 3.48 (s, 3H, -OMe^{maj}), 3.59 (q, *J*=6.2 Hz, 2H, -CH_2OH), 5.43 (t, *J*=1.1 Hz, 1H, min), 5.73 (t, *J*=1.2 Hz, 1H, maj), 5.87 (dd, *J*=5.9 Hz, 1.2 Hz, 1H, min), 5.89 (dd, *J*=6.0 Hz, 1.2 Hz, 1H, maj), 6.01 (dd, *J*=5.8 Hz, 1.2 Hz, 1H, min), 6.03 (dd, *J*=5.9 Hz, 1.1 Hz, 1H, maj)

^{13}C NMR (100 MHz, $CDCl_3$) δ= 27.2+27.3 (-CH_2-), 35.9-36.3 (-CH_2-), 49.9+50.5 (-OMe), 55.8+56.4 (-OMe), 63.0 (-CH_2OH), 107.3+108.5, 114.1+115.2, 131.1+131.3, 133.3+133.8.

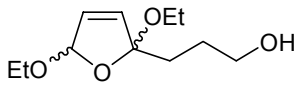
GC-MS (RP50): t_R=8.52 min, m/z=129 (100%), 125 (90%), 101 (50%), 83 (35%).



FAB inactive.

HR-MS (EI): Calculated for the fragment $C_6H_9O_3$ [M-CH_2-CH_2-CH_2-OH] =129.0550 found 129.0572.

3-(2,5-Dihydro-2,5-diethoxy-2-furan)propanol from aminomethylated polystyrene resin



For the experimental setup an undivided beaker-type cell (commerical Metrohm titration vessels and lids were adapted in the local machine shop) was equipped with two carbon electrodes (area of the electrodes immersed in the electrolytic solution: 2.7 cm^2, distance between the two electrodes: 0.5 cm). The cell was charged with 0.41 g (0.35 mmol) aminomethylated polystyrene resin supported 2-furanpropanol and 40 mL 0.2 M tetrabutylammonium bromide in dioxane/EtOH (1/1). The cell was then immersed into a

cooling bath thermo stated at 0°C. The beads were stirred slowly with the help of a magnetic stirrer. For the electrolysis a current density of 0.015 A/cm^2 was applied. The power was supplied by an EA-PS-2032-025 instrument by which the current required for the electrolysis was fixed to 0.04 A and a electronic Coulomb-meter was used to calculate automatically the total charged consumed for the electrolysis. After 0.3752 Ah (40 F/mol) electricity had been consumed the slightly yellow suspension was filtered. The resin was washed with DCM (4x20 mL), THF (4x20 mL), DMF (2x20 mL), DMF/water [2x(10/10 mL)], DCM/MeOH [2x(10/10 mL)], and DCM (4x20 mL). After washing the resin was cleaved with LiOH.

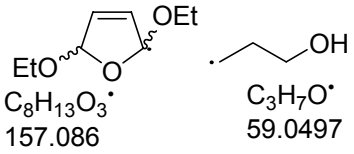
In a fritted funnel aminomethylated polystyrene resin supported 3-(2,5-dihydro-2,5-diethoxy-2)propanol was swelled in 20 mL dioxane and then an aqueous LiOH solution (0.02 g, 1.75 mmol in 2 mL water) was added. The suspension was shaken for 24 h. The resin was filtered and the filtrate was stored in a flask. Again dioxane and LiOH solution were added in same quantity as described above to the resin and the suspension was again shaken for another 24 h. The resin was filtered and the filtrate was added to the previous filtrate. The combined filtrates were concentrated under reduced pressure until a yellowish-white solid structure to precipitate. Then 5 mL water were added and the solution was extracted with ethyl acetate (4x20 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and finally dried in vacuo to furnish 40 mg of 3-(2,5-dihydro-2,5-diethoxy-2)propanol (53 % yield, 98 % purity, *cis/trans* mixture determined by ^{1}H NMR spectroscopy and GC/MS) as a yellow oil.

Ratio: major/minor: 1.5/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.15 (m, 3H, -CH_3), 1.23 (m, 3H, -CH_3), 1.63 (m, 2H, -CH_2-), 1.88 (m, 2H, -CH_2-), 2.25 (s,1H, -OH), 3.30 (m, 2H, -CH_2-), 3.62 (s, 2H, -CH_2-), 3.84 (s, 2H, -CH_2-), 5.54 (t, *J*=1.1 Hz, 1H, min), 5.80 (t, *J*=1.1 Hz, 1H, min), 5.91 (dd, *J*=5.9 Hz, 1.1 Hz, 1H, min), 5.94 (dd, *J*=5.9 Hz, 1.3 Hz, 1H, maj), 6.00 (dd, *J*=5.9 Hz, 1.2 Hz, 1H, min), 6.02 (dd, *J*=5.9 Hz, 1.1 Hz, 1H, maj)

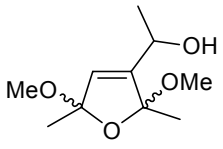
^{13}C NMR (100 MHz, $CDCl_3$) δ= 14.2+14.3 (-CH_3), 17.3, 23.7+23.8 (-CH_2-), 35.0+35.8 (-CH_2-), 57.2, 60.4, 62.0, 64.6, 67.3+67.4, 104.3+105.4, 115.3+116.9, 129.1+129.5, 132.2+132.4

GC-MS (RP50): t_R=9.50 min, m/z=157 (75%), 125 (100%), 97 (35%), 83 (90%).



FAB inactive.

1-(2,5-Dihydro-2,5-dimethoxy-2,5-dimethylfuran-3-yl)ethanol (65)



The experimental set up of the reaction and washing protocol of the resin were as described in the general procedure. The reaction was carried out with 0.28 g (0.24 mmol) of aminomethylated polystyrene resin supported 1-(2,5-dimethylfuran-3-yl)ethanol. After 0.2575 Ah (40 F/mol) electricity was consumed the slightly yellow suspension was filtered, washed and finally the cleavage was carried out with LiOH as described in the general section to afford 30 mg (63% yield, 98 % purity, determined by ^{1}H NMR spectroscopy and GC/MS) of the title compound as a yellow oily *cis/trans* mixture.

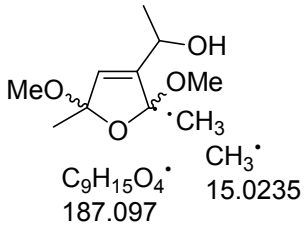
Ratio: major/minor: 2/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.40 (td, *J*=6.6 Hz, 1.5 Hz, 3H, -CH-CH_3), 1.44 (s, 3H, CH_3, min), 1.45 (s, 3H, CH_3, maj), 1.51 (s, 3H, CH_3, min), 1.52 (s, 3H, CH_3, min), 1.53 (s, 3H, CH_3, maj), 1.60 (s, 3H, CH_3, min), 1.61 (s, 3H, CH_3, maj), 2.22 (bs, 1H, -OH), 3.15 (s, -OMe), 3.17 (s, -OMe), 3.18 (s, -OMe): 3.23 (s, -OMe), 3.25 (s, -OMe), 3.26 (s, -OMe), 3.27 (s, -OMe), 3.36 (s, -OMe), 4.45 (m, 1H,-CHOH), 5.65 (d, *J*=1.6 Hz, 1H), 5.72 (d, *J*=1.4 Hz, 1H), 5.76 (dd, *J*=5.9 Hz, 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ=20.0+20.3 (Me), 21.4+21.7+22.13 (Me), 22.9+23.1+23.6(Me), 24.0+24.2 (Me), 48.6+48.7 (OMe), 48.81+48.82 (OMe); 48.9+49.0+49.1+49.2 (OMe); 61.4+61.5, 62.8 (-CH-OH), 107.6, 108.3+108.9, 109.1+109.2+109.6, 110.1+110.2, 125.6, 126.1+126.2+126.4, 147.1+147.2, 148.0+148.1.

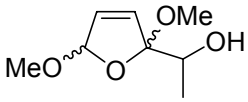
IR [cm^{-1}]: 3437 (br, -OH), 2977 (s, =C-H), 2088 (m), 1697 (m, C=C), 1369, 1294, 1174, 1000, 943, 746, 683, 659, 579, 526.

GC-MS (RP50): t_R=7.65 min, 7.76 min, 7.85 min, 7.96 min, (isomeric mixtures), m/z=187 (90%), 171 (100%), 127 (80%).



FAB inactive

1-(2,5-Dihydro-2,5-dimethoxyfuran-2-yl)ethanol (63)



The experimental setup of the reaction and washing protocol of the resin were as described in the general procedure. The reaction was carried out with 0.51 g (0.45 mmol) of aminomethylated polystyrene resin supported 1-(furan-2-yl)ethanol. After 0.4821 Ah (40 F/mol) electricity had been consumed the slightly yellow suspension was filtered, washed and finally the cleavage was carried out by LiOH as described in the general section to afford 39 mg (50% yield, 95 % purity, determined by ^{1}H NMR spectroscopy and GC/MS) of the title compound as a yellow oily *cis/trans* mixture.

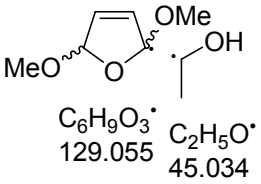
Ratio: major/minor: 2/1

^{1}H NMR (400 MHz, CDCl3) δ=1.05-1.23 (m, 3H, -CH_3), 2.42 (bs, 1H, -OH), 3.14 (s, 2-OMe), 3.20 (s,-OMe), 3.21 (s, -OMe), 3.48 (s, -OMe), 3.49 (s, -OMe), 3.51 (s, 2-OMe), 3.74-3.89 (m, 1H, CH-Me), 5.42 (t, *J*=1.2 Hz, 1H, maj), 5.47(t, *J*=1.2 Hz, 1H, min), 5.72 (q, *J*=1.2 Hz, 1H), 5.92 (dd, *J*=5.8 Hz, 1.1 Hz, 1H, min), 5.97 (m, 1H, maj), 6.12 (dt, *J*=5.8 Hz, 1.1 Hz, 1H, maj), 6.15 (dd, *J*=6.0 Hz, 1.1 Hz, 1H, min).

^{13}C NMR (100 MHz, $CDCl_3$) δ=15.4+15.94+15.97+16.0 (-CH_3), 49.0+49.1+49.5 (-OMe), 55.2+55.3+55.4+55.5 (-OMe), 69.2+69.3 (-CH-OH), 70.1+70.3 (-CH-OH), 106.3+106.4, 114.2+115.7+116.4, 129.3+129.4+129.5, 130.6+131.1+131.4+131.5+131.7.

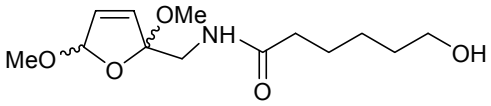
IR [cm^{-1}]: 3485 (br, -OH), 2938 (s, =C-H), 2071 (w), 1631 (m, C=C), 1371, 822, 751, 624, 469.

GC-MS (RP50): t_R=6.81 min, 6.89 min, 6.95 min, (isomeric mixtures), m/z=129 (100%), 101 (90%), 83 (35%).



FAB inactive

***N*-((2,5-Dihydro-2,5-dimethoxyfuran-2-yl)methyl)-6 hydroxyhexanamide (64)**



The experimental set up of the reaction and washing protocol of the resin was as described in the general procedure. The reaction was carried out with 0.32 g (0.21 mmol) of aminomethylated polystyrene resin supported *N*-((furan-2)methyl)-6-hydroxyhexanamide. After 0.2251 Ah (40 F/mol) electricity was consumed the slightly yellow suspension was filtered, washed and finally the cleavage was carried out with LiOH as described in the general section to afford 30 mg (53% yield, 95 % purity, determined by ^{1}H NMR spectroscopy and GC/MS) of the title compound as a yellow oil (*cis/trans* mixture)

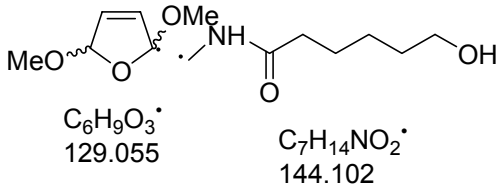
Ratio: major/minor: 1.1/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.35 (m, 2H, -CH_2), 1.58 (m, 2H, -CH_2), 2.15 (m, 2H, -CH_2), 2.4 (bs, 1H, -OH), 3.13 (s, 3H, -OMe^{maj}), 3.18 (s, 3H, -OMe^{min}), 3.38 (m, 1H, -CHNH), 3.48 (s, 3H, -OMe^{min}), 3.50 (s, 3H, -OMe^{maj}), 3.60 (m, 2H, CH_2OH), 3.88 (m, 1H, -CHNH) ,5.45 (t, *J*=1.1 Hz, min), 5.69 (t, *J*=1.1 Hz,1H, maj), 5.83 (dd, *J*=5.8 Hz, 1.1 Hz, 1H, maj), 5.87 (dd, *J*=5.8 Hz, 1.1 Hz, 1H, min), 5.93 (bs, 1H, -NH), 6.03 (dd, *J*=5.8 Hz, 1.1 Hz, 1H, min), 6.06 (dd, *J*=5.8 Hz, 1.1 Hz, 1H, maj)

^{13}C NMR (100 MHz, $CDCl_3$) δ=25.4+25.6+25.7 (CH_2), 32.6+32.7 (CH_2), 36.9+37 (CH_2), 44.9+45.9, 50.4+50.9, 56.6+56.7, 62.7+62.8 (-CH_2-OH), 107.6+ 108.6, 112.9+114.8, 131.7+132.1, 132.2+132.5, 173.1+173.3(-NHCO-).

IR [cm^{-1}]: 3306 (br, -OH), 2936 (s, =C-H), 3100 (br, -N-H), 2069 (m), 1664 (s, C=C), 1545, 1455, 1372, 825, 803, 754, 677, 631.

GC-MS (RP50): t_R=13.17 min, 13.31 min, 13.35 min, 13.43 min, (isomeric mixtures), m/z=241 (12%), 129 (100%), 115 (40%), 101 (70%), 69 (60%).



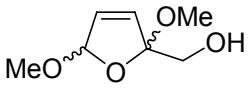
$C_6H_9O_3^{\bullet}$
129.055

$C_7H_{14}NO_2^{\bullet}$
144.102

FAB inactive

HR-MS (EI): Calculated for the fragment $C_6H_9O_3$ [M-CH_2-CH_2-CH_2-OH] =129.0550 found 129.0548.

(2,5-Dihydro-2,5-dimethoxyfuran-2-yl)methanol (69)



The experimental set up of the reaction and washing protocol of the resin were as described in the general procedure. The reaction was carried out with 0.21 g (0.18 mmol) of aminomethylated polystyrene resin supported furfuryl alcohol. After 0.1920 Ah (40 F/mol) electricity were consumed the slightly yellow suspension was filtered, washed and finally the cleavage was carried out with LiOH as described in the general section to afford 5 mg (19% yield, 95 % purity, determined by ^{1}H NMR spectroscopy and GC/MS) of the title compound as a yellow oil (*cis/trans* mixture).

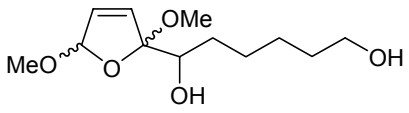
Ratio: major/minor: 1.1/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.60 (s, -1H, -OH), 3.15 (s, 3H, -OMe^{maj}), 3.20 (s, 3H, -OMe^{min}), 3.47 (s, 3H, -OMe^{maj}), 3.48 (s, 3H, -OMe^{min}), 3.60 (m, 2H, -CH_2O), 5.47 (bs, 1H, min), 5.71 (bs, 1H, maj), 5.95 (bs, 1H, min), 5.96 (bs, 1H, maj), 6.08 (bd, *J*=6.4 Hz, 1H, min), 6.11 (bd, *J*=6.4Hz, 1H, maj).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 50.2+50.6 (-OMe), 56.3+56.5 (-OMe), 65.9+66.9 (-CH_2O), 107.6+108.3, 113.2, 115.2, 131.5, 132.3, 132.4, 132.5.

GC-MS (RP50): t_R=6.59 min, m/z=159 (2%), 129 (100%), 101 (50%).

1-(2,5-Dihydro-2,5-dimethoxyfuran-2-yl)hexan-1,6-diol (66)



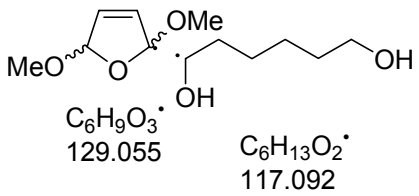
The experimental set up of the reaction and washing protocol of the resin were as described in the general procedure. The reaction was carried out with 0.51 g (0.42 mmol) of aminomethylated polystyrene resin supported 1-(furan-2-yl)hexane-1,6-diol. After 0.4512 Ah (40 F/mol) electricity had been consumed the slightly yellow suspension was filtered, washed and finally the cleavage was carried out with LiOH as described in the general section to afford 54 mg (53% yield, 95 % purity, determined by ^{1}H NMR spectroscopy and GC/MS) of the title compound as a yellow oil (*cis/trans* mixture).

Ratio: major/minor: 3.5/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.3-1.2 (m, 10H, -$(CH_2)_4$ and the 2 hydroxyl groups), 3.08 (s, 3H, -OMe^{maj}), 3.09 (s,3H, -OMe^{min}), 3.14 (s,3H, -OMe^{min}), 3.16 (s,3H, -OMe^{maj}), 3.5-3.7 (m, 3H, -CH-OH and CH_2OH), 5.37 (t, *J*=1.1 Hz, 1H, maj), 5.42 (t, *J*=1.1 Hz, 1H, min), 5.65 (q, *J*= 1.1 Hz, 1H), 5.85 (dd, *J*= 5.8 Hz, 1.1 Hz, 1H, min), 5.90 (m, 1H, maj), 6.04 (m, 1H, maj), 6.07 (m, 1H, min).

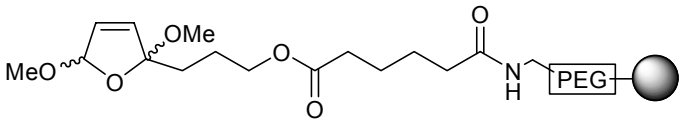
^{13}C NMR (100 MHz, $CDCl_3$) δ=22.3, (-CH_2-), 24.6+24.7 (-CH_2-), 24.9+25.0 (-CH_2-), 29.5+30.2+30.5 (-CH_2-), 31.5 (-CH_2-), 48.9+49.0+49.3+49.4 (-OMe), 55.3+55.4+55.43 (-OMe), 61.6 (-CH_2-OH), 73.1+73.2 (-CH-OH), 74.1+74.2 (-CH-OH),106.3+106.4, 107.1+107.4, 116.0+116.2, 129.5+129.7, 131.1+131.4.

GC-MS (RP50): t_R=11.20 min, 11.22 min, 11.29 min, (isomeric mixtures), m/z=129 8 (100%), 98 (50%).



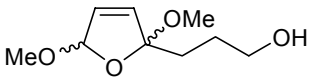
FAB inactive

Formation of aminomethylated tentagel resin supported 3-(2,5-dihydro-2,5-dimethoxy-2-furan)propanol (72)



For the experimental setup an undivided beaker-type cell (commerical Metrohm titration vessels and lids were adapted in the local machine shop) was equipped with two carbon electrodes (area of the electrodes immersed in the electrolytic solution: 2.7 cm^2, distance between the two electrodes: 0.5 cm). The cell was charged with 0.41 g aminomethylated tentagel resin supported 2-furanpropanol (0.10 mmol) and 40 mL 0.3 M ammonium bromide in MeOH. The cell was then immersed into a cooling bath thermostated at 0°C. The beads were stirred slowly with the help of a magnetic stirrer. For the electrolysis a current density of 0.015 A/cm^2 was applied. The power was supplied by an EA-PS-2032-025 instrument by which the current required for the electrolysis was fixed to 0.04 A and a electronic Coulomb-meter was used to calculate automatically the total charged consumed for the electrolysis). After 0.1212 Ah (50 F/mol) electricity had been consumed the slightly yellow suspension was filtered. The resin was washed with DCM (4x20 mL), THF (4x20 mL), DMF (2x20 mL), DMF/water [2x(10/10 mL)], DCM/MeOH [2x(10/10 mL)], and DCM (4x20 mL). After washing the resin was dried in vacuo for 24 h.

Cleavage of 3-(2,5-dihydro-2,5-dimethoxy-2-furan)propanol from aminomethylated tentagel resin (53)

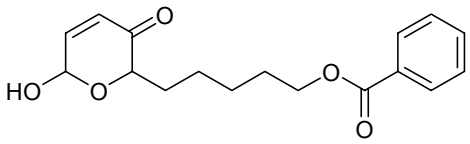


In a fritted funnel aminomethylated tentagel resin supported 3-(2,5-dihydro-2,5-dimethoxy-2-furan)propanol (0.42 g, 0.10 mmol) was swelled in 20 mL dioxane and then an aqueous LiOH solution (0.02 g, 0.53 mmol in 2 mL water) was added. The suspension was shaken for 24 h. The resin was filtered and the filtrate was stored in a flask. Again dioxane and LiOH solution were added to the resin (same quantity as described above) and the suspension was again shaken for another 24 h. The resin was filtered and the filtrate was added to the previous filtrate. The combined filtrates were concentrated under reduced pressure until a yellowish-white solid started to precipitate. Then 5 mL water were added and the solution was extracted with ethyl acetate (4x20 mL). The combined organic layers were dried over

Na_2SO_4, concentrated under reduced pressure and finally dried in vacuo to furnish 10.5 mg 3-(2,5-dihydro-2,5-dimethoxy-2-furan)propanol (55 % yield, 95 % purity, *cis/trans* mixture determined by ^{1}H NMR spectroscopy and GC/MS) as a yellow oil.

6.2.6 Experimental section for chapter 4.1.8

5-(3,6-Dihydro-6-hydroxy-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (80)



To a solution of 6-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)-6-hydroxyhexyl benzoate) (0.21 g, 0.61 mmol) in dioxane (10 mL) was added 2% H_2SO_4 (1.2 mL) at rt. The resulting brown reaction mixture was shaken at rt for 24 h. Solid $NaHCO_3$ was added until the solution reached pH 4. Then 5 mL water were added and the solution was extracted with ethyl acetate (4x20 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure maintaining the water bath temperature below 35°C to afford 0.15 g (80%) of the title compound as a yellow oil (isomeric mixture).

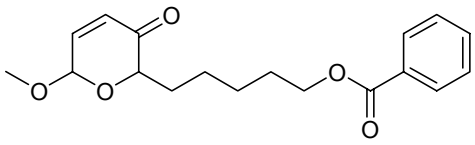
Ratio: major/minor: 2/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.45-2.00 (m, 8H, -$(CH_2)_4$), 3.80 (bs, 1H, -OH), 4.30 (t, *J*=6.5 Hz, 2H, -CH_2O), 4.55 (dd, *J*=8.2 Hz, 3.9 Hz, 1H, 2-H), 5.62 (m, 1H, 6-$H^{maj+min}$), 6.08(d, *J*=10.4 Hz, 1H, 4-H^{maj}), 6.12 (dd, *J*=10.3 Hz, 1.6 Hz, 1H, 4-H^{min}), 6.89 (dd, *J*=10.3 Hz, 3.5 Hz, 1H, 5-H^{maj}), 6.91 (dd, *J*=10.6 Hz, 1.6 Hz, 1H, 5-H^{min}), 7.28-8.05 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 21.2, 22.6, 24.9+25.0, 26.0+26.1, 28.9+29.1, 29.8+30.0, 65.20+65.26 (-CH_2O), 74.1 (C-2), 79.0, 87.8 (C-6), 91.1, 126.6, 127.6, 128.5, 128.7+128.8, 129.7, 130.51+130.53, 133.08+133.09, 144.7, 148.1, 166.9 (-COPh), 196.3+196.6 (-CO).

GC-MS (RP50): t_R=14.15 min, m/z=219 (10%), 207 (5%), 123 (10%), 105 (100%), 85 (30%), 77 (40%).

5-(3,6-Dihydro-6-methoxy-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (91)



To a solution of 5-(3,6-dihydro-6-hydroxy-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (0.61 g, 2.03 mmol) in 15 mL dry CH_2Cl_2, 0.51 mL (5.07 mmol) $CH(OMe)_3$ and 0.02 mL (0.203 mmol) $BF_3.OEt_2$ were added respectively at room temperature. The colour of the reaction mixture was changing from light yellow to light green and finally to bright blue. The reaction mixture was stirred at room temperature and was monitored by TLC (cyclohexane/EtOAc 3:1). After complete conversion of the starting material within 5 minutes the reaction mixture was quenched with 10% $NaHCO_3$ solution (5mL). The solution was extracted with dichloromethane (4x20 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure maintaining the water bath temperature below 35°C to yield 0.55 g (90%) of the title compound as a yellow oil (isomeric mixtures).

Ratio: major/minor: 2/1

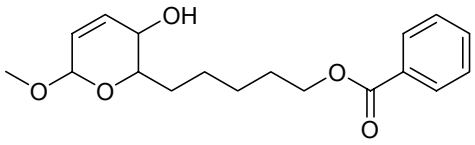
^{1}H NMR (400 MHz, $CDCl_3$) δ=1.45-2.10 (m, 8H -$(CH_2)_4$), 3.47 (s, 3H,-OMe^{maj}), 3.53 (s, 3H,-OMe^{min}), 4.02 (dd, *J*=8.4 Hz, 3.7 Hz, 1H, 2-H^{min}), 4.30 (t, *J*=6.6 Hz, 2H, -CH_2O), 4.37 (dd, *J*=8.4 Hz, 3.5 Hz, 1H, 2-H^{maj}), 5.07 (d, *J*=3.5 Hz, 1H, 6-H^{maj}), 5.20 (m, 1H, 6-H^{min}), 6.06 (d, *J*= 10.5 Hz, 1H, 4-H^{maj}), 6.11 (dd, *J*=10.17 Hz, 1.57 Hz, 1H, 4-H^{min}), 6.82 (dd, *J*= 10.6 Hz, 3.5 Hz, 1H, 5-H^{maj}), 6.85 (dd, *J*= 10.3 Hz, 1.8 Hz, 1H, 5-H^{min}), 7.28-8.05 (m, 5H, -COPh).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 25.6+25.7, 26.1+26.2, 31.17, 32.2, 33.0+33.0 ($(CH_2)_4$), 56.6+56.8 (-OMe, maj+min), 65.2 (-CH_2O), 74.0 (C-2), 79.1, 94.3+96.9 (C-6), 126.5, 127.8, 128.5, 128.7, 128.8, 129.6, 130.6, 132.9, 143.3+146.5 (C-5), 166.7 (-COPh), 196.4+196.5 (-CO).

GC-MS (RP50): t_R=14.33 min, 14.36 min (isomeric mixtures) m/z=318 (10%), 287 (30%), 105 (50%), 98 (100%).

R_f 0.3 (cyclohexane/EtOAc 3:1)

5-(3,6-Dihydro-6-methoxy-3-hydroxy-2*H*-pyran-2-yl)pentyl benzoate (92)

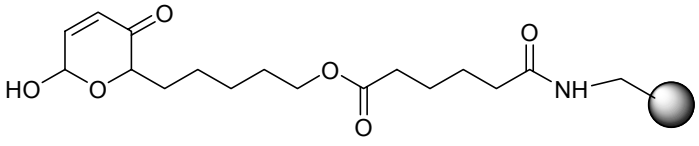


5-(3,6-dihydro-6-methoxy-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (0.30 g, 0.94 mmol) and cerium trichloride heptahydrate (0.41 g, 1.11 mmol) were stirred in 10 mL absolute ethanol at –40 °C and sodium borohydride (0.04 g, 0.94 mmol) were added slowly in small portions. The reaction was monitored by TLC. The mixture was stirred for 4 h and allowed to warm to room temperature. The reaction mixture was quenched with 5 mL water. After a further 10 min of stirring, the ethanol was removed under vacuum, and the residue diluted with water (10 mL). The residue was extracted with chloroform (4x20 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure maintaining the water bath temperature below 35°C and purified by silicagel chromatography (cyclohexane/EtOAc 1:1) to yield 0.29 g (96%) of the title compound as a yellow oil (isomeric mixtures).

Ratio: major/minor: 2/1

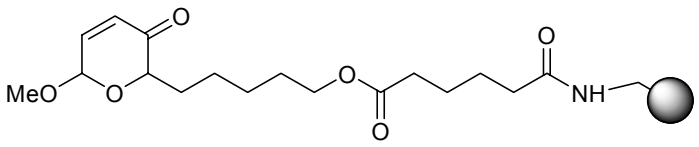
^{1}H NMR (400 MHz, $CDCl_3$) δ= 1.45-2.10 (m, 9H -$(CH_2)_4$ and -OH), 3.40 (s, 3H,-OMe^{maj}), 3.45 (m, 1H, 2-$H^{maj+min}$), 3.50 (s, 3H,-OMe^{min}), 3.70 (bs, 1H, 3-H^{min}), 3.86 (bd, J=8.8 Hz, 1H, 3-H^{maj}), 4.32 (t, 2H, *J*=6.6 Hz, -CH_2O), 4.82 (bs, 1H, 6-H^{maj}), 4.92 (bs, 1H, 6-H^{min}), 5.74 (ddd, *J*=10.1, 2.7, 2.1 Hz, 1H, 5-H^{maj}), 5.81 (bd, *J*=10.0 Hz, 1H, 5-H^{min}), 5.92 (bd, *J*=10.1, 1.1 Hz, 1H, 4-H^{maj}), 6.14 (ddd, *J*= 9.9, 5.2, 1.2 Hz, 1H, 4-H^{min}), 7.54-8.03 (m, 5H, -COPh).
^{13}C NMR (100 MHz, $CDCl_3$) δ= 25.6+25.7, 26.1+26.2, 31.17, 32.2, 33.0+33.0 ($(CH_2)_4$), 56.2+56.3 (-OMe, maj+min), 63.2 (-CH_2OH), 64.2, 68.4 (C-3), 71.9 (C-2), 75.9, 95.5+99.4 (C-6), 126.6, 127.8, 128.5, 129.6, 128.7, 130.9, 131.6, 133.9, 166.7 (-COPh),
GC-MS (RP50): t_R=14.54 min, 14.57 min (isomeric mixtures) m/z=289 (1%), 271 (3%), 123 (10%), 100 (100%), 77 (40%).
R_f 0.30 (cyclohexane/EtOAc 1:1)

Formation of aminomethylated polystyrene resin supported 6-hydroxy-2-(5-hydroxypentyl)-2*H*-pyran-3(6*H*)-one (95)



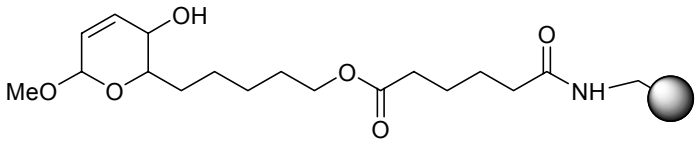
To a mixture of aminomethylated polystyrene resin supported 1-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)hexan-1,6-diol (0.21 g, 0.16 mmol) in dioxane (10 mL) was added 2% H_2SO_4 (1.2 mL) at rt. The reaction mixture was shaken at rt for 48 h. Then the resin was filtered and washed with DCM (4x20 mL), THF (4x20 mL), DMF (2x20 mL), DMF/water [2x(10/10 mL)], DCM/MeOH [2x(10/10 mL)], and DCM (4x20 mL).

Formation of aminomethylated polystyrene resin supported 2-(5-hydroxypentyl)-6-methoxy-2*H*-pyran-3(6*H*)-one (96)



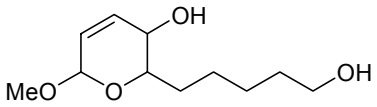
To a mixture of aminomethylated polystyrene resin supported 6-hydroxy-2-(5-hydroxypentyl)-2*H*-pyran-3(6*H*)-one (0.16 mmol, which was prepared in the experiment described above) in DCM (20 mL) cooled at 0°C were added $CH(OMe)_3$ (0.043 mL, 0.39 mmol) and $BF_3.Et_2O$ (0.0035 mL, 0.028 mmol). The resulting red reaction mixture was shaken at rt for 1 h. The resin was filtered and washed with DCM (4x20 mL), THF (4x20 mL), DMF (2x20 mL), DCM/MeOH [2x(10/10 mL)], and DCM (4x20 mL).

Procedure for the formation of aminomethylated polystyrene resin supported 3,6-dihydro-2-(5-hydroxypentyl)-6-methoxy-2*H*-pyran-3-ol (96)



To a mixture of aminomethylated polystyrene resin supported 2-(5-hydroxypentyl)-6-methoxy-2*H*-pyran-3(6*H*)-one (0.16 mmol, which was prepared in the experiment described above) in THF/H_2O (20/1 mL) at rt was added $NaBH_4$ (0.03 g, 0.84 mmol). The resulting reaction mixture was shaken at rt for 4 h. The resin was filtered and washed with DCM (4x20 mL), THF (4x20 mL), DMF (2x20 mL), DCM/MeOH [2x(10/10 mL)], and DCM (4x20 mL). After washing the resin was dried in vacuo for 24 h.

Procedure for the cleavage of aminomethylated polystyrene resin supported 3,6-dihydro-2-(5-hydroxypentyl)-6-methoxy-2*H*-pyran-3-ol (93)



In a fritted funnel resin aminomethylated polystyrene resin supported 3,6-dihydro-2-(5-hydroxypentyl)-6-methoxy-2*H*-pyran-3-ol (0.23 g, 0.16 mmol) was swelled in 20 mL dioxane and then an aqueous LiOH solution (0.03 g, 0.8 mmol equiv in 2 mL water) was added. The suspension was shaken for 24 h at room temperature. The resin was filtered and the filtrate was stored in a flask. Again dioxane and LiOH solution were added to the resin (same quantity as described above) and the suspension was again shaken for another 24 h. The resin was filtered and the filtrate was added to the previous filtrate. The combined filtrates were concentrated under reduced pressure until a yellowish-white solid started to precipitate. Then 5 mL water were added and the solution was extracted with ethyl acetate (4x20 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and finally purified by flash chromatography on basic Al_2O_3 (pH-9.5) using EtOAc/MeOH (50:1) to furnish 11.2 mg (33%) of 3,6-dihydro-2-(5-hydroxypentyl)-6-methoxy-2*H*-pyran-3-ol as a yellow oil (*cis/trans* mixture).

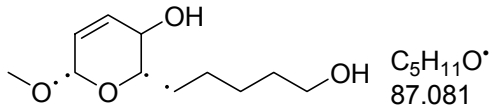
Ratio: major/minor: 2/1

^{1}H NMR (400 MHz, $CDCl_3$) δ= 1.45-2.10 (m, 9H, -$(CH_2)_4$ and -OH), 3.43 (s, 3H,-OMe^{maj}), 3.52 (s, 3H,-OMe^{min}), 3.64 (t, 2H, *J*=6.0 Hz, -CH_2OH), 3.70 (bs, 1H, 3-H^{min}), 3.86 (bs, 1H, 3-H^{maj}), 4.82 (bs, 1H, 6-H^{maj}), 4.92 (bs, 1H, 6-H^{min}), 5.74 (ddd, *J*=10.1, 2.7, 2.1 Hz, 1H, 5-H^{maj}), 5.81 (bd, *J*=10.0 Hz, 1H, 5-H^{min}), 5.92 (bd, *J*=10.1, 1.1 Hz, 1H, 4-H^{maj}), 6.14 (ddd, *J*= 9.9, 5.2, 1.2 Hz, 1H, 4-H^{min}).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 25.6+25.7, 26.1+26.2, 31.17, 32.2, 33.0+33.0 ($(CH_2)_4$), 56.2+56.3 (-OMe, maj+min), 63.2 (-CH_2OH), 64.2, 68.4 (C-3), 71.9 (C-2), 75.9, 95.5+99.4 (C-6), 126.6, 130.9, 131.6, 133.9.

GC-MS (RP50): t_R=10.92 min, m/z=185 (5%), 100 (100%).

$C_5H_7O_2^{\bullet}$
99.0446



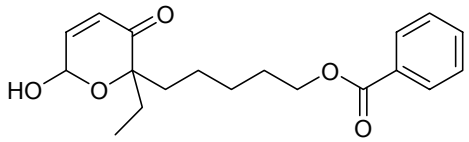
$C_5H_{11}O^{\bullet}$
87.081

$CH_3O^{\bullet}$
31.0184

$C_{10}H_{17}O_3^{\bullet}$
185.118

R_f 0.3 (EtOAc/MeOH 50:1)

5-(2-Ethyl-3,6-dihydro-6-hydroxy-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (85)

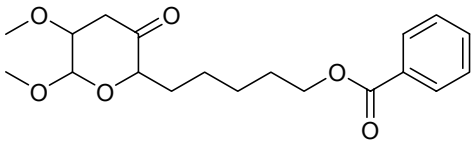


To a solution of (6-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)-6-hydroxyoctyl)benzoate (0.22 g, 0.582 mmol) in dioxane (10 mL) was added 2% H_2SO_4 (2.0 mL) at rt. The resulting brown reaction mixture was stirred at rt for 24 h. Solid $NaHCO_3$ was added until the solution reached pH 4. Then 5 mL water was added and the solution was extracted with ethyl acetate (4x20 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure maintaining the water bath temperature below 35°C to yield 0.15 g (77%) of the title compound as a yellow oil (isomeric mixture).

^{1}H NMR (400 MHz, $CDCl_3$) δ=0.8 (m, 3H, -CH_3), 1.35-2.00 (m, 11H, -$(CH_2)_5$ and –OH), 4.25 (m, 2H, -CH_2O), 5.70 (m, 1H, 6-H), 6.05 (dd, *J*=10.1 Hz, 3.7 Hz, 1H, 4-H), 6.83 (ddd, *J*=10.3 Hz, 2.2 Hz, 1.5 Hz, 1H, 5-H), 7.28-8.05 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=8.1+8.3 (-CH_3), 23.1+23.5, 26.6+26.8, 28.9+29.0, 30.9, 35.2, 36.9, 65.1+65.2, (-CH_2O), 84.9 (C-2), 87.91+87.94 (C-6), 127.3+127.4, 128.5, 129.71+129.73, 130.53+130.54, 133.0, 145.5+145.9, 166.8+166.9 (-COPh), 199.1+199.2 (-CO).

5-(Tetrahydro-5,6-dimethoxy-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (106)

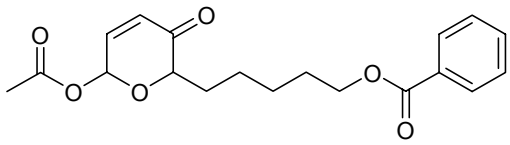


To a solution of 5-(3,6-dihydro-6-methoxy-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (0.19 g, 0.63 mmol) in 10 mL dry methanol, (0.03 g, 0.641 mmol) NaOMe was added at room temperature. The resulting brown reaction mixture was stirred at room temperature and was monitored by GC-MS. 5 mL saturated NH_4Cl was added slowly to the reaction mixture. The solution was extracted with ethylacetate (4x20 mL). The organic layers were separated and dried with Na_2SO_4. The reaction mixture was concentrated under reduced pressure to give 0.132 g (60%) of the title compound as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.3-1.9 (m, 8H -$(CH_2)_4$), 2.60 (dd, *J*=6.1 Hz, 15.4 HZ, 1H,-CH_2), 2.73 (dd, *J*=4.5 Hz, 15.4 HZ, 1H,-CH_2), 3.35 (s, 3H, -OMe), 3.45 (s, 3H, -OMe), 3.5 (m, 1H, -CH), 3.6 (m, 1H, -CH), 4.30 (t, *J*=6.6 Hz, 2H, -CH_2O), 4.5 (m, 1H, -CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 25.6+25.7, 26.1+26.2, 31.17, 32.2, 33.0+33.0 ($(CH_2)_4$), 56.6+56.8 (-OMe, maj+min), 65.2 (-CH_2O), 74.0 (C-2), 79.1, 94.3+96.9 (C-6), 126.5, 127.8, 128.5, 128.7, 128.8, 129.6, 130.6, 132.9, 143.3+146.5 (C-5), 166.7 (-COPh), 196.4+196.5 (-CO).

5-(3,6-dihydro-6-acetoxy-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (104)



To a solution of 5-(3,6-dihydro-6-hydroxy-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (0.043 g, 0.14 mmol) in 10 mL dry CH_2Cl_2, 0.04 mL (0.57mmol) pyridine, 0.008 g (0.065 mmol) DMAP and 0.03 mL (0.35 mmol) CH_3COCl were added respectively at 0°C. The resulting brown reaction mixture was allowed to warm to room temperature and stirred for 12 h. Then 5 mL water were added and the solution was extracted with DCM (3x15 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/EtOAc 3:1) to furnish 0.035 g (71%) of the title compound as a yellow oil.

Ratio: major/minor: 2/1

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.45-2.00 (m, 8H, -$(CH_2)_4$), 2.10 (s, 1H, 3H, -CH_3^{maj}), 2.11 (s, 1H, 3H, -CH_3^{min}), 4.20 (t, *J*=6.6 Hz, 1H , 2-H^{min}), 4.30 (t, *J*=6.5 Hz, 2H, -CH_2O^{maj}), 4.31 (t, *J*=6.5 Hz, 2H, -CH_2O^{min}), 4.45 (dd, *J*=8.2 Hz, 3.9 Hz, 1H, 2-H^{maj}), 6.19 (d, *J*=10.4 Hz, 1H, 6-H^{maj}), 6.20 (dd, *J*=10.4 Hz, 1.4 Hz, 1H, 6-H^{min}), 6.48 (d, *J*=3.7 Hz, 1H, 4-H^{maj}), 6.53 (dd, *J*=2.5 Hz, 1.4 Hz, 1H, 4-H^{min}), 6.83 (dd, *J*=12.9 Hz, 2.5 Hz, 1H, 5-H^{min}), 6.87 (dd, *J*=10.2 Hz, 3.7 Hz, 1H, 5-H^{maj}), 7.28-8.05 (m, 5H, -Ph).

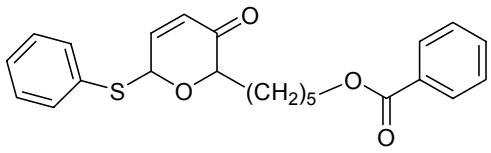
^{13}C NMR (100 MHz, $CDCl_3$) δ= 21.34+21.43 (-CH_3), 24.7, 25.3, 26.1+26.2, 28.9+29.0, 29.9, 32.9, 65.1+65.2 (-CH_2O), 76.0 (C-2), 79.7, 87.3+88.0 (C-6), 128.48+128.49, 128.6,

128.7+128.8, 129.67+129.68, 130.5+130.6, 132.95+132.98, 141.7, 143.1, 166.65+166.68 (-COPh), 169.2+169.5 (-$COCH_3$), 195.4+196.5 (-CO).

GC-MS (RP50): t_R=15.01 min, m/z=304 (5%), 287 (30%), 126 (60%), 105 (100%), 84 (100%).

R_f 0.30 (cyclohexane/EtOAc 3:1).

5-(3,6-Dihydro-6-phenylthio-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (117)



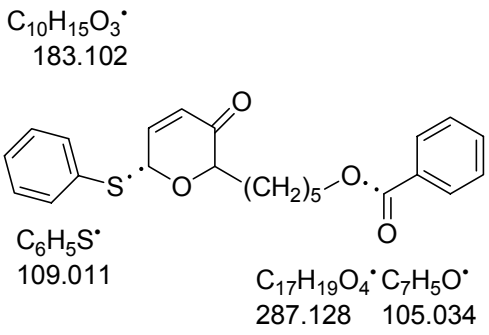
To a yellow solution of 5-(3,6-dihydro-6-hydroxy-3-oxo-2*H* pyran-2-yl)pentyl benzoate (0.51 g, 1.64 mmol) in 15 mL dry CH_2Cl_2, PhSH (0.168 mL, 1.64 mmol) and $BF_3.OEt_2$ (0.15 mL, 0.82 mmol) were added respectively at 0°C. The colour of the reaction mixture changed from yellow to dark brown after addition of $BF_3.OEt_2$, the reaction mixture was stirred for 2h at 0° C. The reaction was monitored by GC-MS. 10% $NaHCO_3$ solution (5mL) was added to to the reaction mixture and the solution was extracted with dichloromethane (4x20 mL). The organic layers were separated and dried over Na_2SO_4. The reaction mixture was concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane / EtOAc 4:1) to give 0.42 g (68%) of the title compound as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.51-1.88 (m, 8H, -$(CH_2)_4$), 4.29 (t, *J*=6.65 Hz, 2H, CH_2O), 4.78 (dd, *J*=8.4 Hz, 3.5 Hz, 1H, 2-H), 5.95 (dd, *J*=4.1 Hz, 1.2 Hz, 1H, 6-H), 6.08 (dd, *J*=9.9 Hz, 1.3 Hz, 1H, 4-H), 7.08 (dd, *J*=10.1 Hz, 3.91 Hz, 1H, 5-H), 7.27-8.05 (m, 10H, -COPh and -SPh).
^{13}C NMR (100 MHz, $CDCl_3$) δ=25.2 (-CH_2), 26.2 (-CH_2), 27.3 (-CH_2), 29.1 (-CH_2), 29.4 (-CH_2), 65.2 (CH_2O), 74.8 (2-C), 83.1 (6-C), 126.8 (-Ph), 127.3(-Ph), 127.6 (-Ph), 128.0 (-Ph), 128.4 (-Ph), 129.3, 129.7, 130.6 (-Ph), 131.7 (-Ph), 132.9 (-Ph), 134.3 (-Ph), 145.13 (C-5), 166.71(-COPh), 195.8 (C-3).

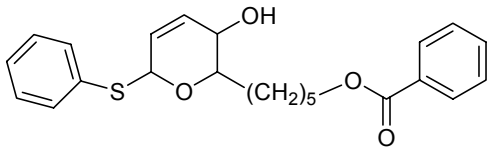
GC-MS (RP50): t_R=14.46 min, m/z=287 (20%), 105 (100%), 98 (30%).

HR-MS (FAB) of $C_{10}H_{15}O_3$: Theoretical 397.1474 $[M+H]^+$, found 397.1478.

R_f 0.2 (cyclohexane/ EtOAc 4:1)



5-(3,6-Dihydro-6-phenylthio-3-hydroxy-2*H* pyran-2-yl)pentyl benzoate (118)



A solution of 5-(3,6-dihydro-6-phenylthio-3-oxo-2*H* pyran-2-yl)pentyl benzoate (0.42 g, 1.21 mmol) in 15 mL THF was added slowly at 0°C to a solution of sodium borohydride (0.040 g, 1.21 mmol) in a mixture of 10 mL THF and 1 mL water. The resulting brown reaction mixture was stirred at room temperature for 2 hours. 5 mL saturated NH_4Cl were added slowly to the reaction mixture. The solution was extracted with ethylacetate (4x20 mL). The organic layers were separated and the combined layers were dried over Na_2SO_4. The reaction mixture was concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/ EtOAc 4:1) to give 0.35 g (74%) of the corresponding alcohol as a yellow oil.

Ratio: major/minor: 2/1

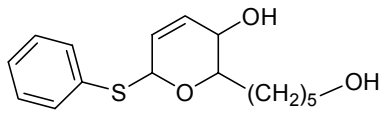
^{1}H NMR (400 MHz, $CDCl_3$) δ=2.00-1.41 (m, 9H,OH,$(-CH_2)_4$), 3.86 (tt, *J*=9 Hz, 2.34 Hz, 1H, 2-$H^{maj+min}$), 3.99 (t, *J*=7.4 Hz, 1H, 3-$H^{maj+min}$), 4.26 (t, *J*=6.6 Hz, 2H, -CH_2O), 5.77 (bq, *J*=1.3 Hz, 1H, 6-$H^{maj+min}$), 5.89 (t, *J*=1.6 Hz, 1H, 4-H^{min}), 5.91 (t, *J*=1.6 Hz, 1H, 4-H^{maj}), 5.97 (dd, J= 3 Hz, 1.8 Hz, 1H, 5-H^{maj}), 5.99 (dd, *J*=2.9 Hz, 1.9 Hz, 1H, 5-H^{min}), 7.27-8.07 (m, 10H, -COPh and -SPh).

^{13}C NMR (100 MHz, $CDCl_3$) δ=25.5 ($-CH_2$), 26.2 ($-CH_2$), 31.3 ($-CH_2$), 31.3 (CH_2), 65.3 (-CH_2O), 68.2 (3-C), 72.4 (2-C), 83.8+83.9 (6-C), 127.1, 127.5, 128.4, 129.1, 129.7, 129.72, 130.6, 130.8, 132..1, 132.9, 136.0, 166.76 (-COPh).

GC-MS (RP50): t_R=18.67 min, 18.75 min, (isomeric mixtures), m/z=398 (10%), 289 (30%), 271 (30%), 105 (100%).

R_f 0.2 (cyclohexane/ EtOAc 4:1)

3,6-Dihydro-2-(5-hydroxypentyl)-6-phenylthio-2*H*-pyran-3-ol (119)



To a solution of 5-(3,6-dihydro-6-phenylthio-3-hydroxy-2*H* pyran-2-yl)pentyl benzoate (0.35 g, 0.75 mmol) in 20 mL dioxane, an aqueous LiOH solution (0.25g, 0.75 mmol LiOH in 2 mL water) was added. The suspension was stirred at room temperature overnight. Then 5 mL water were added and the solution was extracted with ethyl acetate (3x15 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/ EtOAc 1:2) to furnish 0.198 g (90%) of the title compound as a yellow oil.

Ratio: major/minor: 2/1

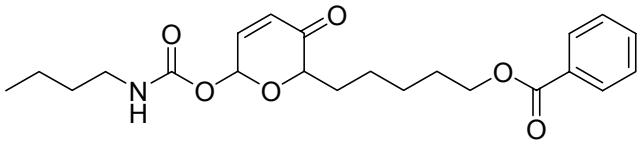
^{1}H NMR (400 MHz, $CDCl_3$) δ=2.00-1.41 (m, 10H,2-OH,(-CH_2)$_4$), 3.68(t, J= 6.78 Hz, 2H, -CH_2OH), 3.86 (tt, *J*=9 Hz, 2.34 Hz, 1H, 2-H$^{maj+min}$), 3.99 (t, *J*=7.4 Hz, 1H, 3-H$^{maj+min}$), 4.26 (t, *J*=6.6 Hz, 2H, -CH_2O), 5.77 (bq, *J*=1.3 Hz, 1H, 6-H$^{maj+min}$), 5.89 (t, *J*=1.6 Hz, 1H, 4-H^{min}), 5.91 (t, *J*=1.6 Hz, 1H, 4-H^{maj}), 5.97 (dd, J= 3 Hz, 1.8 Hz, 1H, 5-H^{maj}), 5.99 (dd, *J*=2.9 Hz, 1.9 Hz, 1H, 5-H^{min}), 7.27-7.55 (m, 5H, -SPh).

^{13}C NMR (100 MHz, $CDCl_3$) δ=25.5 (-CH_2), 26.2 (-CH_2), 31.3 (-CH_2), 31.3 (CH_2), 62.2 (-CH_2O), 68.3 (3-C), 72.4 (2-C), 83.8+83.9 (6-C), 126.8, 127.1, 127.2, 128.9, 129.1, 130.8, 130.9, 131.0, 132.4, 136.1.

HR-MS (FAB) of $C_{16}H_{22}O_3S$: Theoretical 294.1290 [M]$^+$, found 294.1301.

R_f 0.20 (cyclohexane/ EtOAc 1:2)

5-(2-Ethyl-3,6-dihydro-6-butylcarbamate-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (112)



To a solution of 5-(3,6-dihydro-6-hydroxy-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (0.31 g, 0.98 mmol) in 20 mL dry CH_2Cl_2, 0.16 mL (1.48 mmol) butyl isocyanate and 0.07 mL (0.49 mmol) Et_3N were added respectively at 0°C under Ar atmosphere. The resulting brown reaction mixture was allowed to warm to room temperature and stirred for 4 h. Finally the reaction mixture was concentrated under reduced pressure and purified by silicagel chromatography (cyclohexane/EtOAc 2:1) to afford 0.21 g (60%) of the title compound as a yellow oil.

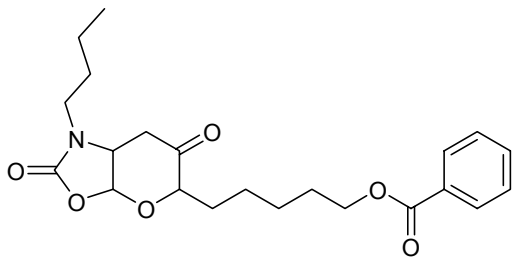
^{1}H NMR (400 MHz, $CDCl_3$) δ=0.92 (t, *J*=7.2 Hz, 3H, -CH_3), 1.30-1.90 (m, 12H -$(CH_2)_6$), 3.22 (q, *J*=6.6 Hz, 2H,-CH_2-N-), 4.20 (t, *J*=6.6 Hz, 1H, 2-H), 4.30 (m, 2H, -CH_2O), 4.37 (dd, *J*=8.4 Hz, 3.5 Hz, 1H, 2-H^{maj}), 4.92 (t, *J*=5.6 Hz, 1H, -NH), 6.18 (dd, *J*=10.3 Hz, 1.4 Hz, 1H, 6-H), 6.51 (dd, *J*=2.4 Hz, 1.4 Hz, 1H, 4-H), 6.84 (dd, *J*=10.3 Hz, 2.4 Hz, 1H, 5-H), 7.28-8.05 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 25.6+25.7, 26.1+26.2, 31.17, 32.2, 33.0+33.0 ($(CH_2)_4$), 56.6+56.8 (-OMe, maj+min), 65.2 (-CH_2O), 74.0 (C-2), 79.1, 94.3+96.9 (C-6), 126.5, 127.8, 128.5, 128.7, 128.8, 129.6, 130.6, 132.9, 143.3+146.5 (C-5), 166.7 (-COPh), 196.4+196.5 (-CO).

GC-MS (RP50): t_R=18.84 min, 18.89 min, (isomeric mixtures), m/z=403 (20%), 281 (20%), 141 (100%), 105 (70%).

R_f 0.30 (cyclohexane/EtOAc 2:1)

5-(1-Butylhexahydro-2,6-dioxo-1*H*-pyrano[3,2-*d*]oxazol-5-yl)pentyl benzoate (113)



To a solution of 5-(3,6-dihydro-6-butylcarbamte-3-oxo-2*H*-pyran-2-yl)pentyl benzoate (0.12 g, 0.0.30 mmol) in 15 mL dry CH_2Cl_2, 0.09 mL (0.61 mmol) 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) were added at room temperature. The colour of the reaction mixture changed from yellow to green and finally to dark brown. The resulting brown reaction was stirred for 12 h at room temperature. Then 10 mL water were added and the solution was extracted with DCM (4x50 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by silicagel chromatography (cyclohexane/EtOAc 2:1) to afford 0.096 g (80%) of the title compound as a yellow oil.

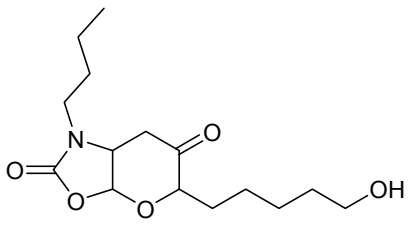
^{1}H NMR (400 MHz, $CDCl_3$) δ=0.92 (t, *J*=7.2 Hz, 3H, -CH_3), 1.30-1.90 (m, 12H -$(CH_2)_6$), 2.70 (dd, *J*=2.5 Hz, 16.0 Hz, 1H, -*CH*-CH-N), 2.80 (dd, *J*=3.1 Hz, 16.0 Hz, 1H, -*CH*-CH-N), 2.95 (m, 1H, -N-CH-), 3.40 (m, 1H, -N-CH), 4.05 (dd, *J*=3.9 Hz, 7.1 Hz, 1H, -OCH), 4.30 (t, *J*=6.6 Hz, 2H, -CH_2O), 4.35 (m, 1H, -CH-N), 5.98 (d, *J*=7.4 Hz, 1H, -O-CH-O), 7.28-8.05 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=14.0 (-CH_3), 20.2, 24.9, 26.1, 27.3, 28.8, 29.4, 30.5, 37.2, 41.8, 65.2 (-CH_2O), 76.6 (C-7), 93.8 (C-9), 128.5, 129.6, 130.5, 133.0, 156.2 (N-CO), 166.7 (-COPh), 207.8 (-CO).

GC-MS (RP50): t_R=18.86 min, 19.03 min, (isomeric mixtures), m/z=403 (20%), 359 (2%), 330 (10%), 288 (10%), 154 (20%), 141 (100%), 105 (70%).

R_f 0.30 (cyclohexane/EtOAc 2:1)

1-Butyl-dihydro-5-(5-hydroxypentyl)-1*H*-pyrano[3,2-*d*]oxazol-2,6(3a*H*,*5H*)-dione (114)



To a solution of 5-(1-butylhexahydro-2,6-dioxo-1*H*-pyrano[3,2-*d*]oxazol-5-yl)pentyl benzoate (0.04 g, 0.09 mmol) in 10 mL dioxane, an aqueous LiOH solution (0.02g, 0.59 mmol in 2 mL water) were added. The suspension was stirred at room temperature overnight. Then 5 mL water was added and the solution was extracted with ethyl acetate (3x15 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by silicagel chromatography (EtOAc) to furnish 0.026 g (88%) of the title compound as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=0.92 (t, *J*=7.2 Hz, 3H, -CH_3), 1.30-1.90 (m, 12H -$(CH_2)_6$), 2.70 (dd, *J*=2.5 Hz, 16.0 Hz, 1H, -*CH*-CH-N), 2.80 (dd, *J*=3.1 Hz, 16.0 Hz, 1H, -*CH*-CH-N), 2.95 (m, 1H, -N-CH-), 3.40 (m, 1H, -N-CH), 3.65 (t, *J*=6.6 Hz, 2H, -CH_2O), 4.05 (dd, *J*=3.9 Hz, 7.1 Hz, 1H, -OCH), 4.35 (m, 1H, -CH-N), 5.98 (d, *J*=7.4 Hz, 1H, -O-CH-O).

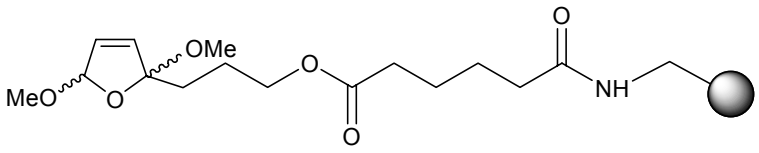
^{13}C NMR (100 MHz, $CDCl_3$) δ=14.0 (-CH_3), 20.2, 24.9, 26.1, 27.3, 28.8, 29.4, 30.5, 37.2, 41.8, 61.5 (-CH_2O), 76.6 (C-7), 93.8 (C-9), 156.2 (N-CO), 207.8 (-CO).

GC-MS (RP50): t_R=14.59 min, m/z=299 (30%), 281 (2%), 226 (10%), 184 (10%), 154 (20%), 141 (100%), 112 (70%).

R_f 0.20 (EtOAc)

6.2.7 Experimental section for chapter 4.1.9

Procedure for the oxidation of aminomethylated polystyrene resin supported 2-furanpropanol with NBS (61)



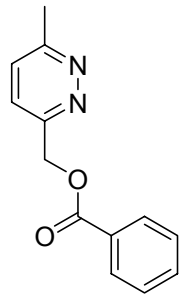
Aminomethylated polystyrene resin supported 2-furanpropanol was prepared following the same reaction conditions and washing protocols described above for the formation of aminomethylated polystyrene resin supported 5-methyl furfuryl alcohol.

To a 50 ml flask containing a mixture of aminomethylated polystyrene resin supported 2-furanpropanol (0.15 g, 0.13 mmol) in THF/MeOH (10/10 mL) were added 1.15 g (13.70 mmol) $NaHCO_3$, 0.54 g (6.65 mmol) NaOAc, and 0.80 g (4.52 mmol) *N*-bromosuccinimide. The flask was wrapped in aluminum foil and shaken at rt for 1 h. The resin was then isolated

by filtration and washed with DCM (4x20 mL), THF (4x20 mL), DCM (2x20 mL). After washing the resin was dried in vacuo for 24 h. Aminomethylated polystyrene resin supported 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanol was cleaved by the procedure described above for the formation of (2,5-dihydro-2,5-dimethoxy-5-methylfuran-2-yl)methanol. Finally 7.5 mg (30%) 3-(2,5-dihydro-2,5-dimethoxy-2)propanol (>95 % purity) was isolated as a *cis/trans* mixture.

6.2.8 Experimental section for chapter 4.1.10

(6-Methylpyridazin-3-yl)methyl benzoate (130)



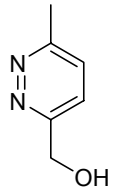
To a solution of (2,5-dihydro-2,5-dimethoxy-5-methylfuran-2-yl)methyl benzoate (0.21 g, 0.72 mmol) in 15 mL dioxane, aq. H_2SO_4 [(0.05 mL (0.44 mmol) conc. H_2SO_4 in 2 mL water] was added at room temperature. The reaction was monitored by TLC and the resulting brown reaction mixture was stirred at room temperature for 5 min. Then 0.03 mL (0.72 mmol) hydrazine hydrate were added to the reaction mixture at room temperature. The reaction was monitored by TLC and the resulting yellow reaction mixture was stirred for 15 minutes. The reaction mixture was concentrated under reduced pressure and purified by silicagel chromatography (EtOAc) to give 0.11 g (70%) of the title compound as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.72 (s, 1H, -CH_3), 4.93 (s, 2H, -CH_2O), 7.33 (d, *J*=8.6 Hz, 1H), 7.43 (d, *J*=8.6 Hz, 1H), 7.42-8.08 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=22.4 (-CH_3), 65.9 (-CH_2O), 125.9, 127.6, 128.4, 128.5, 129.9, 133.5, 156.3, 159.8, 166.2 (-COPh).

R_f 0.30 (EtOAc).

6-Methylpyridazin-3-methanol (135)



In a fritted funnel aminomethylated polystyrene resin supported 5-methyl furyl alcohol (0.25 g, 0.21 mmol) was swelled in 15 mL dioxane at room temperature and aq. H_2SO_4 [(0.04 mL (0.42 mmol) conc. H_2SO_4 in 2 mL water] was added. The reaction mixture was shaken for 20 minutes and then filtered. 15 ml of dioxane was added to the resin and hydrazine hydrate (0.2 mL, 6.42 mmol) was added to the reaction mixture at rt. The reaction mixture was shaken for 15 minutes. The resin was filtered and the filtrate was concentrated under reduced pressure and finally dried in vacuo to furnish 16 mg 6-methylpyridazin-3-methanol (60%, >95 % purity).

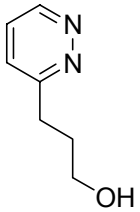
^{1}H NMR (400 MHz, $CDCl_3$) δ=2.72 (s, 1H, -CH_3), 4.93 (s, 2H, -CH_2OH), 7.33 (d, *J*=8.6 Hz, 1H), 7.43 (d, *J*=8.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ=22.4 (-CH_3), 63.7 (-CH_2-), 125.1, 127.7, 159.1, 159.5.

GC-MS (RP50): t_R=8.35 min, m/z=124 (90%), 123 (100%), 95 (90%).

HR-MS (EI) for $C_8H_8N_2O$: Theoretical 124.0637 [M^+], found 124.0631.

3-Pyridazinpropanol (136)



In a fritted funnel aminomethylated polystyrene supported 3-(2,5-dihydro-2,5-dimethoxy-2-furan)propanol (0.20 g, 0.17 mmol) was swelled in 15 mL dioxane at rt and aq. H_2SO_4 [(0.03 mL (0.34 mmol) conc. H_2SO_4 in 2 mL water] was added to it. The reaction mixture was shaken for 30 minutes and then filtered. 15 ml of dioxane were added to the resin and hydrazine hydrate (0.15 mL, 5.1 mmol) was added to the reaction mixture at room temperature. The reaction mixture was shaken for 30 minutes. The resin was filtered and 15 ml of dioxane was added to the resin followed by aqueous LiOH solution (0.03 g, 0.85 mmol

in 2 mL water). The suspension was shaken for 24 h. The resin was filtered and the filtrate was stored in a flask. Again dioxane and LiOH solution were added to the resin (same quantity as described above) and the suspension was again shaken for another 24 h. The resin was filtered and the filtrate was added to the previous filtrate. The combined filtrates were concentrated under reduced pressure until a yellowish-white solid was formed. Then 5 mL water were added and the solution was extracted with ethyl acetate (4x20 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and finally purified by silicagel chromatography (MeOH/EtOAc 1:5) to give 13 mg (55%) of the corresponding pyridazine as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.05 (m, *J*=7.2 Hz, 2H, -CH_2), 3.10 (t, *J*=7.2 Hz, 2H, -CH_2OH), 3.70 (t, *J*=6.1 Hz, 2H, -CH_2), 7.40 (m, 2H), 9.00 (dd, *J*=4.5 Hz, 1.9 Hz, 1H).

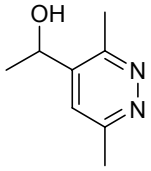
^{13}C NMR (100 MHz, $CDCl_3$) δ=32.0 (-CH_2), 33.0 (-CH_2), 61.7 (-CH_2OH), 126.9 (-CH), 126.9 (-CH), 149.8 (-CH), 163.7 (-C-).

GC-MS (DB_50_S): t_R=6.48 min, m/z=138 (20%), 121 (35%), 94 (100%).

HR-MS (FAB) for $C_7H_{10}H_2O$: Theoretical 139.0871 $[M+H]^+$, found 139.0903.

R_f 0.17 (MeOH/ EtOAc 1:5)

1-(3,6-Dimethylpyridazin-4-yl)ethanol (137)



In a fritted funnel aminomethylated polystyrene supported 1-(2,5-dihydro-2,5-dimethoxy-2,5-dimethylfuran-3-yl)ethanol (0.20 g, 0.16 mmol) was swelled in 15 mL dioxane at rt and aq. H_2SO_4 [(0.05 mL (0.50 mmol) conc. H_2SO_4 in 2 mL water] was added to it. The reaction mixture was shaken for 30 minutes and then filtered. 15 ml of dioxane were added to the resin and hydrazine hydrate (0.15 mL, 4.8 mmol) was added to the reaction mixture at room temperature. The reaction mixture was shaken for 30 minutes. The resin was filtered and 15 ml of dioxane was added to the resin and an aqueous LiOH solution (0.03 g, 0.80 mmol in 2 mL water) was added. The suspension was shaken for 24 h. The resin was filtered and the filtrate was stored in a flask. Again dioxane and LiOH solution were added to the resin (same

quantity as described above) and the suspension was again shaken for another 24 h. The resin was filtered and the filtrate was added to the previous filtrate. The combined filtrates were concentrated under reduced pressure until a yellowish-white solid was formed. Then 5 mL water were added and the solution was extracted with ethyl acetate (4x20 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and finally purified by silicagel chromatography (MeOH/ EtOAc 1:5) to give 15 mg (60%) of the corresponding pyridazine as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ=1.40 (d, *J*=6.5 Hz, 3H, -CH_3(CH)OH), 2.51 (s, 3H, -CH_3), 2.53 (s, 3H, -CH_3), 4.50 (q, *J*=6.5 Hz, 1H, -CHOH), 7.52 (s, 1H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ=18.9 (-CH_3), 21.5 (-CH_3), 23.4 (-CH_3), 64.5 (-CHOH), 123.2 (-CH), 145.2 (-C-), 154.6 (-C-), 158.4 (-C-).

GC-MS (DB_50_S): t_R=6.12 min, m/z=152 (100%), 137 (45%), 109 (55%), 79 (65%).

HR-MS (EI) of $C_8H_{12}N_2O$: Theoretical 152.0949 [M^+], found 152.0948.

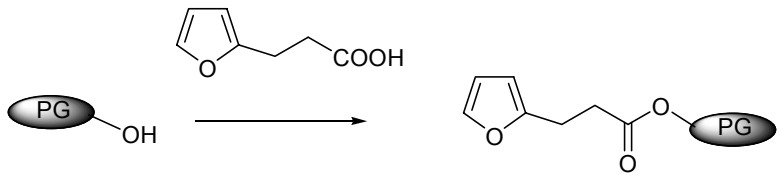
R_f 0.17 (MeOH/ EtOAc 1:5)

6.3 Parallel multistep synthesis of *N*-substituted pyrrole derivatives using dendritic polyglycerol as a high-loading support

Dialysis was performed in benzoylated cellulose dialysis tubes from Sigma-Aldrich (No. D-7884, width: 32mm, molecular weight cut-off (MW CO 1000 g/mol). The dialysis of all the intermediates was performed in chloroform for 24 h. In general the intermediates (2-4 mmol) were dissolved in 10-15 mL chloroform and filled in the 5-10 cm long tubes . The solvent was changed every 1 hour during the first 4 hours of dialysis. The solution outside the dialysis tube was analyzed by GC-MS to check for impurities.

6.3.1 Experimental section for chapter 4.2.2

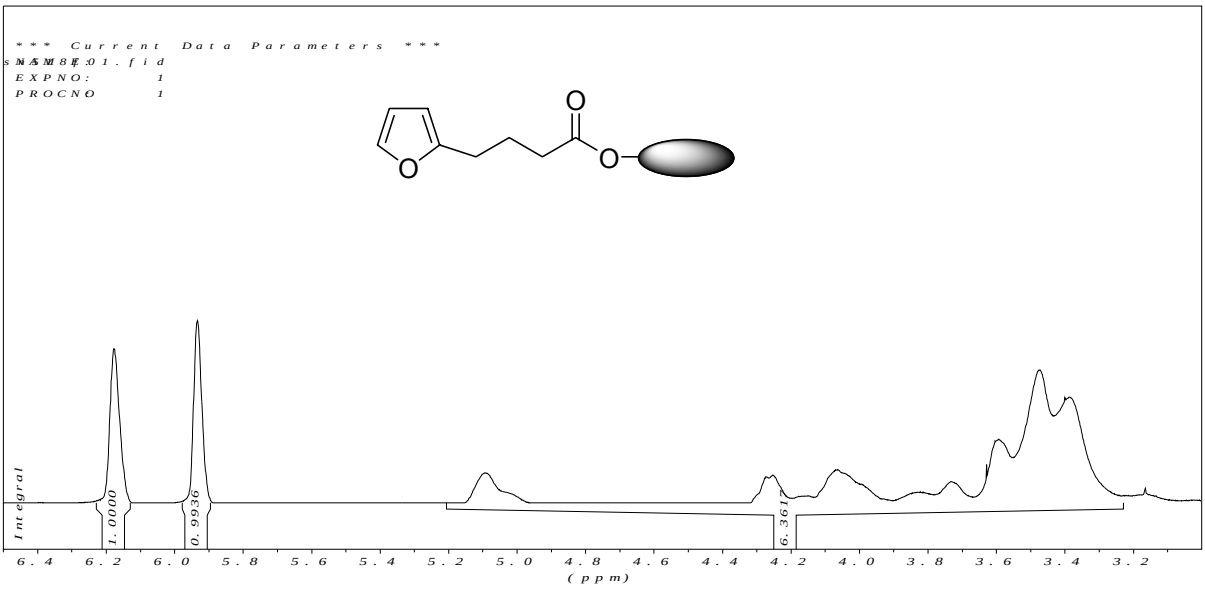
Immobilization of 2-furanpropionic acid on the polyglycerol support 150 via DCC-coupling (153)



This reaction was performed under an inert gas atmosphere and exclusion of water. Polyglycerol **150** (3.10 g, 40.5 mmol OH-groups, 1 equiv) was dissolved in abs. DMF (50 ml) upon ultrasonification. During stirring DMAP (0.47 g, 3.64 mmol, 0.09 equiv.) and 2-furanpropionic acid (6.24 g, 44.55 mmol, 1.1 equiv.) were added. A solution of DCC (8.38 g, 40.50 mmol, 1 equiv.) in abs. DMF (40 ml) was added over 1 h at 0°C. Clouding occured and the reaction was continued at room temperature for 16 h. The formed urea was filtered off through celite, the filtrate was concentrated in vacuo, and subsequently a little portion of $CHCl_3$ was added. After storage at -20°C for 1 h the residual urea was filtered off and the filtrate was dialysed for 48 h in $CHCl_3$. After evaporation of the solvent 4.51 g of a brown oil was obtained which was stored at 0°C.

2-furanpropionic acid polyglycerylester

Conversion: 78%; Yield: 72%.



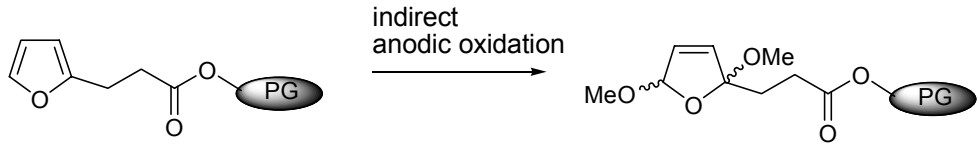
The conversion is the percentage of groups on the polyglycerol support which readily underwent the respective reaction. This value is determined via ^{1}H NMR (±5%) (by integration of polyglycerol units from 3.2 ppm to 5.2 ppm And compared with the product peak at 5.9 ppm which corresponds to one hydrogen atom).

Isolated yield is based on the ratio of obtained mass to expected mass considering the conversion. This is the yield of the crude product. Despite thorough drying of the products, they still contained some solvents from dialysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.65 (m, 2H, -CH_2), 2.92 (m, 2H, -CH_2), 3.40-4.00 (polyglycerol), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 6.00 (m, 1H, 3-H), 6.25 (m, 1H, 4-H), 7.27 (m, 1H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 23.4 (-CH_2), 32.5 (CH_2), 62.0-79.5 (polyglycerol), 105.4 (C-3), 110.3 (C-4), 141.3 (C-5), 154.1 (C-2), 172.3 (-CO-).

Formation of 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanoic acid polyglyceryl ester by indirect anodic oxidation (154)



For the experimental setup an undivided beaker-type cell (commerical Metrohm titration vessels and lids were adapted in the local machine shop) was equipped with two carbon electrodes (area of the electrodes immersed in the electrolytic solution-2.7 cm^2, distance between the two electrodes-0.5 cm). The cell was charged with 0.41 g (2.60 mmol) 2-furanpropionic acid polyglycerylester and 40 mL 0.2 M ammonium bromide in dioxane/MeOH (1/1). The cell was then immersed into a cooling bath thermostated at 0°C. For the electrolysis a current density of 0.015 A/cm^2 was applied. The power was supplied by an EA-PS-2032-025 instrument by which the current required for the electrolysis was fixed to 0.04 A and a electronic Coulomb-meter was used to calculate automatically the total electricity consumed for the electrolysis. After 0.1800 Ah (3 F/mol, which was required for the complete conversion of the starting material) electricity had been consumed, 1 g $NaHCO_3$ was added to the bright yellow solution mixture and the reaction mixture was concentrated under reduced pressure until a yellowish-white solid was formed. Then 50 mL dioxane were added and the solution was filtered through a fritted funnel to remove the salt (as ammonium bromide is insoluble in dioxane). The filtrate was concentrated under reduced pressure and finally dried in vacuo to furnish 0.46 g of 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanoic acid polyglyceryl ester as a yellow oil (*cis/trans* mixture).

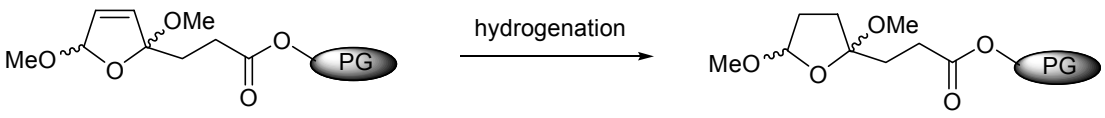
Conversion: quant., Yield: 80%.

^{1}H NMR (400 MHz, CD_3OD) δ=2.09 (m, 2H, -CH_2), 2.40 (m, 2H, -CH_2), 3.09 (m, 3H, -OMe^{min}), 3.15 (m, 3H, -OMe^{maj}), 3.43 (m, 3H, -OMe^{min}), 3.47 (m, 3H, -OMe^{maj}), 3.50-4.00 (polyglycerol), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 5.47 (m, 1H), 5.75 (m, 1H), 5.95 (m, 1H), 6.11 (m, 1H).

^{13}C NMR (100 MHz, CD_3OD) δ= 28.8 (-CH_2-), 33.9 (-CH_2-), 54.9 (-OMe), 55.4 (-OMe), 62.0-79.5 (polyglycerol), 107.4+108.6, 113.5+114.7, 131.7, 132.5, 132.6, 132.9, 173.8 (-CO-).

6.3.2 Experimental section for chapter 4.2.3

Formation of 3-(tetrahydro-2,5-dimethoxyfuran-2-yl)propanoic acid polyglyceryl ester by hydrogenation (152)



To a solution of 3-(2,5-dihydro-2,5-dimethoxyfuran-2-yl)propanoic acid polyglyceryl ester (0.46 g, 2.09 mmol) in 50 mL methanol, catalyst platinum on activated carbon [0.25 g, (5% Pt)] was added under argon atmosphere at room temperature. The solution was flushed five times with Ar using vacuum/Ar cycles. A balloon filled with hydrogen gas was attached to one of the necks of the flask. After evacuating the flask again the flask was flushed with hydrogen gas. The reaction mixture was stirred at room temperature for 1 day. The mixture was then filtered under vacuum and the filtrate was concentrated under reduced pressure to afford 3-(tetrahydro-2,5-dimethoxyfuran-2-yl)propanoic acid polyglyceryl ester (0.35 g) as a dark brown oil.

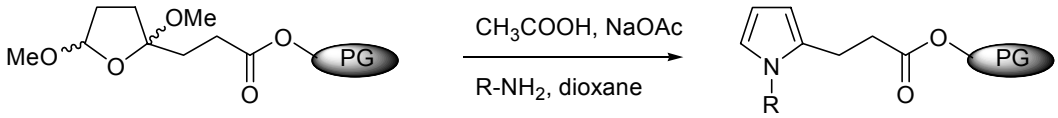
Conversion: quant., Yield: 77%

^{1}H NMR (400 MHz, CD_3OD) δ=1.8-2.6 (m, 2H, -$(CH_2)_4$), 3.18 (m, 3H, -OMe), 3.23 (m, 3H, -OMe), 3.32 (m, 3H, -OMe), 3.39 (m, 3H, -OMe), 3.50-4.00 (polyglycerol), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 5.08 (m, 1H, 5-H).

^{13}C NMR (100 MHz, CD_3OD) δ= 30.5 (-CH_2-), 30.6 (-CH_2-), 30.9 (-CH_2-), 31.2 (-CH_2-), 31.3 (-CH_2-), 31.4 (-CH_2-), 31.5 (-CH_2-), 31.8 (-CH_2-), 32.4 (-CH_2-), 33.04 (-CH_2-), 33.09 (-CH_2-), 52.6 (-OMe), 54.1 (-OMe), 54.9 (-OMe), 62.0-79.5 (polyglycerol), 104.2, 105.1, 105.7, 106.4, 110.1+110.2, 173.5 (-CO), 173.8 (-CO).

6.3.3 Experimental section for chapter 4.2.4

General procedure for the formation of *N*-substituted pyrrole polyglyceryl ester (151)



A solution of NaOAc (0.12 g, 1.57 mmol) in 20 mL of glacial acetic acid was placed in a round bottomed flask at room temperature. During stirring primary amine (2.35 mmol) was added to the solution. A solution of 3-(tetrahydro-2,5-dimethoxyfuran-2-yl)propanoic acid polyglyceryl ester (0.35 g, 1.57 mmol) in 10 mL dioxane was added slowly to the reaction mixture over 5 min. The reaction mixture was heated to 80°c for 2 h, during which time the solution turned dark brown to deep red in colour. The reaction mixture was concentrated in vacuo, and the resulted brown solid was dissolved in 10 mL $CHCl_3$. The solution was dialysed for 24 h in $CHCl_3$. After evaporation of the solvent a brown solid was obtained. Despite thorough drying of the products, they still contained some dioxane.

3-(1-Phenyl-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester (158)

Conversion: quant., Yield: 65%.

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.41-2-80 (m,-$(CH_2)_2$), 3.50-4.00 (polyglycerol), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 6.01 (m, 1H, 3-H), 6.15 (m, 1H, 4-H), 6.71 (1H, 5-H), 7.26-7.50 (m, 5H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=22.9 (-CH_2-), 33.3 (-CH_2-), 62.0-79.5 (polyglycerol), 107.0, 108.0, 115.4, 117.9, 120.0, 121.8, 123.9, 126.0, 128.6, 128.9, 129.3, 131.6, 138.8, 140.4, 178.5 (-CO).

3-(1-Benzyl-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester

Conversion: quant., Yield: 62%.

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.41-2-80 (m, -$(CH_2)_2$), 3.50-4.00 (polyglycerol), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 5.02 (2H, -CH_2Ph), 5.90 (1H, 3-H), 6.07 (1H, 4-H), 6.59 (1H, 5-H), 6.96 (2H, -Ph), 7.15-7.30 (m, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=23.9, 31.3, 53.3, 62.0-79.5 (polyglycerol), 103.9, 106.2, 107.4, 121.5, 126.6, 128.9, 138.4, 127.6, 107.0, 108.0, 115.4, 117.9, 120.0, 121.8, 123.9, 126.0, 128.6, 128.9, 129.3, 131.6, 138.8, 140.4, 173.1 (-CO).

3-(1-Butyl-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester

Conversion: quant., Yield: 60%.

^{1}H NMR (400 MHz, $CDCl_3$) δ=0.85-2-95 (m, (-$CH_2)_5$), 3.50-4.00 (polyglycerol), 3.79 (m, 2H, -CH_2), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 5.82 (1H, 3-H), 6.00 (1H, 4-H), 6.55 (1H, 5-H).

3-(1-(4-Iodophenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester

Conversion: quant., Yield: 70%

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.40-2-85 (m, $-CH_2)_2$), 3.50-4.00 (polyglycerol), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 6.00 (1H, 3-H), 6.14 (1H, 4-H), 6.66 (1H, 5-H), 7.02 (2H, -Ph), 7.73 (2H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=22.7, 33.6, 62.0-79.5 (polyglycerol), 91.2 (=C-I), 106.4 (C-3), 107.6 (C-4), 120.8, 126.9, 130.5, 137.4, 138.7, 171.1(-CO)

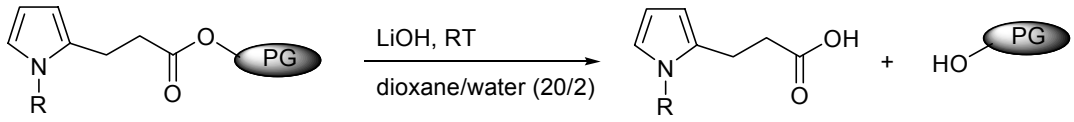
3-(1-(2-Iodophenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester

Conversion: quant., Yield: 70%

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.40-2-70 (m, $-CH_2)_2$), 3.50-4.00 (polyglycerol), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 5.99 (1H, 3-H), 6.17 (1H, 4-H), 6.54 (1H, 5-H), 7.10 (1H, -Ph), 7.39 (2H, -Ph), 7.88 (1H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=22.17, 33.6, 62.0-79.5 (polyglycerol), 99.3 (=C-I), 106.5 (C-3), 108.4 (C-4), 121.6, 129.3, 129.4, 130.3, 131.9, 139.8, 142.9, 171.1 (-CO).

General procedure for the cleavage of *N*-substituted pyrroles from polyglycerol support by base



To a solution of *N*-substituted pyrrole polyglyceryl ester (1.57 mmol) in 20 mL dioxane, an aqueous LiOH solution (o.13 g, 3.14 mmol, in 2 mL water) was added. The suspension was stirred at room temperature overnight. As the desired acid was in salt form, concentrated hydrochloric acid was added to the reaction mixture to acidify the solution to pH 3~4. Then 20 mL water was added and the solution was extracted with ethyl acetate (5x40 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by silicagel chromatography to furnish the *N*-substituted pyrrole.

3-(1-Phenyl-1*H*-pyrrol-2-yl)propanoic acid (160)

Yield: 55% , amount: 185 mg

Texture: Brown solid.

^{1}H NMR (400 MHz, CD_3OD) δ=2.46 (t, *J*=7.4 Hz, 2H, -CH_2), 2.82 (t, *J*=7.4 Hz, 2H, -CH_2), 6.02 (m, 1H, 3-H), 6.12 (t, *J*=3.1 Hz, 1H, 4-H), 6.72 (dd, *J*=2.9 Hz, 1.8 Hz, 1H, 5-H), 7.31-7.41 (m, 5H, -Ph).

^{13}C NMR (100 MHz, CD_3OD) δ=23.1 (-CH_2-), 34.4 (-CH_2-), 107.9, 109.0, 122.8, 127.2, 128.3, 130.3, 133.0, 141.7, 176.5 (-CO).

HR-MS (FAB): Theoretical 215.0946 $[M]^+$, found 215.0943.

R_f 0.30 (cyclohexane/EtOAc 2:1)

3-(1-Benzyl-1*H*-pyrrol-2-yl)propanoic acid (161)

Yield: 52%, amount: 186 mg

Texture: Light brown solid.

^{1}H NMR (400 MHz, CD_3OD) δ=2.48 (t, *J*=7.4 Hz, 2H, -CH_2), 2.72 (t, *J*=7.4 Hz, 2H, -CH_2), 5.10 (s, 1H, -CH_2Ph), 5.90 (m, 1H, 3-H), 6.03 (t, *J*=3.1 Hz, 1H, 4-H), 6.65 (dd, *J*=2.9 Hz, 1.8 Hz, 1H, 5-H), 6.98-7.31 (m, 5H, -Ph).

^{13}C NMR (100 MHz, CD_3OD) δ=22.5 (-CH_2-), 34.4 (-CH_2-), 51.0 (-CH_2Ph), 106.9, 107.9, 122.3, 127.4, 128.2, 129.6, 132.7, 140.3, 176.6 (-CO).

HR-MS (FAB): Theoretical 229.1103 $[M]^+$, found 229.1086.

R_f 0.30 (cyclohexane/EtOAc 2:1).

3-(1-Butyl-1*H*-pyrrol-2-yl)propanoic acid (162)

Yield: 50%, amount: 100 mg

Texture: Light brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ=0.94 (t, *J*=7.4 Hz, 3H, -CH_3), 1.34 (m, 2H, -CH_2), 1.70 (m, 2H, -CH_2), 2.73 (t, *J*=7.4 Hz, 2H, -CH_2), 2.86 (t, *J*=7.4 Hz, 2H, -CH_2), 3.80 (t, *J*=7.4 Hz, -NCH_2), 5.86 (m, 1H, 3-H), 6.06 (t, *J*=3.1 Hz, 1H, 4-H), 6.60 (dd, *J*=2.9 Hz, 1.8 Hz, 1H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$) δ=13.9 (-CH_3), 20.2 (-CH_2-), 21.4 (-CH_2-), 33.1 (-CH_2-), 33.6 (-CH_2-), 46.5 (-CH_2-), 105.3, 106.9, 120.6, 130.7, 178.1 (-CO).

HR-MS (FAB): Theoretical 195.1259 $[M]^+$, found 195.1243.

R_f 0.30 (cyclohexane/EtOAc 2:1).

3-(1-(2-Iodophenyl)-1*H*-pyrrol-2-yl)propanoic acid (162)

Yield: 65%, amount: 300 mg

Texture: Brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.50-2.65 (m, 4H, -$(CH_2)_4$), 6.08 (m, 1H, 3-H), 6.24 (t, *J*=3.1 Hz, 1H, 4-H), 6.60 (dd, *J*=2.9 Hz, 1.8 Hz, 1H, 5-H), 7.14 (ddd, *J*=9.1 Hz, 7.4 Hz, 1.8 Hz, 1H, -Ph), 7.32 (dd, *J*=7.8 Hz, 1.6 Hz, 1H, -Ph), 7.43 (dt, *J*=7.6 Hz, 1.4 Hz, 1H, -Ph), 7.93 (dd, *J*=7.8 Hz, 1.4 Hz, 1H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=21.9 (-CH_2), 33.4 (-CH_2), 99.3 (=C-I), 106.5, 108.4, 121.7, 129.2, 129.4, 130.3, 131.8, 139.8, 142.9 (=C-N), 178.0 (-CO).

HR-MS (FAB): Theoretical 340.9913 $[M]^+$, found 340.9940.

R_f 0.30 (cyclohexane/EtOAc 2:1).

3-(1-(4-Iodophenyl)-1*H*-pyrrol-2-yl)propanoic acid (163)

Yield: 65%, 300 mg

Texture: Brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.60 (t, *J*=7.4 Hz, 2H, -CH_2), 2.85 (t, *J*=7.4 Hz, 2H, -CH_2), 6.08 (m, 1H, 3-H), 6.21 (t, *J*=3.1 Hz, 1H, 4-H), 6.72 (dd, *J*=2.9 Hz, 1.8 Hz, 1H, 5-H), 7.05 (d, *J*=8.6 Hz, 2H, -Ph), 7.76 (d, *J*=8.6 Hz, 2H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=22.0 (-CH_2-), 33.2 (-CH_2-), 92.5 (=C-I), 107.6, 108.8, 122.2, 128.1, 131.6, 138.6, 139.9, 177.4 (-CO).

HR-MS (FAB): Theoretical 341.9991 $[M+H]^+$, found 341.9983.

R_f 0.30 (cyclohexane/EtOAc 2:1).

6.3.4 Experimental section for chapter 4.2.5

General procedure for Suzuki coupling with 3-(1-(4-iodophenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester (174)

To a solution of 3-(1-(4-iodophenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester (0.39 g, 1.09 mmol) in 20 mL DMF, boronic acid (1.63 mmol) and 0.36 g K_2CO_3 (2.72 mmol) were added under argon atmosphere at room temperature. The solution was flushed 3 times with Ar using vacuum/Ar cycles. 12 mg of $Pd(PPh_3)_4$ (0.011 mmol, 1 mol %) were added to the reaction mixture and again purged with argon. The reaction mixture was stirred and heated to 90°C for 18 h. DMF was removed in vacuo and the resulting brown solid was dissolved in 50 mL chloroform. The reaction mixture was filtered through celite and concentrated. Dialysis in chloroform was carried out on the crude product for 24 h. After evaporation of the solvent the product was dried in high vacuum. Despite thorough drying of the products, they still contained some chloroform.

3-(1-(4-Biphenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester

Conversion: quant., Yield: 70%

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.40-2-90 (m,-$(CH_2)_2$), 3.20-4.00 (polyglycerol), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 6.02 (1H, 3-H), 6.15 (1H, 4-H), 6.71 (1H, 5-H), 7.26-7.65 (m, 9H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=22.3 (-CH_2-), 29.9 (-CH_2-), 62.0-79.5 (polyglycerol), 107.2, 108.4, 122.2 126.5, 127.2, 127.8, 128.0, 129.1, 131.9, 139.4, 140.4 (=C-N), 172.8 (-CO).

3-(1-(3´-Nitrobiphenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester

Conversion: quant., Yield: 60%

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.50-2-90 (m,-$(CH_2)_2$), 3.20-4.00 (polyglycerol), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 6.04 (1H, 3-H), 6.19 (1H, 4-H), 6.75 (1H, 5-H), 7.42 (-Ph), 7.66 (-Ph), 7.86 (-Ph), 8.02 (-Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=21.8, 30.4, 62.0-79.5 (polyglycerol), 107.8, 108.3, 121.5, 122.0, 126.3, 127.7, 129.0, 129.6, 131.3, 137.2, 140.0 (=C-N), 141.4, 148.4 (=C-NO_2), 172.9 (-CO).

3-(1-(3´,5´-Bistrifluorobiphenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester

Conversion: quant., Yield: 60%

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.50-2-90 (m,-$(CH_2)_2$), 3.20-4.00 (polyglycerol), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 6.03 (1H, 3-H), 6.18 (1H, 4-H), 6.75 (1H, 5-H), 7.39-7.95 (m, -Ph), 8.18 (1H, -Ph), 8.43 (1H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=22.2, 31.2, 62.0-79.5 (polyglycerol), 107.5, 108.7, 119.3, 121.3, 122.0, 126.7, 127.2, 128.2, 131.7, 132.1, 132.4, 137.1, 140.6 (=C-N), 141.4, 142.3, 172.5 (-CO).

General procedure for the cleavage of Suzuki coupled product form polyglycerol support by base:

To a solution of Suzuki coupled *N*-substituted pyrrole polyglyceryl ester (1.09 mmol) in 20 mL dioxane, an aqueous LiOH solution (0.09 g, 2.18 mmol in 2 mL water) was added. The suspension was stirred at room temperature overnight. As the desired acid was in salt form, concentrated hydrochloric acid was added to the reaction mixture to acidify the solution to pH 3~4. Then 20 mL water was added and the solution was extracted with ethyl acetate (5x40 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by silicagel chromatography to furnish the *N*-substituted pyrroles.

3-(1-(4-Biphenyl)-1*H*-pyrrol-2-yl)propanoic acid (176)

Yield: 60%, amount: 117 mg

Texture: Brown solid

^{1}H NMR (400 MHz, CD_3OD) δ=2.00-2.45 (m, 4H, -$(CH_2)_4$), 5.82 (m, 1H, 3-H), 6.05 (t, *J*=3.1 Hz, 1H, 4-H), 6.59 (dd, *J*=2.9 Hz, 1.8 Hz, 1H, 5-H), 7.04-7.56 (m, 9H, -Ph).

^{13}C NMR (100 MHz, CD_3OD) δ=22.8 (-CH_2-), 34.1 (-CH_2-), 107.2, 109.0, 123.0, 128.2, 129.2, 129.3, 129.4, 129.6, 129.9, 131.8, 133.6, 138.9, 139.9, 140.7, 176.4 (-CO).

HR-MS (FAB): Theoretical 291.1259 $[M]^+$, found 291.1248.

R_f 0.30 (cyclohexane/EtOAc 2:1)

3-(1-(3´-Nitrobiphenyl)-1*H*-pyrrol-2-yl)propanoic acid (177)

Yield: 60%, amount: 120 mg

Texture: Light yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ=2.51 (t, *J*=7.4 Hz, 2H, -CH_2), 2.90 (t, *J*=7.4 Hz, 2H, -CH_2), 6.07 (m, 1H, 3-H), 6.17 (t, *J*=3.1 Hz, 1H, 4-H), 6.80 (dd, *J*=2.9 Hz, 1.8 Hz, 1H, 5-H), 7.48 (d, *J*=8.6 Hz, 2H, -Ph), 7.72 (t, *J*=8.0 Hz, 1H, -PhNO_2), 7.84 (d, *J*=8.6 Hz, 2H, -Ph), 8.10 (ddd, *J*=7.6 Hz, 1.9 Hz, 1.2 Hz, 1H, -PhNO_2), 8.24 (ddd, *J*=7.6 Hz, 2.1 Hz, 1.2 Hz, 1H, -PhNO_2), 8.53 (t, *J*=1.9 Hz, 1H, -PhNO_2).

^{13}C NMR (100 MHz, CD_3OD) δ=23.0 (-CH_2-), 34.2 (-CH_2-), 108.2, 109.2, 122.3, 122.6, 123.0, 127.5, 128.9, 131.0, 132.9, 133.9, 138.6, 141.7, 150.0, 176.2 (-CO).

HR-MS (FAB): Theoretical 336.1110 $[M]^+$, found 336.1138.

R_f 0.20 (cyclohexane/EtOAc 2:1).

3-(1-(3´,5´-Bistrifluorobiphenyl)-1*H*-pyrrol-2-yl)propanoic acid (178)

Yield: 62%, amount: 112 mg

Texture: Light yellow solid.

^{1}H NMR (400 MHz, CD_3OD) δ=2.51 (t, *J*=7.6 Hz, 2H, -CH_2), 2.90 (t, *J*=7.6 Hz, 2H, -CH_2), 6.06 (m, 1H, 3-H), 6.17 (t, *J*=3.1 Hz, 1H, 4-H), 6.80 (dd, *J*=2.9 Hz, 1.8 Hz, 1H, 5-H), 7.50 (d,

J=8.6 Hz, 2H, -Ph), 7.85 (d, *J*=8.6 Hz, 2H, -Ph), 7.97 (brs, 1H, -PhCF$_3$), 8.25 (brs, 2H, -PhCF$_3$).

^{13}C NMR (100 MHz, CD$_3$OD) δ=23.3 (-CH$_2$-), 34.5 (-CH$_2$-), 108.5, 109.5, 122.0, 122.8, 123.5, 126.2, 127.8, 128.4, 129.3, 133.1, 133.2, 133.5, 138.0, 142.3, 144.0, 176.5 (-CO).

HR-MS (FAB): Theoretical 427.1007 [M]$^+$, found 427.1012.

R_f 0.20 (cyclohexane/EtOAc 2:1).

6.3.5 Experimental section for chapter 4.2.6

General procedure for Sonogashira coupling with 3-(1-(4-iodophenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester(179)

A two-neck flask was charged with 7 mg of PdCl$_2$(PPh$_3$)$_2$ (0.011 mmol, 1 mol %) and purged with argon. 10 mL Et$_3$N were added to it at room temperature. The solution was flushed 3 times with Ar using vacuum/Ar cycle. A solution of 3-(1-(4-iodophenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester (0.39 g, 1.09 mmol) in 20 mL dioxane, alkyne (2.18 mmol) and 11 mg of CuI (0.021 mmol) were added to the solution under argon atmosphere. The reaction mixture was stirred and heated to 60°C for 18 h. The solvents were removed in vacuo and the resulting brown solid was dissolved in 50 mL chloroform. The reaction mixture was filtered and concentrated. Dialysis in chloroform was carried out on the crude product. After evaporation of the solvent the product was dried in high vacuum. Despite thorough drying of the products, they still contained some chloroform and dioxane.

3-(1-(4-(3-Hydroxy-3-methylbut-1-ynyl)phenyl)-1*H*-pyrrol-2-yl)propanoicacid polyglyceryl ester

Conversion: quant., Yield: 62%

^{1}H NMR (400 MHz, CDCl$_3$) δ=1.57 (-CH$_3$), 1.80 (-OH), 2.40-2-90 (m,-(CH$_2$)$_2$), 3.20-4.00 (polyglycerol), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 6.00 (1H, 3-H), 6.14 (1H, 4-H), 6.67 (1H, 5-H), 7.19 (2H, -Ph), 7.43 (2H, -Ph).

^{13}C NMR (100 MHz, CDCl$_3$) δ=22.6 (-CH$_2$-), 30.4 (-2CH$_3$), 35.9 (-CH$_2$-), 62.0-79.5 (polyglycerol), 66.0 (-C-OH), 80.0 (≡C-), 94.2 (≡C-), 106.4, 107.5, 120.8, 124.7, 130.5, 131.5, 138.6, 171.0 (-CO).

3-(1-(4-(3-(Dimethylamino) prop-1-ynyl) phenyl) -1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester

Conversion: quant., Yield: 60%

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.35 (-NMe_2), 2.40-2-90 (m,-$(CH_2)_2$), 3.20-4.00 (polyglycerol), 3.25 (-CH_2-N), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 5.99 (1H, 3-H), 6.13 (1H, 4-H), 6.67 (1H, 5-H), 7.20 (2H, -Ph), 7.46 (2H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=22.7 (-CH_2-), 32.2 (-CH_2), 43.3 (-2CH_3), 47.6 (-CH_2-N), 62.0-79.5 (polyglycerol), 83.5 (≡C-), 84.6 (≡C-), 106.3, 107.5, 120.8, 121.1, 124.8, 131.6, 131.5, 138.6, 171.3 (-CO).

3-(1-(4-(2-(pyridine-2-yl)ethynyl)phenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester

Conversion: quant., Yield: 60%

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.40-2-90 (m,-$(CH_2)_2$), 3.20-4.00 (polyglycerol), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 5.98 (1H, 3-H), 6.11 (1H, 4-H), 6.66 (1H, 5-H), 7.15-7.65 (7H, -Ph), 8.55 (1H, -Py).

^{13}C NMR (100 MHz, $CDCl_3$) δ=22.6 (-CH_2-), 32.2 (-CH_2), 62.0-79.5 (polyglycerol), 87.5 (≡C-), 88.4 (≡C-), 106.6, 107.7, 120.0, 120.8, 122.0, 124.7, 126.3, 130.5, 131.9, 135.3, 139.4, 142.0, 149.1, 171.2 (-CO).

3-(1-(4-(2-Phenylethynyl)phenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester

Conversion: quant., Yield: 70%

^{1}H NMR (400 MHz, $CDCl_3$) δ=2.40-2-90 (m,-$(CH_2)_2$), 3.20-4.00 (polyglycerol), 4.10–4.40 (polyglycerol terminal units), 5.00–5.20 (polyglycerol linear units), 6.03 (1H, 3-H), 6.16 (1H, 4-H), 6.71 (1H, 5-H), 7.33 (4H, -Ph), 7.52 (4H, -Ph).

^{13}C NMR (100 MHz, $CDCl_3$) δ=21.0 (-CH_2-), 32.2 (-CH_2), 62.0-79.5 (polyglycerol), 87.5 (≡C-), 89.3 (≡C-), 106.4, 107.5, 120.8, 121.9, 124.8, 127.3, 130.6, 131.4, 138.7, 171.1 (-CO).

General procedure for the cleavage of Sonogashira coupled product form polyglycerol support by base:

To a solution of Sonogashira coupled *N*-substituted pyrrole polyglyceryl ester (1.09 mmol) in 20 mL dioxane, an aqueous LiOH solution (0.09 g, 2.18 mmol in 2 mL water) was added. The suspension was stirred at room temperature overnight. As the desired acid was in salt form, concentrated hydrochloric acid was added to the reaction mixture to acidify the solution to pH 3~4. Then 20 mL water was added and the solution was extracted with ethyl acetate (5x40 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by silicagel chromatography to furnish the *N*-substituted pyrroles.

3-(1-(4-(3-Hydroxy-3-methylbut-1-ynyl)phenyl)-1*H*-pyrrol-2-yl)propanoic acid (181)

Yield: 65%, amount: 200 mg

Texture: Light red solid

^{1}H NMR (400 MHz, CD_3OD) δ=1.57 (s, 6H, -$(CH_3)_2$), 1.98 (brs, 1H, -OH), 2.46 (t, *J*=7.6 Hz, 2H, -CH_2), 2.83 (t, *J*=7.6 Hz, 2H, -CH_2), 6.03 (m, 1H, 3-H), 6.13 (t, *J*=3.1 Hz, 1H, 4-H), 6.71 (dd, *J*=2.9 Hz, 1.8 Hz, 1H, 5-H), 7.27 (d, *J*=8.6 Hz, 2H, -Ph), 7.48 (d, *J*=8.6 Hz, 2H, -Ph).

^{13}C NMR (100 MHz, CD_3OD) δ=23.1 (-CH_2-), 31.6 (-$CH_3)_2$, 34.3 (-CH_2-), 65.8 (-C-OH), 81.7 (≡C-), 96.1 (≡C-), 108.4, 109.4, 122.7, 123.3, 126.9, 132.9, 133.0, 133.5, 141.3, 176.4 (-CO).

HR-MS (FAB): Theoretical 298.1443 $[M+H]^+$, found 298.1418.

R_f 0.20 (cyclohexane/EtOAc 1:2)

3-(1-(4-(3-(Dimethylamino)prop-1-ynyl)phenyl)-1*H*-pyrrol-2-yl)propanoic acid (182)

Yield: 60%, amount: 210 mg

Texture: Bright yellow solid

^{1}H NMR (400 MHz, CD_3OD) δ=2.37-2.45 (m, 8H, -$(CH_3)_2$ and –CH_2), 2.83 (t, *J*=7.6 Hz, 2H, -CH_2), 3.57 (brs, H, -CH_2N), 6.04 (m, 1H, 3-H), 6.12 (t, *J*=3.1 Hz, 1H, 4-H), 6.72 (dd, *J*=2.9 Hz, 1.8 Hz, 1H, 5-H), 7.32 (d, *J*=8.6 Hz, 2H, -Ph), 7.52 (d, *J*=8.6 Hz, 2H, -Ph).

^{13}C NMR (100 MHz, CD_3OD) δ=24.5 (-CH_2-), 34.3 (-CH_2-), 44.1 (-CH_3)$_2$, 48.2 (-CH_2-), 84.5 (≡C-), 86.2 (≡C-), 108.3, 109.4, 122.3, 122.7, 127.0, 133.5, 134.2, 141.8, 176.4 (-CO).

HR-MS (FAB): Theoretical 297.1603 $[M+H]^+$, found 297.1576.

R_f 0.20 (MeOH/EtOAc 1:2)

3-(1-(4-(2-(Pyridine-2-yl)ethynyl)phenyl)-1*H*-pyrrol-2-yl)propanoic acid (183)

This compound contained an impurity which could not be removed even after second column chromatography.

Yield: 65%, amount: 212 mg, 30% impurity

Texture: Yellow solid

^{1}H NMR (400 MHz, CD_3OD) δ=2.45 (t, *J*=7.6 Hz, 2H, -CH_2), 2.86 (t, *J*=7.6 Hz, 2H, -CH_2), 6.06 (m, 1H, 3-H), 6.14 (t, *J*=3.1 Hz, 1H, 4-H), 6.75 (dd, *J*=2.9 Hz, 1.8 Hz, 1H, 5-H), 7.39 (d, *J*=8.6 Hz, 2H, -Ph), 7.42 (m, 1H, -Py), 7.66 (td, *J*=7.8 Hz, 0.9 Hz, 1H, Py), 7.69 (d, *J*=8.6 Hz, 2H, -Ph), 7.87 (dt, *J*=7.8 Hz, 1.8 Hz, 1H, Py), 8.55 (ddd, *J*=5.6 Hz, 1.8 Hz, 0.9 Hz, 1H, Py).

^{13}C NMR (100 MHz, CD_3OD) δ=26.5 (-CH_2-), 32.0 (-CH_2-), 89.5 (≡C-), 89.9 (≡C-), 108.6, 109.6, 121.7, 122.4, 124.7, 127.1, 128.7, 133.9, 138.6, 142.5, 143.8, 150.6, 175.4 (-CO).

HR-MS (FAB): Theoretical 317.3612 $[M+H]^+$, found 317.1281.

R_f 0.20 (cyclohexane/EtOAc 1:2).

6.3.6 Experimental section for chapter 4.2.7

Heck coupling with 3-(1-(4-iodophenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester (190)

$NaHCO_3$ (0.22 g, 2.72 mmol), tetrabutylammonium bromide (0.35 g, 1.09 mmol) and 10 mL dry DMF were treated together with 4Å molecular sieves (10 pellets) under argon atmosphere in a two neck 100 mL flask at room temperature. The mixture was stirred for 15 min at room temperature. A solution of 3-(1-(4-iodophenyl)-1*H*-pyrrol-2-yl)propanoic acid

polyglyceryl ester (0.39 g, 1.09 mmol) in 20 mL DMF and styrene (0.24 mL, 2.18 mmol) were added respectively to the reaction mixture under argon atmosphere and the reaction mixture was stirred another 15 min. 12.2 mg (5 mol %) $Pd(OAc)_2$ were added to the brown reaction mixture and the resulting brown mixture was stirred at 90°C for 24 h. The polymer supported crude product was purified by dialysis in chloroform. Even after dialysis for 24 h, the reaction mixture still contained some black particles and therefore the NMR of the crude reaction mixture was not clear.

Cleavage of the Heck coupled product

To a solution of 3-(1-(4-styrylphenyl)-1*H*-pyrrol-2-yl)propanoic acid polyglyceryl ester (1.09 mmol) in 20 mL dioxane, an aqueous LiOH solution (0.09 g, 2.18 mmol in 2 mL water) was added. The suspension was stirred at room temperature overnight. As the desired acid was in salt form, concentrated hydrochloric acid was added to the reaction mixture to acidify the solution to pH 3~4. Then 20 mL water were added and the solution was extracted with ethyl acetate (5x40 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified by silicagel chromatography to furnish 0.20 g (60%) of 3-(1-(4-styrylphenyl)-1*H*-pyrrol-2-yl)propanoic acid.

3-(1-(4-Styrylphenyl)-1*H*-pyrrol-2-yl)propanoic acid (191)

Yield: 0.20 g (60%)

Texture: Bright yellow solid

^{1}H NMR (400 MHz, CD_3OD) δ=2.49 (t, *J*=7.6 Hz, 2H, -CH_2), 2.86 (t, *J*=7.6 Hz, 2H, -CH_2), 6.04 (m, 1H, 3-H), 6.13 (t, *J*=3.1 Hz, 1H, 4-H), 6.75 (dd, *J*=2.9 Hz, 1.8 Hz, 1H, 5-H), 7.23 (s, -2H), 7.30 (m, -5H, Ph), 7.56 (d, *J*=8.6 Hz, 2H, -Ph), 7.66 (d, *J*=8.6 Hz, 2H, -Ph).

^{13}C NMR (100 MHz, CD_3OD) δ=22.0 (-CH_2-), 33.3 (-CH_3)$_2$, 106.9, 107.9, 121.5, 126.1, 126.4, 127.1, 127.3, 127.6, 128.5, 129.4, 131.9, 136.8, 137.4, 139.6, 175.3 (-CO).

HR-MS (FAB): Theoretical 317.1416 $[M]^+$, found 317.1393.

R_f 0.20 (cyclohexane/EtOAc 1:2).

Abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
brs	broad singlet
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublet
ddd	doublet of doublet of doublet
DIC	diisopropyl carbodiimide
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
dt	doublet of triplet
EI	electron impact
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atom bombardment
GC-MS	gas chromatography-mass spectroscopy
HOBT	1-Hydroxybenzotriazol
HRMS	highresolution massspectroscopy
MeOH	methanol
mmol	millimole
NMO	*N*-methyl-morpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
R*f*	retardation factor (TLC)
t	tertiary
TBAF	tetrabutylammonium fluoride
TBDMSCl	*tert*-butyldimethylsilylchloride
THF	tetrahydrofuran
TMS	trimethylsilane resp. trimethylsilyl-
t_r	retention time

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