Building Blocks for 2-Deoxy-L-Nucleosides

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by

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Referee: Prof. Dr. M.P. Schneider

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I would like to thank Professor Schneider for the interesting subject he chose for my thesis, for daily discussions of my work and the importance of my targets and for having taught me what you will never find in any book: the way to think!

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…there is excitement,

adventure, and challenge,

and there can be great art,

in Organic Synthesis…

R.B. Woodward, 1956.

Ai miei genitori

Summary

The major topic of this work was the development of novel synthetic routes towards enantiomerically pure building blocks for 2-deoxy-L-ribose and non-natural L-nucleosides derived thereof, with their therapeutic importance outlined in Chapter 1.

In Chapter 2 the synthesis of enantiomerically pure *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**) is described, which we chose as chiral starting material for the synthesis of 2-deoxy-L-ribose. **1** was obtained from L-ascorbic acid in 5 steps and 26% overall yield. As an alternative **1** can also be obtained from *R*-(-)-benzylglycidol by either using $PhSeCH_2CO_2H$ (2 steps, 61% overall yield) or $PhSCH_2CO_2H$ (3 steps, 35% overall yield).

In Chapter 3 the synthesis of 2-deoxy-L-ribose and building blocks derived thereof starting from **1** is described. We were able to prepare 2-deoxy-L-ribose following two different routes:
The first route is based on previous experiments described by Fleming *et al.* related to the diastereoselective addition of silyl cuprate reagents to Michael systems, and to the fact that the silyl functions in the resulting derivatives can be transformed into the corresponding hydroxy groups with retention of configuration. We were able to synthesize 2-deoxy-L-ribose (4 steps, 28% overall yield from **1**) and related building blocks in enantiomerically pure form.
The second route involves a) dihydroxylation of **1**, b) selective protection of the 2-OH group and c) selective removal of this function. This way 2-deoxy-L-ribose was obtained from **1** in 5 steps with an overall yield of 18%.
In comparing the two routes we feel that the dihydroxylation route has several advantages in using a) simpler procedures, b) commercially available reagents and c) being faster. The only remaining drawback is the requirement for one additional step and a lower overall yield (18%) as compared to the silyl based procedure (28%). This is, in our opinion, more than compensated by the rapid and facile procedure.

In Chapter 4 the synthesis of two selected 2-deoxy-L-nucleosides is described. The Vorbrüggen procedure was used in the case of L-thymidine and the KI catalyzed procedure in the case of 2-deoxy-L-adenosine. In order to avoid equilibration between the pyranoside and furanoside forms of the free sugar, the 5-*O*-benzyl protected derivative **47** was employed. In order to demonstrate the usefulness of our building block having the backbone of 2-deoxy-L-ribose, we synthesized L-thymidine - a pyrimidine L-nucleoside- and 2-deoxy-L-adenosine, a purinic nucleoside. L-thymidine and 2-deoxy-L-adenosine were obtained in 48% and 30% overall yield, respectively. The major and unresolved remaining problem is the lack of diastereoselectivity in the coupling reactions leading to mixtures of α,β-anomers of the final nucleosides.

In Chapter 5 the instability of δ-lactones towards acid catalysis is investigated. The enantiomerically pure (≥98% ee) *R*-(+)-6-methyl-tetrahydro-pyran-2-one (**87**) was prepared *via* TFA catalyzed cyclization of the corresponding acid. It was observed that this δ-lactone converts into an equilibrium mixture with its trimer (**90**) (monomer/trimer 20:80) corresponding to a $\Delta G \cong -0.8$ kcal mol^{-1} if traces of TFA are still present in the final product. The transformation can be followed by ^1H and ^{13}C-NMR. The structure of **90** was established by chemical correlation with the monomer and its molecular weight determined *via* its colligative properties. *p*-TsOH in contrast was shown to be a highly suitable catalyst for such cyclizations leading to pure and stable δ-lactones.

Contents

Introduction

1 Overview

One of the most exciting developments in nucleic acid chemistry has been the discovery of remarkably efficient routes towards the synthesis of DNA and RNA sequences[1]. These advancements allow for the production of any desired natural sequence as well as sequences having virtually any modification in the basic nucleotide structure. Many of these oligonucleotide analogs, particularly those having phosphate and sugar modifications, are important not only for structural and biological studies but also for the development of new therapeutic agents. Of particular importance in this regard are oligonucleotide analogs that interact selectively with RNA (the "antisense" strategy)[2], double-stranded DNA (the "antigene" strategy)[3], or peptide sequences (the "sense" strategy)[4].

The term nucleoside was originally applied to ribose derivatives of purines that can be isolated from an alkaline RNA hydrolysate. Later, this name was given to all purine and pyrimidine *N*-glycosides of D-ribose and 2-deoxy-D-ribose. Today, this term refers to all natural or synthetic compounds which consist of a heterocyclic nitrogen-containing base (aglycon) and a carbohydrate residue (glycon). The nitrogen atom (*N*-nucleoside) or carbon atom (*C*-nucleoside) of the heterocycle is linked to the anomeric carbon atom of the sugar residue. Ribonucleosides and deoxyribonucleosides are obtained from naturally occurring RNA and DNA by enzymatic or chemical hydrolysis. Most nucleosides are stable within a wide pH range. However, under strongly acidic or alkaline conditions at elevated temperature cleavage of the *N*-glycosidic bond may occur.

The natural purine nucleosides are adenosine, deoxyadenosine, guanosine, and deoxyguanosine. The natural pyrimidine nucleosides are cytidine, deoxycytidine, thymidine, and uridine, all of them carrying the nucleobases in the β-orientation on the anomeric center (Figure 1.1).

A limited number of nucleosides in the α-D configuration (e.g. 5,6-dimethylbenzylimidazole-α-D-ribofuranoside of vitamin B_{12}) can be isolated from natural substances.

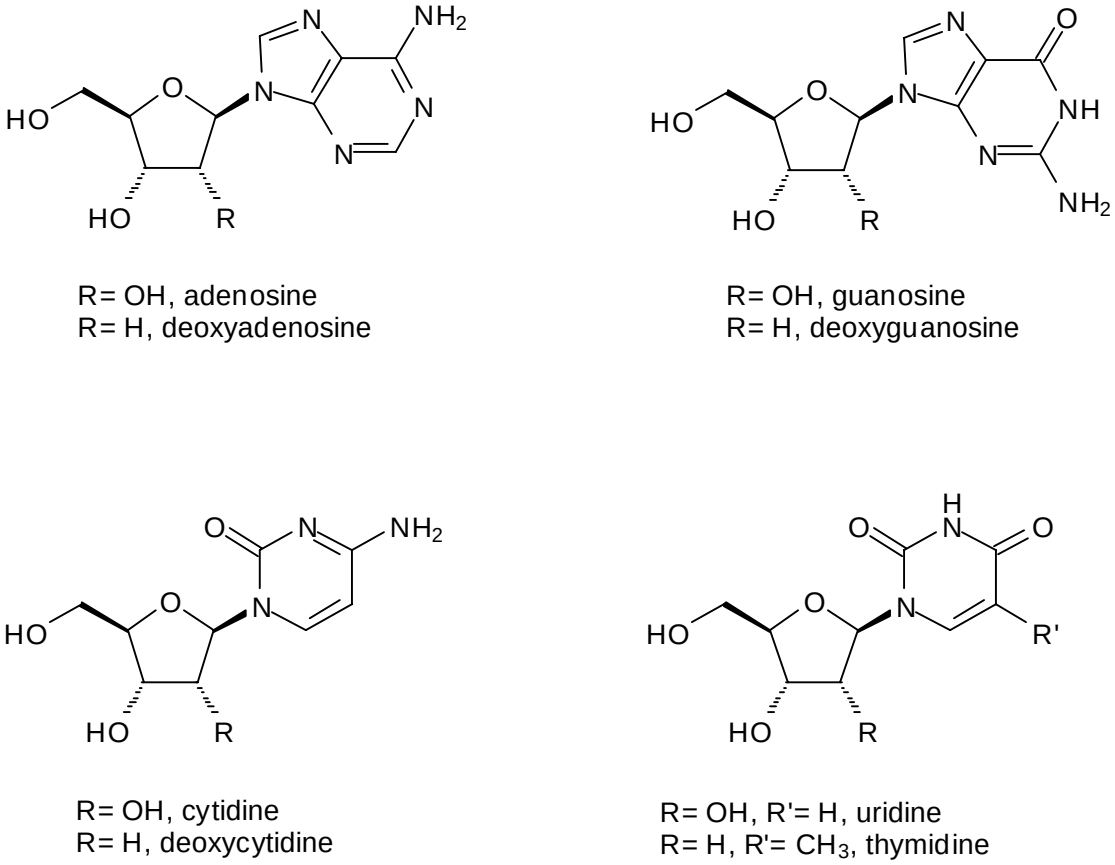


Figure 1.1: Structures of the natural nucleosides present in DNA and RNA.

L-Nucleosides are the enantiomers of the natural nucleosides which have an inverted configuration at all chiral centers. By analogy with the natural D-nucleosides, the aglycon moiety is designated to be β-oriented if it is *cis* to the 4'-hydroxymethyl group of the sugar moiety (Figure 1.2).

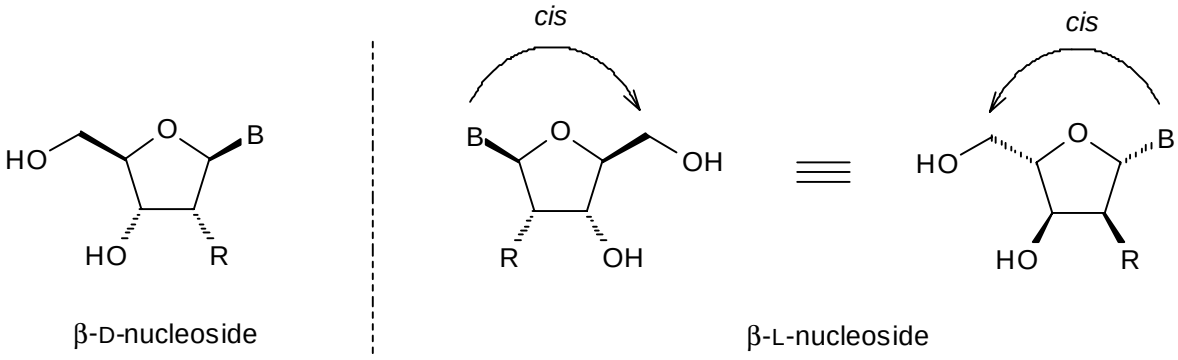
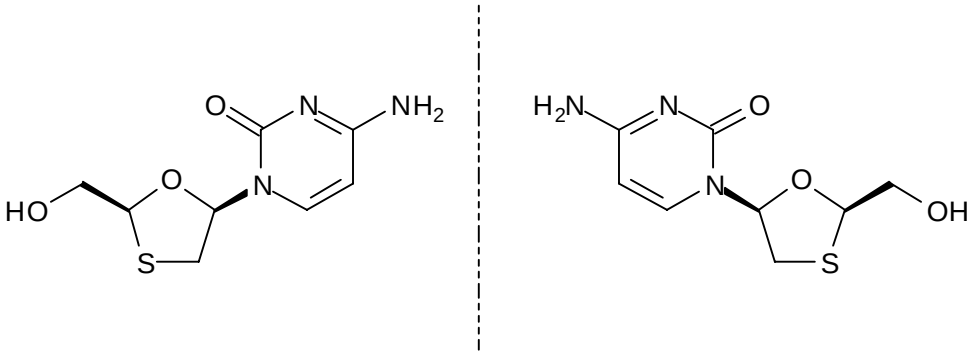


Figure 1.2: Nomenclature of nucleoside enantiomers.

Enzyme catalyzed reactions are normally highly stereoselective and frequently act only on one enantiomer. This may be one possible reason why it took so long to pay attention to L-nucleosides for their use in therapy. It was simply assumed that optically active compounds resembling natural nucleosides would be invariably more active than the unnatural L-enantiomers. Belleau *et al.*[5] first described the synthesis and anti-HIV activity of an unusual nucleoside analogue, racemic (±)-2',3'-dideoxy-3'-thiacytidine (BCH-189). Subsequently, it was - rather surprisingly - discovered that the L-isomer of BCH-189 (3TC) was more potent and less toxic than its D-isomer[6] (Figure 1.3). Since then, a number of L-nucleoside analogs have been synthesized and were biologically evaluated.



(+)-BCH-189 (-)-3TC (lamivudine)

Figure 1.3: 3TC, the first L-nucleoside with anti-HIV activity.

However, the most surprising aspect was the fact that in some instances cellular kinases are able to phosphorylate L-nucleosides to their triphosphates, and thereby induce various biological activities.

With the exception of optical rotation the physical and most of the chemical properties of L-nucleosides are identical with those of the D-counterparts. However, their pharmacological properties can differ for each isomer.

The origin of these differences may be:

- Different modes of nucleoside transport into the cells
- Anabolic and catabolic enzymes which act on these compounds
- Different interactions with the target enzymes (viral, cellular)

1.1 Anticancer activity of L-nucleosides

Several different therapies are available for the treatment of cancer. Some of the most common include surgery, radiation and chemotherapy. However, none of these treatments can be considered a true cure, as all of them have shortcomings which make them unsuitable for treating certain types of cancer. For example, surgery, which is the oldest and most widely used approach at this stage, is quite effective in treating some cancers but cannot be used to treat tumors that are attached to vital organs nor tumors that have metastasized widely throughout the body. Radiation exploits the sensitivity of dividing cells to X-rays, but it is also not effective in treating metastasized tumors, which are the most common cause of cancer death[7]. Both surgery and radiation therapy can be effective in treating localized disease, but the frequent occurrence of metastases means that some form of systemic therapy is needed to increase the chances of a cure[8].

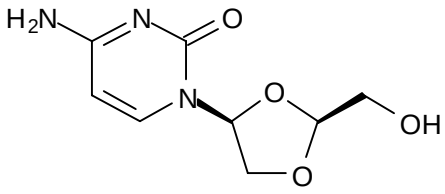
Chemotherapy is systemic and can therefore be used against metastasized tumors. Chemotherapy aims to target the differences between normal and cancer cells and therefore to achieve selective toxicity. However, available chemotherapeutic drugs often display severe side effects. This is due to incomplete selectivity since the differences between normal and cancer cells are often relatively subtle[7].

There are several classes of chemotherapeutic drugs. They include antimetabolites, such as fluorouracil and methotrexate, topoisomerase inhibitors, such as doxorubicin and alkylating agents such as cyclophosphamide and chlorambucil. Many of these drugs interfere with tumor cell replication, and especially target rapidly dividing cells. All rapidly dividing cells require abundant supplies of deoxythymidylate for DNA synthesis. This makes them particulary vulnerable to inhibition of dTMP synthesis. Inhibitors of thymidylate synthesis and dihydrofolate reductase prevent uncontrolled cell proliferation by blocking its production and hence DNA replication.

It has been shown that cellular membrane transport systems used in the uptake of sugars, amino acids, and nucleosides frequently function at higher capacity in transformed cells. Moreover the rate of DNA and RNA production as well as protein synthesis increase in cells undergoing rapid proliferation.

Until recently, it was believed that L-isomers of nucleosides could not be effective anti-cancer and anti-viral drugs as they would not be recognized by the cellular enzymes

responsible for their transport and activation[9]. However, a study by Casillas *et al.*[10] showed that L-adenosine was a substrate for a transporter expressed in chromaffin tissue (homogeneous neural cell population). Today there is a growing body of evidence that enzymes involved in nucleoside metabolism that lack enantioselectivity with respect to D- and L-nucleosides are more common than was previously believed[11]. The L-nucleoside analogue, L-(-)-dioxolane cytidine (β-L-(-)-2',3'-dideoxy-3'-oxacytidine), in addition to having potent anti-HBV and anti-HIV activity is also extremely cytotoxic (Figure 1.4).



β-L-dioxolane cytidine

Figure 1.4: β-L-dioxolane cytidine, an anticancer agent.

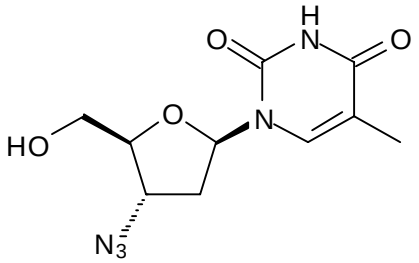
When its anti-cancer potential was evaluated in comparison to arabinoside cytosine -the most effective drug clinically available for the treatment of acute leukemia- the L-nucleoside was found to be effective against both solid and lymphoid tumors. This compound was a good substrate for replicative and repair DNA polymerases but resistant to inactivation by cytidine deaminase, which increased its effectiveness[9]. Toxicity experiments indicated that very high doses of the drug were well tolerated by mice[12]. All these factors may contribute to a greater efficacy of this compound in treating some types of tumors in comparison to currently available antitumor agents[13]. L-(-)-dioxolane cytidine is now at the stage of clinical trials.

1.2 Antiviral activity of L-nucleosides

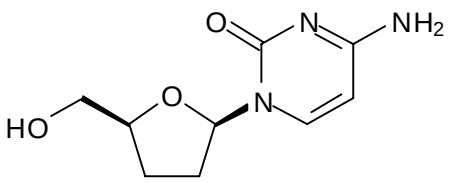
Since the emergence of HIV, a number of nucleoside analogs with anti-HIV and anti-HBV activity have been synthesized. This antiviral activity is generally associated with one of the enantiomers. Interestingly, some unnatural L-nucleosides are more potent in this

respect than their natural D-counterparts. Biochemical studies suggest that among initial enzymes involved in the phosphorylation of the nucleosides, cellular deoxycytidine kinase (dCK) lacks stereoselectivity and often can phosphorylate both enantiomers.

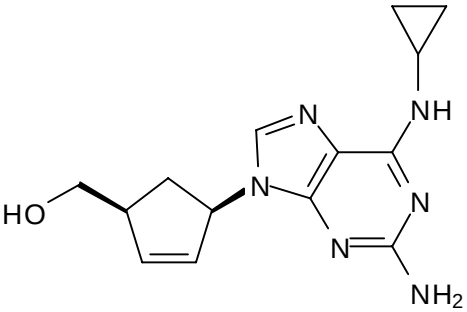
The mode of action of L-nucleosides as antiviral agent has been found to be similar to those of D-nucleosides; their intracellular phosphorylation to 5'-triphosphates inhibits the viral DNA polymerase with the resulting chain terminations of the viral DNA[14]. However, L-nucleosides exhibit different substrate specificities towards catabolizing enzymes, such as deoxycytidine deaminase and adenosine deaminase[15]. This property of L-nucleosides may be related to their enhanced potency as anti-HIV and anti-HBV agents.



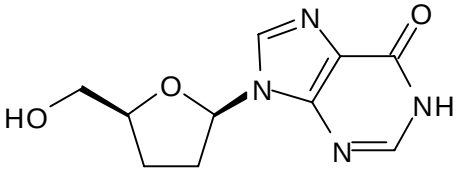
AZT (Glaxo Wellcome)



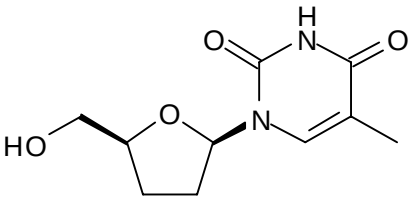
ddC (Hoffman La Roche)



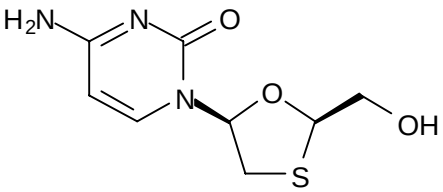
ABV (Glaxo Wellcome)



ddI (Bristol-Myers Squibb)



d4T (Bristol-Myers Squibb)



3TC (Glaxo Wellcome)

Figure 1.5: Nucleoside analogues approved by the FDA as anti-HIV drugs.

To date, only six nucleoside analogues have been approved by the American Food and Drug Administration as inhibitors of HIV replication. They are currently used clinically either alone or in conjunction with other inhibitors[16]. Among these six compounds, five have D-stereochemistry (AZT, ddI, ddC, d_4T, ABV). One is the already described L-configured 3TC (Figure 1.5).

Lamivudine (3TC) or (2*R*,5*S*)-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine has the advantage of being less cytotoxic than the corresponding D-enantiomer. In addition to its anti-HIV properties, this very important compound also displays a powerful activity against the hepatitis B virus, and is currently administered in therapy against this virus[16,17].

1.3 Antimalaria activity of L-nucleosides

Malaria, mostly caused by the parasite *Plasmodium falciparum*, devastates the world's tropical zone. The World Health Organization indicates renewed activity of this endemic disease, with 300 to 500 million cases per year, 2.3 billion persons at risk, and 1.5 to 2.7 million deaths per year[18].

Vaccination is considered to be an approach that will complement other strategies for prevention and control of the disease in the future, and in the last 10 years studies have been aimed at the development of a malaria vaccine.

Due to the resistance of the parasite towards known drugs there is an increased need for novel antimalarials, particularly of those which have no affect on the host. When the malaria parasite invades the red blood cell, it induces a unique transport pathway in their membrane[19]. This transport pathway takes up both natural purine and pyrimidine nucleosides and bases. But surprisingly it also takes up non-physiological L-purine nucleosides. The concept of selective drug design is based on the fact that the malaria parasite must salvage purine nucleosides from the serum as it has no purine *de novo* pathway and thus utilizes preformed purines as nucleosides. Unlike normal erythrocytes, the induced nucleoside transport sites are not stereoselective, and low concentration of L-nucleoside analogues are selectively transported exclusively into infected erythrocytes while normal erythrocytes are not affected[20]. Thus a unique opportunity exists for

exploiting these changes in transport phenomena as a strategy for gaining selective access to the malaria parasite.

The design of substrates or inhibitors of the parasite metabolic pathways which a) gain selective entry to parasitised cells, and b) target only malarial enzymatic pathways, would be a powerful combination in the design of a specific agent against malaria.

1.4 Aim of this thesis

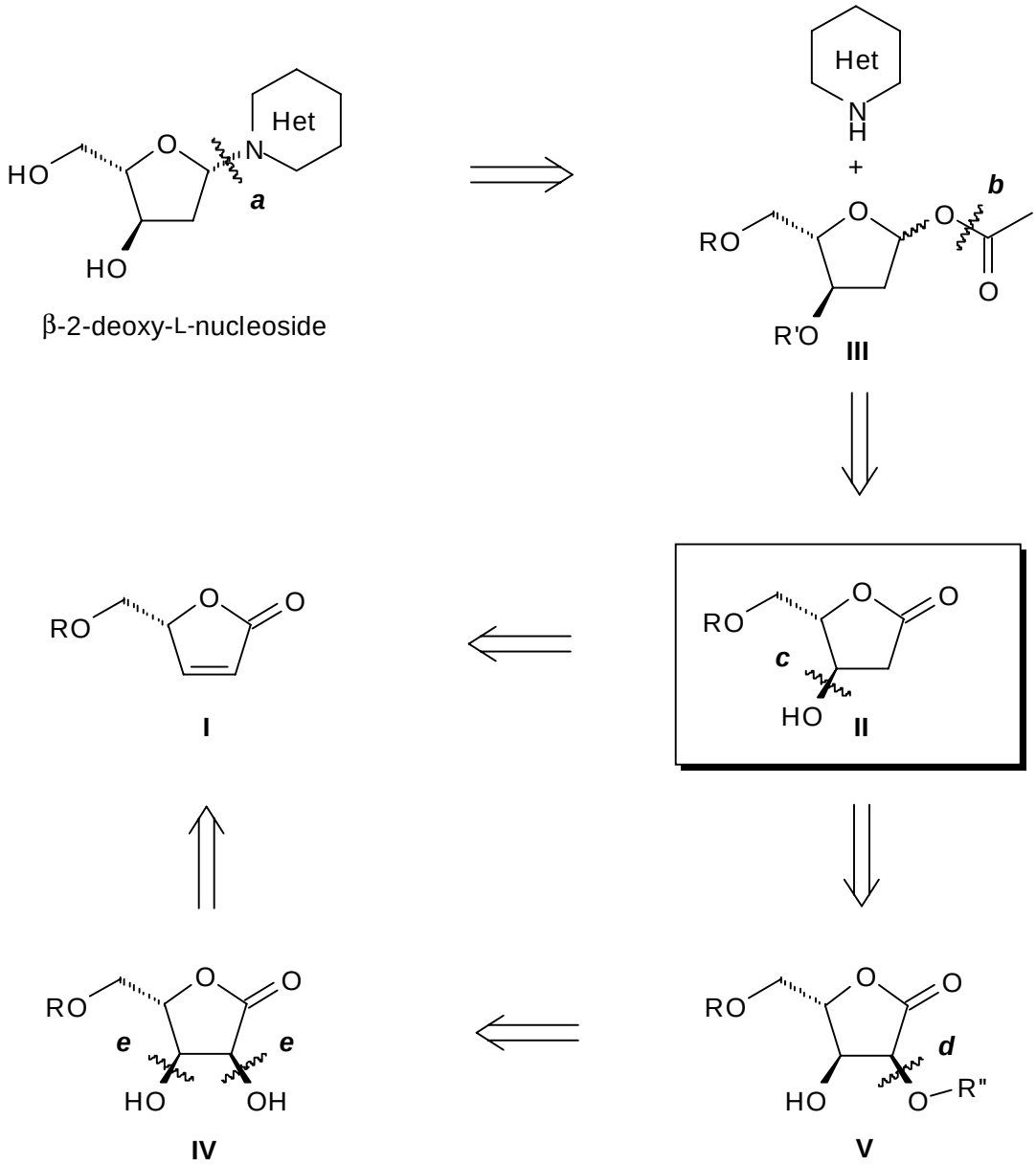
Main goal of this thesis was the development of new strategies towards the synthesis of L-sugars as precursors of their corresponding L-nucleosides. In particular our effort has been focused towards novel routes to 2-deoxy-L-nucleosides whose syntheses are among the most difficult in nucleoside chemistry because total yields are frequently only moderate and the ratio of the β and α anomers are often difficult to control and to reproduce[21].

Our retrosynthetic approach to 2-deoxy-L-nucleosides is summarized in Scheme 1.1. The nucleoside structure can be obtained from a coupling reaction between a nucleobase and a suitable protected sugar carrying on the C-1 anomeric center an "activated" leaving group (i.e. halogens, acyloxy) which allow for S_N displacement with nucleophiles. 1-halogenated sugars, however, are quite instable and reactions employing these starting materials are not always reproducible. On the contrary 1-acyloxy sugars are stable and excellent procedures have been developed over the years for their reactions with nucleobases (see chapter 4).

Taking a general 2-deoxy-L-nucleoside as an example and following Scheme 1.1, we could break the C-N bond in position *a* in order to obtain the 1-acyloxy sugar **III** and the nucleobase. The 2-deoxy-L-ribose moiety **III** contains a protected hemiacetal function and could be synthesized (see cleavage *b*) from the β-hydroxy-γ-lactone **II** by selective reduction followed by acylation. **II** represents in our retrosynthetic analysis the most crucial intermediate. We felt that **II** could be derived from the α,β-unsaturated lactone **I** which contains a Michael 1,4-system which could allow for the insertion of HO^- in the 4-position (cleavage *c*). The suitably protected hydroxymethyl group in **I** could play an important role in terms of diastereoselectivity.

II may be thought to be derived also from the dihydroxy derivative **IV** *via* selective protection (activation) of the 2-hydroxy group followed by its selective removal (cleavage

d). **IV** could also be correlated directly to **I** if one could exploit the reactivity of its double bond and thus allow for a classical *cis*-dihydroxylation (cleavage *e*).



Scheme 1.1: Retrosynthetic analysis of 2-Deoxy-L-nucleosides

This work is divided into four main chapters:

- the first part is dedicated to an investigation of the synthesis and reactivity of chiral γ-lactones; various novel approaches are reported.

- the second part shows the application of γ-lactones as chiral building blocks for the synthesis of carbohydrates; the hydroxy functionalities were introduced by either 1,4-addition of suitable nucleophiles or *syn*-dihydroxylation.

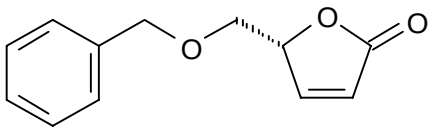
- the third part describes the synthesis of 2-deoxy-L-nucleosides; here the major unresolved problem remains the problem of obtaining pure anomers. When building blocks with the 2-deoxy-L-ribose moieties were used always α,β-mixtures of the final L-nucleosides were obtained.

- The fourth part describes an intensive study on synthesis and reactivity of enantiomerically pure δ-lactones with some new and surprising observations regarding their stability under acidic conditions.

Results and Discussion

2 Synthesis of γ-lactones – Central building blocks for 2-Deoxy-L-ribose

In the previous chapter (retrosynthetic analysis) the utility of γ-lactones for the synthesis of L-sugars as precursors of the corresponding nucleosides was shown. Compounds having structures such as **I** (see chapter 1, Scheme 1.1) could represent ideal starting materials in order to achieve this goal. In particular we felt that the 5-*O*-benzyl protected butenolide **1** (Figure 2.1) could display the suitable characteristics because it carries the acid and base stable benzyl group which could be easily removed by standard catalytic hydrogenation. Moreover, since the derivatization of the double bond in **1** would create additional chiral centers, the bulky benzyl group could direct these transformations diastereoselectively and control the attack from the opposite side of the lactone ring.



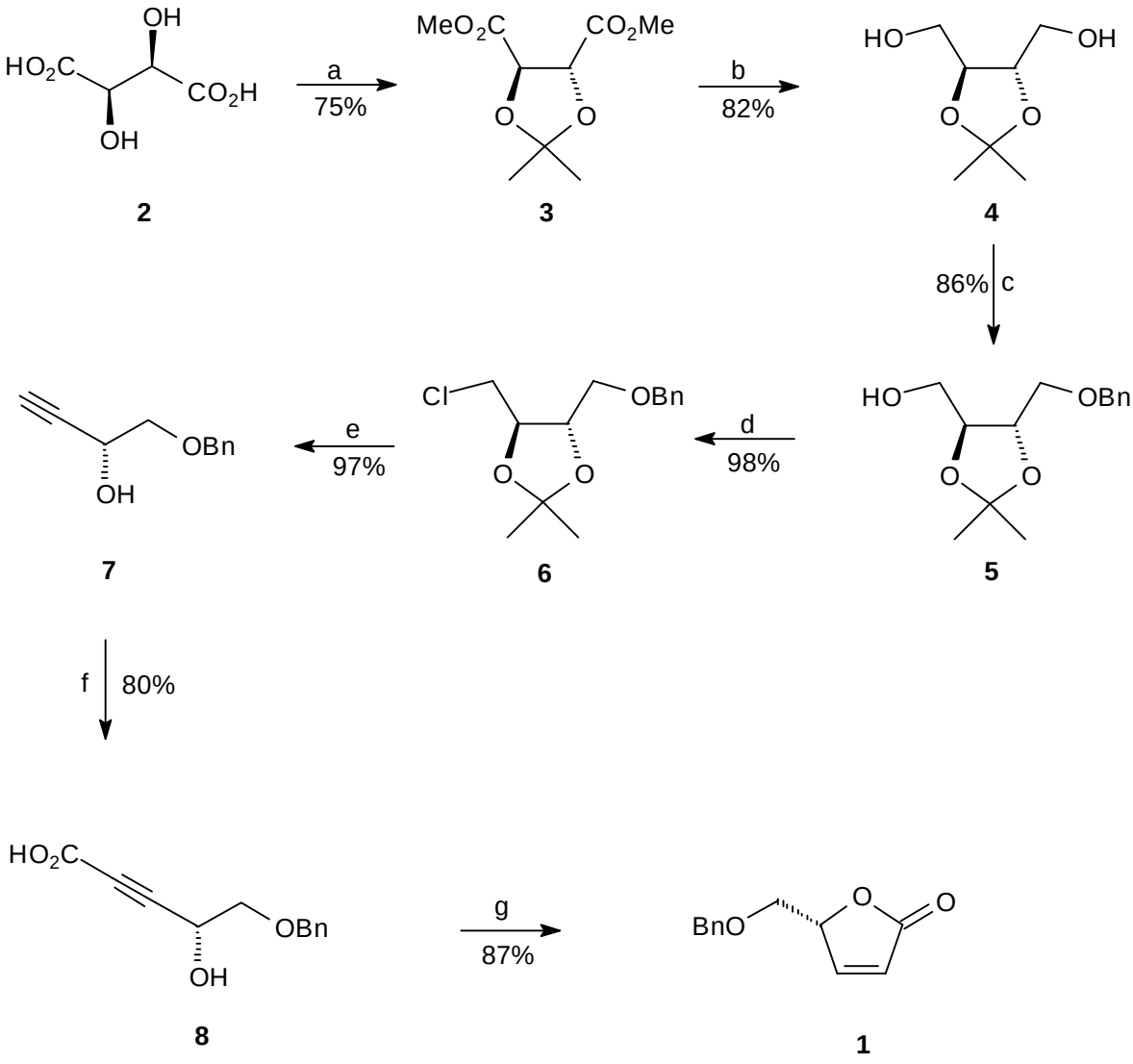
1

Figure 2.1: *R*-(+)-5-Benzyloxymethyl-5*H*-furan-2-one

R-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**) is not commercially available and its precursor *R*-(+)-5-hydroxymethyl-5*H*-furan-2-one (**16**, Scheme 2.2), carrying the free hydroxy group is extremely expensive (452 EUR/g, Fluka). The high cost of this compound prompted us to look for alternative processes which would allow for an economical and large scale preparation of this material.

*2.1 Synthesis of **1** from L-tartaric acid*[22]

In the literature several approaches towards **1** were described. One strategy allows the synthesis of **1** in 7 steps starting from L-tartaric acid with an overall yield of 35% (Scheme 2.1).



Scheme 2.1: a) acetone dimethylacetal, *p*-TsOH, MeOH; b) $LiAlH_4$; c) NaH, BnBr; d) PPh_3, CCl_4; e) *n*-BuLi; f) CO_2, *n*-BuLi; g) H_2, Pd, $BaSO_4$.

The first step employs the diesterification of the carboxylic acid functions in **2** with concomitant acetal formation leading to **3** using acetone dimethylacetal in MeOH in the presence of *p*-TsOH. This is followed by reduction of the ester groups with $LiAlH_4$ affording the diol **4**. Monoprotection of the diol **4** (NaH/BnBr) leads to **5** which is converted into the chloride **6** using PPh_3 in CCl_4. Double deprotonation with *n*-BuLi leads to the alkyne **7** *via* the intermediate alkene. Carbonylation to **8** and selective reduction with concomitant cyclization finally leads to **1**. Although this way a high overall yield can be achieved, we felt that the large number of steps and the use of moisture sensitive

organometallic reagents would render this method not very convenient for preparations on a large scale.

*2.2 Synthesis of **1** from L-ascorbic acid*

Another attractive starting material for the preparation of **1** certainly is (*S*)-glyceraldehyde (**12**) which can be obtained both from L-ascorbic acid[23] and L-mannitol[24].

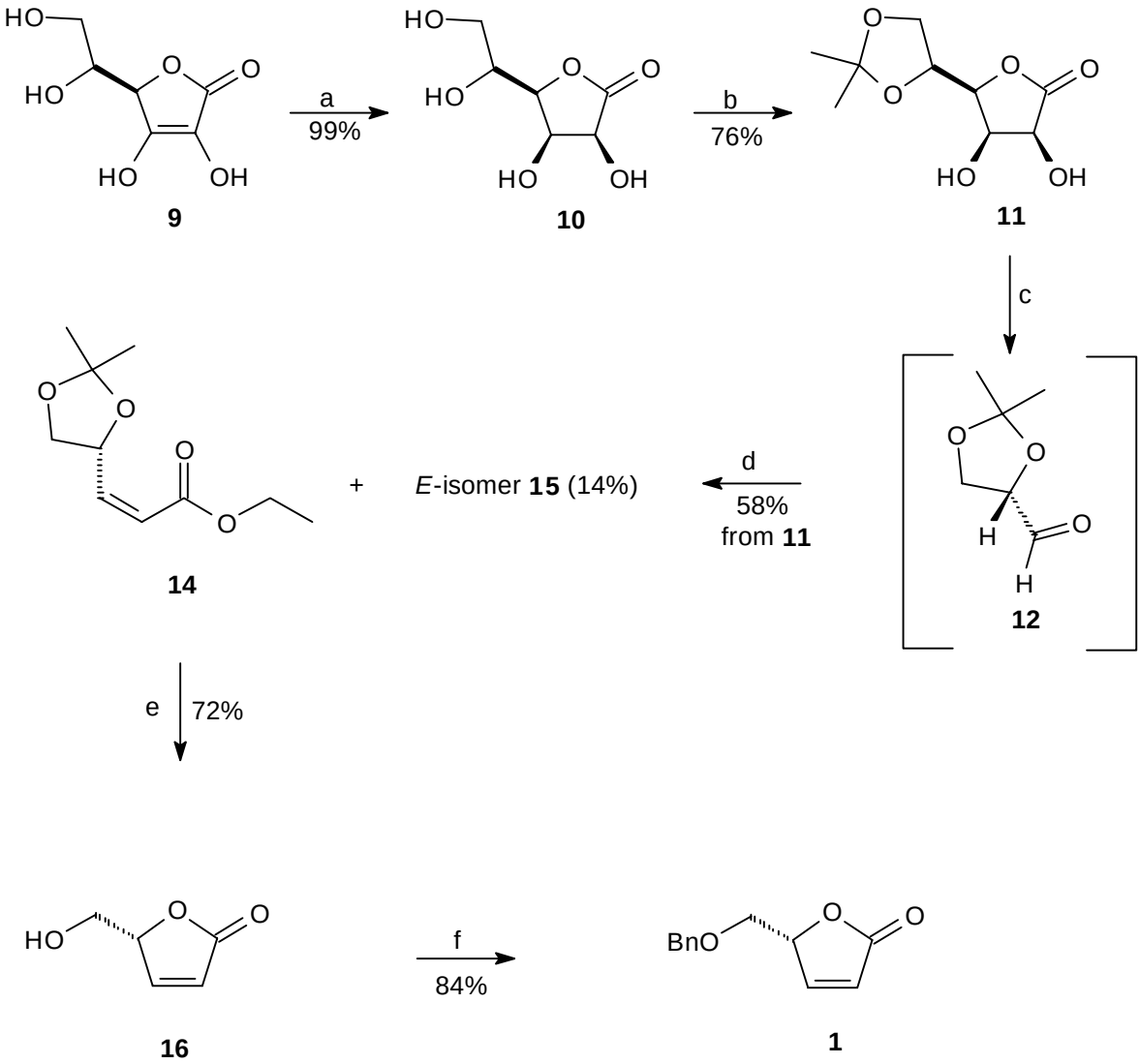
We decided to use the route starting from L-ascorbic acid (**9**) because of its low cost and the limited number of steps required in this procedure.

Starting from L-ascorbic acid (**9**) Hubschwerlen[23c] described the synthesis of *R*-(-)-*Z*-3-(2,2-Dimethyl-[1,3]-dioxolan-4-yl)-acrylic acid ethyl ester (**14**) in good overall yield (Scheme 2.2).

14 represents an excellent intermediate for our purpose since the cleavage of the acetal function under acidic conditions and subsequent cyclization would directly lead to *R*-(+)-5-hydroxymethyl-5*H*-furan-2-one (**16**) which could possibly be transformed into the desired benzyl protected derivative **1**.

The first step involves the catalytic hydrogenation of an aqueous solution of **9** using Pd/C 10% over a period of 24h with a H_2 pressure of 5 Bar. The completely hydrogenated product **10** was isolated in quantitative yield and with high chemical purity. The second step involves the regioselective protection of one diol function using isopropenyl methylether as reagent. This reaction was carried out in DMF using *p*-TsOH as catalyst. The acetal **11** was isolated in 76% yield. Oxidation of the *cis* diol function in **11** with $NaIO_4$ produced the instable (*S*)-glyceraldehyde (**12**) which was reacted without isolation with the Wittig reagent (Triphenyl-λ^5-phosphanylidene)-acetic acid ethyl ester[25] (**13**) leading to a mixture of the desired α,β-unsaturated *Z*-ester **14** and *E*-ester **15**. This mixture was easily separated by column chromatography on silica gel leading to pure **14** in 58% yield starting from **11**.

In order to prepare our target compound *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**), the acetal function was cleaved under acidic conditions[26] (aqueous 10% H_2SO_4) leading to a concomitant, spontaneous cyclization under the formation of *R*-(+)-5-hydroxymethyl-5*H*-furan-2-one (**16**) in 72% yield.



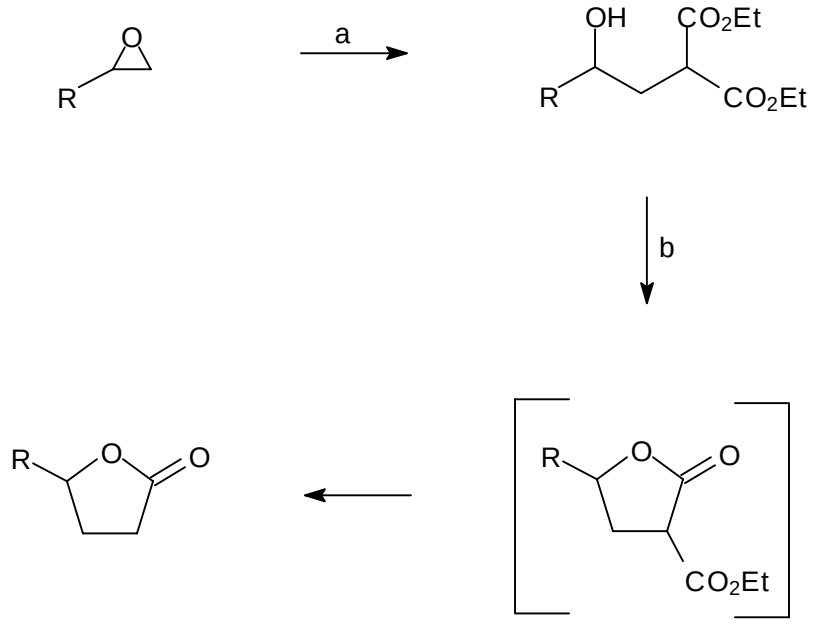
Scheme 2.2: a) H_2, Pd/C 10%, water, 50 °C, 24h; b) Isopropenylmethylether, *p*-TsOH, DMF, rt, 24h; c) $NaIO_4$, water, rt, 2h; d) $Ph_3P{=}CHCO_2Et$ (**13**), dichloromethane/H_2O, rt, over night. e) H_2SO_4 (10% in water), MeOH, rt, 2h; f) $Cl_3CC(=NH)OBn$ (**17**), CF_3SO_3H, dichloromethane/cyclohexane (2/1), rt, 2h.

While more classical methods for the introduction of the benzyl group (NaH/BnBr, Ag_2O/BnBr[27]) failed, **1** was obtained from **16** in 84% yield using 2,2,2-Trichloro-acetimidic acid benzyl ester[28] (**17**) in the presence of CF_3SO_3H (Scheme 2.2).

This way **1** was obtained in 29% overall yield starting from L-ascorbic acid (**9**). The synthesis can be carried out conveniently on a 100g scale using standard equipment. In view of the facile procedure further up-scaling into the Kg scale should be possible without difficulty.

2.3 *Synthesis of **1** from R-(-)-2-benzyloxymethyl oxirane using the Krapcho method*

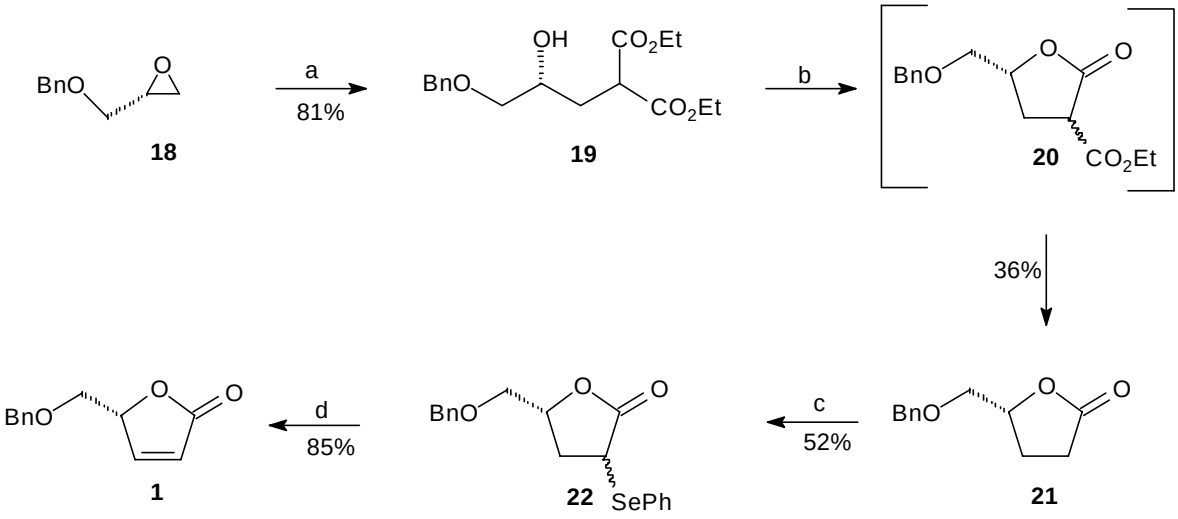
One of the procedures described in the literature for the synthesis of γ-lactones is the Krapcho method[29]. This strategy consists in the reaction of an epoxide with the ester enolate of a malonic ester in order to obtain a γ-hydroxy diester which upon heating cyclizes to γ-lactone *via* concomitant decarboxylation (Scheme 2.3).



Scheme 2.3: Krapcho method. a) M-CH(CO_2Et)$_2$; b) NaCl, H_2O, DMSO, 150 °C

In our case the epoxide of choice was obviously *R*-(-)-2-benzyloxymethyl oxirane (**18**), a compound which is commercially available. As outlined in Scheme 2.4 reaction of **18** with the lithium salt of malonic acid diethyl ester at –78 °C in THF using BF_3-Et_2O for the activation of the epoxide towards the nucleophilic attack led to **19** in 81% yield. If this reaction is carried out in ethanol using sodium ethoxide as base, the yield is reduced to only 50%. This can probably be explained by the lack of regioselectivity in the ring opening reaction under these conditions. For the cyclization reaction **19** was heated in DMSO in the presence of H_2O and NaCl at 150 °C for 6h to afford the lactone **21** in only 36% yield *via* decarboxylation of the intermediate β-carboxyl ester **20**. The conversion of

the saturated lactone **21** into **1** was already described[30]. Deprotonation with LDA at –78 °C and quenching with PhSeBr produced **22** as mixture of diastereoisomers in 52% yield after chromatographic separation on silica gel. Oxidation to the selenium oxide was accomplished with $NaIO_4$[31] followed by concomitant *syn*-elimination[32] to produce **1** with a yield of 85%. If the oxidation is carried out with H_2O_2[32e] **1** is isolated in only 65% yield (Scheme 2.4).

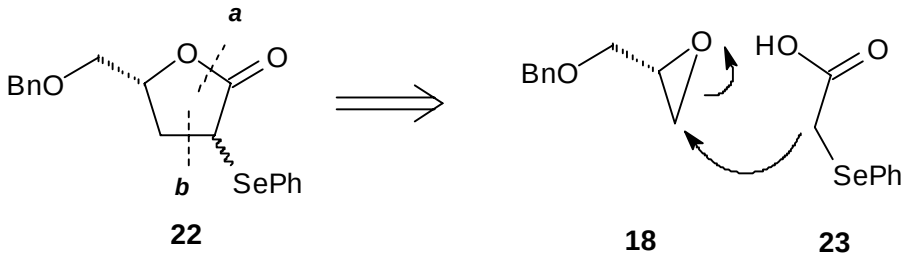


Scheme 2.4: a) diethylmalonate, BuLi, BF_3-Et_2O, THF, -78 °C, 1.30h; b) NaCl, H_2O, DMSO, 150 °C, 6h; c) HMDS, BuLi, PhSeBr, THF, -78 °C, 5min; d) $NaIO_4$, MeOH/H_2O, rt, 1h.

Although in this procedure the number of steps can be reduced to 4, the low overall yield of this process (13%) provides no advantage over the preparation of **1** starting from L-ascorbic acid. Furthermore, requirement for toxic selenium derivatives for the introduction of the double bond in the lactone ring renders this method not very attractive from an ecological point of view.

2.4 *Synthesis of **1** from R-(-)-2-benzyloxymethyl oxirane using $PhSeCH_2CO_2H$ or $PhSCH_2CO_2H$*

In order to improve the above method, alternative approaches towards **1** were explored. Thus, as an alternative to the introduction of the double bond following the Krapcho method, retrosynthetic analysis of **22** reveals the interesting possibility to obtain **22** starting from *R*-(-)-2-benzyloxymethyl oxirane (**18**) and phenylselanyl acetic acid (**23**) by breaking the bonds in positions *a* and *b* as represented in Scheme 2.5.

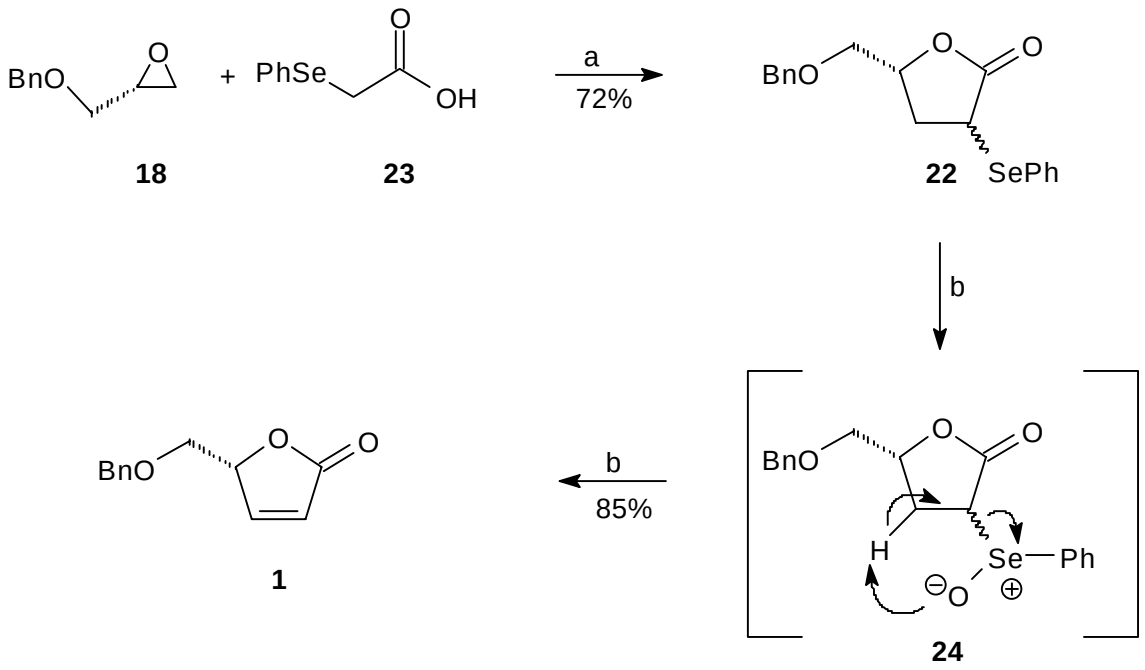


Scheme 2.5: Retrosynthesis of (3*R*,*S*-5*R*)-Benzyloxymethyl-3-(phenylselanyl)-dihydro-furan-2-one (**22**)

Thus, deprotonation of the acidic proton α to the carbonyl group (together with the OH proton) in **23** would form a di-enolate which could add regioselectively to the epoxide **18** leading to **22** which, as previously shown, can be transformed into **1** in 85% yield by oxidative *syn*-elimination[32]. Using commercially available *R*-(-)-2-benzyloxymethyl oxirane (**18**) (≥98% ee), we were indeed able to obtain **1** this way in two steps with an overall yield of 61% (Scheme 2.6).

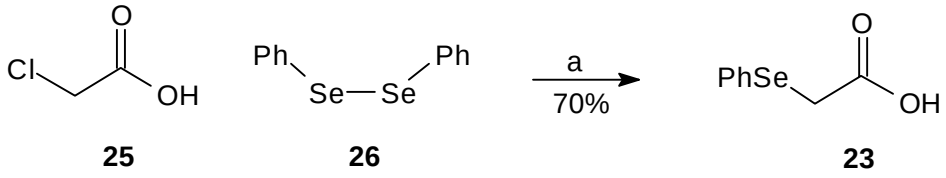
Thus, nucleophilic ring opening of **18** with the dilithium salt of $PhSeCH_2CO_2H$ at −78 °C followed by refluxing with AcOH overnight led to (3*R*,*S*-5*R*)-benzyloxymethyl-3-(phenylselanyl)-dihydro-furan-2-one (**22**) in 72% yield as mixture of diastereoisomers. Oxidation of the phenylselenide function with $NaIO_4$ was accomplished with concomitant formal *syn*-elimination of benzeneselenenic acid (PhSeOH) in **24** leading directly and in 85% yield to **1**.

In comparison to the routes using L-tartaric acid or L-ascorbic acid as starting materials this method is of course much more convenient since it requires only two steps and produces **1** with an overall yield of 61%.



Scheme 2.6: a) 1. LDA, THF, -78 °C – rt, 3h; 2. AcOH, reflux, overnight. b) $NaIO_4$, $MeOH/H_2O$, rt, 1h.

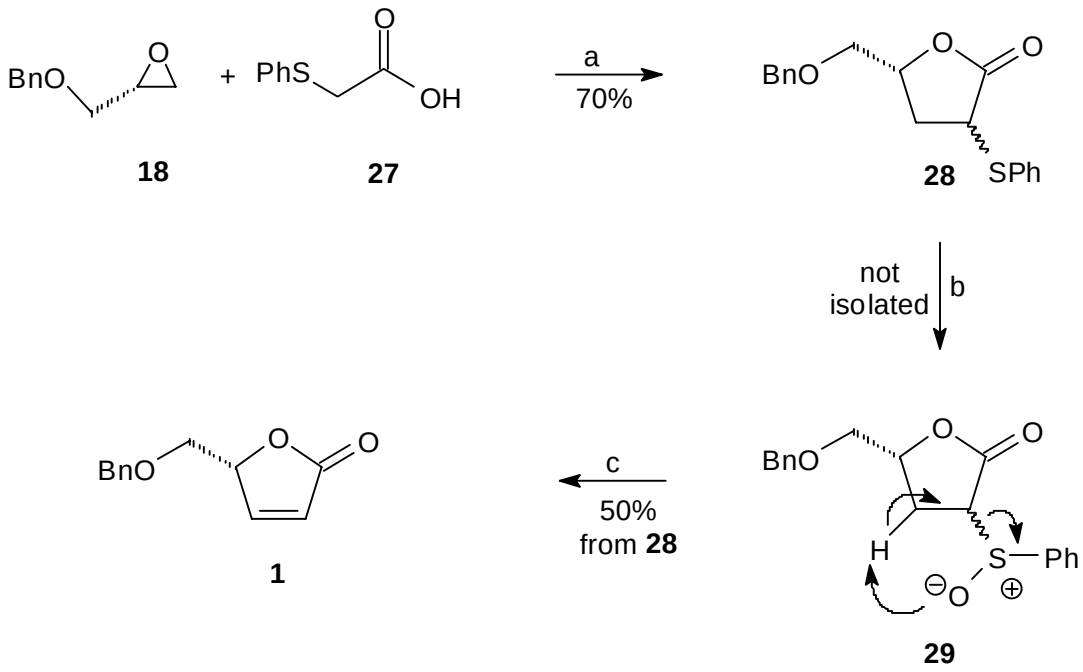
$PhSeCH_2CO_2H$ is not commercially available but can be prepared[33] easily and in a preparative scale simply by reacting chloroacetic acid (**25**) and diphenyldiselenide (**26**, Scheme 2.7).



Scheme 2.7: a) $NaBH_4$, EtOH, 7h, rt.

The major drawback of this method is the use of toxic selenium compounds which, especially for large scale preparations, represents an ecological problem.

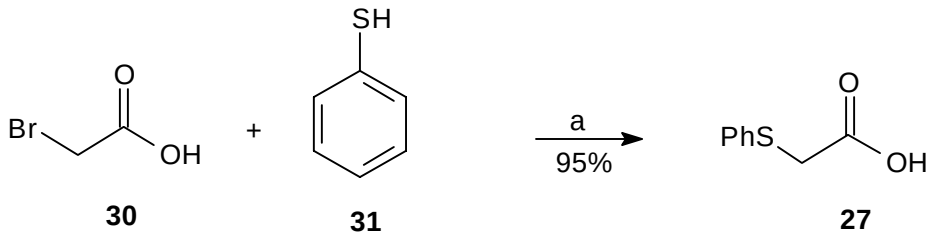
An alternative for the introduction of the required double bond and mechanistically related would be the *syn*-elimination of the corresponding aryl sulfoxides[34]. Thus, based on the retrosynthetic Scheme 2.5, we decided to exchange selenium by sulfur, in reacting **18** with phenylsulfanyl acetic acid (**27**, Scheme 2.8).



Scheme 2.8 a) 1. LDA, THF, -78 °C – rt, 3h; 2. AcOH, reflux, overnight. b) $NaIO_4$, $MeOH/H_2O$, rt, over night. c) toluene, reflux, 30 min.

Thus, ring opening of **18** with the dilithium salt of $PhSCH_2CO_2H$ led to (3*R*,*S*- 5*R*)-5-benzyloxymethyl-3-(phenylsulfanyl)-dihydro-furan-2-one (**28**) in 70% yield again as mixture of diastereoisomers. Oxidation with $NaIO_4$ produced a diastereoisomeric mixture of the corresponding sulfoxides **29**, which in this case are stable and can be isolated. After work up and without further purification this mixture was refluxed in toluene for 30min leading to **1** in 50% yield.

Also **27** is not commercially available but can be prepared[35] in one step reaction from bromoacetic acid (**30**) and thiophenol (**31**) using NaOH as base (Scheme 2.9).



Scheme 2.9: a) NaOH, THF/H_2O, 30min, rt.

While the use of $PhSeCH_2CO_2H$ thus allows the production of **1** in only two steps with an overall yield of 61%, the use of $PhSCH_2CO_2H$ (three steps, 35% yield) may be of advantage from an ecological point of view by avoiding the employment of toxic selenium compounds. Both reactions can be scaled up to 5g without any difficulties.

*2.5 Determination of the optical purity of **1***

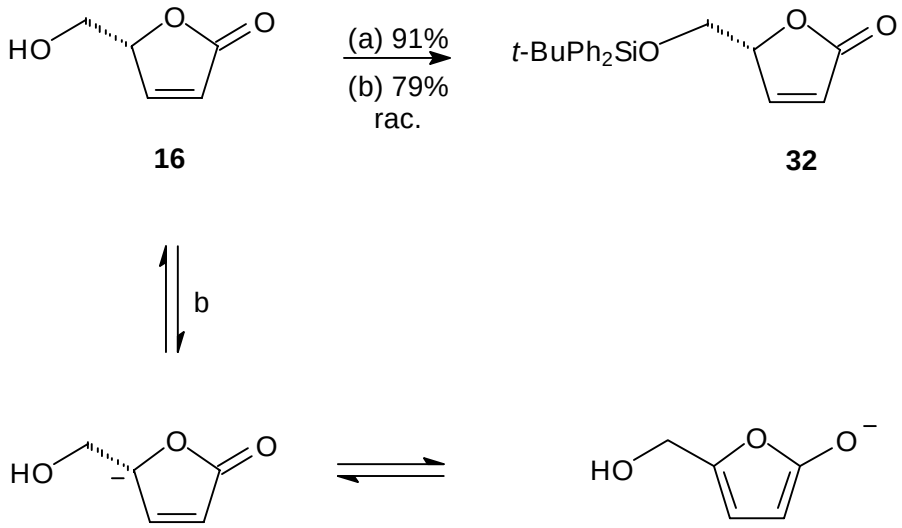
For the determination of the optical purity of **1** an HPLC method on a chiral support had to be developed. As reference for the HPLC separation *ent*-**1** was prepared from commercially available *S*-(-)-5-hydroxymethyl-5*H*-furan-2-one *ent*-(**16**) using the procedure described in Scheme 2.2. Due to the presence of a benzyl group as chromophor, UV detection could be employed.

Although a wide variety of different columns were tried, no satisfactory separation of the *R,S* mixture was achieved. Therefore we decided to investigate other protective groups for the 5-hydroxymethyl function in **1**.

The characteristics of this protecting group should be a) the simplicity of introduction together with b) the requirement of a suitable chromophor for UV detection. This prompted us to investigate the use of silyl ethers carrying phenyl groups.

Unfortunately, the introduction of these silyl groups proved to be not straightforward. Using more standard conditions (Et_3N, DMAP, *t*-$BuPh_2SiCl$[36]) and depending on the employed reaction times various degrees of racemization were observed. We attribute this to the transient deprotonation of the allylic proton (homologous acid) at C-5 (Scheme 2.10). If, however, *t*-$BuPh_2SiCl$ and NH_4NO_3[37] are used, the desired *R*-(+)-5-(*tert*-butyl-diphenyl-silanyloxymethyl)-5*H*-furan-2-one (**32**) was obtained with excellent yield and free of racemization.

Excellent separations were achieved using the column LiChoCART 250-4 (*S,S*)-Whelk-5µm and the following conditions: eluent *n*-hexane/isopropanol (97/3 *v/v*), flow rate 1 ml/min, detector UV 254 nm. As shown in Figure 2.2a a base line separation of the racemic mixture was achieved under these conditions allowing a reliable determination of the enantiomeric purities of **1** derived from the various employed routes.



Scheme 2.10 a) *t*-$BuPh_2SiCl$, NH_4NO_3, DMF, rt, 24h; b) *t*-$BuPh_2SiCl$, Et_3N, DMAP, dichloromethane, 0 °C – rt, 4h.

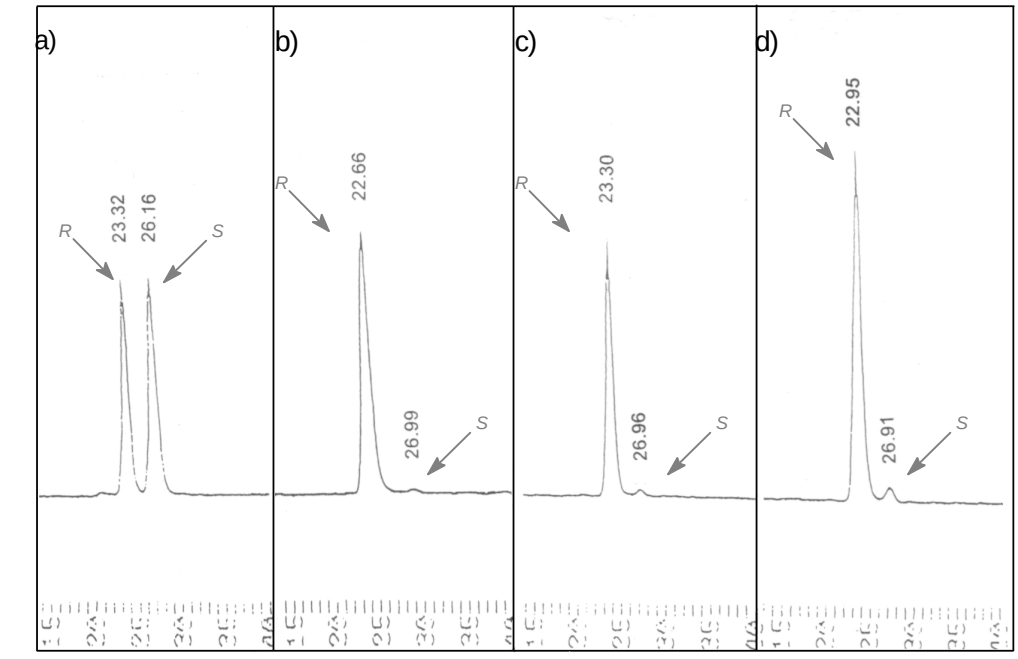
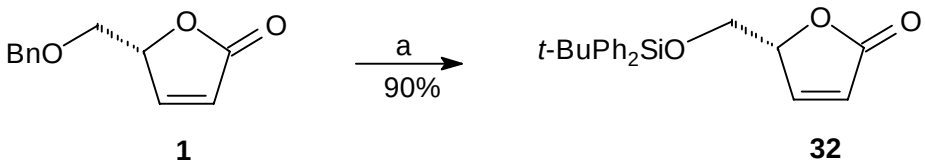


Figure 2.2: HPLC analysis. Column LiChoCART 250-4 (*S*,*S*)-Whelk-5µm eluent *n*-hexane/isopropanol (97/3 *v/v*), flow rate 1 ml/min, detector UV 254 nm. a) racemic mixture of **32**; b) *R*-(**32**) from L-ascorbic acid, ee ≥98%; c) *R*-(**32**) from Krapcho method and from $PhSeCH_2CO_2H$, ee ≥97%; d) *R*-(**32**) from $PhSCH_2CO_2H$, ee ≥95%.

Starting from L-ascorbic acid the resulting **16** was converted directly into **32**. In contrast, starting from *R*-(-)-2-benzyloxymethyl oxirane (**18**), the benzyl group had to be first removed (H_2, Pd/C) and the resulting **16** then transformed into **32** using the sequence described in Scheme 2.11.



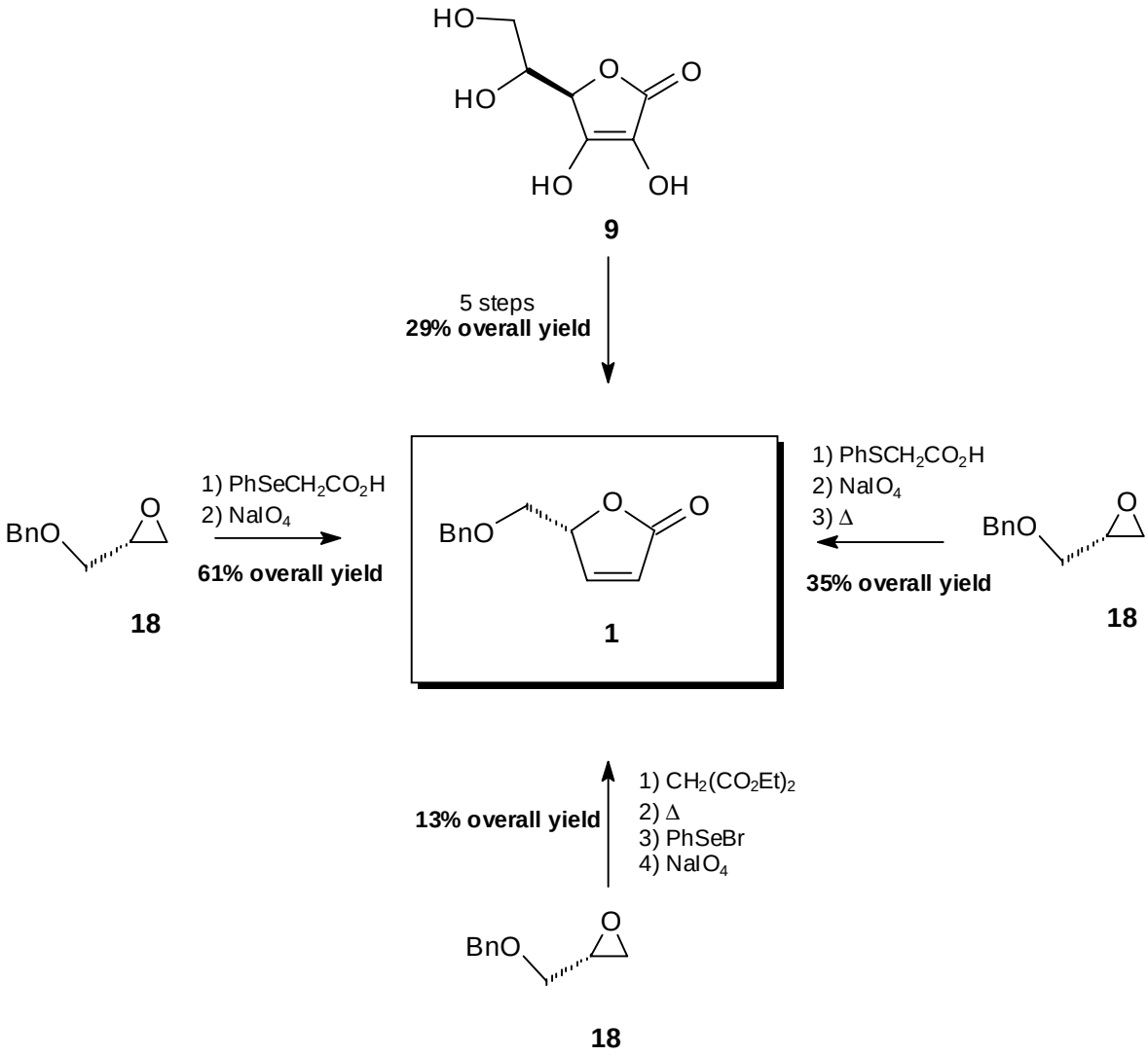
1 **32**

Scheme 2.11: a) 1. Pd/C 10%, AcOEt, rt, 1h; 2. *t*-$BuPh_2SiCl$, NH_4NO_3, DMF, rt, 24h.

2.6 Synthesis of γ-lactones – Summary

In conclusion, four different methods have been developed towards the synthesis of *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**) with all routes having various advantages and also drawbacks (Scheme 2.12).

The first route uses L-ascorbic acid as starting material and produces the product with the highest enantiomeric purity (≥98% ee). This should always be taken into consideration when - as in our case - the synthesis of biologically active molecules is planned. On the other hand this route requires the largest number of steps with an overall yield from L-ascorbic acid of 29%. The Krapcho method starting from *R*-(-)-2-benzyloxymethyl oxirane (**18**) results in a poor overall yield of only 13% and furthermore utilizes toxic selenium derivatives. The enantiomeric purity is also very high (≥97% ee). A much better alternative – although also using selenium compounds as intermediates – is the route using *R*-(-)-2-benzyloxymethyl oxirane (**18**) and $PhSeCH_2CO_2H$. Only two steps are required and an overall yield of 61% is achieved. Again the enantiomeric purity is very high. The last procedure using $PhSCH_2CO_2H$ eliminates all problems regarding toxic compounds. In this case we have to accept a lower overall yield (35%) and the lowest enantiomeric purity (≥95% ee) observed among all studied procedures.



Scheme 2.12: 4 routes to *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**)

In summary, the enantiomeric excess achieved in the syntheses of *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**) *via* these all four different routes are as follows:

- from L-ascorbic acid: **≥**98% ee
- from *R*-(-)-2-benzyloxymethyl oxirane using the Krapcho method: **≥**97% ee
- from *R*-(-)-2-benzyloxymethyl oxirane using $PhSeCH_2CO_2H$: ≥97% ee
- from *R*-(-)-2-benzyloxymethyl oxirane using $PhSCH_2CO_2H$: ≥95% ee

3 2-Deoxy-L-ribose and building blocks derived thereof

3.1. Introduction – State of the art

This chapter describes new methodologies for the synthesis of carbohydrates of the L-series and derivatives thereof. Next to constituting building blocks for L-nucleosides with both natural and non-natural nucleobases and thus attractive candidates for numerous therapeutic applications in treating cancer, viral diseases and malaria (chapter 1) these L-riboses are the building blocks for *enantio*-DNA which could code for D-proteins and an enantiomeric living world.

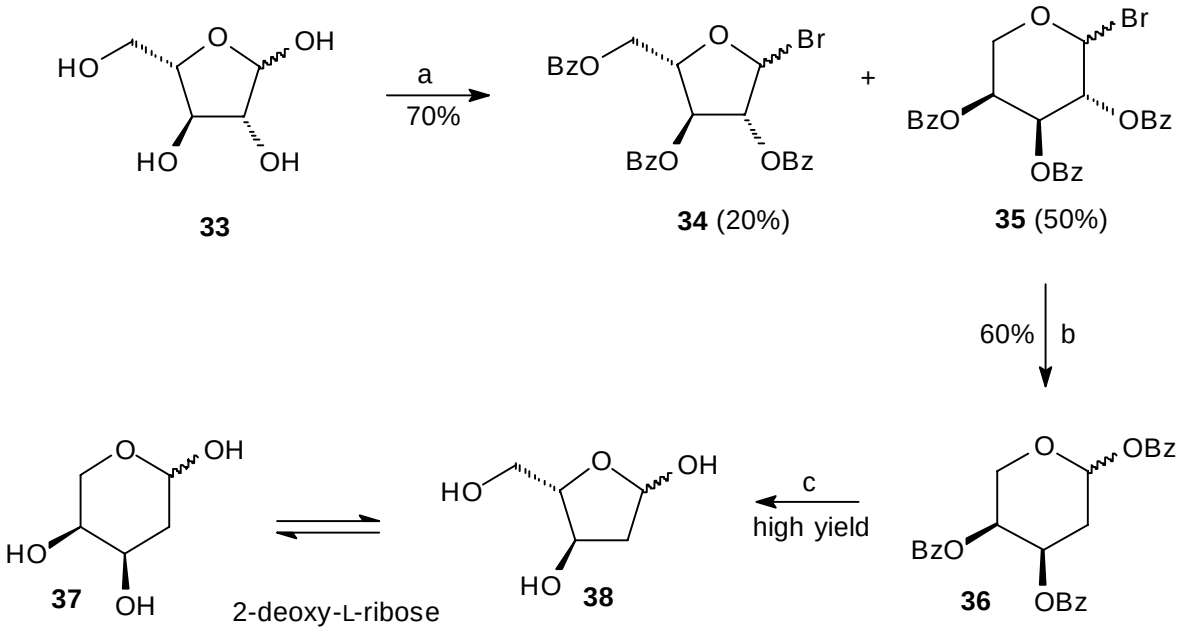
Several synthetic approaches to 2-deoxy-L-ribose have been published in recent years, most of them starting with molecules of the "chiral pool" such as L-arabinose or L-ascorbic acid[38]. Alternatively, the required absolute configuration was introduced by asymmetrization of an achiral starting material e.g. by employing the Sharpless epoxidation[39].

The most attractive methods, largely developed by Michael Jung *et al.* are described below.

3.1.1 2-Deoxy-L-ribose starting from L-arabinose[40]:

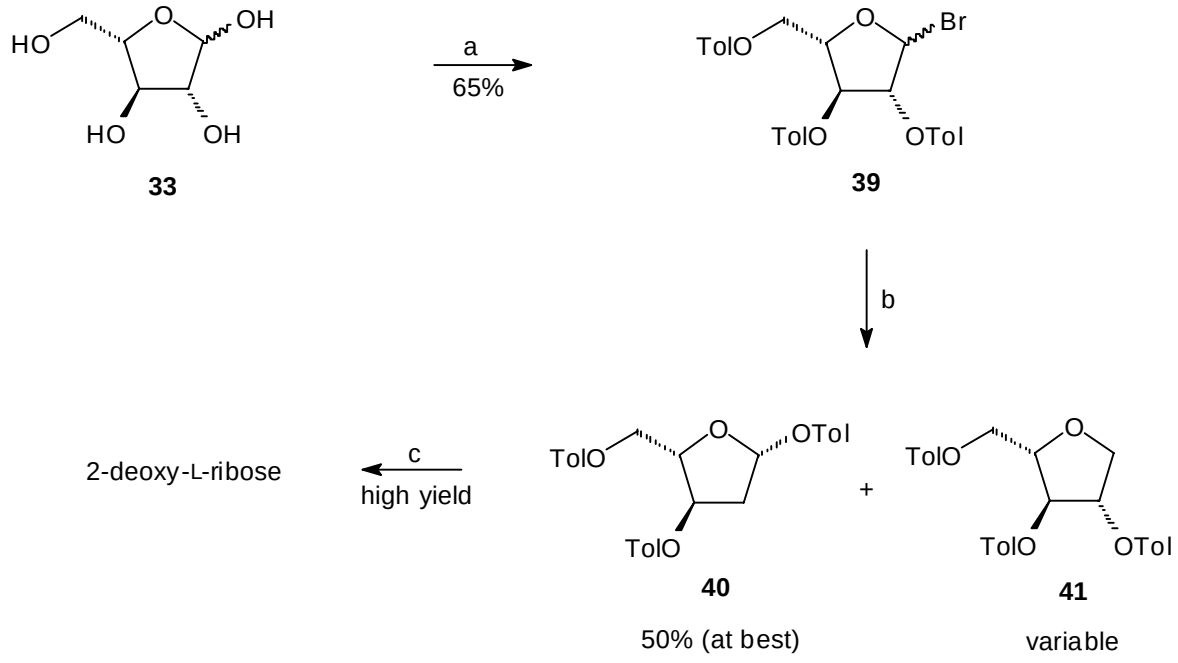
Perbenzoylation of L-arabinose (**33**) followed by treatment with HBr/AcOH affords the isomeric furanose **34** and the pyranose **35** which are separable *via* column chromatography. Reductive radical rearrangement of the bromopyranose **35** under the Giese[41] conditions leads to the deoxygenated intermediate **36** in 60% yield which can be hydrolyzed leading to 2-deoxy-L-ribose (**37** + **38**) in high yield (Scheme 3.1).

As an alternative[42] and shown in Scheme 3.2, L-arabinose (**33**) was first transformed into its methyl glycoside and then esterified with 4-methylbenzoic acid chloride (TolCl). Reaction with HBr/AcOH led to the bromo-derivative **39** in 67% overall yield. Also in this case, using the Giese[41] 1,2-acyloxy shift rearrangement the desired 2-deoxygenated intermediate **40** was produced in 50% yield. **40** can then be easily hydrolyzed to 2-deoxy-L-ribose.



Scheme 3.1: a) 1. BzCl, pyridine; 2. HBr, AcOH; b) Bu_3SnH, AIBN; c) hydrolysis.

The major importance of this intermediate resides in the fact that it has been employed in some cases for the diastereoselective formation of single anomers of 2-deoxy-L-nucleosides[42] (see chapter 4).

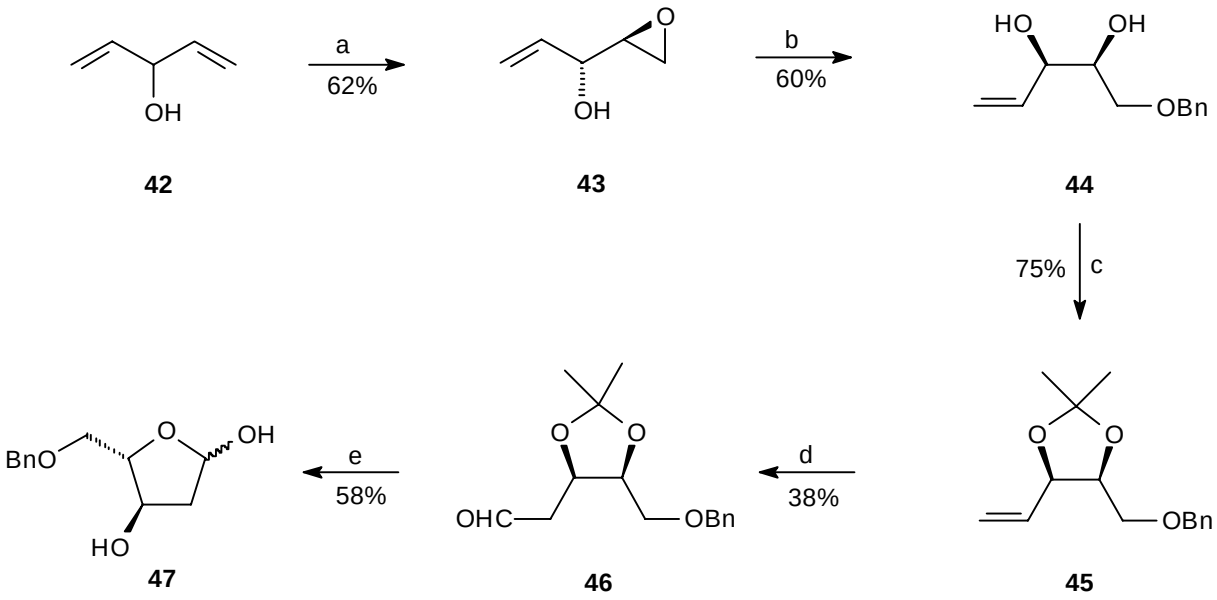


Scheme 3.2: a) 1. MeOH, HCl. 2. TolCl, pyridine. 3. HBr/AcOH; b) Bu_3SnH, AIBN; c) hydrolysis.

One limitation of these procedures resides in the fact that under the Giese[41] conditions (Bu_3SnH/AIBN) is not always possible to completely control the 1,2-acyloxy shift. This causes the production of variable amounts of "direct reduction" products of **39** to **41** with sometimes severe losses of chemical yield.

3.1.2 2-Deoxy-L-ribose *via* Sharpless Epoxidation[39]

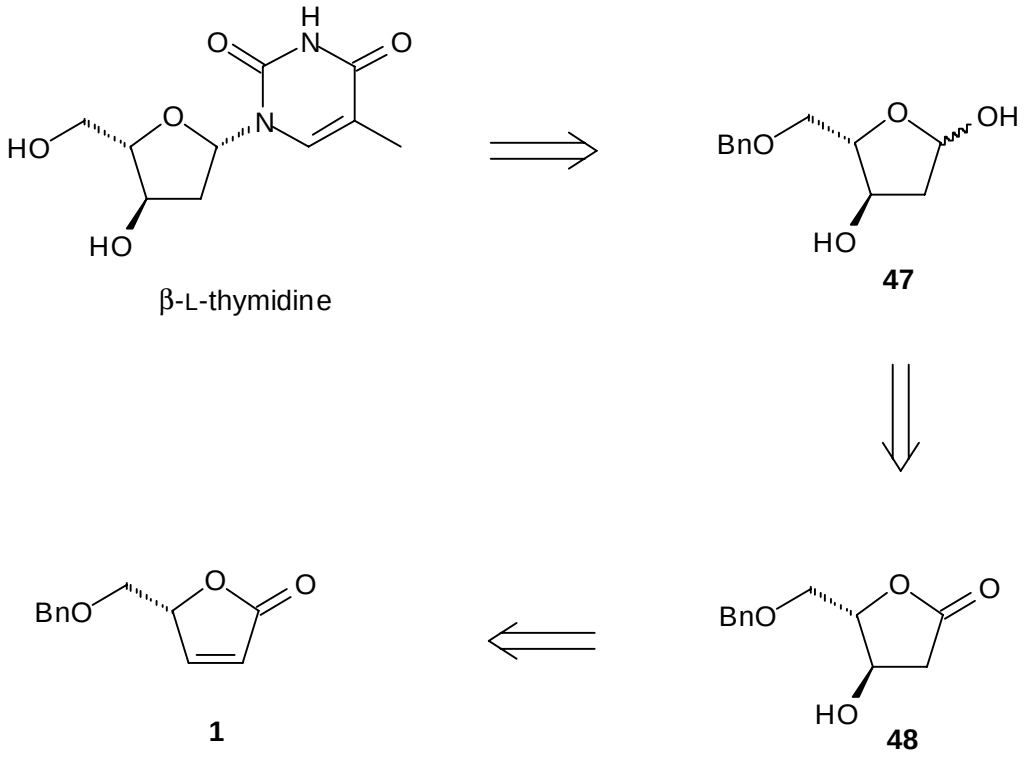
Sharpless epoxidation of the dienol **42** produces the epoxide **43** in 62% yield and with 100% enantiomeric excess. Ring opening of the activated [Ti(*i*OPr)$_4$] epoxide with BnOH leads to **44** in 60% yield. **44** can then be transformed into the acetal **45** in 75% yield. Wacker oxidation of the terminal olefin produced the aldehyde **46** in 38% yield. The benzyl protected 2-deoxy-L-ribose **47** was finally obtained *via* acid catalyzed cyclization of **46** in 58% yield (Scheme 3.3).



Scheme 3.3: a) D-(-)DIPT, Ti(*i*OPr)$_4$, *t*BuOOH, CH_2Cl_2; b) BnOH, Ti(*i*OPr)$_4$; c) acetone, $CuSO_4$, TsOH; d) $PdCl_2$ (0.2eq), CuCl, O_2, DMF/H_2O 7:1; e) 1N HCl.

3.2 Retrosynthetic analysis

As outlined in Scheme 1.1 of chapter 1 and largely discussed in chapter 2, our retrosynthetic approach towards the synthesis of 2-deoxy-L-ribose and of the corresponding 2-deoxy-L-nuceosides employs as starting material the butenolide **1**. L-thymidine as an example, can thus be formed by coupling the nucleobase thymine and peracetylated **47. 47** could be obtained by selective reduction of the β-hydroxy-γ-lactone **48** which in turn could be obtained by diastereoselective, formal 1,4-addition of OH^- to the Michael system in **1** (Scheme 3.4).



Scheme 3.4: Retrosynthesis of β-L-thymidine: correlation with **1**

*3.3 The reactivity of nucleophilic oxygen species in 1,4-additions to **1***

In a Michael system such as in **1** (Figure 3.1), there are two electrophilic positions present: the C=O group (hard 2-position) and the C=C group (soft 4-position). In accordance with

the "hard-soft-acid-base" (HSAB) rationale[43], most oxygen nucleophiles (hard) would react preferentially with the carbonyl group although some selected examples for Michael additions of alcohols are reported in the literature[44].

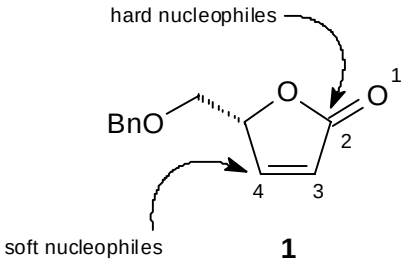
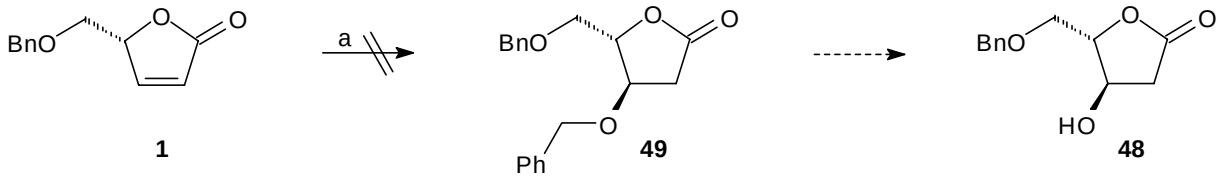


Figure 3.1: sites of reactivity of **1**.

3.3.1 1,4-Addition of benzyl alcoholates - Attempts

Our first attempts along these lines employed benzyl alcoholates, because once introduced, the benzyl group could be easily removed by catalytic hydrogenation leading to the β-hydroxy-γ-lactone **48**. Unfortunately, the formation of 3-benzyloxy derivative **49** was not observed. The basic conditions employed (NaH, BnOH) probably favored the opening of the lactone ring and thus 1,2-addition (Scheme 3.5).

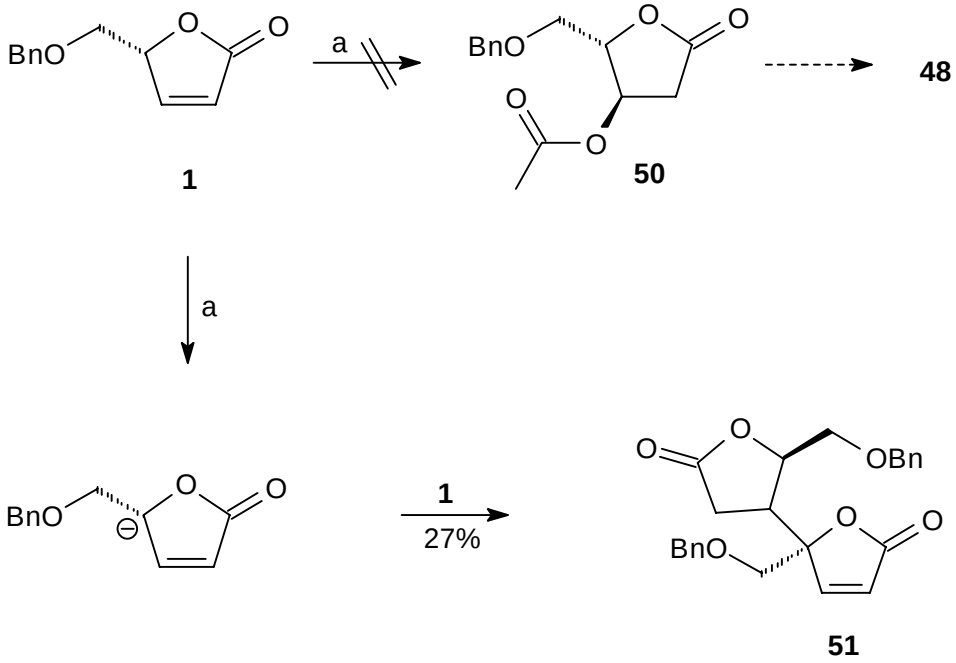


Scheme 3.5: a) BnOH, NaH, DMF

3.3.2 1,4-Addition of acetates - Attempts

As another nucleophilic oxygen species we considered the acetate anion. Following its successful introduction, the hydrolysis of the thus generated **50** would lead to β-hydroxy-γ-

lactone **48** (Scheme 3.6). Although polar aprotic solvents (HMPT/DMSO) and a large counter ion (Cs^+) were employed– conditions that enhance nucleophilicity – the formation of the 3-acetoxy derivative **50** was not observed. In this case, however, a different product was isolated, which was identified as having the dimeric structure **51**. Evidently, the basicity of the reaction system favored deprotonation of the acidic transient allylic proton in **1** to form the corresponding enolate which could then react in a 1,4-addition with itself leading to **51**. The literature evidence supported such reactions[45] and the chemical analyses clearly confirmed the structure of **51**.



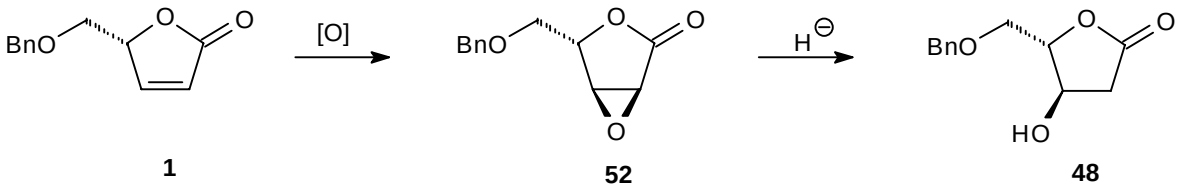
Scheme 3.6: a) CsOAc, DMSO, HMPT, rt, 1h.

These results clearly indicate the difficulties encountered in the direct introduction of the "hard" oxygen atom *via* a Michael addition to systems such as **1.** The lability of the lactone ring under basic conditions favors the formation of open chain products (1,2-addition) and the acidic allylic proton in the 5-position generates carbanions which can further react with Michael systems as described above (Scheme 3.6).

*3.4 Epoxidation of the double bond in **1** - Attempts*

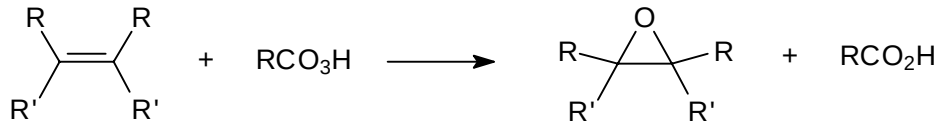
3.4.1 Epoxidation using peroxycarboxylic acids

Diastereoselective epoxidation of **1** (Scheme 3.7) would lead to a highly attractive intermediate **52** which could possibly be regioselectively opened to the β-hydroxy-γ-lactone **48**, whose importance was already described in the retrosynthetic Scheme 3.4 (paragraph 3.2).



Scheme 3.7: Diastereoselective epoxidation of **1**.

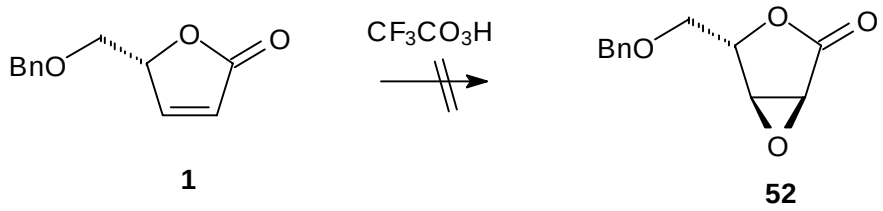
General reagents for the direct conversion of alkenes to epoxides are peroxycarboxylic acids. *m*-Chloroperoxybenzoic acid (*m*-CPBA), peroxyacetic acid (CH_3CO_3H), peroxybenzoic acid ($PhCO_3H$) and peroxytrifluoroacetic acid (CF_3CO_3H) are particularly convenient reagents due either a) to their simplicity of application (*m*-CPBA and CH_3CO_3H are commercially available) or b) for their strong oxidizing properties such as CF_3CO_3H (Scheme 3.8).



Scheme 3.8: Epoxidation of simple olefins

These epoxidations usually work well when the alkene is substituted with electron-donating groups. However, if electron-attracting substituents such as carbonyl groups are directly attached to the double bond, no epoxidation is usually observed. Here only the

strongly oxidizing agent CF_3CO_3H found limited applications[46]. No epoxidations of **1** were observed with any of the above reagents (Scheme 3.9).

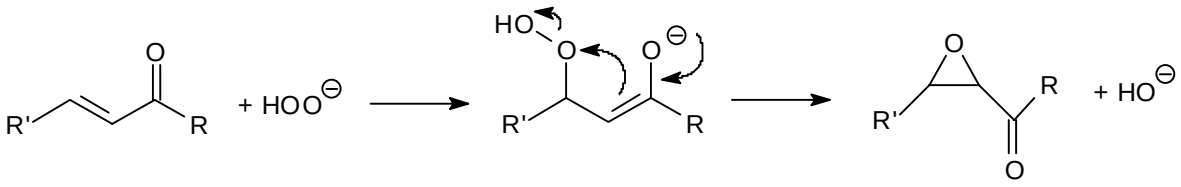


1 **52**

Scheme 3.9: Attempts to epoxidize **1** using CF_3CO_3H

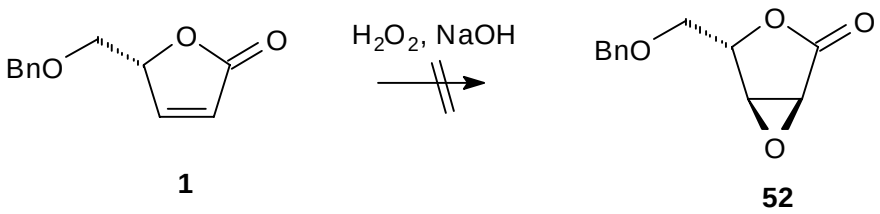
3.4.2 Epoxidation using H_2O_2

Another general method for the direct conversion of alkenes to epoxides employs the use of H_2O_2. The mechanism is completely different as observed in the case of peroxycarboxylic acids. Here, the reactive species is the deprotonated form of the peroxides and thus reactions have to be carried out under basic conditions (Scheme 3.10).



Scheme 3.10: Mechanism of olefin epoxidation by H_2O_2

1 was thus reacted under standard conditions using 30% aqueous H_2O_2 in MeOH and 4N NaOH as base. Unfortunately, again **52** could not be obtained following this procedure (Scheme 3.11). Tishler *et al.*[47] reported an extensive study on the epoxidation of butenolides. This paper confirms the difficulty to epoxidize butenolides such as **1** under standard conditions (the paper reports butenolides to be unreactive under all the published epoxidation methods).

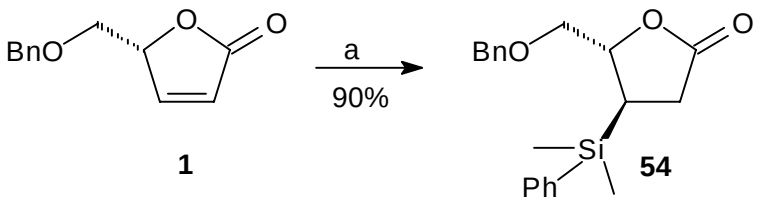


Scheme 3.11: Attempts to epoxidize **1** using H_2O_2

Also the use of dioxiranes[48] (e.g. dimethyl dioxiranes), which are reported to be capable to epoxidize double bonds conjugated with carbonyl groups were unsuccessful when applied to **1**.

3.5 Using the dimethyl-phenyl-silyl group as nucleophile

The β-hydroxy-γ-lactone **48** can potentially be synthesized from **1** using known Fleming chemistry[49] *via* Michael addition of the dimethyl-phenylsilyl group which, once introduced, can easily be transformed to an OH group[50]. The actual reagent for this 1,4-addition is the organocuprate with the formula $(PhMe_2Si)_2Cu(CN)Li_2$ which can be prepared directly from dimethyl-phenylsilyl chloride and lithium metal. This cuprate reagent has the disadvantage of being unstable and therefore must be prepared *in situ* immediately prior to use. Following this route cuprate addition of $(PhMe_2Si)_2Cu(CN)Li_2$ (**53**) to **1** indeed afforded the desired, corresponding silyl derivative **54** in 90% yield. As to judge from the ^{13}C-NMR, only the desired diastereoisomer was produced (Scheme 3.12).

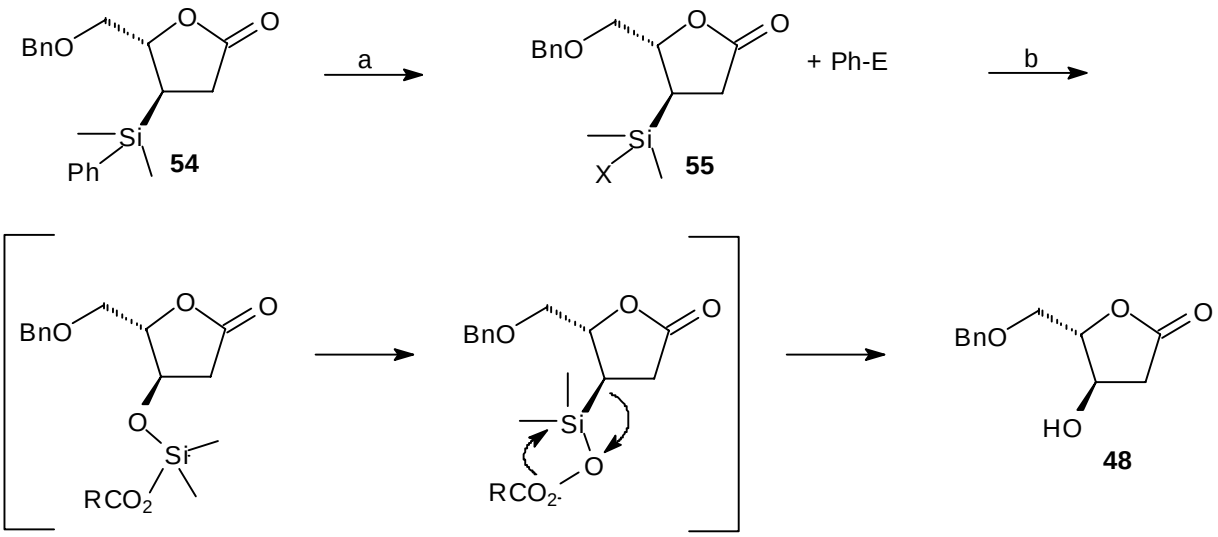


Scheme 3.12: a) $(PhMe_2Si)_2Cu(CN)Li_2$ (**53**), THF, -45 °C, 1h.

Normally the reagent is used in double excess to the substrate. This, of course, can cause some economical problems in large scale syntheses.

3.6 Conversion of the dimethyl-phenylsilyl group into-OH group

Fleming at al. also reported that a variety of reagents can transform the dimethyl-phenylsilyl function into an OH group[50]. As shown in Scheme 3.13, protodesilylation of the phenyl group can be accomplished in the simplest way by using HCl or HBF_4. If these two reagents are employed, the halogenosilyl intermediate **55** must first be isolated and then further reacted with peracids to afford the desired β-hydroxy-γ-lactone **48**. This is obtained with retention of configuration following the mechanism outlined in Scheme 3.13.

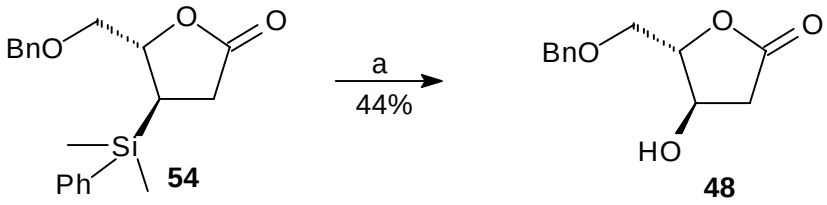


Scheme 3.13: Mechanism of peracid oxidation of the dimethyl-phenyl silyl group; a) E^+X^- = [$Hg(OAc)_2$, Br_2, HCl, HBF_4]; b) peracids.

However, also other reagents were described allowing the accomplishment of both steps a and b (Scheme 3.13) in the sense of a "one pot procedure", thus avoiding the isolation of the intermediate **55**.

3.6.1 Desilylation using $Hg(OAc)_2/AcO_2H$[50b]

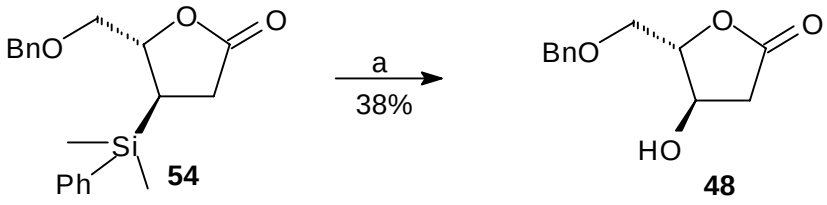
For this transformation an excess of AcO_2H and $Hg(OAc)_2$ was added to **54** and the resulting mixture stirred for 3h at rt. After work up the desired **48** was isolated in 44% yield with complete retention of configuration (Scheme 3.14).



Scheme 3.14: a) $Hg(OAc)_2$, AcO_2H, AcOH, rt, 3h.

3.6.2 Desilylation using $Hg(CF_3CO_2)_2/AcO_2H$[50c]

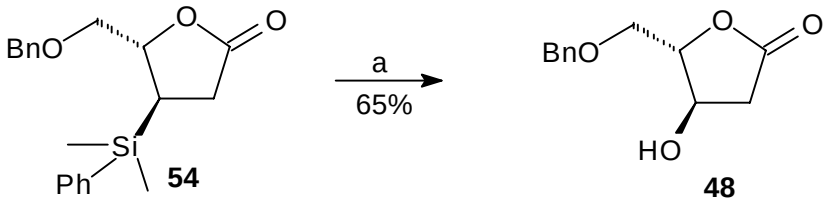
It was reported in the literature that the more active $Hg(CF_3CO_2)_2$ in some cases led to higher yields for this transformation. However, in our hands and using similar conditions as described for the $Hg(OAc)_2$ procedure (paragraph 3.6.1), **48** was produced with lower yield (38%, Scheme 3.15).



Scheme 3.15: a) $Hg(CF_3CO_2)_2$, AcO_2H, AcOH/CF_3CO_2H, 0 °C - rt, 3.5h.

3.6.3 Desilylation using Br_2/AcO_2H[50b]

Finally, conversion of the silyl derivative **54** into the corresponding β-hydroxy-γ-lactone **48** was achieved in 65% yield by using Br_2/AcO_2H at rt for 5h. In addition to producing the highest yield, this method has also the advantage of avoiding mercury containing reagents (Scheme 3.16).



Scheme 3.16: a) Br_2 (1M in AcOH), AcO_2H, 0 °C - rt, 5h.

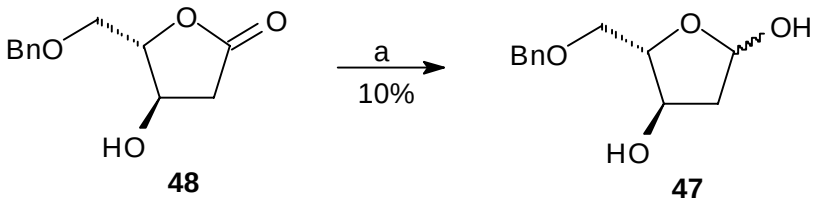
Furthermore this method can be carried out without using elemental bromine which can be produced *in situ* by oxidation of KBr to Br_2. The yields are comparable with those obtained if Br_2 is used directly.

*3.7 Reduction of lactone **48** to lactol **47***

For the reduction of the lactone **48** to the lactol **47** two different method were tested.

3.7.1 Using DIBAL

Diisobutylaluminum hydride (DIBAL) is reported to reduce selectively esters and lactones to aldehydes and hemiacetals respectively[51]. Using three equivalents of DIBAL for the reduction of **48** at –78 °C for 4h led to **47** in only 10% yield together with unreacted starting material. All attempts to increase the yield by extending the reaction times or increasing the temperature (e.g. –50 °C for 7h) did not lead to any improvement (Scheme 3.17).

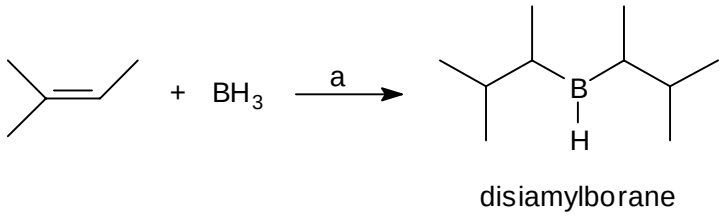


48 **47**

Scheme 3.17: a) DIBAL, THF, -78 °C, 4h.

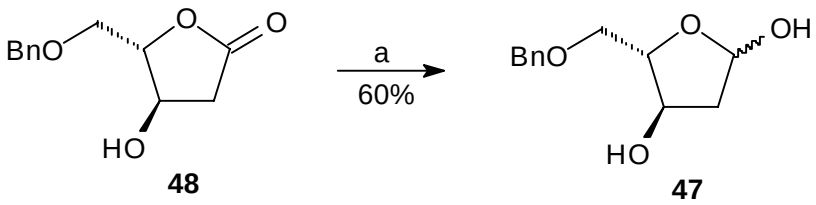
3.7.2 Using Disiamylborane

It is reported in the literature[52] that disiamylborane can selectively reduce lactones to lactols. Disiamylborane is not commercially available, but can be easily prepared *in situ* from BH_3 (1M solution in THF) and 2-methyl-2-butene (Scheme 3.18)



Scheme 3.18: *In situ* preparation of disiamylborane a) THF, 0 °C, 20min

Thus, the β-hydroxy-γ-lactone **48** was reacted with an excess of disiamylborane in THF for 24h at rt and the corresponding lactol **47** was obtained in 60% yield as anomeric mixture ($\alpha/\beta \cong 70/30$ in $CDCl_3$, Scheme 3.19).



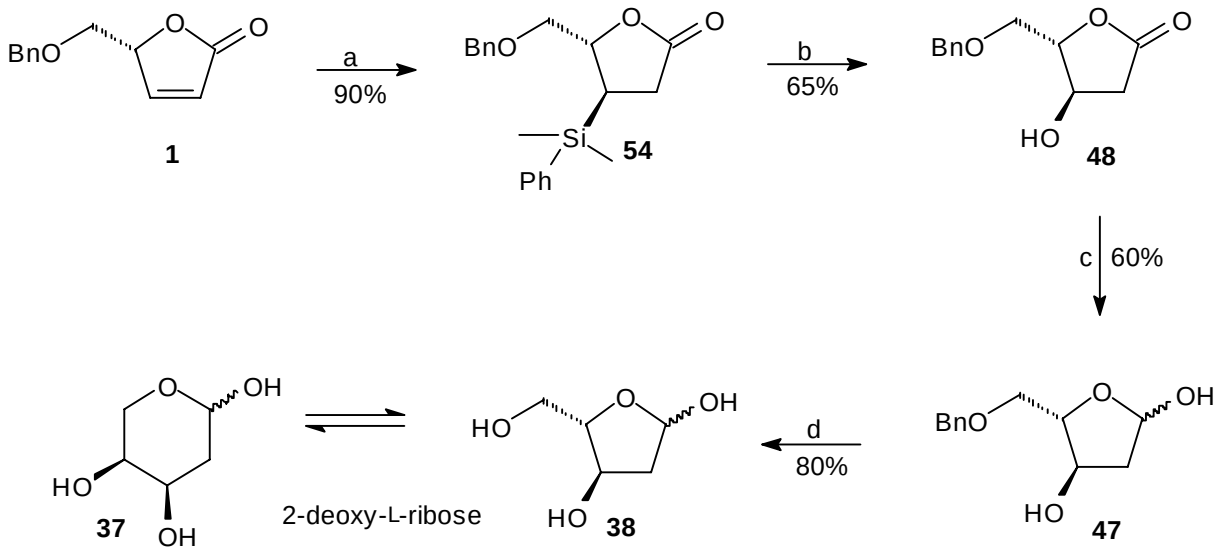
48 **47**

Scheme 3.19: a) disiamylborane, THF, rt, 24h.

47 represents the desired building block for the synthesis of 2-deoxy-L-nucleosides. Starting from *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**) we were able to produce **47** this way in 35% overall yield. The applications of **47** for the syntheses of nucleosides are described in chapter 4.

3.8 Synthesis of 2-Deoxy-L-ribose: removal of the benzyl protecting group

The removal of the benzyl group in **47** would led directly to 2-deoxy-L-ribose. It was known from the literature[53] that we would obtain a mixture of the pyranoside and furanoside forms this way. Therefore, for synthesis of nucleosides, the benzyl protected building block **47** would have to be employed. However, in order to show the effectiveness of our route and in order to allow a comparison of the final sugar with natural 2-deoxy-D-ribose, we carried out the deprotection by using transfer hydrogenation[54] (HCOOH, Pd/C 10%) in MeOH at rt for 1h.



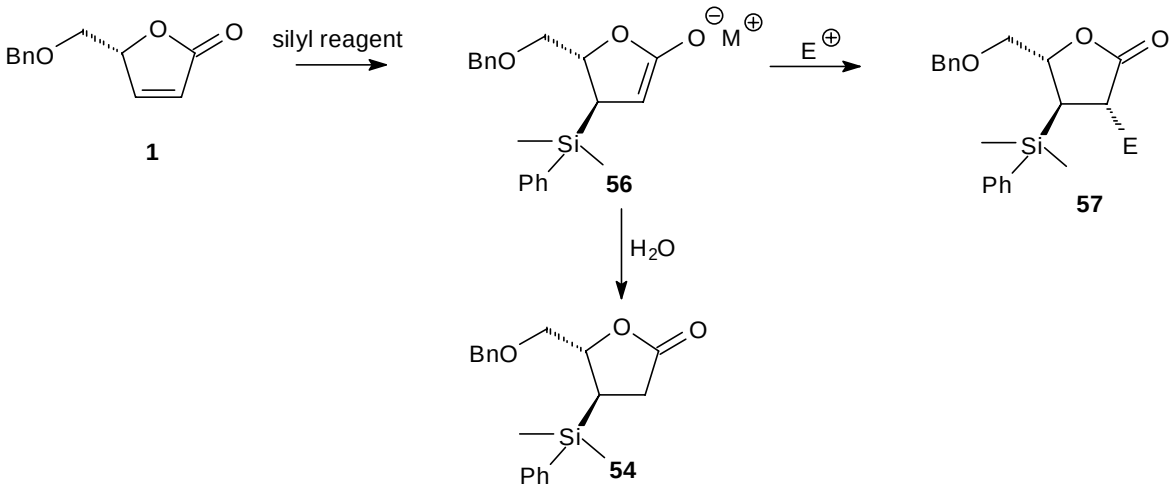
Scheme 3.20: a) $(PhMe_2Si)_2Cu(CN)Li_2$ (**53**), THF, -45 °C, 1h; b) Br_2, AcOOH, AcOH, rt, 5h; c) disiamylborane, THF, rt, 24h; d) HCOOH, 10% Pd/C, MeOH, rt, 1h.

As shown in Scheme 3.20 (which also summarizes the complete, optimized route from **1**), this way 2-deoxy-L-ribose was obtained in 80% yield as a mixture of the α,β-pyranose **37** and the α,β-furanose **38** in a ratio of 72:28. The anomeric ratios for **37** and **38** were nearly 1:1 in both cases (^{1}H-NMR analysis).

In summary, the above described route allowed the synthesis of 2-deoxy-L-ribose with an overall yield of 28% starting from *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**).

*3.9 Enolate trapping with electrophiles: 2-hydroxylation of **54***

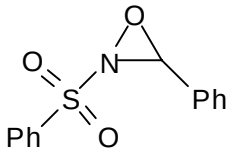
Another synthetic possibility offered by the silyl derivative **54** involves the insertion of a substituent into the 2-position. In paragraphs 3.7 and 3.8 we have described the utility of the cuprate reagent $(PhMe_2Si)_2Cu(CN)Li_2$ (**53**) as "masked" OH group. When this cuprate reagent reacts with α,β-unsaturated carbonyl systems such as in **1**, the enolate **56** is first formed which, upon quenching with water, yields the desired β-silyl derivative **54** (Scheme 3.21). If, however, **56** could be trapped with an electrophile, the 2-substituted derivatives with the general structure of **57** could be formed. As a further advantage, the bulky dimethyl-phenylsilyl group could direct this addition diastereoselectively from the opposite face.



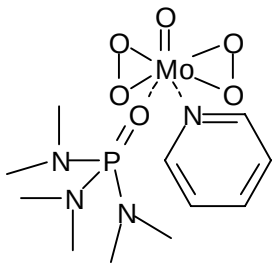
Scheme 3.21: Enolate trapping with electrophiles

Clearly, in planning the synthesis of nucleosides an introduction of an hydroxy group into the 2-position was of major interest (chapter 4). We were therefore looking for an "electrophilic OH-reagent". In the literature essentially two reagents are described for this propose:

- 3-phenyl-2-(phenylsulfonyl)-oxaziridine (Davis' reagent, **58**)[55] and
- Oxodiperoxy molybdenum-(pyridine)-hexamethyl-phosphoric triamide (MoOPH, Mimoun' reagent, **59**[56], Figure 3.2).



58



59

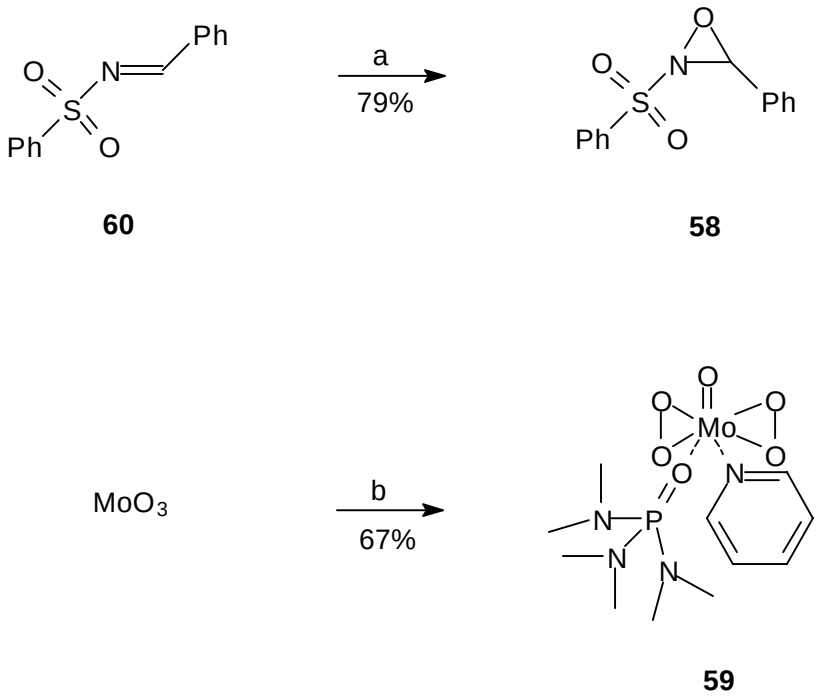
Figure 3.2: The Davis' and Mimoun' reagents

Both are instable and therefore not commercially available. However, once prepared they can be stored in a freezer for several months.

58 was prepared by oxidation of *N*-benzylidene-benzensulfonamide (**60**) in a biphasic system consisting of toluene/H_2O and using potassium monopersulfate triple salt Oxone® ($2KHSO_5.KHSO_4.K_2SO_4$) as oxidant. **58** was isolated in 79% yield (Scheme 3.22).

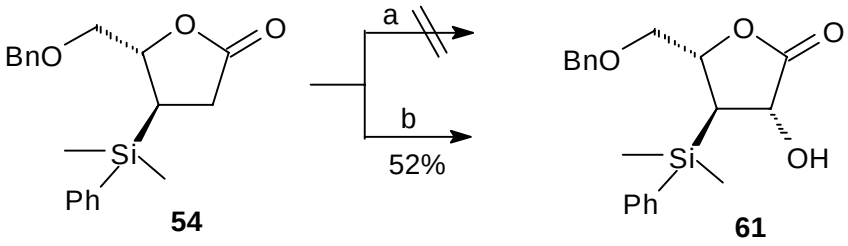
The preparation of **59** was accomplished by oxidation of MoO_3 with 30% H_2O_2 followed by precipitation of the resulting yellow solid by addition of pyridine and HMPT in anhydrous THF (Scheme 3.22).

Our first attempts to introduce the OH group by trapping the enolate **56** (Scheme 3.21) in the presence of either **58** or **59** completely failed. It seemed that the complex salt mixture present following the cuprate addition to **1** interferes with these reagents. Therefore, subsequently we decided to first isolate the β-silyl derivative **54** prior to these reactions.



Scheme 3.22: a) Oxone®, K_2CO_3, toluene, H_2O, rt, 30min; b) 1. 30% H_2O_2, 40 °C, 3.5h, HMPT. 2. pyridine.

Using the Davis' reagent **58** in THF at –78 °C, and employing different bases for the deprotonation (KMDS, LDA), no product was isolated. In contrast, however, and under similar conditions, the Mimoun' reagent **59** indeed led to (3*S*,4*R*,5*S*)-(-)-5-benzyloxymethyl-4-(dimethyl-phenyl-silanyl)-3-hydroxy-dihydro-furan-2-one (**61**) in 52% yield as a single diastereoisomer (^{13}C-NMR). The use of 2 equivalents of base (KMDS) at –60 °C for 1h proved to be the optimal reaction conditions (Scheme 3.23). **61** could be an attractive starting material for L-arabinose.



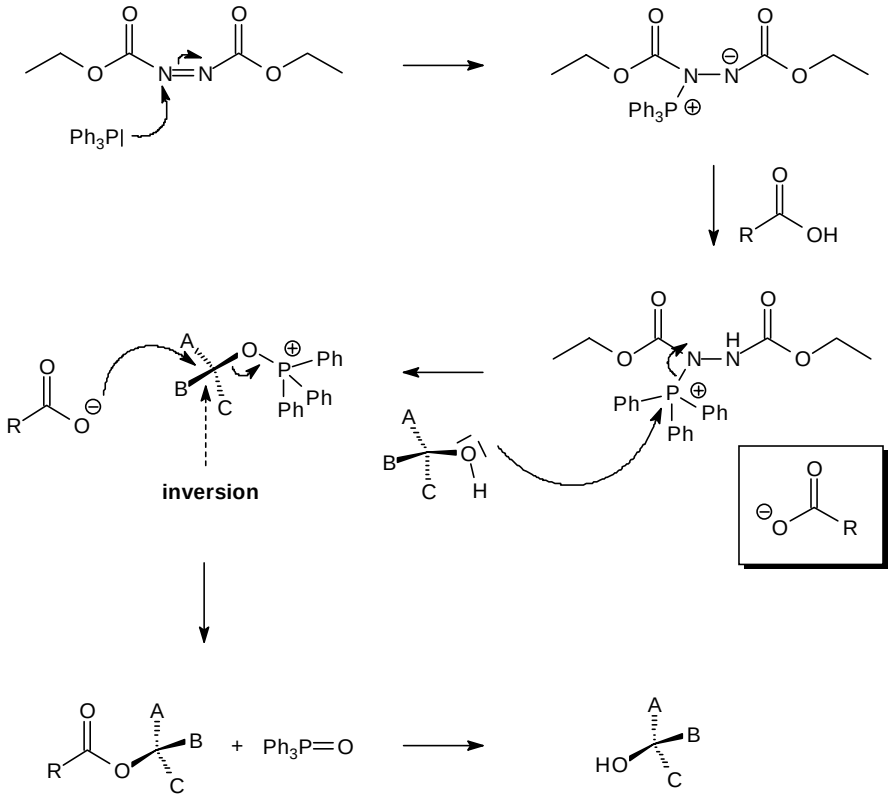
Scheme 3.23: a) Davis' reagent **58**, THF, LDA or KMDS; b) Mimoun' reagent **59**, KMDS, THF, -60 °C, 1h.

*3.10 Inversion of the 2-OH group in **61** - Attempts*

The successful synthesis of diastereomerically pure **61** opened a variety of additional synthetic possibilities. Thus, in the synthesis of nucleosides the 2-OH group could direct the diastereoselective insertion of a nucleobase from the opposite face leading to α-configurated anomers of L-nucleosides. We also considered the possibility to invert the configuration of the 2-OH group in order to prepare the corresponding building blocks for both the synthesis of α and β-L-nucleosides.

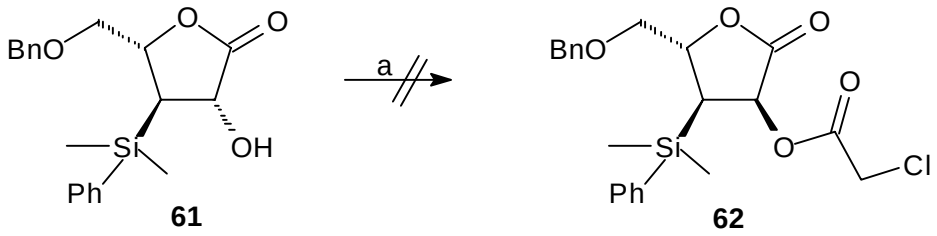
3.10.1 The Mitsunobu reaction[57]

The Mitsunobu reaction is one of the most widely used methods for the inversion of hydroxy groups (Scheme 3.24).



Scheme 3.24: Mechanism of the Mitsunobu reaction

However, according to the literature problems are encountered when the hydroxy function to be inverted is sterically hindered such as in the case of secondary OH groups in γ-lactones[58]. As standard reagent for the Mitsunobu reaction carboxylic acids are employed which serve as nucleophile and thus lead to the inverted alcohol in form of its carboxylic ester. For the inversion of the 2-OH group in **61** we decided to employ chloroacetic acid mainly for two reasons: a) chloroacetic acid is a small nucleophile and therefore could avoid sterical problems and b) the chloroacetate of the desired **62** can be selectively hydrolyzed in the presence of the lactone moiety by using thiourea/$NaHCO_3$[59].
Unfortunately, however, no reaction was observed when these Mitsunobu conditions were applied to **61** (Scheme 3.25).

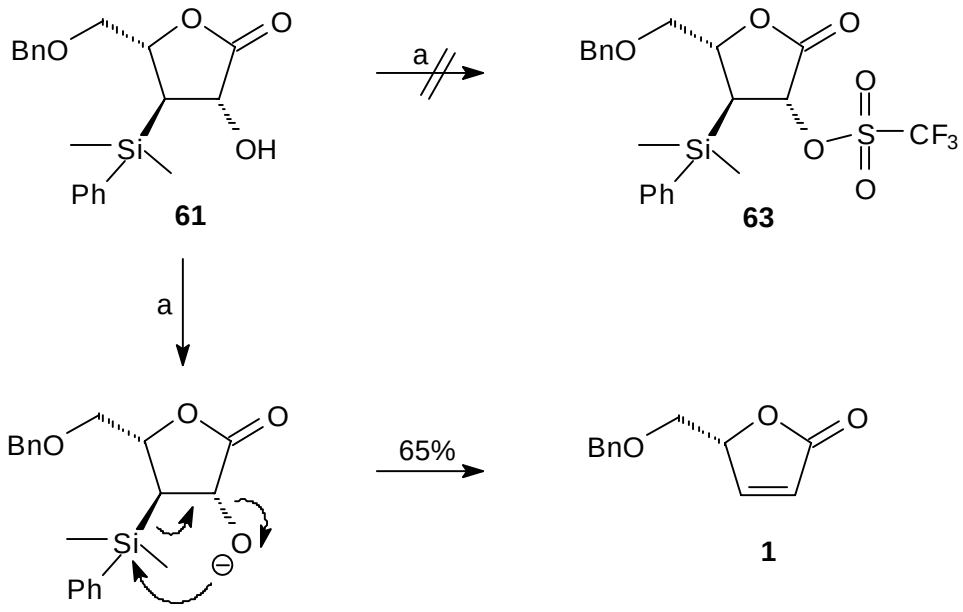


61 **62**

Scheme 3.25: a) Ph_3P, DEAD, $ClCH_2COOH$, toluene, rt – reflux.

3.10.2 The KNO_2/triflate method

In an article published by Moriarty *at al.*[58] the superiority of KNO_2 for the inversion of hindered alcohols was reported. For this, the OH group must first be activated by transformation into its triflate ester which could then be displaced following a S_N2 mechanism into the corresponding, inverted alcohol. Thus, **61** was reacted in dichloromethane at 0 °C with triflic anhydride (Tf_2O) using pyridine as base. Under this conditions, however, the triflate ester **63** was not obtained. In contrast, Peterson elimination[60] occurred leading to **1** with the double bond in the 2,3 positions (Scheme 3.26).

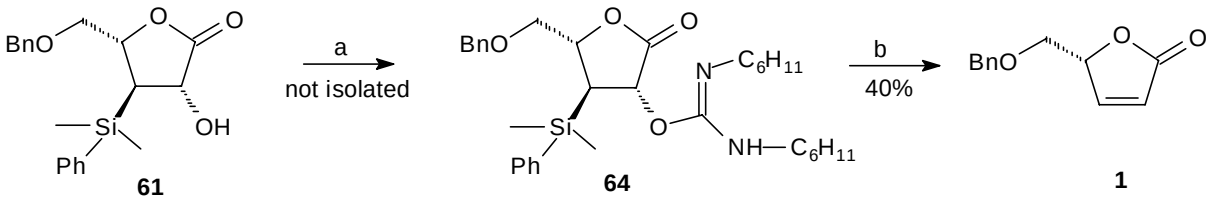


Scheme 3.26: a) Tf_2O, pyridine, CH_2Cl_2, 0 °C, 3h.

Since this elimination is catalyzed both by bases and acids and independent of the order of addition of the reagents, **1** is always formed. A recent publication by Lambert *et al.*[61] confirms the high instability of such *trans* β-hydroxysilanes even when activated in form of the less reactive mesylate esters.

3.10.3 The DCC/CuCl method[62]

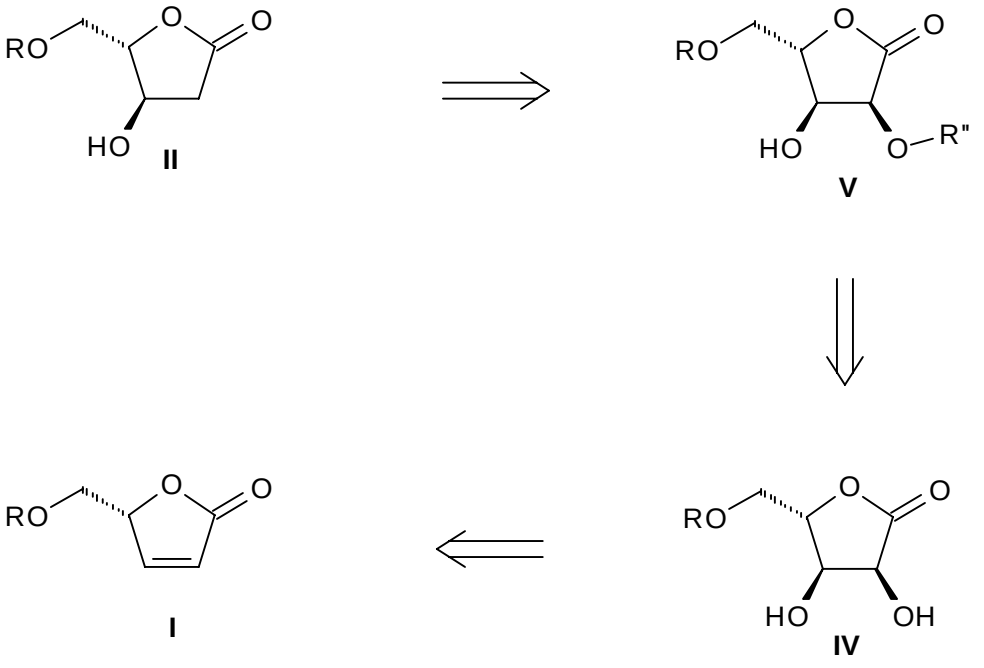
In the literature it was reported that the system dicyclohexylcarbodiimide (DCC)/CuCl can activate alcohols so that they can be displaced with carboxylic acids. This reaction, in comparison to the Mitsunobu reaction[57], employs the "smaller" activating agent DCC in contrast to the bulky DEAD/triphenylphosphonium complex formed during the Mitsunobu reaction (compare Scheme 3.24). Clearly the intermediate **64** is first formed. However, when **64** was reacted with chloroacetic acid, the butenolide **1** was again the only product (Scheme 3.27).



Scheme 3.27: a) DCC, CuCl, dioxane, 3 days, 50°C; b) $ClCH_2CO_2H$.

*3.11 Dihydroxylation of the double bond of **1***

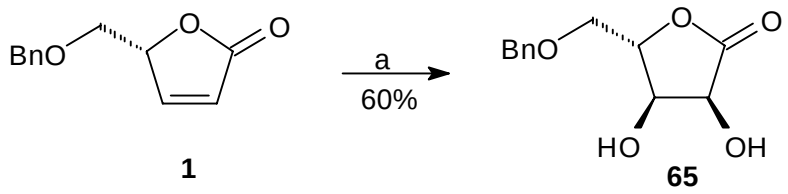
As already described in the retrosynthetic Scheme 1.1 (chapter 1), the insertion of two hydroxy groups in the crucial 2 and 3 positions of **1** could open another route towards the synthesis of 2-deoxy-L-ribose *via* regioselective deoxygenation of the 2-OH group in the thus produced **V** (Scheme 3.28).



Scheme 3.28: Retrosynthesis of β-hydroxy-lactone **II** *via* dihydroxylation of the double bond in **1**

Mukaiyama *at al.*[63] described the dihydroxylation of butenolides using $KMnO_4$ in dichloromethane in the presence of crown ethers. Following this procedure ($KMnO_4$, dicyclohexano-18-crown-6, CH_2Cl_2, -42 °C, 2h), **1** was thus reacted and indeed the

dihydroxylated product **65** was obtained in 50% yield as a single isomer (NMR analyses) together with unreacted starting material (60% recovered yield, Scheme 3.29).



1 **65**

Scheme 3.29: a) $KMnO_4$, dicyclohexano-18-crown-6, dichloromethane, -42 °C, 2h

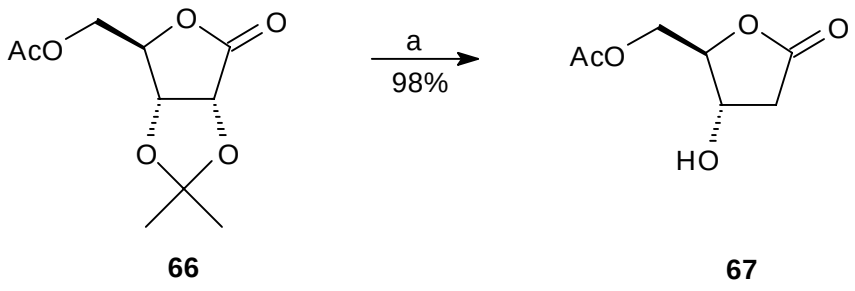
If the same reaction is carried out employing the one phase system acetone/H_2O[64], a yield of only 27% is obtained.

*3.12 Regioselective 2-deoxygenation of **65***

Once **65** was obtained this way, the next step of course was the regioselective removal of the 2-OH group in this material. Several methods to this effect are described in the literature.

3.12.1 2-Deoxygenation using SmI_2

Hanessian *at al.*[65] reported the deoxygenation of cyclic acetals such as **66** (easily obtainable from *cis* diols) *via* the one-electron-transfer reagent samarium iodide (SmI_2) leading to α-deoxy-lactones **67**. A number of such examples were described, leading to the corresponding products in very good yields and in very short reaction times (Scheme 3.30).



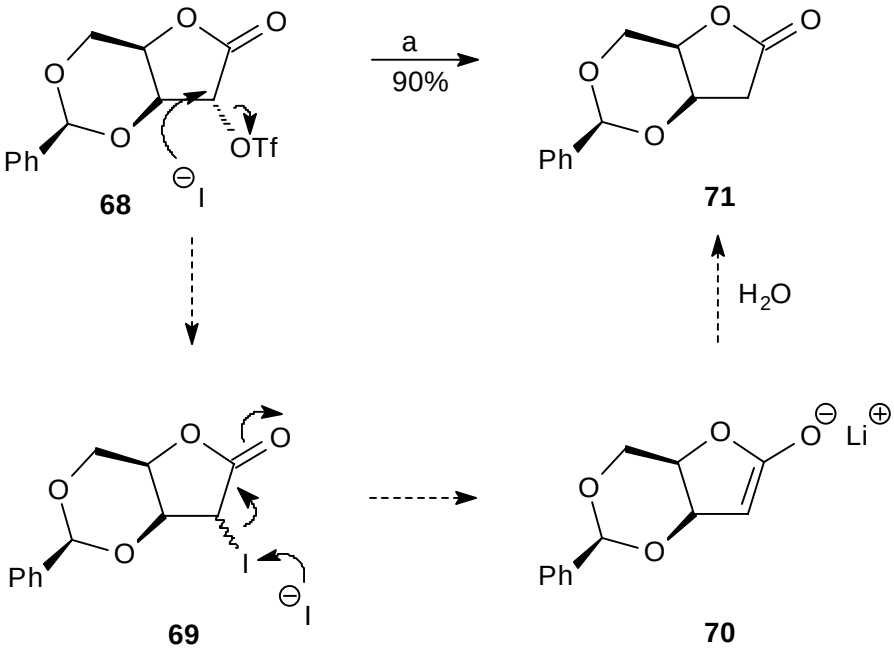
66 **67**

Scheme 3.30: a) SmI_2, ethylene glycol, THF, rt, 3h.

Samarium iodide, however, is weakly radioactive (α-rays, spec. activity 1.2 Bq/ml) and is not commercially available in Germany by standard suppliers.

3.12.2 Deoxygenation of the corresponding 2-triflate esters

Fleet *et al.*[66] reported several examples for the deoxygenation of a triflate function in the α-position of a lactone moiety using lithium iodide.



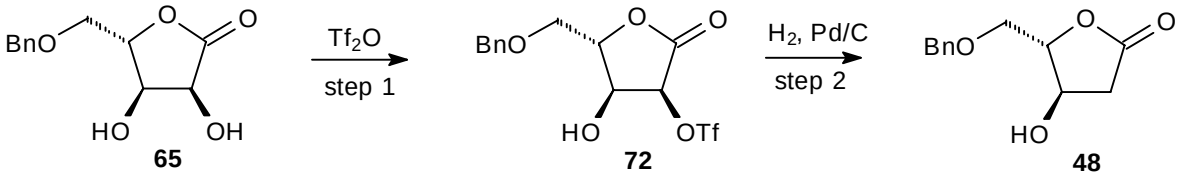
68 **71** **69** **70**

Scheme 3.31: a) LiI-$3H_2O$, THF, AcOH, reflux, 12h.

As shown in Scheme 3.31, the mechanism of this reaction involves the nucleophilic attack of the iodide anion to the activated electrophilic 2-carbon atom of the lactone **68**. By this the corresponding 2-iodo-derivative **69** is obtained as a mixture of diastereoisomers (S_N1 type reaction also involved). Further reaction of the 2-iodo-derivative **69** with a second iodide forms the corresponding enolate **70** which upon aqueous work-up forms the desired 2-deoxy-lactone **71**.

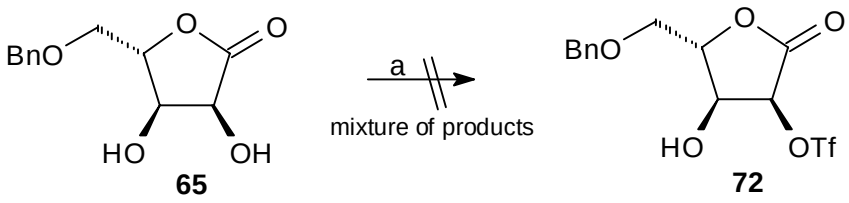
The reported yields are very high. However, based on the described examples it seemed necessary to protect all OH groups, requiring for our substrate **65** several additional steps for the required protections and deprotections.

However another good method for the deoxygenation of triflates in the α-position of the lactone moiety is described in the literature[67]. Hydrogenolysis using 10% Pd/C in the presence of a base in order to neutralize the produced TfOH leads to the deoxygenated products in high yields (Scheme 3.32).



Scheme 3.32: Deoxygenation of the 2-OH group in **65**

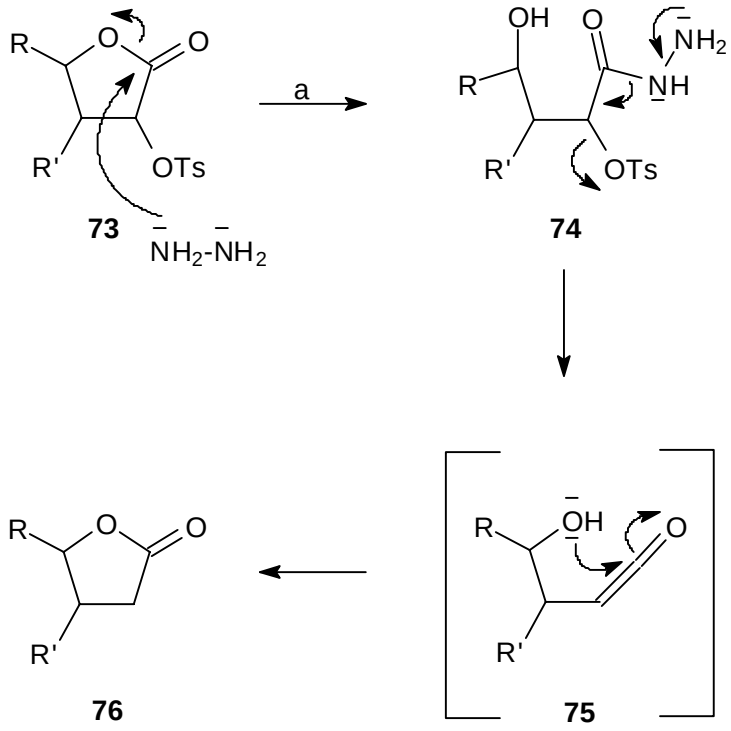
For our target products the 2-*O*-Tf derivative **72** clearly is the substrate of choice. For this, however, a regioselective protection of **65** is required. Examples for this are already reported in the literature[67,68]. However, when **65** was reacted in THF/pyridine at –20 °C using 1 equivalent of triflic anhydride (Tf_2O), a complex mixture of products was obtained which renders this method not advantageous for our propose (Scheme 3.33)



Scheme 3.33: a) Tf_2O, THF/pyridine, –20 °C.

3.12.3 Deoxygenation of tosylate esters

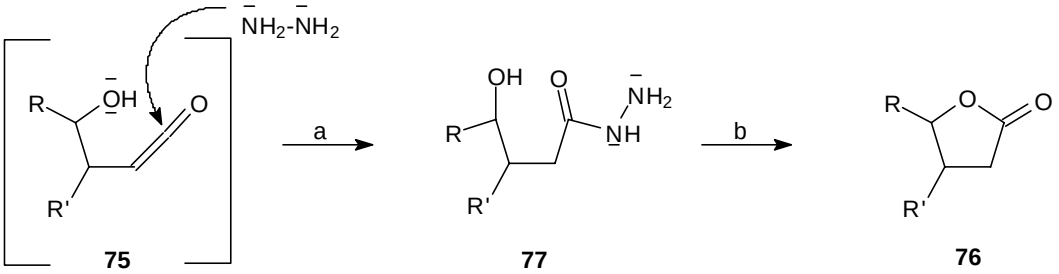
Paulsen and Stoye[69] reported the deoxygenation of tosylates in the α-position of lactones using hydrazine. A detailed mechanistic study of this deoxygenation reaction is reported. Stoichiometric amounts of hydrazine and anhydrous conditions are required in order to favor the formation of the desired 2-deoxy-lactones (Scheme 3.34).



Scheme 3.34: a) 1eq NH_2NH_2, dry solvent

Nucleophilic addition of hydrazine to the carbonyl group of the lactone **73** forms the hydrazide **74**, which spontaneously eliminates diimide. This, in turn disproportionates to hydrazine and nitrogen. The resulting ketene **75** is highly instable and if the reaction is carried out without an excess of hydrazine and in complete absence of water, the cyclization to the 2-deoxy-lactone **76** occurs.

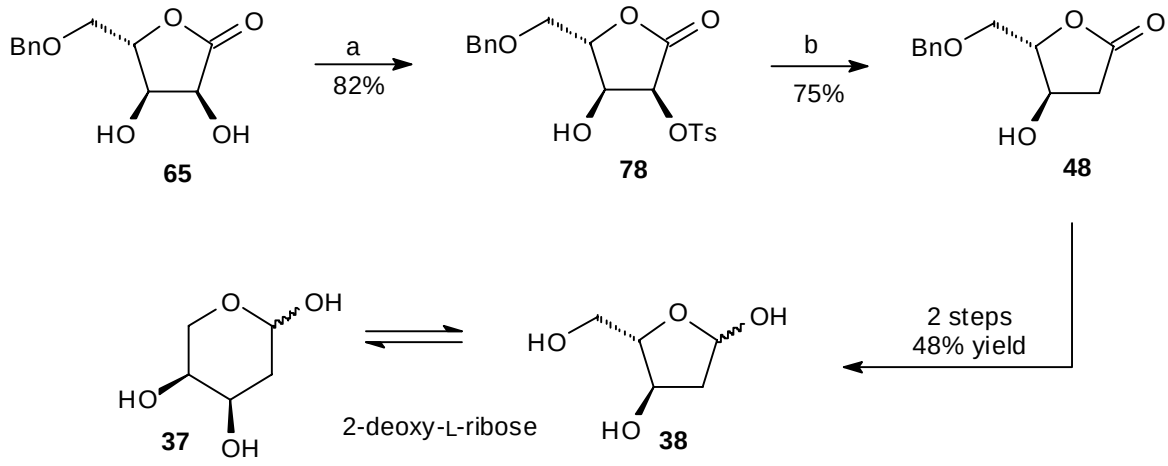
In a modification[70] of this procedure and with an excess of hydrazine hydrate the hydrazide **77** can be formed resulting from the reaction of hydrazine with the ketene **75**. **77** is stable and can be isolated if needed. It can also be oxidized *in situ* with Br_2/H_2O to the corresponding lactone **76** (Scheme 3.35).



Scheme 3.35: a) excess of 80% aqueous NH_2NH_2; b) Br_2, H_2O.

3.12.4 Synthesis of 2-Deoxy-L-ribose *via* deoxygenation of tosylate esters

With this background we tested the reactivity of TsCl towards **65** in order to regioselectively protect its 2-OH group. This reaction proved to be highly sensitive to the employed temperature and the solvent used. Thus, first attempts carried out in acetone at 0 °C yielded the tosylate **78** in only 50% yield. Furthermore. the reaction was not completely regioselective. Finally and after several attempts, regioselective protection of the 2-OH group was accomplished successfully with *p*-TsCl in dichloromethane at –20 °C for 18h leading to the regioisomer **78** in 82% yield. This was then further reacted with an 80% aqueous solution of hydrazine and bromine in THF at 0 °C leading to the desired β-hydroxy γ-lactone **48** in 75% yield (Scheme 3.36).



Scheme 3.36: a) *p*-TsCl, Et_3N, dichloromethane, -20 °C, 18h; b) aq. NH_2NH_2, Br_2, THF, 0 °C-rt, 30min.

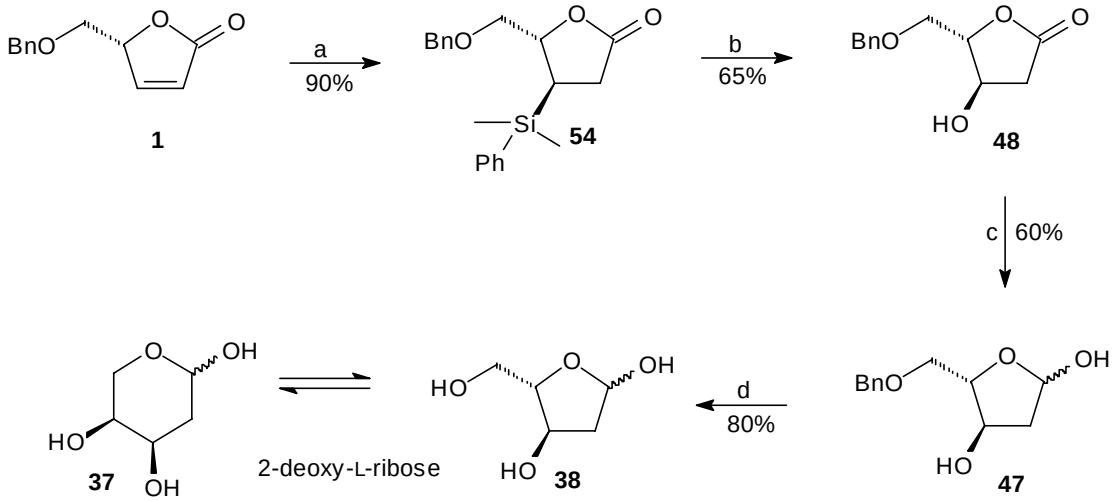
As already described in paragraphs 3.7 and 3.8 (compare also scheme 3.20) **48** can be transformed in 2-deoxy-L-ribose in two steps with an overall yield of 48%.

In comparison to the previously reported method for the synthesis of 2-deoxy-L-ribose (using the dimethyl-phenyl silyl group, paragraph 3.5) we feel that this route has several advantages in using a) simpler procedures, b) commercially available reagents and c) being faster. The only remaining drawback is the requirement for one additional step to transform *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**) into 2-deoxy-L-ribose and this with a lower overall yield (18%) as compared to the silyl based procedure (28%). This, however in our opinion, is more than compensated by the above rapid and facile procedure.

3.13 2-Deoxy-L-ribose and building blocks derived thereof - Summary

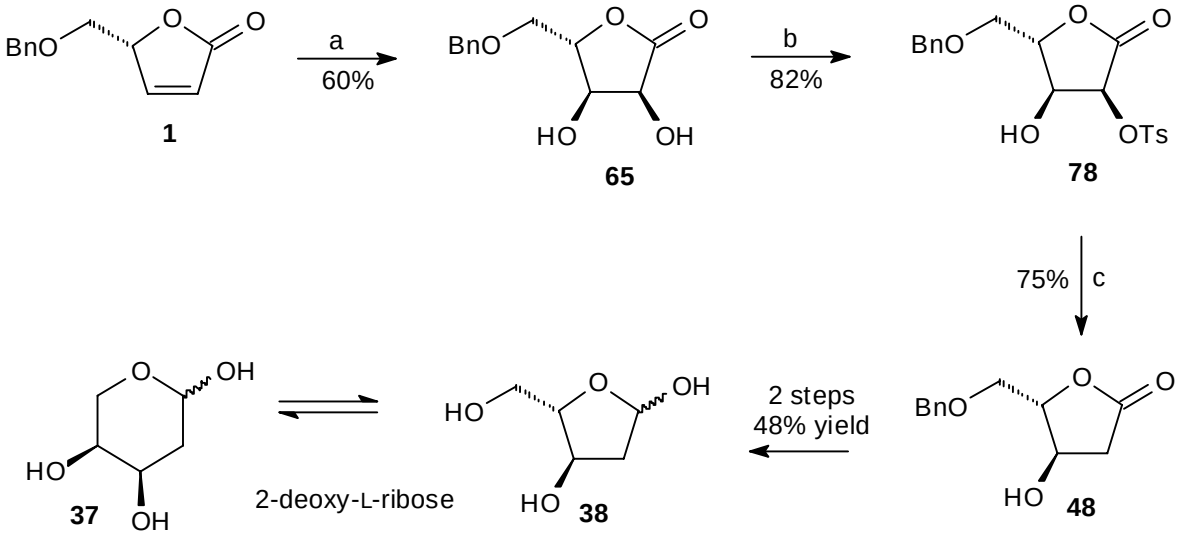
In conclusion, we have devised two novel and efficient routes to the above target molecules starting from our central building block **1** and based on two different concepts for the regioselective hydroxylation of the 3 (3')-position:

a) Diastereoselective 1,4-addition of a silyl cuprate followed by the **introduction** of the 3-OH group under retention of configuration (Scheme 3.37)



Scheme 3.37: a) $(PhMe_2Si)_2Cu(CN)Li_2$ (**53**), THF, -45 °C, 1h; b) Br_2, AcOOH, AcOH, rt, 5h; c) disiamylborane, THF, rt, 24h; e) HCOOH, 10% Pd/C, MeOH, rt, 1h.

b) Diastereoselective dihydroxylation of 1 followed by regioselective **removal** of the 2-OH group (Scheme 3.38).



Scheme 3.38: a) $KMnO_4$, dicyclohexano-18-crown-6, dichloromethane, -42 °C, 2h; b) *p*-TsCl, Et_3N, dichloromethane, -20 °C, 18h; c) aq. NH_2NH_2, Br_2, THF, 0 °C-rt, 30min.

4 2-Deoxy-L-nucleosides – Formation of *N*-glycosidic bonds

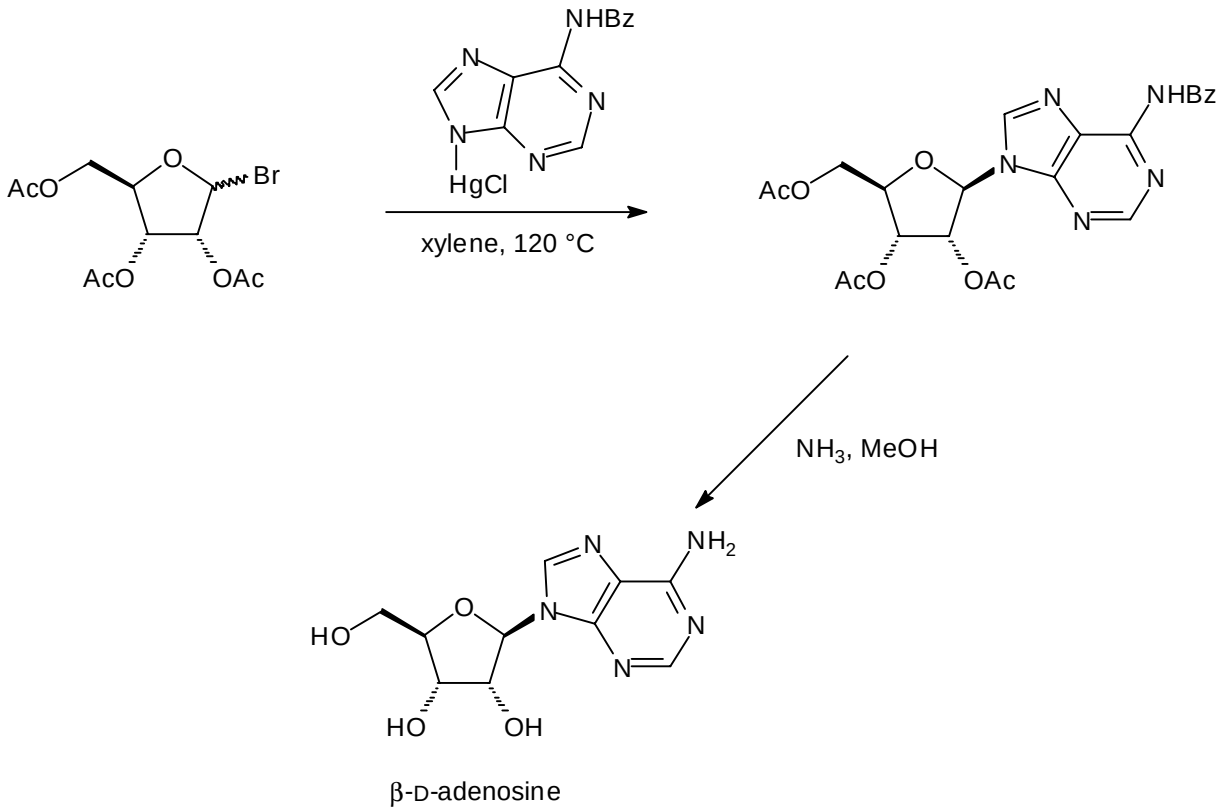
In the past most syntheses of nucleosides were designed to prove the structures of various ribo- and deoxyribonucleosides. Now such syntheses are aimed mainly at producing nucleoside analogues of therapeutic value. In spite of many advances in this area, it remains more economical to produce the major natural nucleosides by degrading nucleic acids rather than by total synthesis[71].

Several general methods for the synthesis of nucleosides have been developed over the years mainly focused at the stereoselective formation of *N*-glycosidic bonds.

4.1 Formation of N-glycosidic bonds: Coupling reactions using heavy metal salts

Fischer and Helferich[72] introduced the use of heavy metal salts [initially silver (I)] of a purine base to catalyze the nucleophilic displacement of a halogen substituent at *C*-1 of a protected sugar. In a later modification[73] mercury (II) salts were used in order to improve the yields of the resulting products. These syntheses lead to products with the desired regioselectivity, i.e. bonding to *N*-9 of the purine base and in most cases also the β-stereoselectivity at *C*-1 of the sugar moiety is achieved (Scheme 4.1).

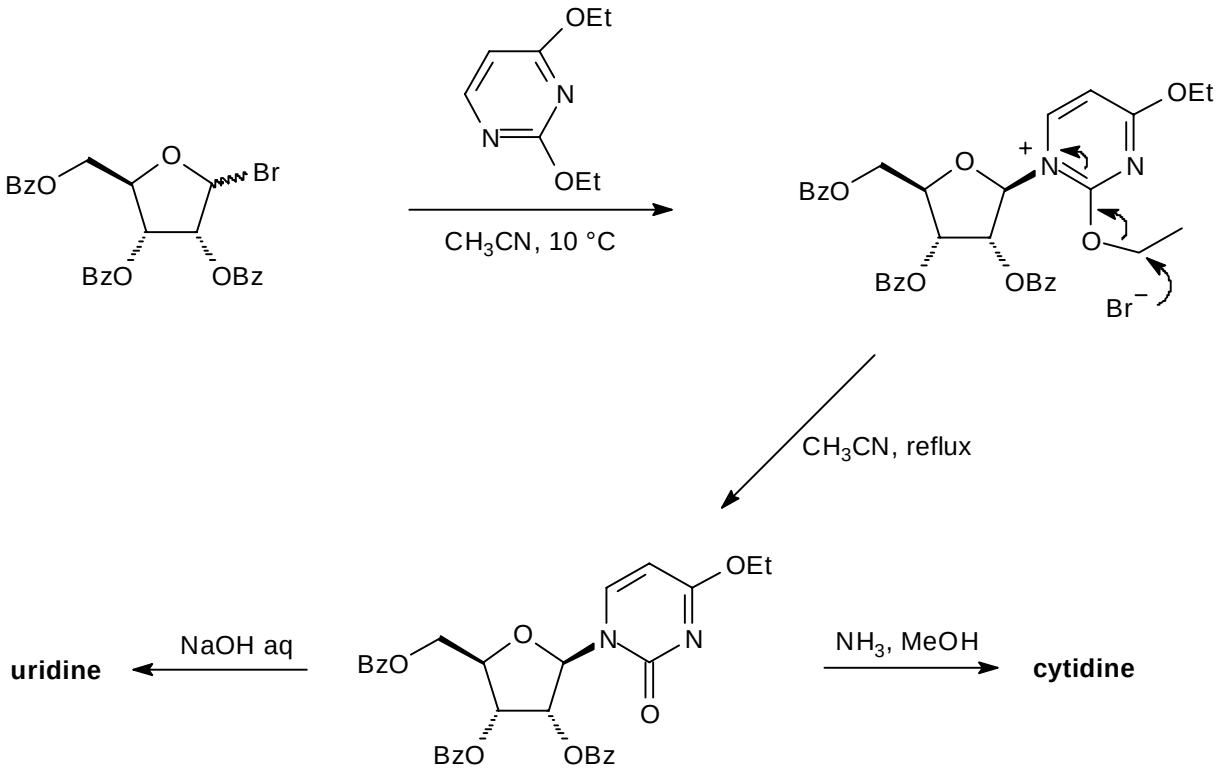
Major disadvantages of the above described methods are a) the low solubility of the mercury derivatives and b) the instability of the 1-halogenated sugar. The methods can be somewhat improved if the 1-halogenated sugar is generated *in situ* by the use of $TiCl_4$ or $SnCl_4$.



Scheme 4.1: Synthesis of adenosine using heavy metal salts of nucleobases.

4.2 Nucleoside synthesis: the quaternization procedure

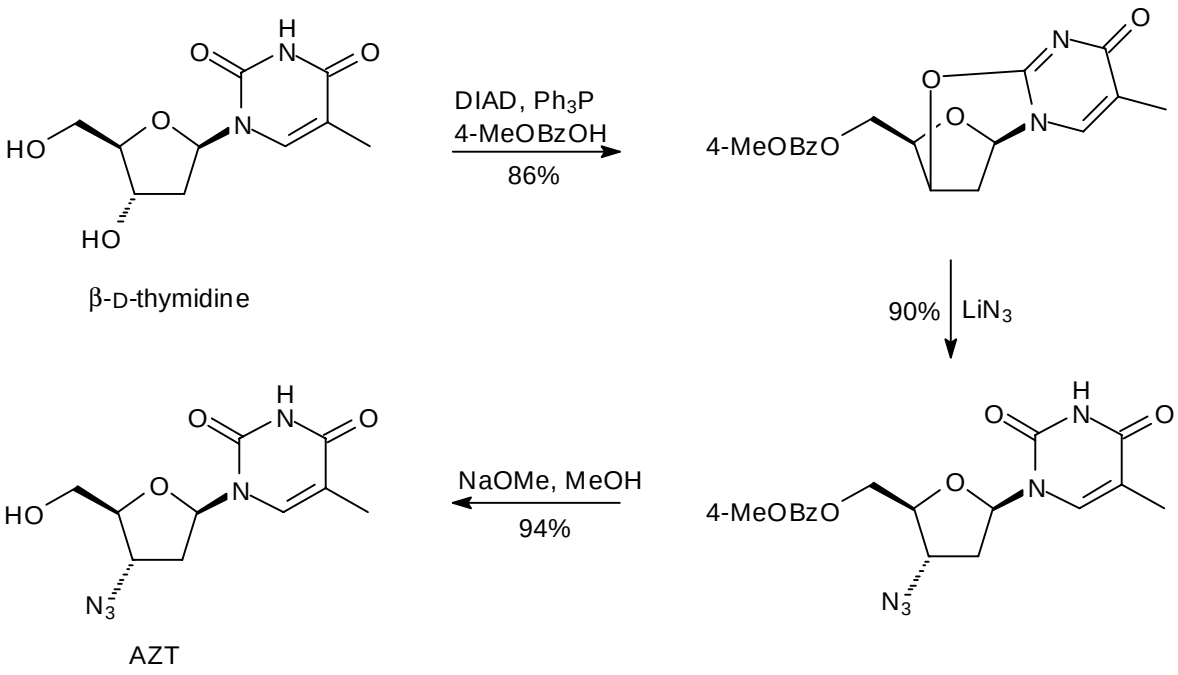
Hilbert and Johnson[74] noticed that pyrimidines are sufficiently nucleophilic in order to react directly with halogenated sugars without the need for a catalyst. The initial product is a quaternary salt which, at higher temperature, eliminates alkyl halide leading to a condensation product which can be further modified to produce natural nucleosides (Scheme 4.2) The major disadvantage of this method is the formation of mixtures of α and β anomers, although the use of $HgBr_2$ increases the proportion of the desired β-anomers.



Scheme 4.2: Nucleoside synthesis *via* the quaternization method

4.3 Nucleoside synthesis via transglycosylation

Sometimes it is possible to convert natural nucleosides into nucleosides having a modified sugar moiety. This way, the antiviral AZT has been synthesized using thymidine as starting material[75]. For this the natural thymidine was reacted under the Mitsunobu conditions to afford a cyclic intermediate which upon treatment with lithium azide and hydrolysis of the 5'-*O*-carboxylic ester afforded AZT in 73% overall yield (Scheme 4.3).

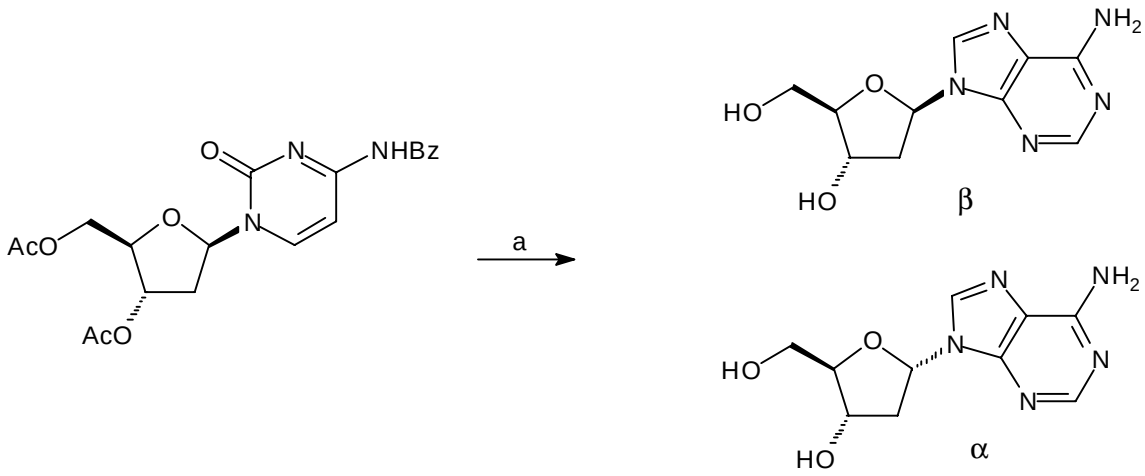


Scheme 4.3: Synthesis of AZT[75]

When such transformations are not possible (i.e. in 2'-deoxyadenosine) the sugar moiety can be transferred from one nucleobase to another by a process known as transglycosidation.

This method is particularly effective in transferring sugars from pyrimidines (π-deficient heterocycles) to purines (π-rich heterocycles). Disadvantages are associated with the typical problems of all S_N1 mechanisms: formation of diastereoisomeric mixtures of α and β anomers and the lack of regioselectivity (formation of *N*-7 and *N*-9 regioisomers).

This method allowed the synthesis of α-anomers of purine nucleosides which sometimes can be separated by chromatography from the corresponding β-anomers (Scheme 4.4). The use of the Friedel Crafts catalyst TMS-triflate allows for the formation of the carbocation at C-1 which reacts with the more basic silylated adenine to form a mixture of α and β acetyl protected anomers. Subsequently, aminolysis of the ester groups produces the mixture of α and β adenosine.



Scheme 4.4: a) 1. TMS-benzoyladenine, TMS-triflate; 2. NH_3, MeOH.

4.4 Nucleoside synthesis via the Vorbrüggen method

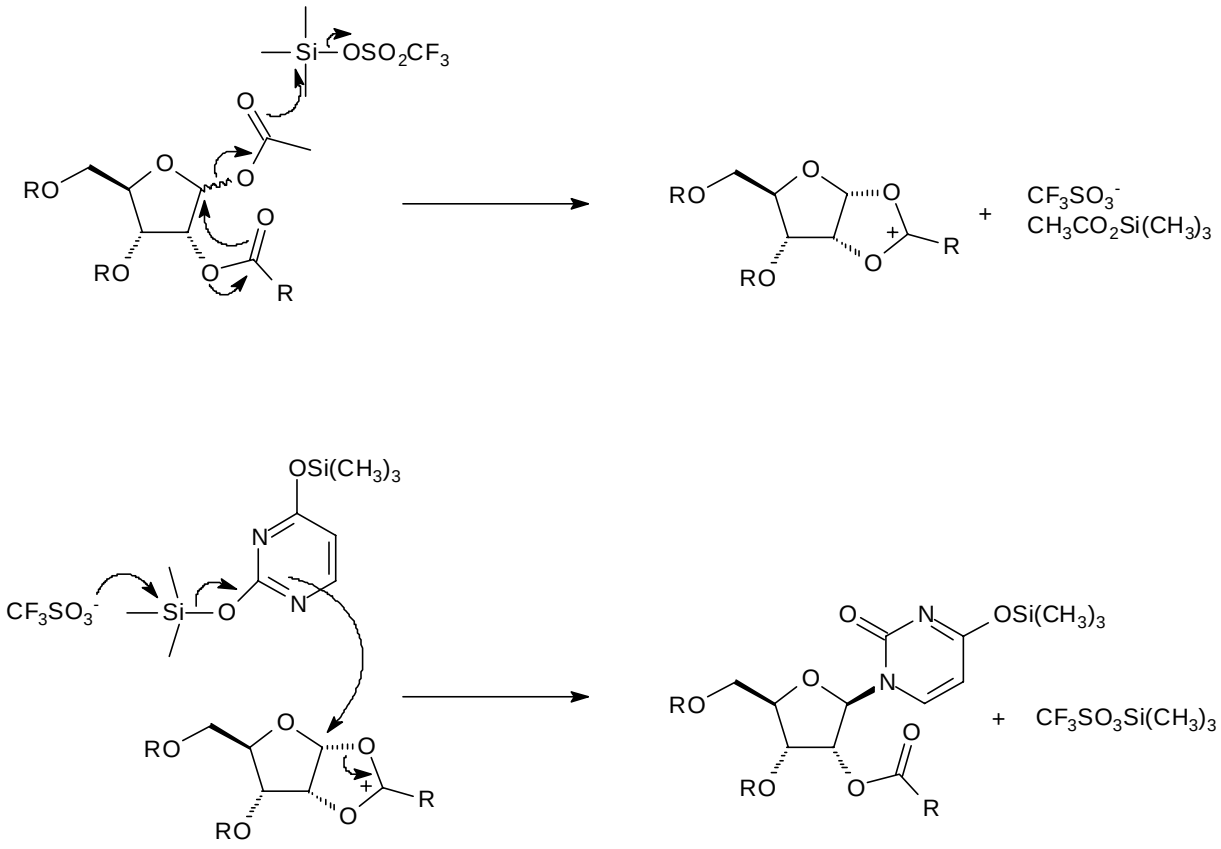
Today one of the most widely used methods for the synthesis of nucleosides is the Vorbrüggen method using silylated bases[76]. Silylated bases have the major advantage to be easily prepared and to react smoothly with stable sugars in a homogeneous solution.

The reactions are carried out using a peracylated sugar, the corresponding silylated base and a Friedel-Crafts catalyst [$SnCl_4$, $AgClO_4$, $(CH_3)_3SiOSO_2C_4F_9$, $(CH_3)_3SiOSO_2CF_3$] (Scheme 4.5).

Vorbrüggen *et al.*[76b] studied the differences in reactivity of different Friedel-Crafts catalysts and discovered the superiority of TMS-triflate for these transformations.

The mechanism involves 2 stages[76a]:

- The reaction of the peracylated sugar with the Friedel-Crafts catalyst leading to an electrophilic sugar cation.
- The formation of a σ-complex between the Friedel-Crafts catalyst and the silylated bases which generates the *N*-nucleophile that will attack the carbocation from the opposite β-side following the Baker's 1,2-trans rule.



Scheme 4.5: Mechanism of nucleoside formation *via* the Vorbrüggen method.

After basic work up - typically aqueous $NaHCO_3$ and dichloromethane - the nucleosides are normally obtained in good yield.

4.5 Control of anomeric stereochemistry

One major goal still unresolved in nucleoside chemistry is the complete control of stereochemistry at the *C*-1 anomeric center of the sugar moiety.

In the case of riboses carrying a 2'-OH group the nucleosides are formed by attack from the opposite face with good to excellent stereoselectivity. In contrast, for 2'-deoxy-nucleosides no efficient method is available for a comparable stereocontrol. The missing 2'-OH group does not allow the formation of the cyclic intermediate (compare Scheme 4.5) and therefore normally leads to a mixture of α and β isomers. Their separation by

chromatography is mostly tedious[77] and the success depends largely on the particular molecular structure.

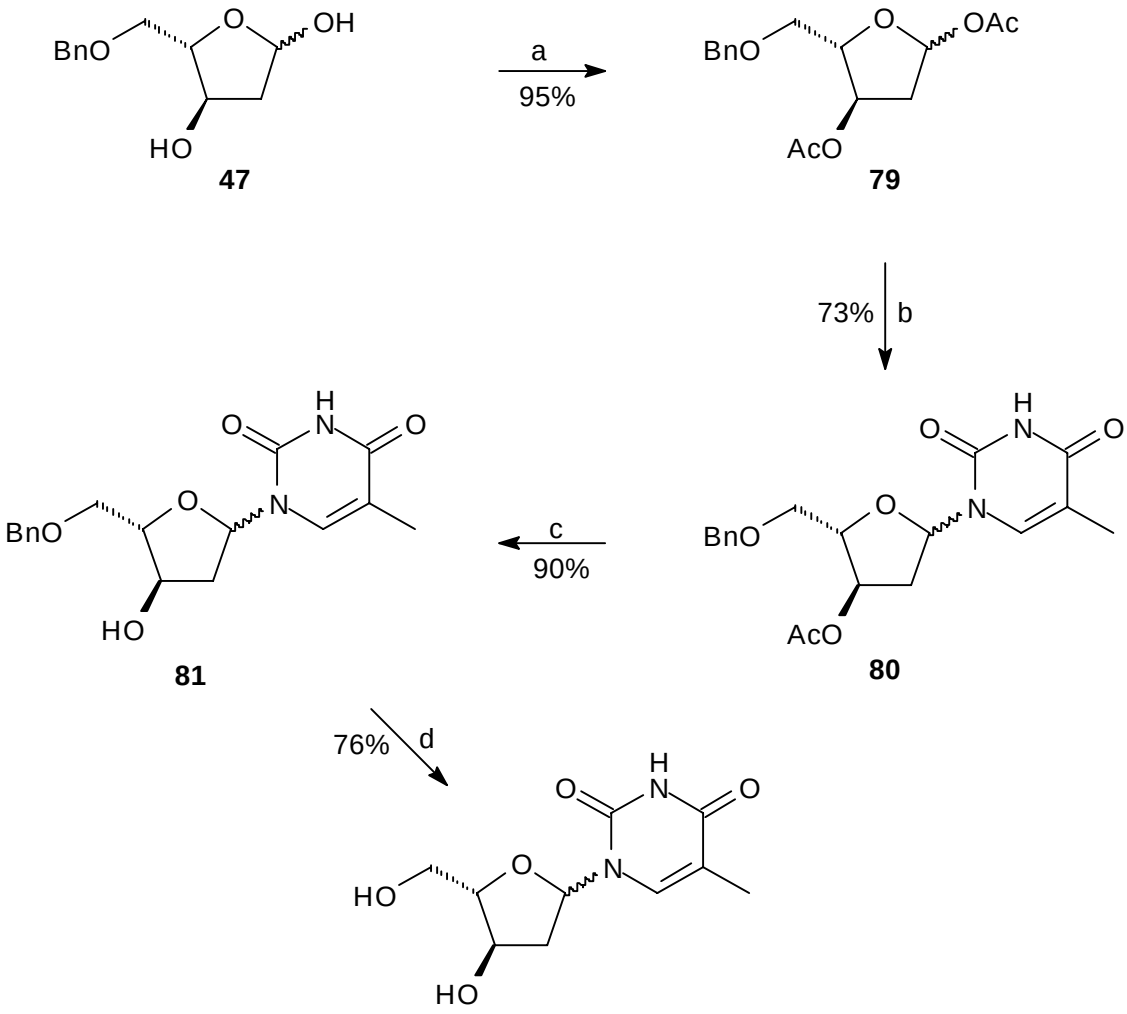
4.6 Synthesis of α,β-L-thymidine

One of the major goals of this thesis was the synthesis of L-thymidine by using the newly developed procedures for the synthesis of the 2-deoxy-L-ribose derivatives. L-thymidine displays various biological activities[78], could be the starting material for the synthesis of important drugs (e.g. *enantio*-AZT)[75] and, moreover, *via* transglycosidations purinic bases can be easily exchanged with the pyrimidinic base thymine.

The starting material of choice for the synthesis of 2-deoxy-L-nucleosides was the 5-benzyl protected 2-deoxy-L-ribose **47**.

Among several available methods, we decided to opt for the Vorbrüggen procedure for the reasons outlined in the previous paragraphs. For the coupling reaction we needed to prepare first the peracylated form of **47** which could be then reacted with silylated nucleobases under Friedel-Crafts catalysis (Scheme 4.6).

Thus, **47** was first esterified to form the diacetyl derivative **79** using Ac_2O/pyridine in THF. **79** was isolated as 1:1 mixture of α and β anomers in 95% yield. Subsequently, the coupling reaction with silylated thymine was achieved in acetonitrile using as catalyst TMS-triflate. The diprotected L-nucleoside **80** was obtained in 73% yield as anomeric mixture ($\alpha/\beta \cong 1/2$, ^{1}H-NMR). The removal of the protecting groups was carried out in the following sequence: first the acetate function was hydrolized *via* aminolysis using *n*-butylamine to afford the 5'-benzyl protected L-thymidine **81** in 90% yield. Second, catalytic hydrogenation (10% Pd/C) in MeOH produced the desired 2-deoxy-L-thymidine **82** in 76% yield again as anomeric mixture ($\alpha/\beta \cong 1/2$, ^{1}H-NMR). Here, the major and yet unresolved problem is the chromatographic separation of the α and β anomers. Several HPLC columns have been tested for this propose but none gave encouraging results.



Scheme 4.6: a) Ac_2O, pyridine, THF, rt, 18h; b) TMS-thymine, TMS-triflate, acetonitrile, -30 °C – 0 °C, 30min; c) *n*-$BuNH_2$, MeOH, rt, 3h; d) H_2, 10% Pd/C, MeOH, rt, 1h.

As shown in Figure 4.1. partial separation could be observed using the following conditions: column LiChroCART 250-4, LiChroSpher 100, RP-8 (5μm), UV 262, eluent: methanol - phosphate buffer pH 4.4 – water (0.1:5:94.9), flow rate 1ml/min.

Using natural β-D-thymidine as reference we were able to establish that the most abundant product in the mixture was the desired β-anomer. This observation has also been confirmed by the ^{1}H and ^{13}C-NMR spectra of our product **82** and natural β-D-thymidine (Figure 4.2).

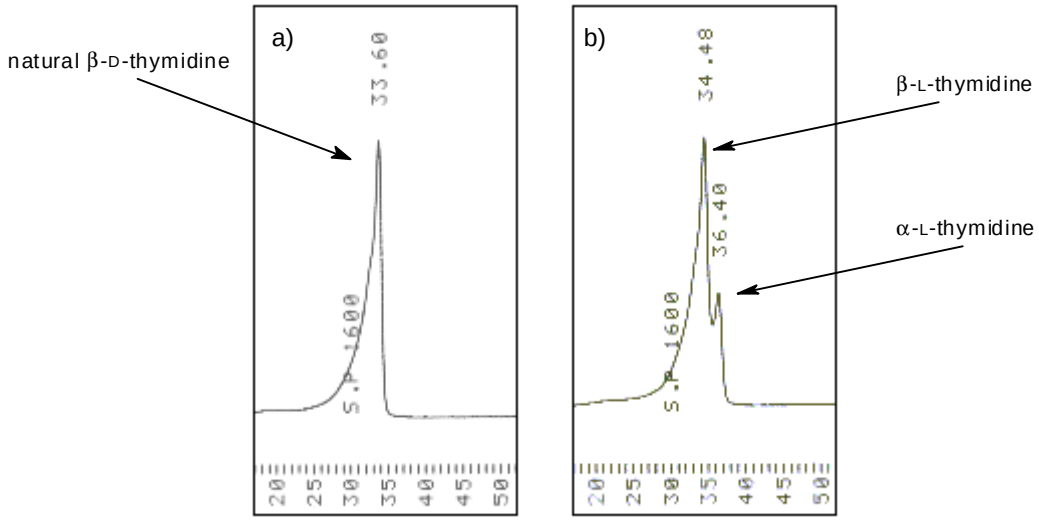


Figure 4.1: HPLC analysis. column LiChroCART 250-4, LiChroSPHER 100, RP-8 (5µm), UV 262, eluent: methanol - phosphate buffer pH 4.4 – water (0.1:5:94.9.), flow rate 1ml/min; a) natural β-D-thymidine b) α,β-L-thymidine

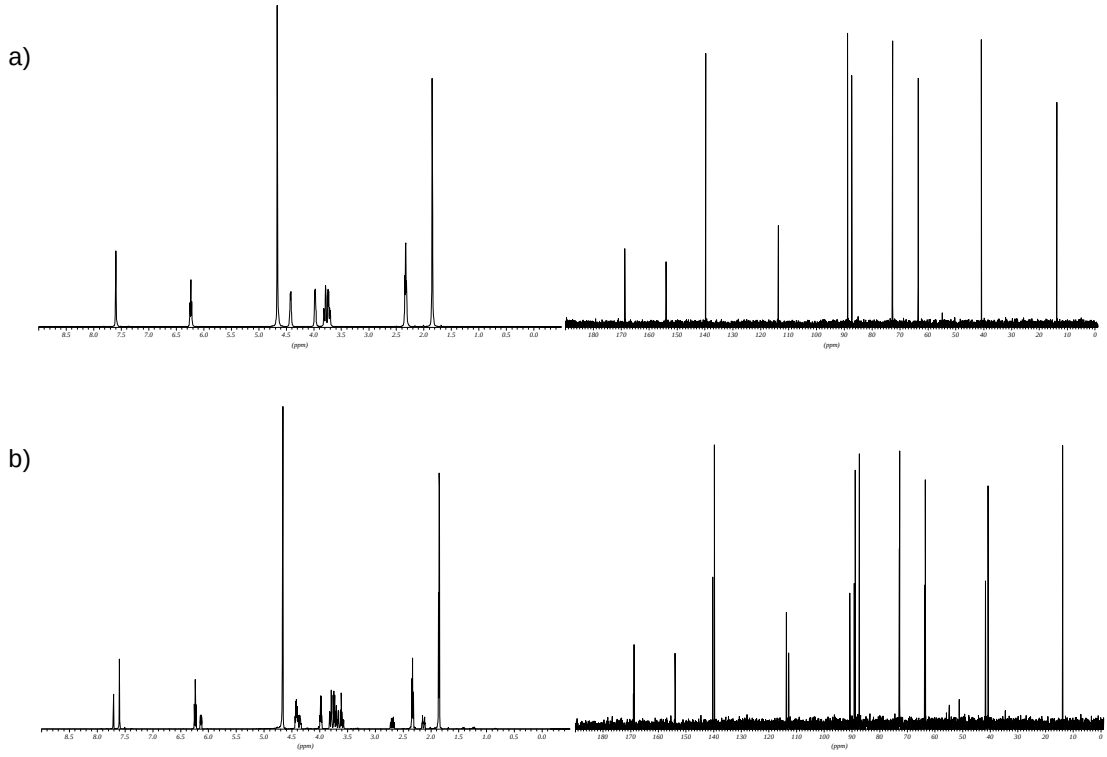
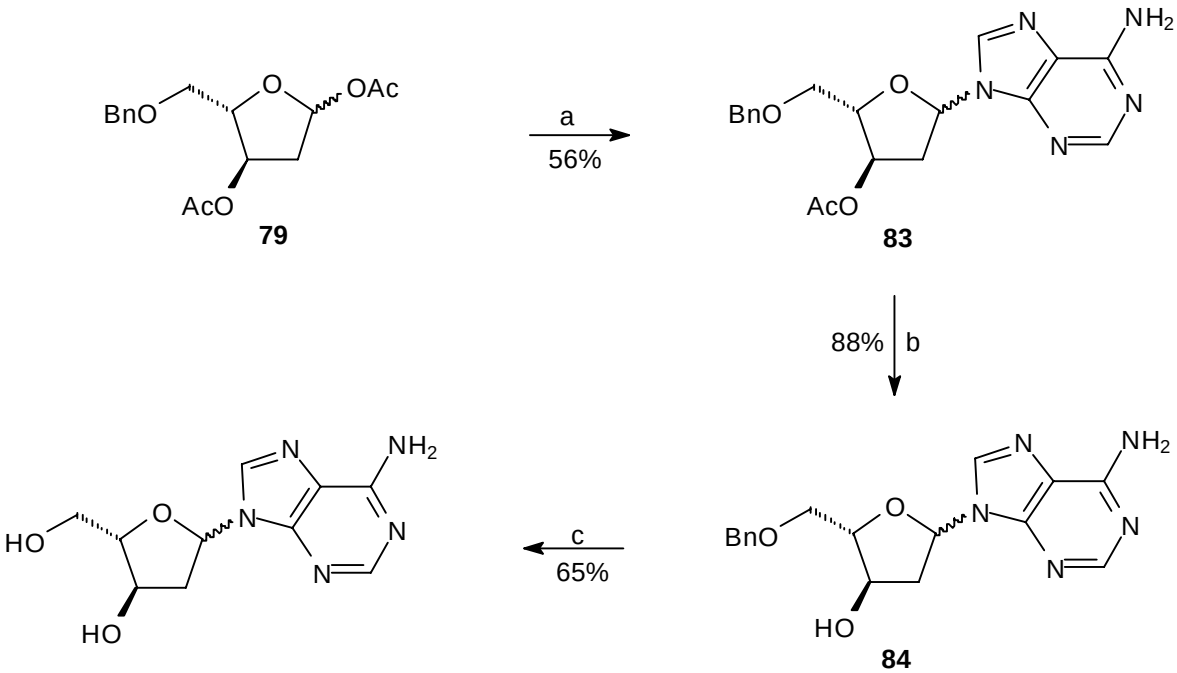


Figure 4.2: ^{1}H and ^{13}C NMR's (400 MHz, D_2O) of a) natural β-D-thymidine b) α,β-L-thymidine

4.7 Synthesis of α,β-2-deoxy-L-adenosine

The use of our building block **79** was also tested for the synthesis of 2-deoxy-L-adenosine. Here, the nucleobase adenine cannot be directly silylated as in the case of thymine because it contains an exocyclic amino group which must be first protected (e.g. as *N*-benzoyl derivative). However, it is reported in the literature[79] that nucleobases with exocyclic amino groups can be directly reacted in toluene/CH_3CN in the presence of KI and dibenzo-18-crown-6 (Scheme 4.7) This way the diacetyl derivative **79** was transformed into the anomeric mixture ($\alpha/\beta \cong 2/1$, ^{1}H-NMR) **83** in 56% yield. **83** was then deprotected with *n*-butylamine in MeOH to yield the **84** in 88% yield. Finally, removal of the benzyl group using $Pd(OH)_2$/C in EtOH/cyclohexene (2/1) produced the desired anomeric mixture of α,β-2-deoxy-L-adenosine **85** in 65% yield (Scheme 4.7).



Scheme 4.7: a) TMS-adenine, KI, dibenzo-18-crown-6, toluene/CH_3CN (1/1), reflux, 4h; b) *n*-$BuNH_2$, MeOH, rt, 1h; c) $Pd(OH)_2$/C, EtOH, cyclohexene, reflux, 2h.

Separations of the α and β anomers of **85** by HPLC are particularly tedious. Although different columns were employed, no encouraging results were obtained in our hands.

However, the α,β-ratio of **85** could be measured *via* ^{1}H-NMR using as reference natural β-2-deoxy-D-adenosine. As readily interpretable from the Figure 4.3, the resulting anomeric ratio hare was α/β ≅ 2/1. Thus, unlike in the case of thymidine, here the α configured-anomer is produced preferentially.

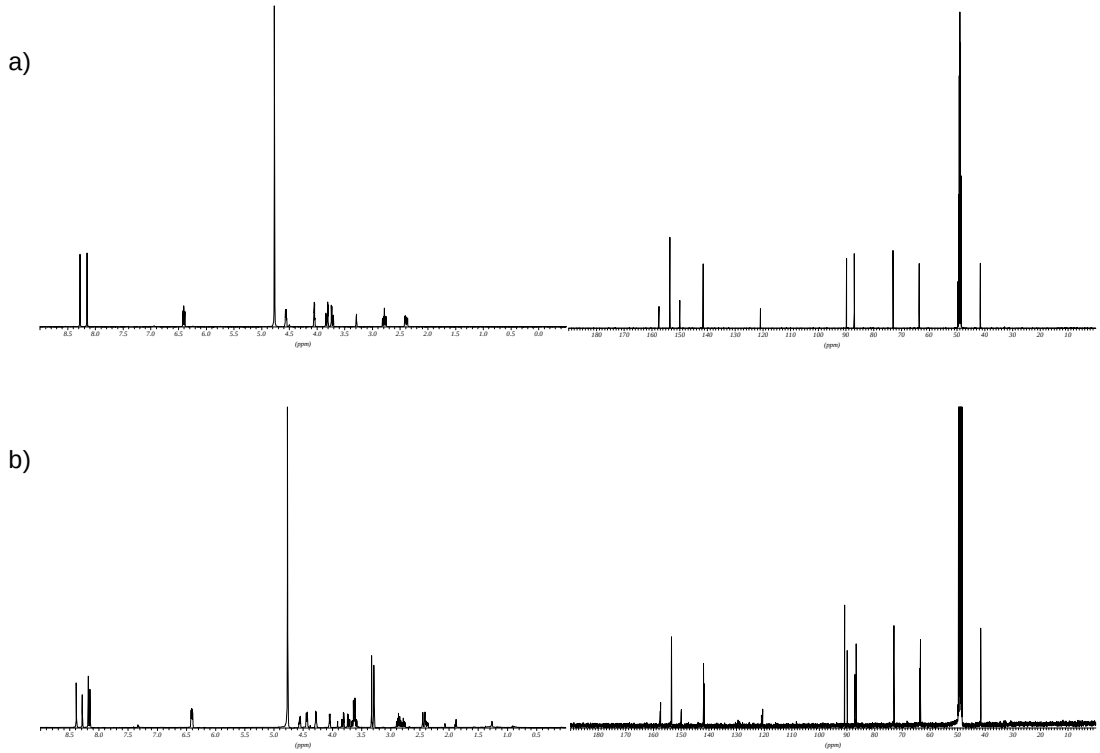
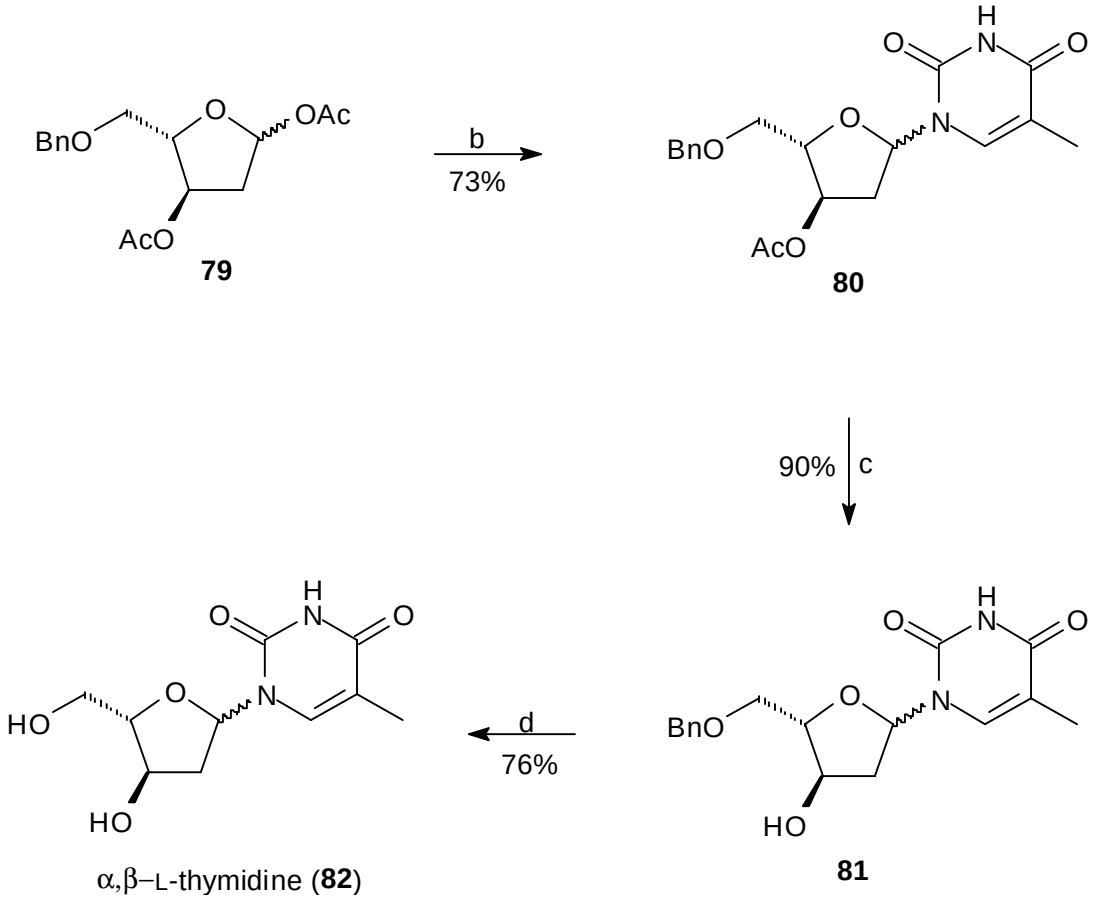


Figure 4.3: ^{1}H and ^{13}C NMR's (400 MHz, CD_3OD) of a) natural β-2-deoxy-D-adenosine b) α,β-2-deoxy-L-adenosine.

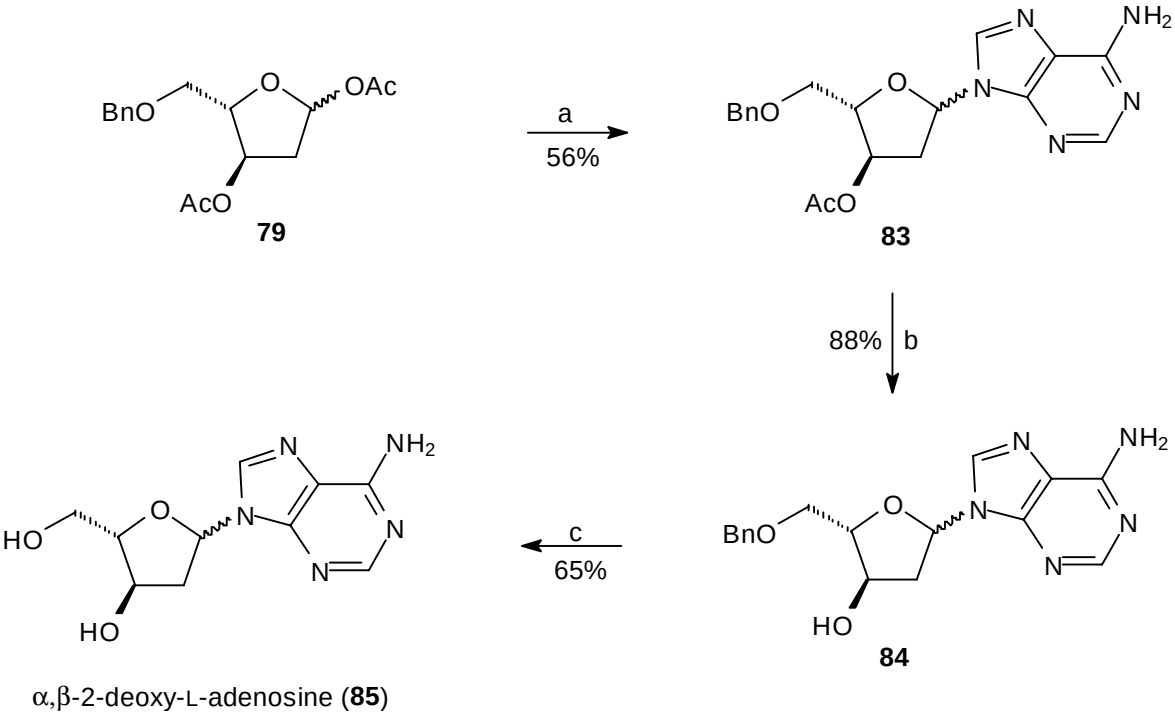
4.8 Synthesis of α,β-nucleosides - Summary

In summary, using our enantiomerically pure building block **47** two 2-deoxy-L-nucleosides were synthesized. For the synthesis of α,β-L-thymidine (**82**) the classical Vorbrüggen procedure was employed for the coupling reaction followed by standard removal of the protecting groups. **82** was obtained in 3 steps (50% overall yield) starting from **79** as anomeric mixture (α/β ≅ 1/2, Scheme 4.8).



Scheme 4.8: a) TMS-thymine, TMS-triflate, acetonitrile, -30 °C – 0 °C, 30min; b) *n*-$BuNH_2$, MeOH, rt, 3h; c) H_2, 10% Pd/C, MeOH, rt, 1h.

In a second example the synthesis of α,β-2-deoxy-L-adenine (**85**) was carried out in 3 steps (32% overall yield). In this case the coupling reaction between the silylated adenosine and the peracetylated sugar **79** was accomplished in the presence of KI and dibenzo-18-crown-6. After removal of protecting groups, 2-deoxy-L-adenine (**85**) was obtained as mixture of the α and β anomers (α/β ≅ 1/2, Scheme 4.9).



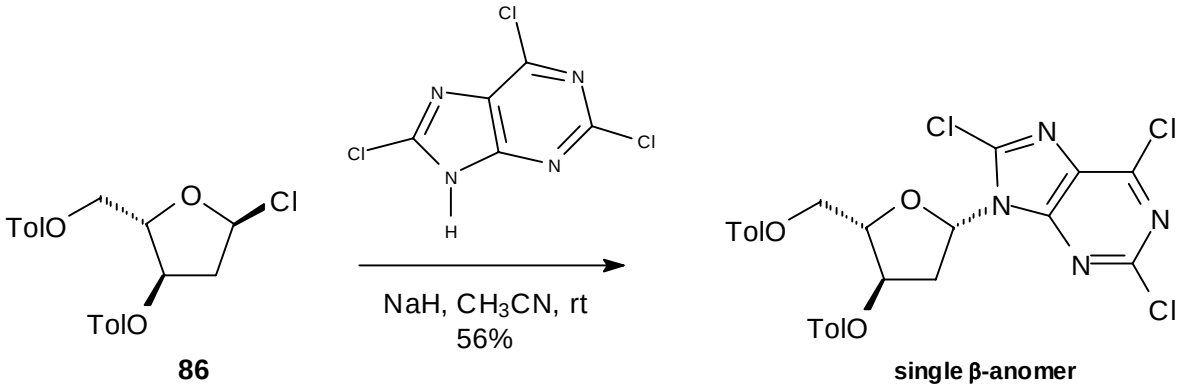
Scheme 4.9: a) TMS-adenine, KI, dibenzo-18-crown-6, toluene/CH_3CN (1/1), reflux, 4h; b) *n*-$BuNH_2$, MeOH, rt, 1h; c) $Pd(OH)_2/C$, EtOH, cyclohexene, reflux, 2h.

4.9 Conclusions and outlook

The control of stereochemistry in the Vorbrüggen coupling reaction of protected 2-deoxy-sugars with nucleobases remains an unresolved problem. In all of our examples mixtures of α,β-isomers were obtained.

In the literature we found however, a single example of a sugar derivative leading to only one diastereoisomer of 2-deoxy-L-nucleosides, the chloro derivatives **86**[42] and *ent*-**86**[80] (Scheme 4.10).

A number of disadvantages are however associated with reactions using these building blocks. High diastereoselectivity is only obtained when the sodium salt of "activated" purine bases carrying chloro substituents on the aromatic ring are employed[81] (Scheme 4.10).



Scheme 4.10: Synthesis of β-nucleosides from **86**.

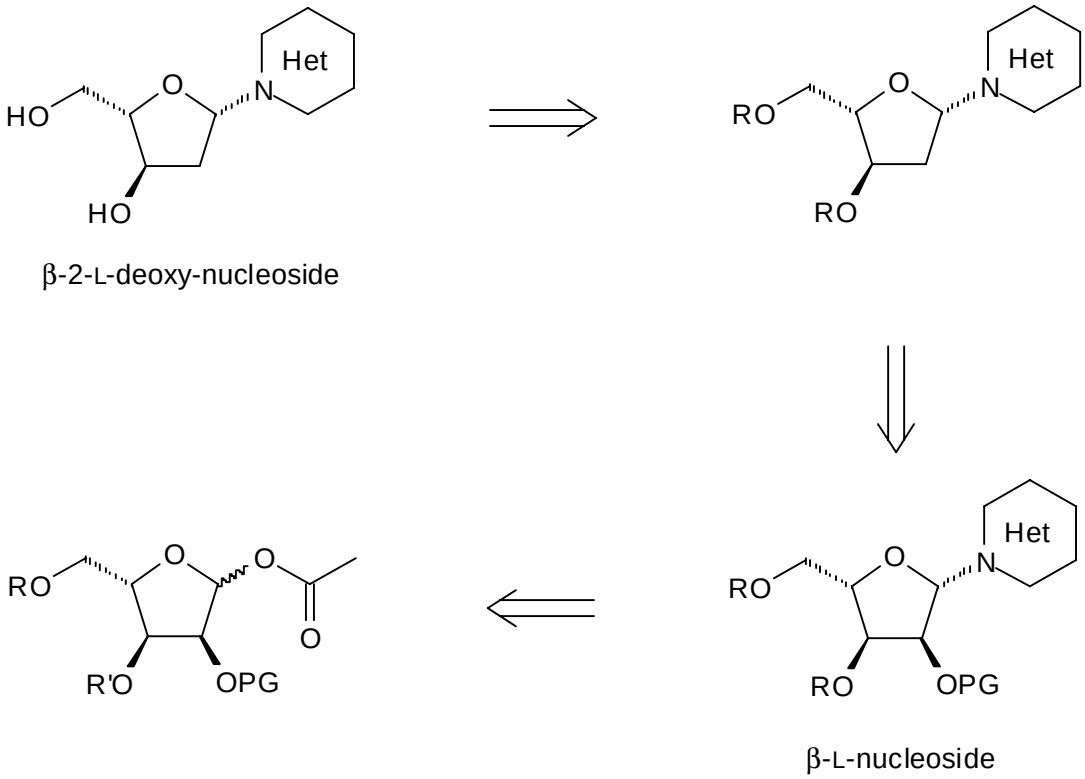
Moreover the reaction is not always regiospecific regarding the base. **86** is also rather unstable, it can isomerize[82] to the β-derivative, especially in polar solvents and in the presence of Lewis acids. Furthermore there is a tendency of **86** to eliminate HCl and *p*-toluic acid[83]. Regardless of this situation, it has been possible in a number of cases to obtain pure β-anomers by recrystallization of the impure reaction mixtures[84] and **86** is up to now the only building block which in some cases leads to single β-anomers of 2-deoxy-nucleosides.

An alternative possibility for the synthesis of single β-anomers of 2-deoxy-nucleosides is the deoxygenation of the 2'-OH group in the already formed nucleoside (Scheme 4.11).

This way it is possible to exploit first the "directing effect" of the 2'-OH moiety with the result that a single β-anomer can be obtained.

Among the most frequently used methods for such deoxygenations are:

- photochemical removal of the 2'-*O*-(3-trifluoromethylbenzoyl) group[85]
- Barton radical fragmentation of 2'-thionocarbonates[86]
- reduction of 2'-tosylates with $Li(HBEt_3)$[87]



Scheme 4.11: Retrosynthesis of 2-deoxy-L-nucleosides *via* regioselective 2-deoxygenation.

Clearly, in these cases the selective removal of the OH group is of major importance. This requires additional steps for the introduction and removal of suitable protection groups. Furthermore in some cases only highly diluted solutions are prone to deoxygenation rendering the scale up of these transformations problematic[85].

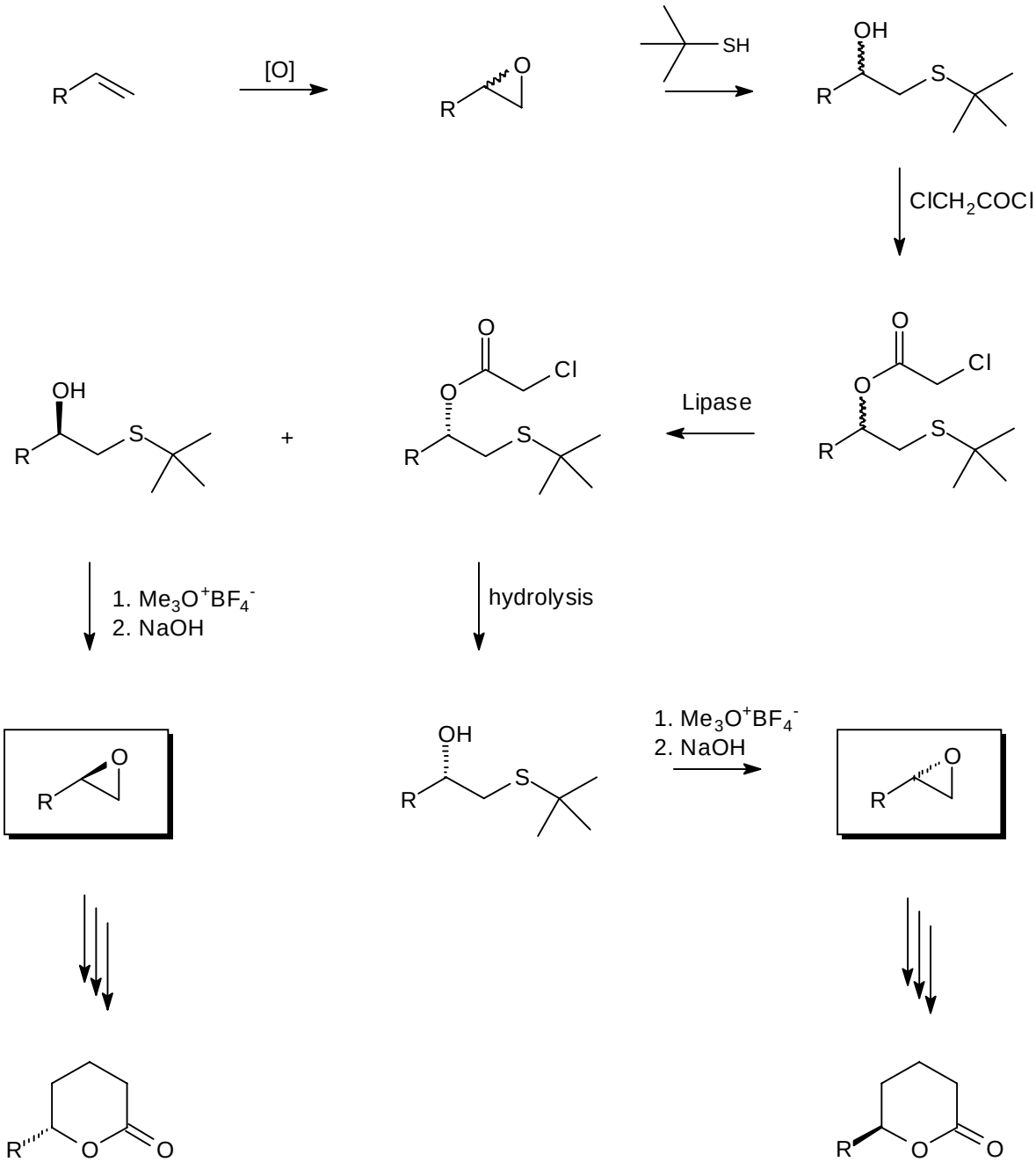
5 δ-lactones

Chiral 6-substituted δ-lactones have been identified as insect pheromones[88]. Due to their frequently low sensory threshold concentrations they represent key aroma constituents in various fruits and plants.

Interestingly enough – although natural products – these molecules are isolated from natural sources frequently not in enantiomerically pure form but as mixture of enantiomers[88c] in which the *R*-configurated compounds are usually dominating. Since the physiological activities – odor or taste – are possibly dependent on the absolute configuration of these molecules, as a consequence the flavour notes of fruits can vary according to the region of growth, condition of storage and degree of ripeness. In spite of the importance of these molecules as aroma constituents there seems to exist no systematic study in which the relationship between organoleptic properties and their absolute configurations has been studied in detail, e.g. by a systematic determination of sensory threshold concentrations. Moreover there seem to be uncertainties regarding absolute configurations in a number of cases. The reason for this situation probably resides in the fact that enantiomerically pure δ-lactones of both absolute configurations are not easily accessible in multigram quantities.

5.1 Synthesis of δ-lactones

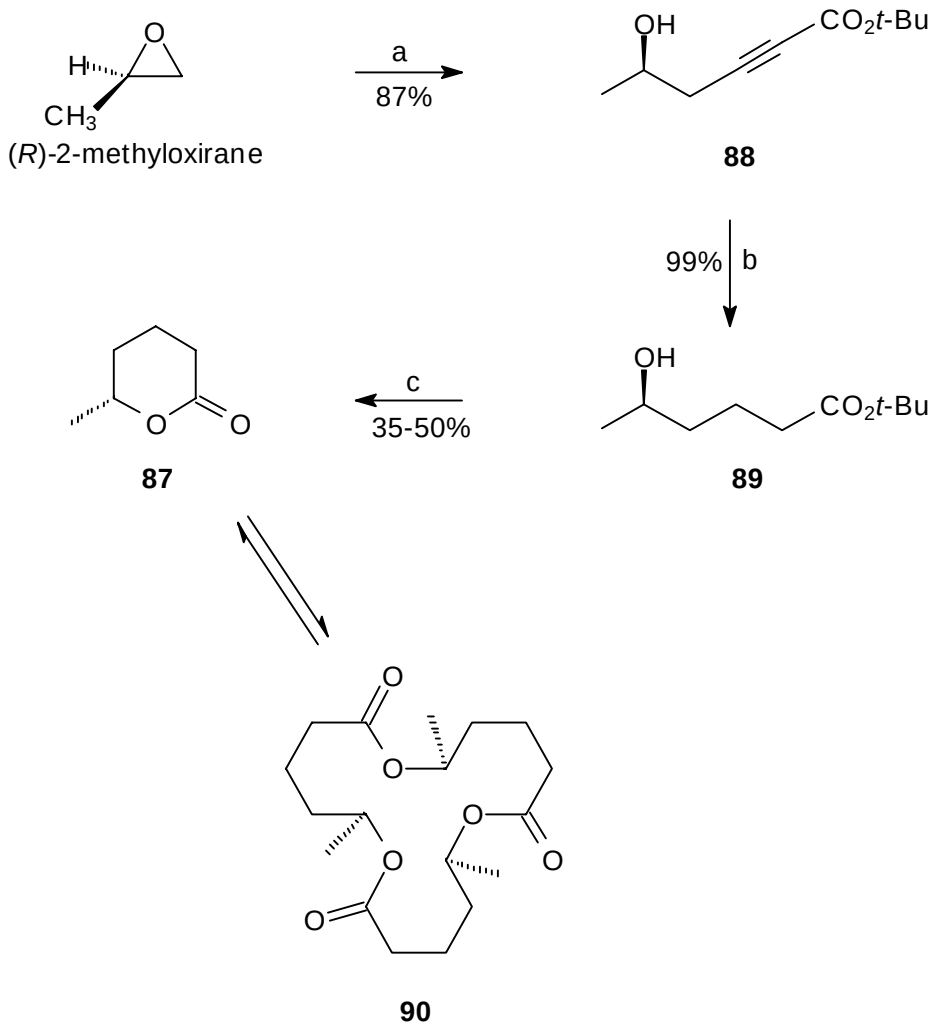
In view of a systematic study of organoleptic properties and detailed determinations of sensory threshold concentrations, the synthesis of both enantiomeric series of these molecules was accomplished in our laboratory[89] (Scheme 5.1).



Scheme 5.1: Synthesis of enantiomerically pure *R* and *S*-δ-lactones.

5.2 Acid catalyzed trimerization of δ-lactones

Surprisingly and quite unexpectedly we found, however, that when e.g. *R*-(+)-6-methyl-tetrahydro-pyran-2-one (**87**) was prepared, it proved to be instable upon storage in neat form even at low temperatures (Scheme 5.2). This became evident when *crystalline* **87** slowly turned into a *liquid*, the change in physical appearance being accompanied by a change of optical rotation from $[\alpha]_D^{20}$ = +36 (*c* 0.7, $CHCl_3$) to $[\alpha]_D^{20}$ = -7 (*c* 1.0, $CHCl_3$) for what turned out to be an equilibrium mixture of **87** and a newly formed compound for which we assigned the trimeric structure **90**.



Scheme 5.2: a) *tert*-butyl propiolate, *n*-BuLi, BF_3-Et_2O, THF, -78 °C, 2.5h; b) H_2, 5% Pd/C, AcOEt, -20 °C, 6h; c) TFA, CH_2Cl_2, rt, 24h.

Nucleophilic ring opening of (*R*)-2-methyloxirane by the anion of *tert*-butyl propiolate led to *R*-(-)-5-hydroxy-hex-2-ynoic acid *tert*-butyl ester **88** which was hydrogenated (5% Pd/C, AcOEt, -20 °C; 6h, 99%) quantitatively to the saturated derivative **89** which was in turn, cyclized to **87** in presence of catalytic amounts of trifluoroacetic acid. **87** was isolated by column chromatography on silica gel [Et_2O/*n*-hexane (2/1)], followed by short path distillation (Kugelrohr, 70 °C, 10^{-3} mBar) as white solid (m.p. 31 °C). Although monitoring of the reaction by T.l.c. and GC confirmed quantitative conversion the yield was only 50%, probably due to the solubility of **87** in the aqueous solution used for work up.

The thus prepared **87** showed a chemical purity of ≥99% (GC analysis) which was further confirmed by the clean and readily interpretable ^{1}H and ^{13}C-NMR spectra (Figure 5.1a). **87** was optically pure with an optical rotation of $[\alpha]_D^{20} = +36$ (*c* 0.7, $CHCl_3$ stab. with 1% EtOH).

However, upon storage in neat form at rt, **87** slowly equilibrates with its trimer **90**. This trimerization surprisingly turned out to be a very clean transformation, no other oligomers or polymers are observed. It can be conveniently monitored *via* the corresponding ^{1}H and ^{13}C-NMR spectra which were taken in regular (7 days) intervals. Thus pure **87** (Figure 5.1a) having a characteristic multiplet at δ= 4.39 ppm in the ^{1}H-NMR spectrum (and a signal at δ= 171.67 ppm for the carbonyl carbon in the ^{13}C-NMR) was slowly transformed into (6*R*,12*R*,18*R*)- (-)-6,12,18-trimethyl-1,7,3-trioxa-cyclooctadecane-2,8,14-trione **90**, having a corresponding multiplet at δ= 4.90 ppm (3 carbonyl carbons at 172.84 ppm in the ^{13}C-NMR) (Figure 5.1b). After ca. 35 days an equilibrium mixture of **87** and **90** is obtained with a ratio (determined by integration of the ^{1}H-NMR signals) of ca. 20:80 (Figure 5.1C). The existence of a true thermodynamic equilibrium was supported by the fact that the same mixture is obtained starting from either pure **87** or **90** (Scheme 5.3).

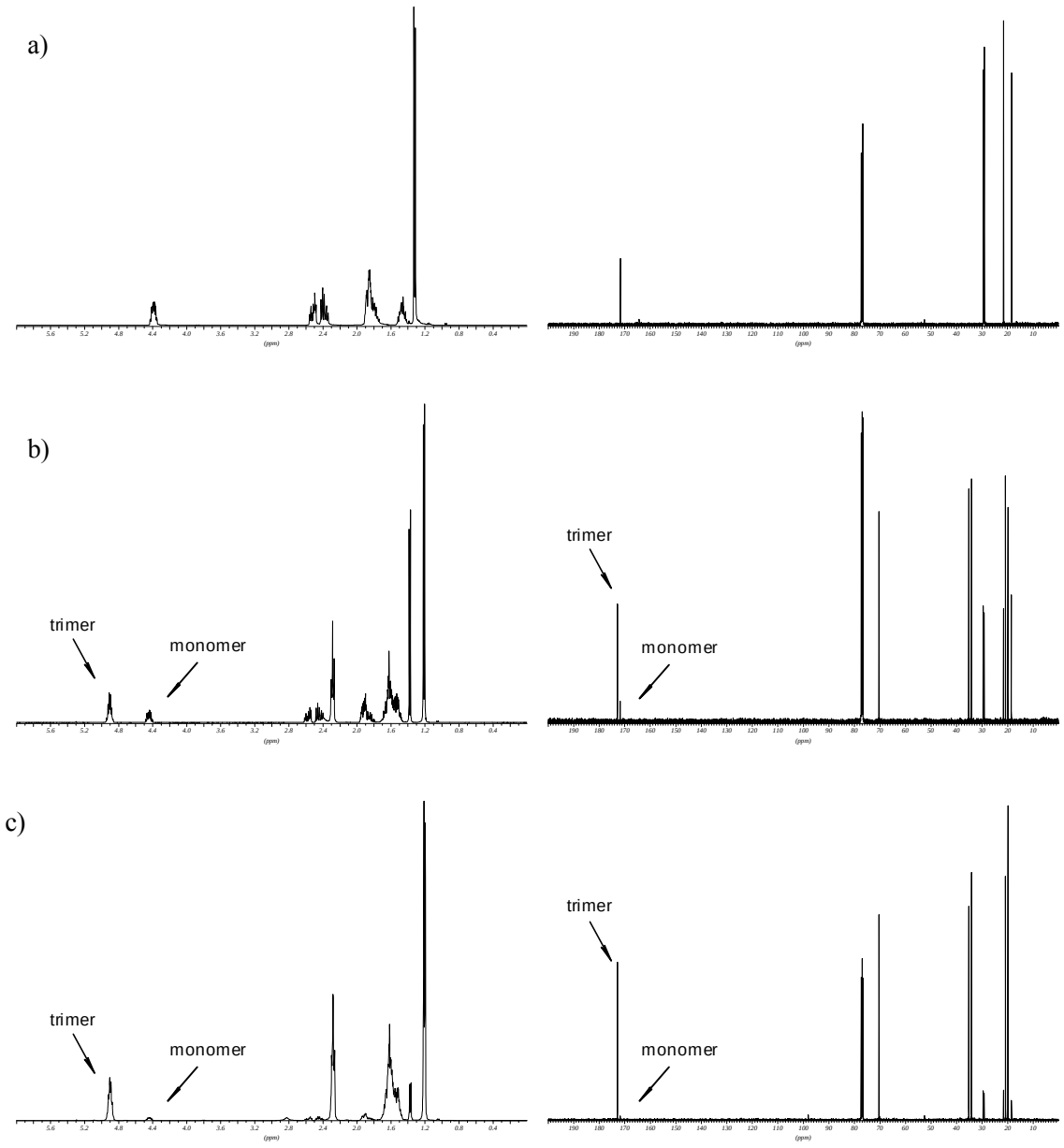
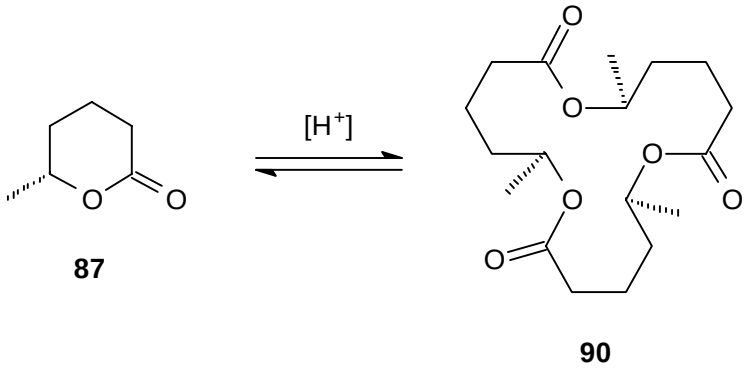
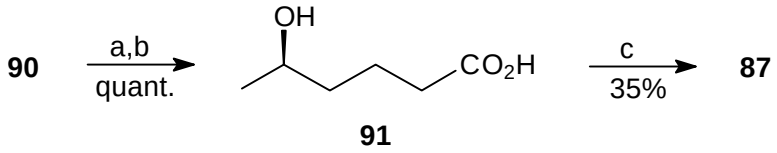


Figure 5.1: ^{1}H and ^{13}C-NMR spectra ($CDCl_3$, 400 MHz). (A) freshly synthesized **87**; (B) product stored at 20 °C for 21 days; (C) product stored at 20 °C for 35 days.



Scheme 5.3: Acid catalyzed equilibration of **87** and **90**

Pure **90** was obtained by removal of **87** from the equilibrium mixture by short path distillation (Kugelrohr, 100 °C, 10^{-3}mBar). Next to a correct elemental analysis and the obvious similarity of the ^{1}H and ^{13}C-NMR spectra of **87** and **90** which allowed a facile interpretation[4], **90** was chemically correlated with **87**. Hydrolysis of **90** with 2N NaOH in H_2O/THF led to the corresponding sodium salt of *R*-(-)-5-hydroxy-hexanoic acid **91**. After acidification with aqueous conc. HCl and removal of all solvents, the resulting **91** was recyclized to **87** without loss of optical purity (Scheme 5.4).



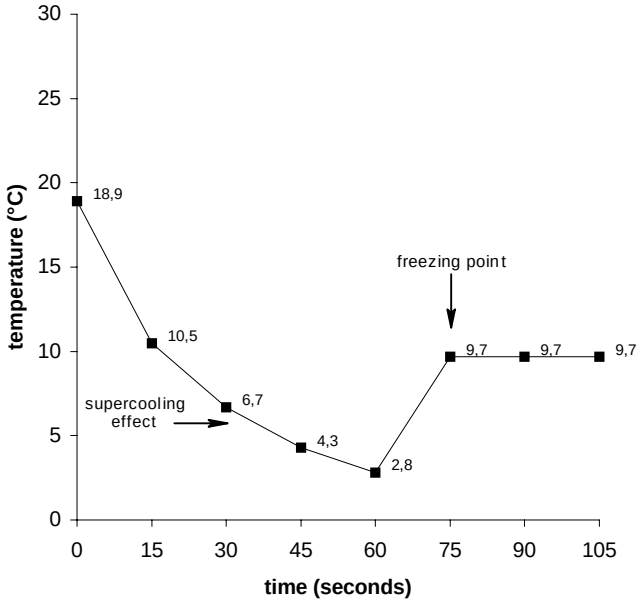
Scheme 5.4: a) 2N NaOH, THF/H_2O, 0 °C – rt, 30min; b) conc. HCl, 0 °C; c) TFA, CH_2Cl_2, rt, 24h.

Next to proving the molecular constitution of **90** this sequence also allows a regeneration of **87** from the impure mixture.

However, in spite of all these informations the correct structure of **90** remained unclear, with other oligomeric structures such as the corresponding dimer or tetramer being obvious options. All of them being symmetric (*n*-fold axes C_n) they would all display 6 carbon atoms in the ^{13}C-NMR. Also the determination of the molecular weight by various MS techniques (EI, CI, electrospray)[90] proved to be unsuccessful. The thermal instability of **90**

led to signals resulting of monomer, dimer and oligomers with unit differences of *m/z* = 114.

Thus the molecular weight of **90** had to be determined the "old fashioned way" exploiting the colligative properties of this material. Using the freezing point depression in 1,4-dioxane we were able to calculate a molecular weight for **90** of 367.16 (theor. 342.43) (Figure 5.2).



$$\text{M.W. of } \mathbf{90} = \frac{(K_f)\,(g_{\,solute})}{\Delta T_f\,(Kg_{\,solvent})} = \frac{-\,4.63 \times 0.091}{-\,0.9 \times (1.27 \times 10^{-3})} = 367.16 \quad \text{(theor. 342.43)}$$

Figure 5.2: Determination of molecular weight of **90** by its freezing point depression in 1,4-dioxane.

In this formula K_f represents the cryoscopic constant (-4.63 for 1,4-dioxane) and $\Delta T_f = T_{f\,solution} - T_{f\,solvent}$ is the difference of the freezing points between pure 1,4-dioxane and the under described solution of **90** in the same solvent (see chapter 6.6.6). We found for **90** a M.W. of 367.16 (theor. 342.43), the error thus was 7.2%.

From the equilibrium constant at 20 °C it can be calculated that the trimeric structure **90** is thermodynamically more stable than **87** by a $\Delta G° \cong -0.8$ kcal mol^{-1}, a difference which is clearly sufficient to partially transform **87** into **90** (Equation 5.1).

$$\Delta G° = - RT \ln k = -2.303 RT \log k$$

$$\text{At } 20\ °C,\ k \cong 80/20 \cong 4$$

$$\Delta G° \cong -1.34 \log 4 \cong \mathbf{-\ 0.8}\ \text{kcal mol-1.}$$

Equation 5.1: calculation of $\Delta G°$ for an equilibrium constant ≅ 4

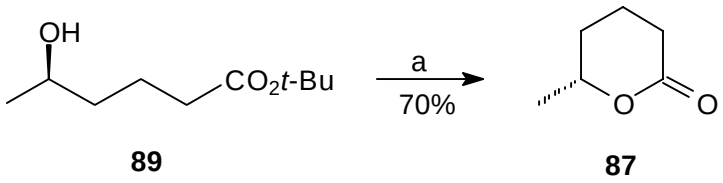
It is interesting to speculate why only the trimer, having an 18 membered ring is formed in this transformation so cleanly without any trace of the corresponding dimer, tetramer or other oligomers and polymers.

The relative stabilities of lactones having 3 to 23 ring members had been determined earlier, revealing clearly the higher stability of the 18-membered ring system[91] over the 6 and the 12-membered rings (i.e. monomer and dimer). This is in good agreement with our observations and the calculated $\Delta G° \cong -0.8$ kcal mol^{-1}.

With enantiomerically pure δ-lactones being important flavour compounds and thus attractive synthetic targets we were curious to elucidate the reasons for the surprising trimerization of such a δ-lactone. Clearly, the instability of **87** could only be the result of an acid catalyzed process initiated by the presence of traces of TFA introduced during the cyclization of **89** (Scheme 5.1). Since δ-lactones are instable towards base, the removal of TFA during work up by extraction with aqueous Na_2CO_3 solution causes considerably reduced product yields. We therefore initially opted for column chromatography and short path distillation in the hope that the last traces of TFA would be completely removed this way. Evidently this was not the case. If the organic phase during work up is indeed washed with Na_2CO_3, the resulting **87** (isolated in greatly reduced yield of only 35%) is perfectly stable upon storage. The addition of a trace of TFA immediately initiates again the above described trimerization.

Clearly TFA is not the method of choice for the cyclization reaction leading to **87**.

Since **87** is both base labile and soluble in an aqueous environment we now optimized the cyclization procedure by using *p*-TsOH in toluene (Scheme 5.5). No aqueous work up is required in this case. Considerably improved yields of 70% were obtained and the resulting product is perfectly stable during storage at room temperature.

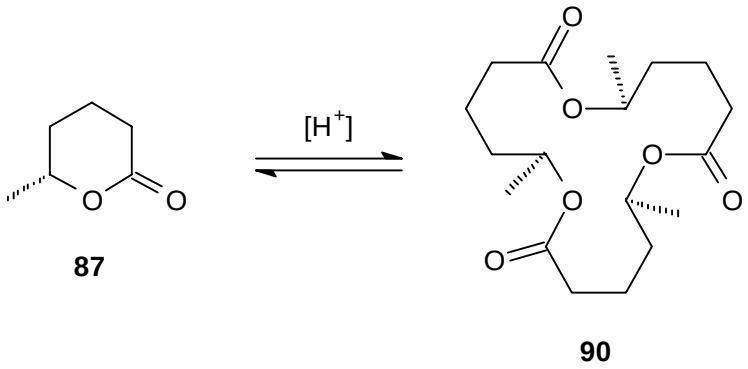


89 **87**

Scheme 5.5: a) *p*-TsOH, toluene, reflux, 1.30h.

5.3 δ-lactones - Summary

The enantiomerically pure (≥98% ee) *R*-(+)-6-methyl-tetrahydro-pyran-2-one **87** in the presence of traces of trifluoroacetic acid (TFA) converts into an equilibrium mixture with its trimer **90** [**87**:**90** = 20:80] corresponding to a $\Delta G \cong -0.8$ kcal mol^{-1} (Scheme 5.6). The transformation can be followed by ^{1}H and ^{13}C-NMR. The structure of **90** was established by chemical correlation with **87** and its molecular weight determined *via* its colligative properties.



87 **90**

Scheme 5.6: Acid catalyzed equilibration of **87** and **90**

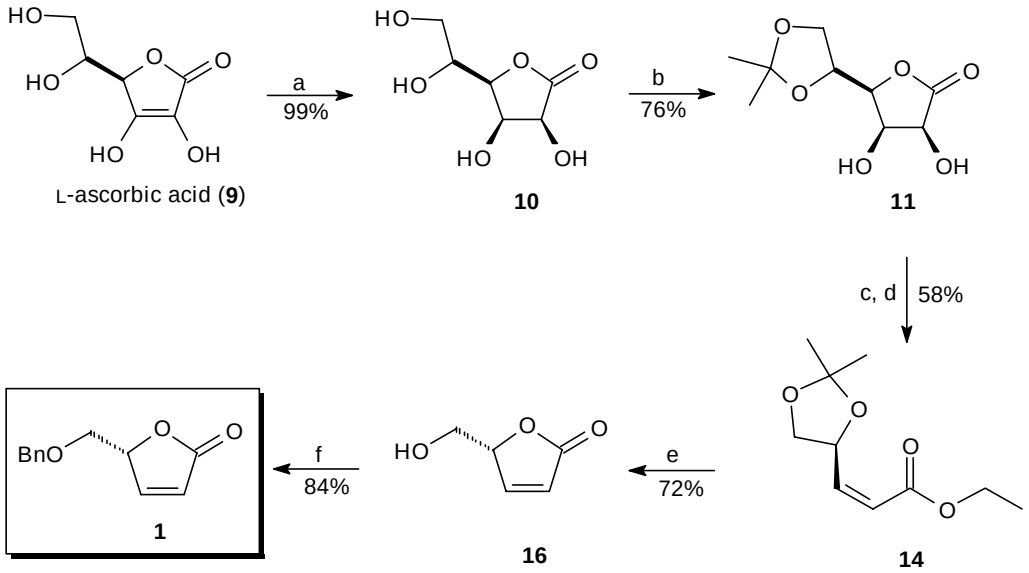
Although base catalyzed oligomerization of δ-lactones has already been reported in the literature[92], this to the best of our knowledge seems to be the first example for an acid (TFA) catalyzed oligomerization of δ-lactones.

6. Summary

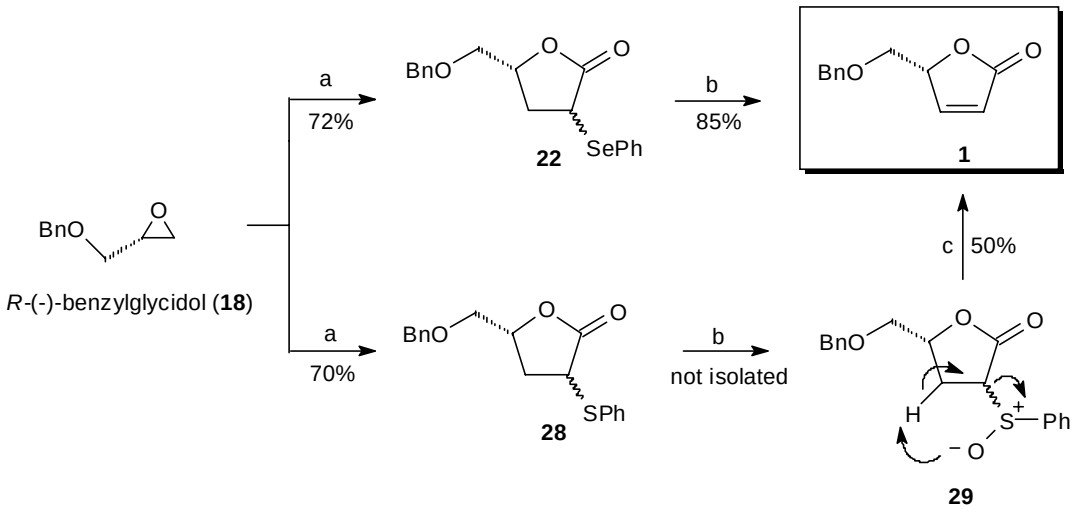
The major topic of this work was the development of novel synthetic routes to enantiomerically pure building blocks for 2-deoxy-L-ribose and non-natural L-nucleosides derived thereof.

*6.1 Synthesis of R-(+)-5-Benzyloxymethyl-5H-furan-2-one (**1**)*

We chose as chiral starting material for the synthesis of 2-deoxy-L-ribose enantiomerically pure *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**) which was obtained from L-ascorbic acid in 5 steps and 26% overall yield (Scheme 6.1). As an alternative **1** was obtained starting from *R*-(-)-benzylglycidol by either using $PhSeCH_2CO_2H$ (2 steps, 61% overall yield) or $PhSCH_2CO_2H$ (3 steps, 35% overall yield, Scheme 6.2).



Scheme 6.1: a) H_2, Pd/C 10%, water, 50 °C, 24h; b) Isopropenylmethylether, *p*-TsOH, DMF, rt, 24h; c) $NaIO_4$, water, rt, 2h; d) $Ph_3P{=}CHCO_2Et$, dichloromethane/H_2O, rt, over night; e) H_2SO_4 (10% in water), MeOH, rt, 2h; f) $Cl_3CC(=NH)OBn$, CF_3SO_3H, dichloromethane/ cyclohexane (2/1), rt, 2h.

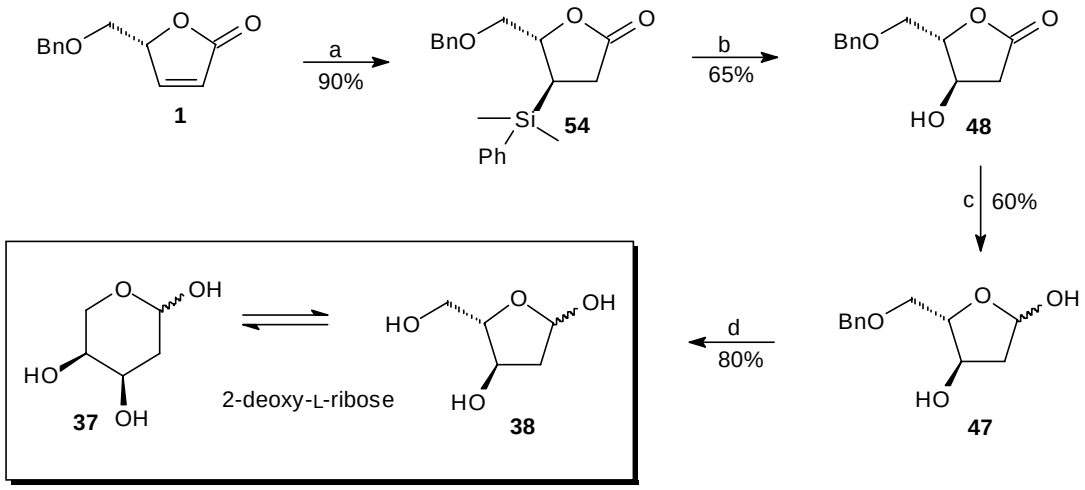


Scheme 6.2: a) 1. $PhXCH_2CO_2H$ (X=Se or S), LDA, THF, -78 °C – rt, 3h; 2. AcOH, reflux, overnight. b) $NaIO_4$, $MeOH/H_2O$, rt, 1h from Se, overnight from S. c) toluene, reflux, 30 min.

From **1** we were able to prepare 2-deoxy-L-ribose and building blocks derived thereof following two different routes.

6.2 2-Deoxy-L-ribose via Michael 1,4-addition of silyl cuprates

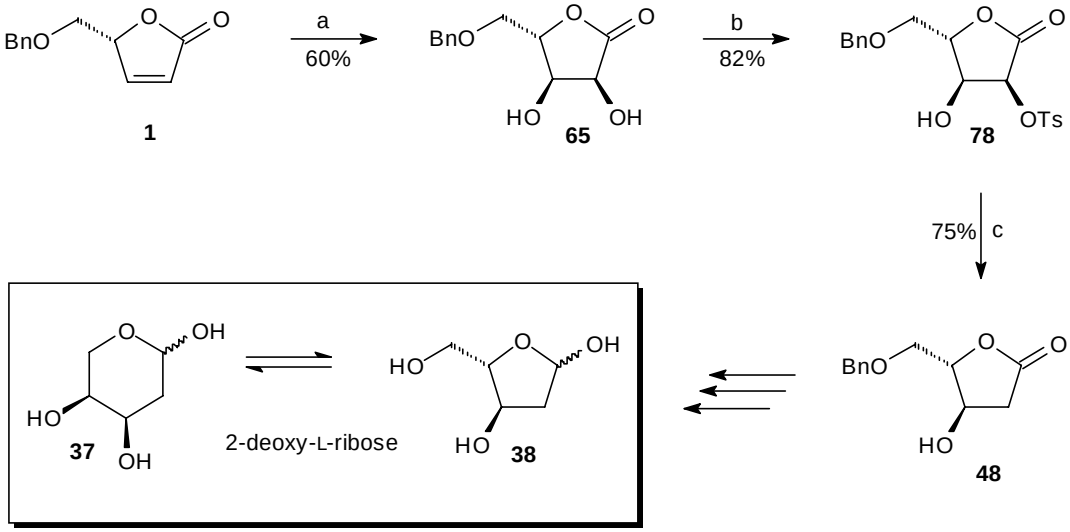
Based on previous experiments described by Fleming *et al*[49] related to the diastereoselective addition of silyl cuprate reagents to Michael systems, and due to the fact that the silyl functions in the resulting derivatives can be transformed into the corresponding hydroxy groups with retention of configuration, we were able to synthesize 2-deoxy-L-ribose (4 steps, 28% overall yield from **1**) and related building blocks in enantiomerically pure form (Scheme 6.3).



Scheme 6.3: a) $(PhMe_2Si)_2Cu(CN)Li_2$, CuCN, THF, -45 °C, 1h; b) Br_2, AcOOH, AcOH, rt, 5h; c) disiamylborane, THF, rt, 24h; d) HCOOH, Pd/C 10%, MeOH, rt, 1h.

6.3 2-deoxy-L-ribose via Mukaiyama[63] dihydroxylation

This route involves a) dihydroxylation of **1**, b) selective protection of the 2-OH group and c) selective removal of this function (Scheme 6.4). This way 2-deoxy-L-ribose was obtained from **1** in 5 steps with an overall yield of 18%.

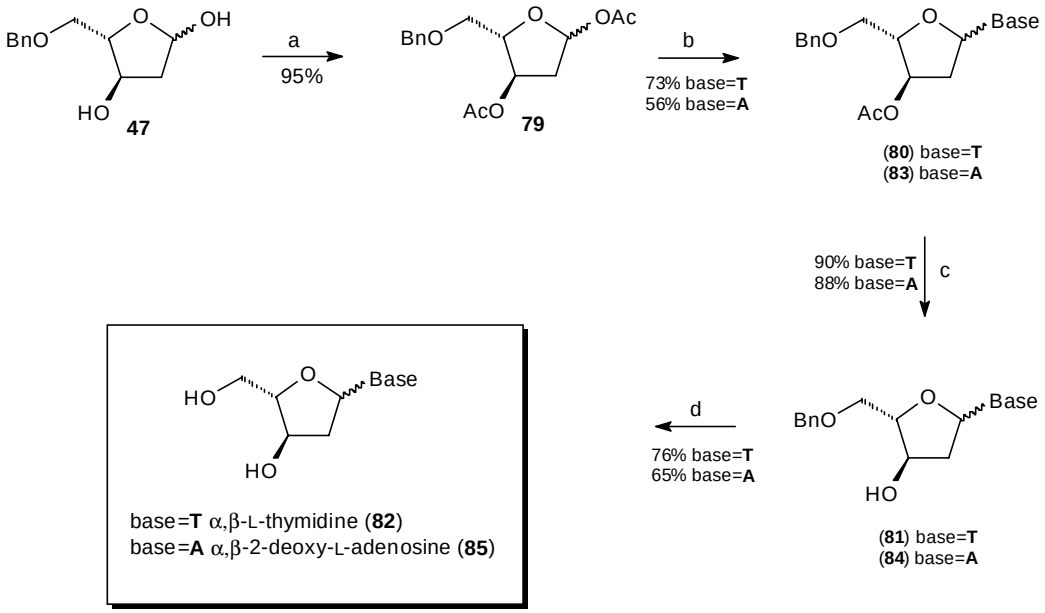


Scheme 6.4: a) $KMnO_4$, dicyclohexano-18-crown-6, dichloromethane, -42 °C, 2h; b) *p*-TsCl, Et_3N, dichloromethane, -20 °C, 18h; c) aq. NH_2NH_2, Br_2, THF, 0 °C-rt, 30min.

In comparing the two routes we feel that the dihydroxylation route has several advantages in using a) simpler procedures, b) commercially available reagents and c) being faster. The only remaining drawback is the requirement for one additional step and a lower overall yield (18%) as compared to the silyl based procedure (28%). This is, in our opinion, more than compensated by the rapid and facile procedure.

6.4 Synthesis of 2-deoxy-L-nucleosides

The two 2-deoxy-L-nucleosides were synthesized using the Vorbrüggen procedure in the case of L-thymidine and the KI catalyzed procedure in the case of 2-deoxy-L-adenosine. In order to avoid equilibration between the pyranoside and furanoside forms of the free sugar, the 5-*O*-benzyl protected derivative **47** was employed as starting material. In order to demonstrate the usefulness of our building block with the backbone 2-deoxy-L-ribose, we synthesized L-thymidine - a pyrimidine L-nucleoside- and 2-deoxy-L-adenosine, a purinic nucleoside. As summarized in Scheme 6.5, L-thymidine and 2-deoxy-L-adenosine were obtained in 48% and 30% overall yield, respectively.

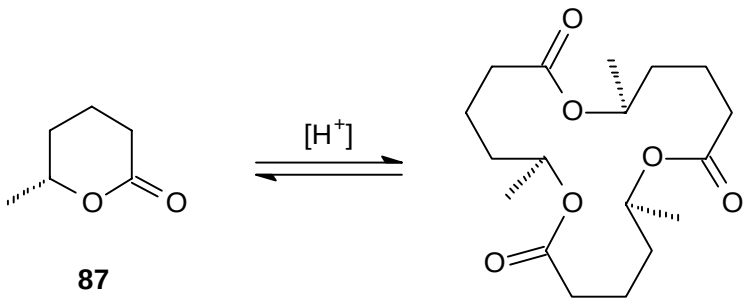


Scheme 6.5: a) Ac_2O, pyridine, THF, rt, 18h; b) base=**T**: TMS-thymine, TMS-triflate, acetonitrile, -30 °C – 0 °C, 30min; base=**A**: TMS-adenine, KI, dibenzo-18-crown-6, toluene/CH_3CN (1/1), reflux, 4h; c) *n*-$BuNH_2$, MeOH, rt, 3h (base=**T**), 1h (base=**A**); d) $Pd(OH)_2$/C, EtOH, cyclohexene, reflux, 2h.

The major and unresolved problem remains the lack of diastereoselectivity in coupling reaction leading to mixtures of α,β-anomers of the final nucleosides.

6.5 TFA catalyzed trimerization of R-(+)-6-Methyl-tetrahydro-pyran-2-one

The enantiomerically pure (≥98% ee) *R*-(+)-6-methyl-tetrahydro-pyran-2-one was prepared *via* TFA catalyzed cyclization of the corresponding δ-hydroxy carboxylic acid. It was observed that this δ-lactone converts into an equilibrium mixture with its trimer form (monomer/trimer 20:80) corresponding to a $\Delta G \cong -0.8$ kcal mol^{-1} if traces of TFA are still present in the final product. The transformation can be followed by ^{1}H and ^{13}C-NMR. The structure of the trimer was established by chemical correlation with the monomer and its molecular weight determined *via* its colligative properties (Scheme 6.6).



87 **90**

Scheme 6.6: trimerization of *R*-(+)-6-Methyl-tetrahydro-pyran-2-one catalyzed by TFA

p-TsOH in contrast was shown to be a highly suitable catalyst for such cyclizations leading to pure and stable δ-lactones.

Experimental Section

7 Syntheses and analyses

7.1 Analytical Instruments

^{1}H-NMR	Bruker WM 250 (250.133 MHz) Bruker WM 400 (400.132 MHz)
^{13}C-NMR	Bruker WM 250 (62.896 MHz) Bruker WM 400 (100.625 MHz)
IR	Perkin-Elmer Infrared Spectrophotometer 1420
Polarimeter	Perkin-Elmer 241 (thermostated at +20 °C)
GC	Shimadzu GC 14B, FID 250 °C, Integrator HP 3390A
HPLC	Merck L-6200 Intelligent Pump, L-4000 UV detector
TLC	SiO_2 $60F_{254}$ (Merck), detection with UV, Vanillin/H_2SO_4
MS	Varian MAT 311 A (EI, 70 eV).
EA	Elementar Vario EL
Melting points	Büchi 510

7.2 General

The chemical reagents used in this dissertation were obtained from standard suppliers (Fluka, Sigma-Aldrich, Merck) and, if not differently specified in the description of the particular reaction, used without further purifications. Solvents employed in reactions were normally distilled and when necessary dried using standard procedures[93] and drying agents. For standard work up procedures they were directly used as purchased. Solvents used for HPLC analyses were of gradient quality and degassed in a sonicator for 20min prior to use. Particular attention was given to reactions carried out under anhydrous conditions. In these cases all glassware, stoppers, septa, magnetic stirrers and syringes were dried over night in a oven thermostated at 80 °C, allowed to cool in a desiccator which was opened only prior to use. For the transfer of reagents sterile packaged one-way plastic syringes were employed. Hypodermic needles for medical use were used together with long metal needles (especially to transfer anhydrous solvents) and the latter dried in an oven as described for the glassware. The inert gas used for all reactions was argon 4.8. Merck silica gel 60 (70-230 mesh) was used for column chromatography. Vacuum distillations were accomplished with standard equipment using either membrane pumps or oil pumps. Alternatively, short path distillations (Kugelrohr) were also used. Deuterated solvents for NMR analyses were obtained from the Aldrich company and used without any internal standard. In the NMR analyses the letters s,d,t,q,m, refer to singlet, doublet, triplet, quartet and multiplet respectively with all various combinations possible (e.g. dd is double doublet). Reported melting points are uncorrected.

7.2.1 List of abbreviations

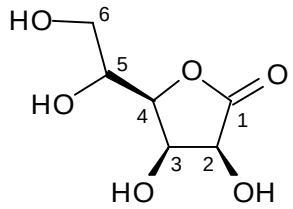
$[\alpha]_D^{20}$	specific rotation [expressed without units; the actual units, deg mL/(g dm) are understood]
Ac	acetyl
AcO_2H	peracetic acid
AIBN	2,2'-azobisisobutyronitrile
atm	atmosphere(s)
Bn	benzyl
bp	boiling point
br	broad
calcd	calculated
CI	chemical ionization
cm	centimeters
δ	chemical shift in parts per million
d	doublet; day(s)
DCC	*N*,*N*-dicyclohexylcarbodiimide
DEAD	diethyal azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electron impact
FAB	fast atomic bombardment
GC	gas chromatography
h	hour(s)
HMDS	hexamethyldisilazane
HMPT	hexamethyphosporic triamide
Hz	Hertz

J	coupling constant
LDA	lithium diisopropylamide
KHMDS	potassium hexamethyldisilazane
µ	micro
m	multiplet, meter(s), milli
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	mass spectrometry
m/z	mass to charge ratio
Ph	phenyl
ppm	parts per million
q	quartet
R_f	retention factor
rt	room temperature
s	singlet, second(s)
t	triplet
Tf	trifluoromethanesulfonyl (triflyl)
Tf_2O	trifluoromethanesulfonic acid anhydride (triflic anhydride)
TFA	trifluoroacetic acid
Tlc	thin layer chromatography
Ts	tosyl (*p*-toluenesulfonyl)

7.3 γ-lactones

7.3.1 (3*S*,4*S*,5*R*)-(+)-5-[(*S*)-1,2-dihydroxy-ethyl]-3,4-dihydroxy-dihydro-furan-2-one (**10**)[23c]

This reaction was carried out using a Büchi hydrogenation apparatus equipped with 1L vessel connected with a water thermostat, a plug valve for gas-discharging and introduction of H_2, a manometer, a metal finger for the insertion of a contact thermometer and a security 6 Bar limit-pressure valve. 65.0g (369mmol) of L(+)-ascorbic acid (**9**) were dissolved in 500ml of distilled water and introduced into the 1L vessel. To this solution 6.5g of Pd/C-10% were added and the mixture was degassed under stirring for 5min by connecting the valve for gas-discharging with a membrane pump. After this period, the plug valve was closed thereby taking great care to avoid any entry of air and the flask was connected under vacuum with a hydrogen source *via* a rubber hose. The mixture was stirred under 5 Bar pressure of hydrogen for 24h at 50 °C. Then, the catalyst was separated by filtration and the water removed from the reaction mixture using a rotavapor at 45 °C. 65.7g (369mmol; quantitative yield) of **10** were obtained as colorless crystals. Recrystallization from EtOH/H_2O afforded **10** in very high purity. In order to collect more material this reaction was repeated twice.



10

m.p.: 180 – 181 °C (EtOH/H_2O).

$[\alpha]_D^{20}$ = +56.7 (*c* = 0,88, H_2O).

^{1}H NMR (d_6-DMSO):

δ 5.75 (d, 1H, *J*=7.5 Hz, C-2-OH), 5.3 (d, 1H, *J*=3.75 Hz, C-3-OH), 4.9 (d, 1H, *J*=5.2 Hz, C-5-OH), 4.6 (t, 1H, *J*=5.6 Hz, C-6-OH), 4.4 (dd, 1H, *J*=7.3 Hz, *J*=4.5 Hz, C-4), 4.2 (d, 1H, *J*=8.1 Hz, C-2), 4.1 (d, 1H, *J*=3.3 Hz, C-3), 3.7 (m, 1H, C-5), 3.45 (m, 2H, C-6).

^{13}C NMR (d_6-DMSO):

δ 176.3 (C-1), 80.9 (C-2), 70 7 (C-4), 70.1 (C-5), 69.4 (C-3), 61.9 (C-6).

IR (KBr, cm^{-1}):

3550 (OH), 3470 (OH), 2980 ($-CH_{2-asym}$), 2890 ($-CH_{2-sym}$), 1780 (C=O).

MS m/z:

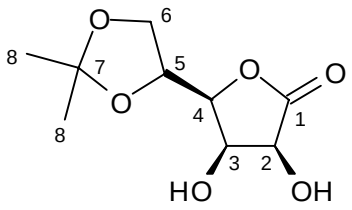
160 ($M^+ - H_2O$), 147 (M+ - $\cdot CH_2OH$), 100 ($C_4H_4O_3^+$), 85, 73 ($C_2H_2O_3^+$), 61 ($C_2H_5O_2^+$), 57, 43.

Elemental Analysis:

Anal. Calcd for $C_6H_{10}O_6$: C, 40.45; H, 5.66. Found: C, 40.22 ; H, 6.17.

7.3.2 (3*S*,4*S*,5*R*)-(+)-5-{(*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl}-3,4-dihydroxy-dihydro-furan-2-one[23c] (**11**)

To a stirred solution of 126g of **10** (710mmol) in 1.3L of dry DMF, at 0 °C, under argon, *p*-TsOH (6.7g, 35mmol, 0.05eq) was added. To this solution 2-methoxy-propene (86.6ml, 910mmol, 1.3eq) was slowly added from a dropping funnel and the resulting mixture was stirred for 24h at rt. The reaction progress was monitored via T.l.c. Then, 130g of $Na_2CO_3 \cdot 10H_2O$ were added and the resulting suspension vigorously stirred for a further 2h. After filtration over Celite and removal of DMF by vacuum distillation (oil bath 70 °C, membrane pump), 118g (530mmol, 76% yield) of a yellow-brown solid was isolated which was reacted without further purification. For analyses a few grams of crude **11** were purified by column chromatography on silica gel using as eluent AcOEt. After removal of the solvent, a white solid was obtained.



11

m.p.: 119-120 °C.

R_f: 0.26 AcOEt.

$[\alpha]_D^{20}$ = +55.8 (*c*= 0.52, methanol).

^{1}H NMR (d_6-DMSO):

δ 5,8 (d, 1H, *J*=6.0 Hz, C-3-OH), 5.4 (d, 1H, J=2.5 Hz, C-2-OH), 4.4 (s, 1H, C-4), 4.2 (m, 1H, C-2), 4.0 (dd, 1H, *J*=8.8 Hz, *J*=6.2 Hz, C-3), 3.7 (dd, 1H, *J*=8.8 Hz, *J*=6.1 Hz, C-5), 3.3 (s, 2H, C-6), 1.3 (s, 3H, C-8), 1.25 (s, 3H, C-8).

^{13}C NMR (d_6-DMSO):

δ 175,9 (C-1), 109,0 (C-7), 81,2 (C-4), 75,0 (C-5), 70,2 (C-2), 69,1 (C-3), 64,3 (C-6), 26,6 (C-8), 25,3 (C-8).

IR (KBr, cm^{-1}):

3520 (OH), 3460 (OH), 2990 (CH_3), 2930 ($-CH_2-_{asym}$), 2870 ($-CH_2-_{sym}$), 1760 (C=O).

MS m/z:

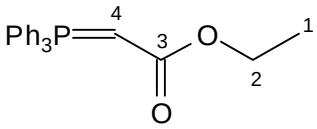
218 (M^+), 203 (M^+ - $\cdot CH_3$), 187 ($C_8H_{11}O_5^+$), 175 ($C_6H_8O_6^+$), 160 ($C_6H_8O_5^+$), 125, 115($C_6H_{10}O_2^+$), 101 ($C_5H_9O_2^+$), 85 ($C_4H_6O_2^+$), 69, 60, 55, 43.

Elemental Analysis:

Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 47.91; H, 7.01.

7.3.3 (Triphenyl-λ^5-phosphanylidene)-acetic acid ethyl ester[25] (**13**)

A 2000ml three-necked flask, equipped with a mechanical stirrer and dropping funnel was charged with triphenylphosphine (153.5g, 590mmol) and 1L toluene. To this stirred solution bromoacetic acid ethyl ester (64.8ml, 590mmol, 1eq) was added dropwise at rt. After 12h the white solid was collected by suction and remaining traces of toluene were removed *in vacuo*. The solid was dissolved in 1.5L distilled water and a 2N aqueous solution of NaOH was added until a positive reaction with phenolphthalein was observed. Filtration by suction and removal of traces of water with the help of a rotavapor first (bath 45 °C) followed by high vacuum afforded 184.4g (530mmol, 90% yield) of **13** as a white solid.



13

m.p.: 127-129 °C.

^{1}H NMR ($CDCl_3$):

δ 7.9 – 7.3 (m, 15H, C-6 – C-8), 3.9 (q, 2H, *J*=6.6 Hz, C-2), 2.9 (br, 1H, C-4), 1.1 (br, 3H, C-1).

^{13}C NMR ($CDCl_3$):

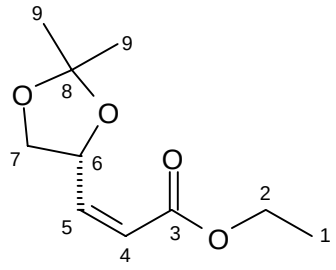
δ 171.25 (C-3), 132.92 (d, $J_{C\text{-}P}$=9.1 Hz, $C_{ar.}$), 131.83 ($C_{ar.}$), 131.80 ($C_{ar.}$), 128.59 (d, $J_{C\text{-}P}$=12.2 Hz, $C_{ar.}$), 57.77 (C-2), 30.03 (d, $J_{C\text{-}P}$=125.1 Hz, C-4), 14.75 (C-1).

IR (KBr, cm^{-1}):

3440, 3060 (-CH-$_{aromat}$), 2980 (=CH-), 2900 (-CH_2-), 1610 (C=O)

7.3.4 *R*-(-)-*Z*-3-(2,2-Dimethyl-[1,3]-dioxolan-4-yl)-acrylic acid ethyl ester[23c] (**14**)

To a solution of 118g (530mmol) of **11** in 600ml of distilled water, $NaIO_4$ (227.3g, 1060mmol, 2eq) was added and the pH was maintained at pH≅5.5 by addition of 4N NaOH using an autotitrator. After stirring for 2h at rt, the mixture was saturated with NaCl, filtered by suction and the pH of the solution adjusted to 6.5 – 7.0. The resulting solution was added under vigorous stirring to (Triphenyl-λ^5-phosphanylidene)-acetic acid ethyl ester **13** (201.2g, 577mmol, 1.1eq) dissolved in 400ml dichloromethane and the biphasic mixture was vigorously stirred over night. The organic layer was separated, the aqueous phase extracted twice with 150ml dichloromethane, and the collected organic fractions were washed with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, a pale yellow solid was obtained which contained the *Z*-ester *Z*-**14**, the *E*-ester *E*-**15** and the by-product triphenylposphine oxide. The latter was removed from the mixture exploiting its different solubility in respect to the products. Thus, to the crude solid product mixture 300ml *n*-hexane/AcOEt (4/1) were added after which the insoluble Ph_3PO was removed by suction. Evaporation of the organic phase afforded a yellow oil containing **14** and **15** in a *Z*/*E* mixture of 80/20 (^{1}H-NMR analysis).
The stereoisomeric mixture was purified by column chromatography using as eluent *n*-hexane/AcOEt (4/1) leading to the isomers *Z*-**14** and *E*-**15** in 58% (61.5g) and 14% (14.8g) respectively as colorless oils.



Z-**14**

Analytical data for *Z*-**14**:

R_f: 0.48 (*n*-hexane/AcOEt 4/1).

$[\alpha]_D^{20}$ = -124.8 (*c*= 1,05, $CHCl_3$).

^{1}H NMR ($CDCl_3$):

δ 6.35 (dd, 1H, *J*=11.6 Hz, *J*=6.6Hz, C-5), 5.83 (dd, 1H, *J*=11.6 Hz, *J*=1,8 Hz, C-4), 5.49 (dq, 1H, *J*=6.8 Hz, *J*=1.7 Hz, C-6), 4.37 (dd, 1H, *J*=8.3 Hz, *J*=6.9 Hz, C-7), 4.16 (q, 2H, *J*=7.1 Hz, C-2), 3.60 (dd, 1H, *J*=8,2 Hz, *J*=6.6 Hz, C-7), 1.44 (s, 3H, C-9), 1.38 (s, 3H, C-9), 1.28 (t, 3H, *J*=7.1, C-1).

^{13}C NMR ($CDCl_3$):

δ 165,6 (C-3), 149,1 (C-5), 120,8 (C-4), 109,7 (C-8), 73,5 (C-6), 69,4 (C-7), 60,4 (C-2), 26,5 (C-9), 25,4 (C-9), 14,1 (C-1).

IR (film, cm^{-1}):

2990(=CH-), 2940(-CH_3), 2910(-CH_2-$_{asym}$), 2880(-CH_2-$_{sym}$), 1720(C=O), 1640(C=C).

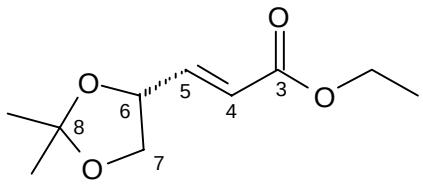
MS m/z:

200 (M^+), 185 (M^+ - $\cdot CH_3$), 170 (M^+ - $2\cdot CH_3$), 155 (M^+ - $EtO^\cdot$), 142 ($C_7H_{10}O_3^+$), 125, 112 ($C_6H_8O_2^+$), 97, 84 ($C_4H_4O_2^+$), 72 ($C_4H_8O^+$), 59, 52, 43.

Elemental Analysis:

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 57.61; H, 8.70.

Analytical data for *E*-**15**:



E-**15**

R_f: 0.38 (*n*-hexane/AcOEt 4/1).

$[\alpha]_D^{20}$ = -41.1 (*c*= 0.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$):

δ 6,86 (dd, 1H, *J*=15.7 Hz, *J*=5.6 Hz, C-5), 6.08 (dd, 1H, *J*=15.7 Hz, *J*=1,4 Hz, C-4), 4.65 (dq, 1H, *J*=5,6 Hz, *J*=1.3 Hz, C-6), 4.20 (q, 2H, *J*=14.1 Hz, *J*=7.0 Hz, C-2), 4.17 (dd, 1H, *J*=8.3 Hz, *J*=6.4 Hz, C-7), 3.66 (dd, 1H, *J*=8.2 Hz, *J*=7.2 Hz, C-7), 1.44 (s, 3H, C-9), 1.40 (s, 3H, C-9), 1.28 (t, 3H, *J*=7.1Hz, C-1).

^{13}C NMR ($CDCl_3$):

δ 165,9 (C-3), 144,6 (C-5), 122,4 (C-4), 110,1 (C-8), 74,9 (C-6), 68,8 (C-7), 60,5 (C-2), 26,5 (C-9), 25,7 (C-5), 14,2 (C-1).

IR (film, cm^{-1}):

2990 (=CH-), 2940 ($-CH_3$), 2880 ($-CH_2-$), 1720 (C=O), 1660 (C=C)

MS m/z:

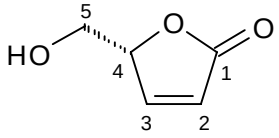
200 (M^+), 185 ($M^+ - {}^{\cdot}CH_3$), 170 ($M^+ - 2{}^{\cdot}CH_3$), 155 ($M^+ - EtO^{\cdot}$), 142 ($C_7H_{10}O_3^+$), 125, 112 ($C_6H_8O_2^+$), 97, 84 ($C_4H_4O_2^+$), 72 ($C_4H_8O^+$), 59, 52, 43.

Elemental Analysis:

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 58,4; H, 8,8.

7.3.5 *R*-(+)-5-Hydroxymethyl-5*H*-furan-2-one (**16**)

To a stirred solution of *R*-(-)-*Z*-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylic acid ethyl ester (**14**, M.W. 200.23, 46.1 g, 230mmol) in 150ml of MeOH, 6ml of a 10% aqueous solution of H_2SO_4 was added at rt. After 4h the weakly basic ion exchange resin Amberlite IRA-93 was added portionwise until the pH was adjusted to 6-6.5. The resin was filtered off and the organic phase was evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel using AcOEt as eluent to afford 18.8g of **16** in 72% yield as white crystals.



16

m.p. 43-44 °C (from $CHCl_3/Et_2O$).

R_f : 0.45 AcOEt.

$[\alpha]_D^{20} = +124.7$ (*c* 1.08, $CHCl_3$).

^{1}H NMR ($CDCl_3$):

δ 7.49 (dd, *J*=5.83 Hz, *J*=1.57 Hz, 1H, C-3), 6.19 (dd, *J*=5.76 Hz, *J*=2.03 Hz, 1H, C-2), 5.15 (m, 1H, C-4), 3,98 (dd, *J*=12.19 Hz, *J*=3.37 Hz, 1H, C-5), 3.79 (dd, *J*=12.19 Hz, *J*=4.88 Hz, 1H, C-5'), 2.58 (br, 1OH).

^{13}C NMR ($CDCl_3$):

δ 173.02 (C-1), 153.45 (C-3), 122.97 (C-2), 83.98 (C-4), 62.39 (C-5).

IR (KBr, cm^{-1}):

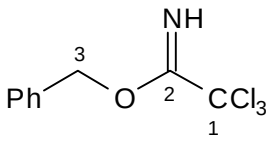
3350 (OH), 3085 (=C-H), 2920 ($-CH_2-_{asym}$), 2860 ($-CH_2-_{sym}$), 1735 (C=O), 1595 (C=C).

Elemental Analysis:

Anal. Calcd for $C_5H_6O_3$: C, 52.58; H, 5.25. Found: C, 52.30; H, 5.21 .

7.3.6 2,2,2-Trichloro-acetimidic acid benzyl ester[28] (**17**)

500ml of a 50% aqueous solution of KOH were added at –15 °C to a stirred solution of $PhCH_2OH$ (50ml, 480mmol) in 500ml dichloromethane. To this biphasic mixture the phase transfer catalyst tetrabutylammonium hydrogensulfate (500mg) was added followed by the dropwise addition of trichloroacetonitrile (58ml, 580mmol; 1.2eq) *via* a dropping funnel. After stirring for 30min at –15 °C, the temperature was increased to rt and the mixture stirred for an additional 30min. The phases were separated, the aqueous layer was extracted with dichloromethane (2x100ml) and the collected organic phases reduced to 1/3 of their volume. The pale yellow solution was filtered over Celite and the solvent was evaporated *in vacuo* to afford 101g (400mmol, 83% yield) of **17** as yellow oil. Without any further purification, this reagent was used for further transformations.



17

^{1}H NMR ($CDCl_3$):

δ 8.4 (s, 1H, NH), 7.5 – 7.3 (m, 5H, Ph), 5.4 (s, 2H, C-3).

^{13}C NMR ($CDCl_3$):

δ 162.5 (C-2), 135.4 (C_{ar}), 128.5 (C_{ar}), 128.2 (C_{ar}), 127.9 (C_{ar}), 91.3 (C-1), 70.7 (C-3).

IR (film, cm^{-1}):

3340 (NH), 3070 (-CH-$_{aromat}$), 3030 (-CH-$_{aromat}$), 2950 (-CH_2-), 1660 (C=N).

MS m/z:

251 (M^+), 186 (M^+ - $Ph^{\cdot}$), 145 ($C_2OCl_3^+$), 134 ($PhCH_2OCH{=}NH^+$), 125 ($C_2HNOCl_2^+$), 107 ($PhCH_2O^+$), 91 (tropyllium ion), 79, 65, 51, 39.

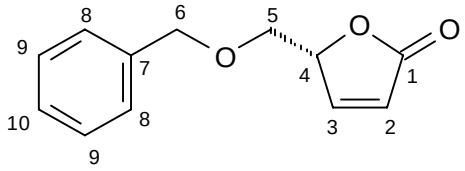
Elemental Analysis:

Anal. Calcd for $C_9H_8Cl_3NO$: C, 42.81; H, 3.19; N, 5.55. Found: C, 42.31; H, 3.51; N, 5.90.

7.3.7 *R*-(+)-5-Benzyloxymethyl-5*H*-furan-2-one (**1**) from **16**

A solution of *R*-(+)-5-hydroxymethyl-5*H*-furan-2-one (**16**, M.W. 114.10, 4.0g, 35.05 mmol) in a 300ml mixture of anhydrous dichloromethane/cyclohexane (2/1) was stirred under argon. The reaction mixture was cooled to 0 °C and trichloroacetamidic acid benzyl ester (**17**, M.W. 252.53, 7.2ml, 38.55mmol, 1.1eq) and trifluoromethanesulfonic acid

(M.W. 150.08, 305.6µl, 3.50mmol, 0.1eq) were added. After10 min at 0 °C the temperature was increased to rt and the mixture was stirred for an additional 2 hours. The solution was filtered to remove the solid trichloroacetamide and the solvents were removed under reduced pressure. The crude product was suspended in 60ml *n*-hexane/dichloromethane (2/1) and filtered again to remove residual trichloroacetamide. Purification by column chromatography on silica gel using as eluent Et_2O/*n*-hexane (2/1)→Et_2O afforded 6.0g of **1** (84% yield), as colorless oil.



1

R_f: 0.28 Et_2O/hexane (2/1).

$[\alpha]_D^{20}$ = +137.3 (*c* 1.31, $CHCl_3$).

ee ≥98% (conditions: see paragraph 7.3.18)

^{1}H NMR ($CDCl_3$):

δ 7.50 (dd, *J*=5.67 Hz, *J*= 1.39 Hz, 1H, C-3), 7.38-7.27 (m, 5H, Ph), 6.17 (dd, *J*=5.67 Hz, *J*=1.96 Hz, 1H, C-2), 5.17 (m, 1H, C-4), 4.58 (s, 2H, C-6), 3.74 (dd, *J*=10.35 Hz, *J*=5.19 Hz, 1H, C-5), 3.69 (dd, *J*=10.50 Hz, *J*=5.05 Hz, 1H, C-5').

^{13}C NMR ($CDCl_3$):

δ 172.63 (C-1), 153.80 (C-3), 137.27 (C-7), 128.46 ($C_{ar.}$), 127.93 ($C_{ar.}$), 127.67 ($C_{ar.}$), 122.55 (C-2), 82.13 (C-4), 73.74 (C-6), 69.47 (C-5).

IR (film, cm^{-1}):

3070 (=C-H), 3045 (=C-H_{arom}), 3015 (=C-H_{arom}), 2890 (-CH_2-$_{asym}$), 2845 (-CH_2-$_{sym}$), 1750 (C=O), 1590 (C=C).

MS *m/z*:

204 (M^+), 161, 151 ($C_9H_{10}O_2^+$), 126, 108 ($PhCH_2O^+$), 98 [(M+1) -$PhCH_2O^{\cdot}$]$^+$, 91 (tropyllium ion), 82 ($C_5H_5O^+$), 77 (Ph^+), 62, 49, 44 (100%), 36.

Elemental Analysis:

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.51; H, 5.87. Found: C, 69.95 ; H, 5.76 .

7.3.8 *R*-(+)-2-(3-Benzyloxy-2-hydroxy-propyl)-malonic acid diethyl ester (**19**)

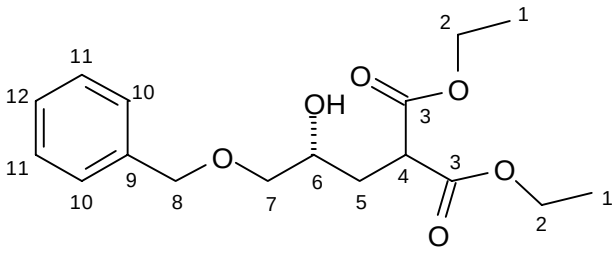
Method A:

In a 250ml three-necked flask, equipped with two dropping funnels, diethyl malonate (2.7ml, 18.28mmol, 1.4eq) was dissolved in 50ml dry THF. To this solution, at –78 °C and under argon, 9.8ml of *n*-butyllithium (1.6M in *n*-hexane, 15.66mmol, 1.2eq) were added dropwise under stirring. After 15min one dropping funnel was charged with *R*-(-)-2-benzyloxymethyl oxirane (**18**, 2ml, 13.05mmol), dissolved in 10ml dry THF and the other

with neat BF_3-Et_2O (1.9ml, 15.66mmol, 1.2eq). **18** and BF_3-Et_2O were added simultaneously and the mixture was stirred for 1.30h at –78 °C. After this time the temperature was increased to rt and 20ml of a saturated aqueous solution of NH_4Cl were added to quench the base. The mixture was transferred to a separatory funnel and 30ml of AcOEt were added. The organic layer was separated, washed with brine and dried over anhydrous Na_2SO_4. Column chromatography on silica gel [*n*-hexane/AcOEt (3/1)] afforded 3.4g of **19** (81% yield) as colorless oil. **19** is unstable, it cyclizes spontaneously with loss of ethanol.

Method B:

Sodium (360mg, 15.66mmol, 1.2eq) was added portionwise at 0 °C to 20ml of dry ethanol in a flask with an attached bubbler to allow escape of produced H_2. When all the sodium was consumed, diethyl malonate (2.7ml, 18.28mmol, 1.4eq), dissolved in 10ml of dry ethanol was added *via* a syringe. After 10min at 0 °C, *R*-(-)-2-benzyloxymethyl-oxirane (**18**, 2ml, 13.05mmol) was added dropwise and the resulting mixture stirred for 2h at 0 °C. After this time, 10ml of a saturated aqueous solution of NH_4Cl were added and the entire mixture transferred to a separatory funnel. 30ml of AcOEt were added, the organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvents, the crude product was purified by column chromatography on silica gel [*n*-hexane/AcOEt (3/1)] to afford 2.1g of **19** (50% yield) as colorless oil. **19** is unstable, it cyclizes spontaneously with loss of ethanol.



19

R_f: 0.23 *n*-hexane/AcOEt (3/1)

$[\alpha]_D^{20}$ = +2.1 (*c* 2.87, $CHCl_3$)

^{1}H NMR ($CDCl_3$):

δ 7.40-7.25 (m, Ph), 4.56 (s, 2H, C-8), 4.20 (m, 4H, C-2), 3.86 (m, 1H, C-4), 3.67 (dd, 1H, *J*=8.64 Hz, *J*=5.59 Hz, C-6), 3.53 (dd, 1H, *J*=9.66 Hz, *J*=3.56 Hz, C-7), 3.38 (dd, 1H, *J*=9.66 Hz, *J*=7.12 Hz, C-7'), 2.06 (m, 2H, C-5), 1.27 (m, 6H, C-1).

^{13}C NMR ($CDCl_3$):

δ 169.72 (C-3), 169.44 (C-3), 137.82 (C-9), 128.44 (C_{ar}), 127.81 (C_{ar}), 127.71 (C_{ar}), 74.13 (C-7), 73.41 (C-8), 68.31 (C-4), 61.44 (C-2), 48.67 (C-6), 32.23 (C-5), 14.03 (C-1), 13.99 (C-1').

IR (film, cm^{-1}):

3512 (OH), 2982 ($-CH_2-_{asym}$), 2866 ($-CH_2-_{sym}$), 1731 (C=O).

MS m/z:

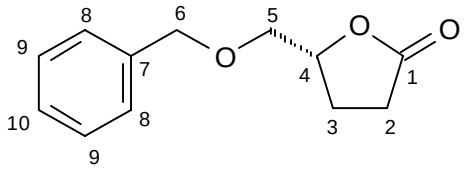
324 (M^+), 278 (M^+ - $PhCH_2OCH_2^{\cdot}$), 172, 157 ($C_8H_{13}O_3^+$), 129, 111, 91 (tropyllium ion).

Elemental Analysis:

Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.23 ; H, 7.31.

7.3.9 *R*-(-)-5-Benzyloxymethyl-dihydro-furan-2-one (**21**)

2.0g of **19** (6.16mmol) were dissolved in 20ml of DMSO. To this solution H_2O (222µl, 12.32mmol, 2eq) was added together with NaCl (720mg, 12.32mmol, 2eq) and the mixture was heated at 150 °C for 6h, allowed to cool to rt, diluted with 20ml Et_2O and washed with brine. The organic phase was dried over anhydrous Na_2SO_4 and the resulting crude product purified by column chromatography on silica gel using as eluent *n*-hexane/AcOEt (2/1). **21** was isolated as colorless oil in 36%yield (576mg).



21

R_f: 0.18 *n*-hexane/AcOEt (2/1)

$[\alpha]_D^{20}$ = -22.0 (*c* 2.95, $CHCl_3$)

^{1}H NMR ($CDCl_3$):

δ 7.37-7.27 (m, Ph), 4.67 (m, 1H, C-4), 4.57 (d, *J*=2.54 Hz, 2H, C-6), 3.68 (dd, *J*=10.68 Hz, *J*=3.56 Hz, 1H, C-5), 3.59 (dd, *J*=10.68 Hz, *J*=4.07 Hz, 1H, C-5'), 2.61 (m, 1H, C-2), 2.47 (m, 1H, C-2'), 2.28 (m, 1H, C-3), 2.12 (m, 1H, C-3').

^{13}C NMR ($CDCl_3$):

δ 177.20 (C-1), 137.62 (C-7), 128.45 (C_{ar}), 127.75 (C_{ar}), 127.54 (C_{ar}), 78.90 (C-4), 73.51 (C-6), 71.51 (C-5), 28.30 (C-2), 24.04 (C-3).

IR (film, cm^{-1}):

2939 ($-CH_2-_{asym}$), 2865 ($-CH_2-_{sym}$), 1770 (C=O).

MS m/z:

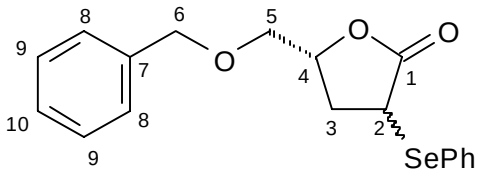
206 (M^+), 107 ($PhCH_2O^+$), 100 (M^{+1}-$PhCH_2O^{\cdot}$), 91 (tropyllium ion), 85 (M^+-$PhCH_2OCH_2^{\cdot}$).

Elemental Analysis:

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.72 ; H, 6.80.

7.3.10 (3*R*,*S*-5*R*)-Benzyloxymethyl-3-phenylselanyl-dihydro-furan-2-one (**22**) from **21**

To a stirred solution of HMDS (425µl, 2.03mmol, 1.4eq) in 3ml of dry THF, under argon, at –78 °C, *n*-butyllithium (1.6M in *n*-hexane, 1.1ml, 1.74mmol, 1.2eq) was added dropwise. After 5min, *R*-(-)-5-benzyloxymethyl-dihydro-furan-2-one (**21**, 300mg, 1.45mmol), dissolved in 2ml of dry THF was added. The reaction was stirred for 30min and then PhSeBr (378mg, 1.60mmol, 1.1eq), dissolved in 3ml of dry THF was added *via* a syringe and after 2min 5ml aqueous 1N HCl was added in one portion. The mixture was diluted with AcOEt (20ml) and the separated organic layer washed with brine and then dried over anhydrous Na_2SO_4. Column chromatography using as eluent *n*-hexane/AcOEt (2/1) afforded 277mg of the diastereoisomeric mixture **22** (52%). No effort was made to separate the diastereoisomers.



22

R_f : 0.29 and 0.38 (*n*-hexane/AcOEt: 2/1)

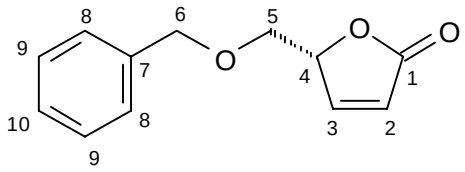
7.3.11 *R*-(+)-5-Benzyloxymethyl-5*H*-furan-2-one (**1**) from **22**

Method A:

The diastereoisomeric mixture **22** (277mg, 0.76mmol) was dissolved in 10ml of H_2O/MeOH: 1/1 (*v/v*) and $NaIO_4$ (487g, 2.28mmol, 3eq) was added at rt. After 1h the reaction mixture was diluted with AcOEt (10ml) and successively washed with H_2O (5ml), an aqueous solution of $Na_2S_2O_3$ (5ml). The organic phase was washed with brine and then dried over anhydrous Na_2SO_4. Purification by column chromatography on silica gel using as eluent Et_2O/*n*-hexane (2/1)→Et_2O afforded **1** in 85% yield (132mg) as colorless oil.

Method B:

500 mg of the diastereoisomeric mixture **22** (1.38mmol) were placed in a 25ml round bottom flask equipped with a magnetic stirrer and containing 5ml of THF. This solution was cooled to 0 °C and 3 drops of acetic acid were added *via* a Pasteur pipette. Then, 1.5ml of a 30% aqueous solution of H_2O_2 were added and the resulting mixture stirred at 0 °C for 30min. After this period the entire solution was transferred to a separatory funnel containing 10ml of dichloromethane. The separated organic phase was washed successively with a saturated aqueous solution of $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4. Purification by column chromatography on silica gel using as eluent Et_2O/*n*-hexane (2/1)→Et_2O afforded **1** in 65% yield (183mg) as colorless oil.



1

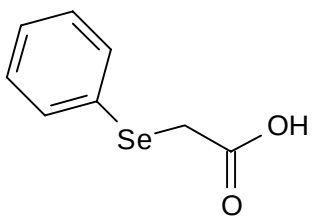
$[\alpha]_D^{20}$ = +136 (*c* 1.30, $CHCl_3$).

ee ≥97% (conditions: see paragraph 7.3.18)

All spectroscopic data were consistent with those reported above (paragraph 7.3.7).

7.3.12 Phenylselanyl acetic acid[33] (**23**)

To a stirred solution of diphenyldiselenide (**26**, 3.1g, 10.0mmol) in 60ml of dry EtOH, under argon, 850mg (22.4mmol, 2.2eq) of $NaBH_4$ were added portionwise and the mixture was stirred until a clear solution was obtained. Then, chloroacetic acid (**25**, 1.9g, 20.0mmol, 2eq), dissolved in 7ml of dry EtOH was added and the reaction mixture stirred for 7h at rt. After that, 10ml of a saturated water solution of $NaHCO_3$ were added, the solution was diluted with 30ml water and extracted with 2x50ml Et_2O/*n*-hexane (2/1). The aqueous phase was acidified to pH=1 and extracted with 2x50ml Et_2O/*n*-hexane (2/1). Removal of the solvents afforded **23** in 70% yield (3.0g) as yellow powder.



23

m.p. 35-36 °C

^{1}H NMR ($CDCl_3$):

δ 10.31 (br, 1OH), 7.63-7.60 (m, 2H, C-4), 7.31-7.27 (m, 3H, C-5 – C-6), 3.53 (s, 2H, C-2).

^{13}C NMR ($CDCl_3$):

δ 177.26 (C-1), 133.43 ($C_{ar.}$), 129.26 ($C_{ar.}$), 128.93 ($C_{ar.}$), 128.05 ($C_{ar.}$), 27.24 (C-2).

IR (film, cm^{-1}):

3000 (OH), 1700 (C=O), 1580

MS m/z:

216 (M^+), 171 ($PhSeCH_2^+$), 156 ($PhSe^+$).

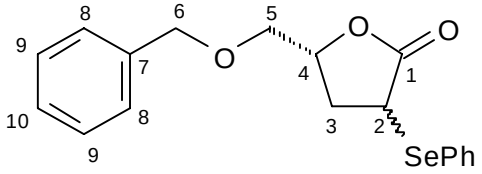
Elemental Analysis:

Anal. Calcd for $C_8H_8O_2Se$: C, 44.67; H, 3.75. Found: C, 44.21 ; H, 3.56.

7.3.13 (3*R*,*S*-5*R*)-Benzyloxymethyl-3-(phenylselanyl)-dihydro-furan-2-one (**22**) from **23**

To a stirred solution of diisopropylamine (2.0ml, 14.36mmol, 2.2eq) in 15ml of dry THF, at -78 °C under argon, *n*-butyllithium (1.6 M in *n*-hexane, 9.0ml, 14.36mmol, 2.2eq) was added dropwise and the mixture stirred for 15min. Then, 6.52mmol (1eq) of $PhSeCH_2CO_2H$ in 5ml of dry THF was added dropwise and, after stirring for 1h at -78 °C,

R-(-)-2-benzyloxymethyl oxirane (**18**, 1ml, 6.52mmol), dissolved in 10ml of dry THF was added. The mixture was stirred for 3h at rt. After this period at 0 °C 5ml of AcOH were added and the resulting solution was refluxed under argon over night. The mixture was diluted with 20ml of Et_2O, washed with a saturated aqueous solution of $NaHCO_3$ (3x10ml), brine and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product containing the mixture of diastereoisomers **22** purified by column chromatography on silica gel using as eluent *n*-hexane/AcOEt: 2/1 leading to 1.7g of the diastereoisomeric mixture **22** (72% yield). No effort was made to separate the diastereoisomers.



22

R_f : 0.29 and 0.38 (*n*-hexane/AcOEt: 2/1)

7.3.14 *R*-(+)-5-Benzyloxymethyl-5*H*-furan-2-one (**1**) from **22**

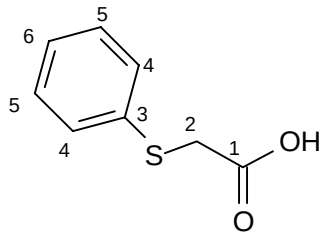
This transformation has been carried out under the same conditions already described above (paragraph 6.3.11) to obtain **1** also in this case with high enantiomeric purity.

$[\alpha]_D^{20}$ = +136.2 (*c* 1.37, $CHCl_3$).

ee ≥97% (conditions: see paragraph 7.3.18)

7.3.15 Phenylsulfanyl acetic acid[35] (**27**)

To a stirred solution of thiophenol (**31**, 5g, 44.1mmol) in a mixture of 20 ml THF and 30ml water at 0 °C, tetrabutylammonium bromide (100mg) was added. Then, NaOH (3.3g, 80.3mmol) was added portionwise, followed by a solution of bromoacetic acid (**30**, 6.4g, 45.1mmol) in 50ml of THF. The mixture was stirred for 30min at rt, acidified with concentrated HCl and diluted with 20ml of diethyl ether. The aqueous phase was extracted with diethyl ether (3x50ml) and the combined organic layers dried over anhydrous Na_2SO_4. Removal of the solvent yielded **27** as pale yellow solid in 95% yield (7.1g) and high chemical purity (NMR analyses).



27

m.p. 61-62 °C

^{1}H NMR ($CDCl_3$):

δ 10.25 (br, 1OH), 7.64-7.61 (m, 2H, C-4), 7.33-7.26 (m, 3H, C-5 – C-6), 3.53 (s, 2H, C-2).

^{13}C NMR ($CDCl_3$):

δ 177.34 (C-1), 133.45 ($C_{ar.}$), 129.28 ($C_{ar.}$), 129.13($C_{ar.}$), 127.82 ($C_{ar.}$), 27.22 (C-2).

IR (film, cm^{-1}):

3000 (OH), 1710 (C=O), 1600, 1200.

MS m/z:

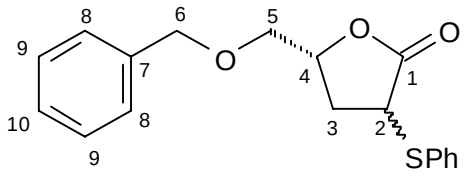
168 (M^+), 123 ($PhSCH_2^+$), 109 (PhS^+).

Elemental Analysis:

Anal. Calcd for $C_8H_8O_2S$: C, 57.12; H, 4.79; S, 19.06. Found: C, 56.89; H, 4.72; S, 18.95.

7.3.16 (3*R*,*S*-5*R*)-Benzyloxymethyl-3-(phenylsulfanyl)-dihydro-furan-2-one (**28**)

To a stirred solution of diisopropylamine (2.0ml, 14.36mmol, 2.2eq) in 15ml of dry THF, at -78 °C under argon, *n*-butyllithium (1.6 M in *n*-hexane, 9.0ml, 14.36mmol, 2.2eq) was added dropwise and the mixture stirred for 15min. Then, 6.52mmol (1eq) of $PhSCH_2CO_2H$ in 5ml of dry THF was added dropwise and after stirring for 1h at -78 °C, *R*-(-)-2-benzyloxymethyl oxirane (**18**, 1ml, 6.52mmol) dissolved in 10ml of dry THF was added. The mixture was stirred for 3h at rt. Then at 0 °C 5ml of AcOH were added and the resulting solution was refluxed under argon over night. The mixture was diluted with 20ml of Et_2O, washed with a saturated aqueous solution of $NaHCO_3$ (3x10ml), brine and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product containing the mixture of diastereoisomers **28** purified by column chromatography on silica gel using as eluent *n*-hexane/AcOEt: 2/1. Obtained were 1.4g of the diastereoisomeric mixture **28** (70% yield). No effort was made to separate the diastereoisomers.

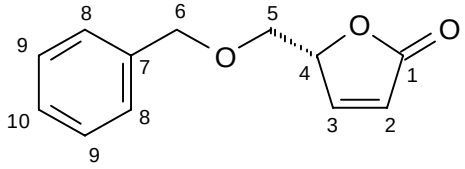


28

R_f : 0.29 and 0.38 (*n*-hexane/AcOEt: 2/1)

7.3.17 *R*-(+)-5-Benzyloxymethyl-5*H*-furan-2-one (**1**) from **28**

28 (1.4g, 4.56mmol) was dissolved in 50ml of H_2O/MeOH: 1/1 (*v/v*) and $NaIO_4$ (2.9g, 13.68mmol, 3eq) was added in one portion at rt. After stirring over night, the reaction mixture was diluted with AcOEt (50ml), washed successively with H_2O (20ml), an aqueous solution of $Na_2S_2O_3$ (20ml), brine and then dried over anhydrous Na_2SO_4. After removal of the solvents under vacuum, the crude product was dissolved in toluene (10ml) and refluxed for 30min. The solution was allowed to cool at rt and the toluene evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using as eluent Et_2O/*n*-hexane: 2/1. **1** was isolated in 50% yield (465mg) as colorless oil.



1

$[\alpha]_D^{20} = +134.1$ (*c* 1.28, $CHCl_3$).

ee ≥95% (conditions: see paragraph 7.3.18)

All spectroscopic data were consistent with those reported above (paragraph 7.3.7).

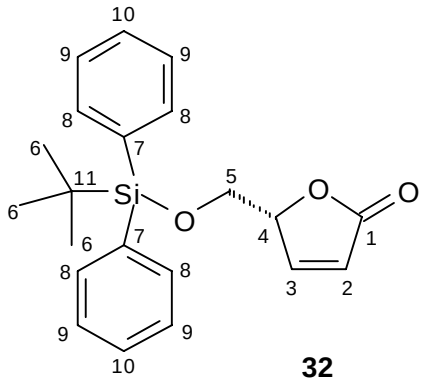
7.3.18 *R*-(+)-5-(*tert*-Butyl-diphenyl-silanyloxymethyl)-5*H*-furan-2-one (**32**) from **16**

Method A:

To a stirred solution of *R*-(+)-5-hydroxymethyl-5*H*-furan-2-one (**16**, 100mg, 0.87mmol) in 10ml of dry dichloromethane, at 0 °C, under argon, Et_3N (146µl, 1.05mmol, 1.2eq) was added *via* a syringe followed by addition of DMAP (10.7mg, 0.08mmol, 0.1eq). The mixture was allowed to warm to rt and was then stirred for 4h. After that the solvent was evaporated and, without any additional work-up, the crude product was purified by column chromatography on silica gel using as eluent *n*-hexane/AcOEt (4/1). **32** was obtained in 79% yield (242mg) as white solid. Under these conditions, complete racemization of **32** was observed (see discussion section).

Method B:

To a stirred solution of *R*-(+)-5-hydroxymethyl-5*H*-furan-2-one (**16**, 50mg, 0.44mmol) in 2ml of dry DMF, under argon, at room temperature were added NH_4NO_3 (105.2mg, 1.31mmol, 3eq) and *tert*-butyl-diphenylsilylchloride (145.7µl, 0.57mmol, 1.3eq). After stirring for 24h, water (10ml) was added and the mixture was extracted with Et_2O (3x10ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using as eluent *n*-hexane/AcOEt (4/1) to afford the title compound **32** in 91% yield (140mg) as white crystals. Under these conditions **32** was isolated without any racemization.



32

m.p. 79-80 °C (from pentane/Et_2O).

R_f : 0.37 *n*-hexane/AcOEt (4/1).

$[\alpha]_D^{20}$ = +76.4 (*c* 1.15, $CHCl_3$); ee ≥98% (HPLC analysis, column LiChoCART 250-4 (*S*,*S*)-Whelk-5µm, eluent *n*-hexane/isopropanol (97/3 *v/v*), flow rate 1 ml/min, detector UV 254 nm, see Figure 2.2, chapter 2).

^{1}H NMR ($CDCl_3$):

δ 7.62-7.36 (complex, 11H, 2Ph + C-3), 6.15 (dd, *J*=5.77 Hz, *J*=1.76 Hz, 1H, C-2), 5.04 (m, 1H, C-4), 3,93 (dd, *J*=10.68 Hz, *J*=4.57 Hz, 1H, C-5), 3.88 (dd, *J*=11.18 Hz, *J*=5.08 Hz, 1H, C-5'), 1,02 (s, 9H, C-6).

^{13}C NMR ($CDCl_3$):

δ 172.82 (C-1), 153.94 (C-3), 135.58 ($C_{ar.}$), 132.79 ($C_{ar.}$), 130.00 ($C_{ar.}$), 127.86 ($C_{ar.}$), 122.71 (C-2), 83.19 (C-4), 63.43 (C-5), 26.70 (C-6), 19.21 (C-11).

IR (KBr, cm^{-1}):

3090 (=C-H), 3050 (=C-H_{arom}), 2880 (-CH_2-), 1740 (C=O), 1595 (C=C).

MS *m/z*:

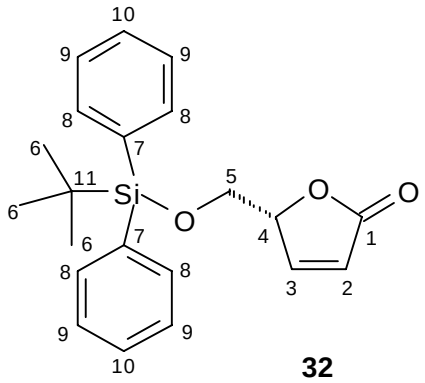
295 (M^+ - *t*-Bu), 199 (100%, Ph_2SiO^+), 181, 135, 77 (Ph^+), 55.

Elemental Analysis:

Anal. Calcd for $C_{21}H_{24}O_3Si$: C, 71.48; H, 6.80. Found: C, 70.89 ; H, 6.45.

7.3.19 *R*-(+)-5-(*tert*-Butyl-diphenyl-silanyloxymethyl)-5*H*-furan-2-one (**32**) from **1**

To a solution of **1** (80mg, 0.39mmol) in 10ml of AcOEt, 10mg of 10% Pd/C were added and the suspension was degassed for 5 min under stirring by applying vacuum using an aspirator. Then, the flask was connected with a source of H_2 *via* a rubber hose and stirred for 1h at rt. The catalyst was removed by filtration and the solvent evaporated under reduced pressure. Quantitative deprotection was observed *via* NMR. The crude product was dissolved in 2ml of dry DMF and under argon at rt NH_4NO_3 (94mg, 1.17mmol, 3eq) and *tert*-butyl-diphenylsilylchloride (130µl, 0.51mmol, 1.3eq) were added. After 24h, water (10ml) was added and the mixture was extracted with Et_2O (2x10ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel using as eluent *n*-hexane/AcOEt (4/1) to afford **32** in 90% yield (124mg) as white crystals.



32

m.p. 79-80 °C.

$[\alpha]_D^{20}$ = +76.2 (*c* 1.18, $CHCl_3$) from *R*-(-)-2-benzyloxymethyl oxirane (**18**) using the Krapcho method (paragraphs 7.3.8 – 7.3.11); ee ≥97% (HPLC analysis, column LiChoCART 250-4 (*S*,*S*)-Whelk-5µm, eluent *n*-hexane/isopropanol (97/3 *v/v*), flow rate 1 ml/min, detector UV 254 nm, see Figure 2.2, chapter 2).

$[\alpha]_D^{20}$ = +76.4 (*c* 1.30, $CHCl_3$) from *R*-(-)-2-benzyloxymethyl oxirane (**18**) using $PhSeCH_2CO_2H$ (paragraphs 7.3.12 – 7.3.14); ee ≥97% (HPLC analysis, column LiChoCART 250-4 (*S*,*S*)-Whelk-5µm, eluent *n*-hexane/isopropanol (97/3 *v/v*), flow rate 1 ml/min, detector UV 254 nm, see Figure 2.2, chapter 2).

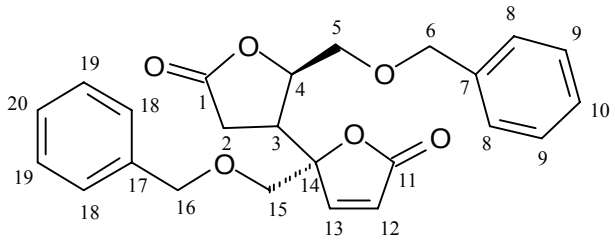
$[\alpha]_D^{20}$ = +75.1 (*c* 1.42, $CHCl_3$) from *R*-(-)-2-benzyloxymethyl oxirane (**18**) using $PhSCH_2CO_2H$ (paragraphs 7.3.15 – 7.3.17); ee ≥95% (HPLC analysis, column LiChoCART 250-4 (*S*,*S*)-Whelk-5µm, eluent *n*-hexane/isopropanol (97/3 *v/v*), flow rate 1 ml/min, detector UV 254 nm, see Figure 2.2, chapter 2).

All spectroscopic data were consistent with those reported above (paragraph 7.3.18).

7.4 2-Deoxy-L-ribose

7.4.1 2,2'-Bis-benzyloxymethyl-3',4'-dihydro-2*H*,2'*H*-[2,3']bifuranyl-5,5'-dione (**51**)

To a stirred solution of *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**) (50mg, 0.22mmol) in 1ml of DMSO and 0.2ml of HMPT, cesium acetate (43.6mg, 0.22mmol, 1eq) was added under an argon atmosphere and the mixture stirred at rt for 1h. Then 10ml of AcOEt were added and the solution was washed consecutively with 10% aqueous HCl (2x5ml), water and brine. The organic layer was dried over anhydrous Na_2SO_4 and the resulting crude product purified by column chromatography on silica gel using as eluent Et_2O/*n*-hexane (4/1) to afford **51** in 27% yield.



51

R_f : 0.20 Et_2O/*n*-hexane (4/1).

$[\alpha]_D^{20}$ = +9.7 (*c* 0.87, $CHCl_3$).

^{1}H NMR ($CDCl_3$):

δ 7.39-7.17 (m, 11H, 2Ph + C-13), 6.17 (d, *J*=6.10 Hz, 1H, C-12), 4.58 (d, *J*=11.68 Hz, 1H, C-6), 4.51 (s, 2H, C-16), 4.48 (d, *J*=12.20 Hz, 1H, C-6'), 4.39 (m, 1H, C-4), 3.69 (d, *J*=10.17 Hz, 1H, C-15), 3.67 (dd, *J*=11.18 Hz, *J*=3.05 Hz, 1H, C-5), 3.47 (dd, *J*=10.68 Hz,

J=3.05 Hz, 1H, C-5'), 3.47 (d, *J*=9.66 Hz, 1H, C-15'), 3.12 (m, 1H, C-3), 2.70 (dd, *J*=18.31 Hz, *J*=10.17 Hz, 1H, C-2), 2.50 (dd, *J*=17.80 Hz, *J*=5.59 Hz, 1H, C-2').

^{13}C NMR ($CDCl_3$):

δ 174.80 (C-1), 170.71 (C-11), 155.57 (C-13), 137.28, 136.57 (C-7 + C-17), 128.62 (C_{ar}), 128.54 (C_{ar}), 128.29 (C_{ar}), 128.03 (C_{ar}), 127.90 (C_{ar}), 127.72 (C_{ar}), 123.59 (C-12), 88.40 (C-14), 78.19 (C-4), 73.98 (C-6), 73.62 (C-16), 72.05 (C-15), 70.45 (C-5), 40.17 (C-3), 30.01 (C-2).

IR (film, cm^{-1}):

3030 (=C-H_{arom}), 2865 (-CH_2-$_{sym}$), 1758 (C=O).

MS *m/z*:

408 (M^+), 317 (M^+ - $PhCH_2^{\cdot}$), 211 ($C_{10}H_{10}O_5^+$), 181 ($C_9H_8O_4^+$), 91 (tropyllium ion), 43.

Elemental Analysis:

Anal. Calcd for $C_{24}H_{24}O_6$: C, 70.57; H, 5.92. Found: C, 69.92 ; H, 6.07.

7.4.2 Dimethylphenylsilyl lithium

A three-neck flask equipped with an argon inlet and a bubbler was charged with lithium powder (Aldrich 37,239-0, 897mg, 129.27mmol, 3eq) and under argon at 0 °C a solution of phenyldimethylchlorosilane (7.1ml, 43.09mmol) in 40ml of dry THF was added

dropwise. After completion of the addition, the flask was immersed into a sonicator for 15min and the purple solution was stirred overnight at –5 °C. This mixture was used directly and was always prepared freshly prior to the application. In our experience this reagent must always be transferred *via cannula* for best results.

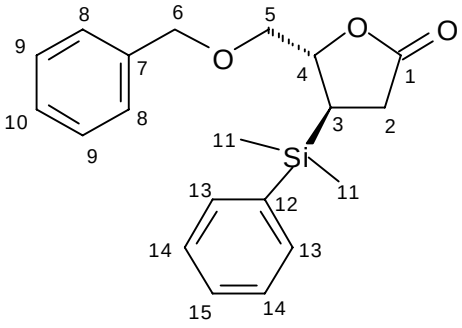
7.4.3 Dimethylphenylsilyl lithium – Determination of concentration

0.50ml of the solution obtained above (paragraph 6.4.2, ≅ 0.50mmol) were poured into 50ml of distilled water. To this solution a catalytic amount of phenolphthalein was added and the violet solution was titrated with a standard solution of 0.1N HCl in water until decolorization was observed (equivalent point). 55ml of 0.1N HCl solution (0.55mmol HCl) were consumed corresponding to 0.55mmol of OH^- equivalents produced by quenching the original solution with water and therefore the conversion could be considered quantitative corresponding to a 1.1 M solution of dimethylphenylsilyl lithium in THF.

7.4.4 (4*R*,5*S*)-(-)-5-Benzyloxymethyl-4-(dimethyl-phenyl-silanyl)-dihydro-furan-2-one (**54**)

A suspension of CuCN (dried over night at 120 °C under high vacuum, 1.9g, 21.54mmol, 1.1eq) in 100ml of dry THF was stirred under argon at –45 °C. To this suspension $Ph(Me)_2SiLi$ (see above, 43.09mmol, 2.2eq) was added *via cannula* and the mixture was vigorously stirred for 30min. Then, at –45 °C, *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**, 4.0g, 19.58mmol) in 15ml of dry THF was slowly added *via* a syringe. The reaction mixture was stirred for 1h and quenched at –45 °C with 10ml of a saturated aqueous solution of NH_4Cl. The mixture was filtered by suction using an aspirator, AcOEt (20ml) was added and the entire mixture transferred to a separatory funnel. The organic layer was separated, successively washed with water and brine, and then dried over anhydrous Na_2SO_4. Chromatographic separation was carried out on silica gel using as eluent *n*-

hexane/AcOEt (3/1). **54** was isolated in 90% yield (6.0g) as a colorless oil. The ^{13}C-NMR analysis showed the formation of a **single** diastereoisomer.



54

R_f : 0.44 *n*-hexane/AcOEt (3/1).

$[\alpha]_D^{20}$ = -22.5 (*c* 1.08, $CHCl_3$).

^{1}H NMR ($CDCl_3$):

δ 7.48-7.27 (m, 10H, 2Ph), 4.51 (m, 1H, C-4), 4.49 (s, 2H, C-6), 3.57 (dd, *J*=11.18 Hz, *J*=2.49 Hz, 1H, C-5), 3.36 (dd, *J*=11.19 Hz, *J*=4.68 Hz, 1H, C-5'), 2.64 (dd, *J*=17.70 Hz, *J*=9.96 Hz, 1H, C-2), 2.38 (dd, *J*=17.74 Hz, *J*=11.06 Hz, 1H, C-2'), 1.96 (q, *J* =9.66 Hz, 1H, C-3), 0.37 (s, 3H, C-11), 0.35 (s, 3H, C-11).

^{13}C NMR ($CDCl_3$):

δ 176.87 (C-1), 137.68 (C-7), 135.26 (C-12), 133.70 (C-13), 129.88 ($C_{ar.}$), 128.21 ($C_{ar.}$), 127.75 ($C_{ar.}$), 127.67 ($C_{ar.}$), 82.05 (C-4), 73.45 (C-6), 71.38 (C-5), 31.33 (C-2), 24.07 (C-3), -4.53 (C-11), -5.15 (C-11).

IR (film, cm^{-1}):

3045 (=C-H_{arom}), 3010 (=C-H_{arom}), 2930 (-CH_{3asym}), 2890 (-CH_2-), 2840 (-CH_2-), 1760 (C=O), 1580 (C=C_{arom}).

MS *m/z*:

340 (M^+), 325 (M^+ - $^{\cdot}CH_3$), 280, 271, 262 [(M-1) - $Ph^{\cdot}]^+$, 241, 219 (M^+ - $PhCH_2OCH_2^{\cdot}$), 191 ($C_{11}H_{14}OSi^+$), 165, 156 (M^+ - $Ph^{\cdot}$ – $PhCH_2O^{\cdot}$), 136 ($PhMe_2SiH^+$), 117, 105, 91 (100%, tropyllium ion), 84 (M^+ - $PhMe_2Si^{\cdot}$ – $PhCH_2OCH_2^{\cdot}$), 75, 65, 57, 43.

Elemental Analysis:

Anal. Calcd for $C_{20}H_{24}O_3Si$: C, 70.48; H, 7.04. Found: C, 69.78; H, 6.97.

7.4.5 (4*R*,5*S*)-(-)-5-Benzyloxymethyl-4-hydroxy-dihydro-furan-2-one (**48**) from **54**

Method A:

To a stirred solution of **54** (5.0g, 14.68mmol) in 15ml of AcOOH (39% in AcOH, 6eq), at 0 °C, under argon, Br_2 (1M in AcOH, 7.3ml, 0.5eq) was added dropwise and the mixture was stirred for 5h at rt. The solution was then diluted with Et_2O (100ml) and under stirring at 0 °C 20ml of an aqueous solution of $Na_2S_2O_3$ were carefully added. The organic layer was separated, treated under stirring with 20ml of a saturated aqueous solution of $NaHCO_3$ followed by addition of $NaHCO_3$ powder until no further gas evolution was observed. The organic phase was washed again successively with 20ml of a saturated aqueous solution of $NaHCO_3$, brine and then dried over anhydrous Na_2SO_4. Chromatographic purification was achieved on silica gel using as eluent *n*-hexane/AcOEt (1/1) to afford **48** in 65% yield (2.1g) as a colorless oil.

Method B:

To a stirred solution of **54** (642mg, 1.88mmol) in 4ml of AcOH were added successively KBr (269mg, 2.26mmol, 1.2eq) and AcONa (580mg, 7.07mmol, 3.7eq). The mixture was cooled to 0 °C and 2.4ml of a 39% solution of AcO_2H in AcOH (14.14mmol, 7.5eq) was slowly added. After stirring for 30min, more AcONa (1.7g, 21.21mmol, 11.3eq) and AcO_2H (39% in AcOH, 7.2ml, 22.5eq) were added and the mixture stirred for 5h at rt. Work up and purification as described for **method A** afforded 250mg of **48** (60% yield) as a colorless oil.

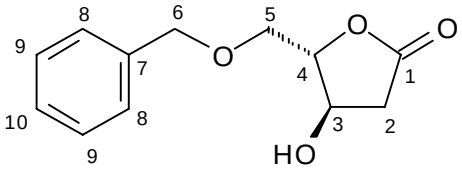
Method C:

To a stirred solution of **54** (220mg, 0.64mmol) in 1ml of AcOH, a 39% solution of AcO_2H in AcOH (2.8ml, 16.79mmol, 26eq) was added followed by $Hg(OAc)_2$ (308mg, 0.96mmol, 1.5eq). This mixture was stirred under an argon atmosphere for 3h at rt, diluted with Et_2O (10ml) and washed consecutively with a saturated aqueous solution of $Na_2S_2O_3$ (2x5ml), H_2O, a saturated aqueous solution of $NaHCO_3$ and finally brine. The organic layer was dried over anhydrous Na_2SO_4 and the crude product purified by column chromatography on silica gel using as eluent *n*-hexane/AcOEt (1/1) to afford **48** in 44% yield (62mg) as colorless oil.

Method D:

54 (500mg, 1.46mmol) was dissolved in 8ml of a mixture 1:1 (*v/v*) of AcOH and CF_3CO_2H. Then 752mg of $Hg(O_2CCF_3)_2$ (1.76mmol, 1.2eq) were added, the resulting mixture cooled to 0 °C and a 39% solution of AcO_2H in AcOH (0.7ml, 4.40mmol, 3eq) was slowly added. After stirring for 3.5h at rt, the mixture was diluted with dichloromethane (10ml), poured into 10ml of a 1:1 (*v/v*) mixture of a saturated aqueous solution of $NaHCO_3$ and NaCl and treated with powdered $NaHCO_3$ until pH=5 was reached. Then, the mixture was extracted with dichloromethane (3x20ml) and the collected

organic phases dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel using as eluent *n*-hexane/AcOEt (1/1) to afford **48** in 38% yield (124mg) as a colorless oil.



48

R_f : 0.26 hexane/AcOEt (1/1).

$[\alpha]_D^{20}$ = -5.0 (*c* 1.38, $CHCl_3$).

^{1}H NMR ($CDCl_3$):

δ 7.38-7.27 (m, 5H, Ph), 4.60-4.47 (complex, 4H, C-6, C-4, C-3), 3.70 (dd, *J*=10.70 Hz, *J*=3.21 Hz, 1H, C-5), 3.66 (dd, *J*=10.73 Hz, *J*=3.59 Hz, 1H, C-5'), 2.93 (dd, *J*=18.05 Hz, *J*=6.8 Hz, 1H, C-2), 2.45 (dd, *J*=17.96 Hz, *J*=2.65 Hz,1H, C-2'), 2.09 (br, 1 OH).

^{13}C NMR ($CDCl_3$):

δ 175.89 (C-1), 137.28 (C-7), 128.53 (C-9), 127.98 (C-8), 127.65 (C-10), 86.26 (C-4), 73.75 (C-6), 69.71 (C-5), 69.41 (C-3), 38.37 (C-2).

IR (film, cm^{1}):

3440 (OH), 3060 (=C-H_{arom}), 3030 (=C-H_{arom}) , 2920 (-CH_2-$_{asym}$), 2860 (-CH_2-$_{sym}$), 1770 (C=O).

MS *m/z*:

222 (M^+), 176, 159, 133, 116 (M^+ - $PhCH_2O^{\cdot}$), 105, 98 ($C_5H_6O_2^+$), 91 (100%, tropyllium ion), 83 ($C_4H_4O_2^+$), 77 (Ph^+), 70, 65, 57, 51, 43.

Elemental Analysis:

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.79; H, 6.30. Found: C, 64.21; H, 6.12.

7.4.6 (2*R*,*S*-4*R*,5*S*)-(-)-5-Benzyloxymethyl-tetrahydro-furan-2,4-diol (**47**)

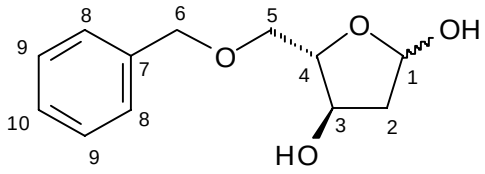
Method A:

To a stirred solution of 2-methyl-2-butene (19ml, 182.23mmol, 22.5eq) in 20ml of dry THF, at 0 °C, under argon, a 1 M solution of BH_3-THF (45.3ml, 5.6eq) was added and the mixture was stirred for 20min. Then, (4*R*,5*S*)-(-)-5-benzyloxymethyl-4-hydroxy-dihydro-furan-2-one (**48**, 8.09mmol, 1.8g) in 10ml of dry THF was added dropwise. After stirring for 24 hours, water (20ml) was added and the reaction mixture was refluxed for 30min. After this time at 0 °C 20ml of a 30% aqueous solution of H_2O_2 was added dropwise and the pH was adjusted to pH=8 with 2N NaOH. The mixture was stirred for an additional 10min, AcOEt (30ml) was added and the organic layer was separated. The aqueous phase was extracted twice with AcOEt and the collected organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvents were removed under vacuum (bath temperature max 30 °C). Chromatographic purification was carried out on silica gel using

as eluent AcOEt/*n*-hexane (3/1) to afford **47** in 60% yield (1.1g) as a colorless oil. **47** constitutes an anomeric mixture ($\alpha/\beta \cong 70/30$ in $CDCl_3$).

Method B:

(4*R*,5*S*)-(-)-5-benzyloxymethyl-4-hydroxy-dihydro-furan-2-one (**48**, 3.06mmol, 684mg) was dissolved in 10ml of dry THF and the resulting solution was stirred at –78 °C under argon. Then, a 1 M solution of DIBAL in toluene (9.2ml, 9.22mmol, 3eq) was added dropwise and the mixture stirred at –78 °C for 4h. The monitoring of the reaction progress (T.l.c.) showed only partial conversion together with unreacted starting material (main spot). The reaction was quenched with a saturated aqueous solution of NH_4Cl followed by extraction with AcOEt (3x10ml). The separated organic phases were collected and dried over anhydrous Na_2SO_4. After removal of the solvents, the crude product was purified by column chromatography on silica gel using as eluent AcOEt/*n*-hexane (3/1) to afford **47** in only 10% yield (68mg) as colorless oil. Again as anomeric mixture ($\alpha/\beta \cong 70/30$ in $CDCl_3$).



47

R_f :0.26 AcOEt/hexane (3/1).

$[\alpha]_D^{20}$ = -32.3 (*c* 1.22, $CHCl_3$, 2h).

^{1}H NMR ($CDCl_3$):

β anomer: δ 7.37-7.27 (m, 5H, Ph), 5.54 (d, *J*=4.78 Hz, 1H, C-1), 4.57 (d, *J*=6.10 Hz, 2H, C-6), 4.44 (m, 1H, C-3), 4.05 (q, *J*=4.06, 1H, C-4), 3.61 (d, *J*=4.22, 2H, C-5), 3.45 (br, 2 OH), 2.13 (d, *J*=3.05 Hz, 1H, C-2), 2.11 (d, *J*=5.08 Hz, 1H, C-2').

^{13}C NMR ($CDCl_3$):

β anomer: δ 137.21 (C-7), 128.51 (C-9), 127.98 (C-8), 127.85 (C-10), 99.03 (C-1), 84.95 (C-4), 73.66 (C-6), 73.10 (C-3), 71.26 (C-5), 43.61 (C-2).

^{1}H NMR ($CDCl_3$):

α anomer: δ 7.37-7.27 (m, 5H, Ph), 5.54 (d, *J*=4.78 Hz, 1H, C-1), 4.52 (s, 2H, C-6), 4.35 (dt, *J*=4.48 Hz, *J*=1.50 Hz, 1H, C-4), 4.23 (d, *J*=5.98 Hz, 1H, C-3), 3.50 (dd, *J*=10.18 Hz, *J*=4.73 Hz, 1H, C-5), 3.45 (br, 2 OH), 3.41 (dd, *J*=10.17 Hz, *J*=5.09 Hz, 1H, C-5'), 2.13 (d, *J*=13.40 Hz, 1H, C-2), 1.98 (d, *J*=13.73 Hz, 1H, C-2').

^{13}C NMR ($CDCl_3$):

α anomer: δ 137.78 (C-7), 128.37 (C-9), 127.71 (C-8), 127.61 (C-10), 99.24 (C-1), 85.86 (C-4), 73.44 (C-6), 73.33 (C-3), 70.49 (C-5), 41.30 (C-2).

IR (film, cm^{-1}):

3350 (OH), 3000 (=C-H_{arom}), 2900 (-CH_2-$_{asym}$), 2840 (-CH_2-$_{sym}$).

MS *m/z*:

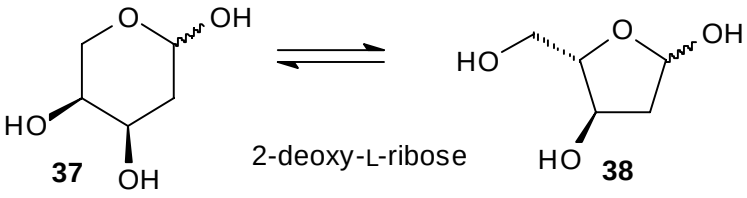
206 (M^+ - H_2O), 115 (M^+ - H_2O - tropyllium ion), 107 ($PhCH_2O^+$), 91 (tropyllium ion), 71, 59, 45 (100%).

Elemental Analysis:

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.21; H, 7.13. Found: C, 64.05; H, 7.08.

7.4.7 2-Deoxy-L-ribose (**37** + **38**)

A (10% *v/v*) solution of formic acid in methanol was degassed under vacuum for 5 min. 20ml of this solution were added carefully under argon to 1g of 10%Pd/C in a Schlenk flask equipped with a magnetic stirrer. To this suspension α,β-(4*R*,5*S*)-(-)-5-benzyloxymethyl-tetrahydro-furan-2,4-diol (**47**, 0.89mmol, 200mg), dissolved in 10ml of this solution, was added dropwise under stirring. After 1 hour the catalyst was filtered off, washed with 5ml of distilled water and the solvents were removed under vacuum (membrane pump, bath temperature max 30 °C). The crude product was purified by column chromatography using as eluent AcOEt/MeOH (9/1). The mixture of **37** + **38** was isolated as a syrup in 80% yield (95mg) which crystallized slowly from AcOEt/MeOH 4/1. After 24h in D_2O at rt the product mixture was analyzed by NMR. It consisted of the α,β-pyranose **37** and the α,β-furanose **38** in a ratio of 72:28. The anomeric ratios for **37** and **38** were nearly 1:1 in both cases.



m.p. 89-90 °C (from AcOEt/MeOH 4/1).

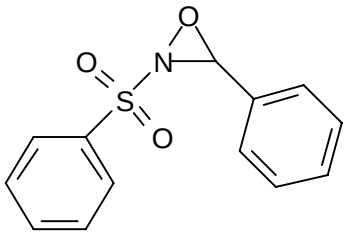
R_f : 0.25 AcOEt/MeOH (9/1).

$[\alpha]_D^{20}$ = +52.0 (*c* 1.0, H_2O, 24h; Lit.[94] +52 (*c* 0.5, H_2O); Lit. for 2-deoxy-D-ribose, -51 (*c* 1.3, H_2O)[95], -52 (*c* 1.05, H_2O)[96].

The spectroscopic data were consistent with those of commercially available, **natural** 2-deoxy-**D**-ribose.

7.4.8. 3-Phenyl-2-(phenylsulfonyl)-oxaziridine (**58**)[55]

To a stirred solution of *N*-benzylidene-benzenesulfonamide (**60**, 1g, 4.10mmol) in 40ml toluene, at rt and under mechanical stirring, a solution of K_2CO_3 (4.7g, 34.36mmol, 8eq) in 25ml water was added and the resulting biphasic mixture was vigorously stirred. After this period, Oxone® [$2KHSO_5$, $KHSO_4$, K_2SO_4, 3g, 4.87mmol (9.74 referred to $KHSO_5$, 2.3eq)] dissolved in 25ml water was added dropwise *via* a dropping funnel over a period of 30min. The separated aqueous phase was extracted with 2x20ml toluene, the collected organic phases washed with a freshly prepared 10% aqueous solution of $NaHSO_3$, and then dried over anhydrous Na_2SO_4. The filtered solution was evaporated (bath temperature <40 °C) and the crude product was allowed to solidify over night in the freezer. The crude product was then triturated with pentane and after removal of traces of solvents **58** was obtained in 89% yield as a white solid. At –20 °C **58** is stable for several months.



58

m.p. 93 - 94 °C (from pentane).

^{1}H NMR ($CDCl_3$):

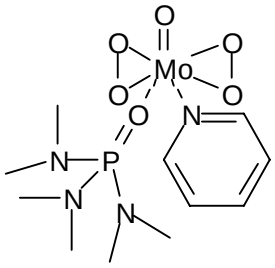
δ 5.50 (s, 1H, C-1), 8.08-7.41 (m, 10H, 2Ph).

^{13}C NMR ($CDCl_3$):

δ 135.00 ($C_{ar.}$), 133.49 ($C_{ar.}$), 131.39 ($C_{ar.}$), 131.31 ($C_{ar.}$), 129.34 ($C_{ar.}$), 129.32 ($C_{ar.}$), 128.71 ($C_{ar.}$), 128.19 ($C_{ar.}$), 76.27 (C-1).

7.4.9 Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric-triamide) (MoOPH) (**59**)[56]

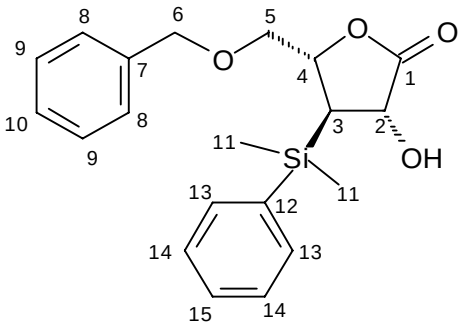
MoO_3 (30g, 0.2mol) was suspended in 150ml of a 30% aqueous solution of H_2O_2 and the mixture vigorously stirred. The mixture was immersed into a preheated oil bath (40 °C) until the internal temperature reached 35 °C. Then the bath was removed and the temperature maintained between 35 and 40 °C by cooling with a water bath if necessary. After the initial exothermic period, the mixture was stirred for 3.5h at 40 °C. After cooling to 20 °C, the reaction mixture was filtered to remove all solids, and the resulting yellow solution was cooled to 10 °C. HMPT (37.3g) was added under stirring and the crystalline precipitate was collected by suction. The solid was dried in a desiccator containing P_2O_5 for 24h under vacuum.
18g (51.9mmol) of the anhydrous complex (MoO_5-HMPA) were dissolved in 40ml dry THF and at 20 °C (water bath) dry pyridine (4.11g, 51,9mmol, 1eq) was added dropwise under stirring. The yellow, crystalline precipitate was collected and washed successively with a small amount of THF (10ml) and dry diethyl ether (100ml). The product was dried under vacuum and stored at –20 °C in a dark glass flask.



59

7.4.10 (3*S*,4*R*,5*S*)-(-)-5-Benzyloxymethyl-4-(dimethyl-phenyl-silanyl)-3-hydroxy-dihydro-furan-2-one (**61**)

200mg (0.58mmol) of (4*R*,5*S*)-(-)-5-benzyloxymethyl-4-(dimethyl-phenyl-silanyl)-dihydro-furan-2-one (**54**) were dissolved in 15ml of dry THF and the resulting solution stirred under argon at –78 °C. Then, KHMDS (0.5M in toluene; 2.4ml, 1.23mmol, 2.1eq) was added dropwise and after 10min solid MoOPH (**59**, 255mg, 0.58mmol, 1eq) was added in one portion. The mixture was stirred for 1h at –60 °C, poured at this temperature into 20ml of a 5% aqueous solution of $NaHSO_3$, and was then extracted with 50 ml Et_2O. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel using as eluent *n*-hexane/AcOEt (3/1) to afford **61** in 52% yield (220mg) as colorless oil.



61

R_f : 0.28 *n*-hexane/AcOEt (3/1).

$[\alpha]_D^{20}$ = -10.2 (*c* 1.48, $CHCl_3$).

^{1}H NMR ($CDCl_3$):

δ 7.51-7.27 (m, 10H, 2Ph), 4.46 (s, 2H, C-6), 4.39 (m, 1H, C-4), 4.28 (m, 1H, C-2), 3.55 (dd, *J*=11.69 Hz, *J*=2.03 Hz, 1H, C-5), 3.41 (br, OH), 3.29 (dd, *J*=11.69 Hz, *J*=5.08 Hz, 1H, C-5), 1.92 (t, *J*=10.17 Hz, 1H, C-3), 0.44 (s, 3H, C-11), 0.40 (s, 3H, C-11).

^{13}C NMR ($CDCl_3$):

δ 177.28 (C.1), 137.22 (C-7), 134.97 (C-12), 133.78 (C-13), 129.94 ($C_{ar.}$), 128.44 ($C_{ar.}$), 128.22 ($C_{ar.}$), 127.87 ($C_{ar.}$), 127.77 ($C_{ar.}$), 79.24 (C-4), 73.41 (C-6), 70.59 (C-5), 70.50 (C-2), 32.94 (C-3), -3.82 (C-11), -5.28 (C-11).

IR (film, cm^{-1}):

3431 (OH), 3068 (=C-H_{arom}), 2955 (-CH_2-$_{asym}$), 2901 (-CH_2-$_{sym}$), 1774 (C=O).

MS *m/z*:

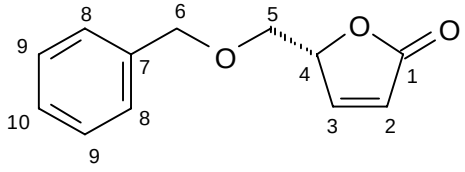
356 (M^+), 341 (M^+ - $CH_3^{\cdot}$), 232 ($C_{13}H_{16}O_2Si^+$), 217 ($C_{12}H_{14}O_2Si^+$), 135 ($PhMe_2Si^+$), 113 ($C_5H_6O_3^+$), 92, 75 ($C_2H_2O_3^+$), 43.

Elemental Analysis:

Anal. Calcd for $C_{20}H_{24}O_4Si$: C, 67.38; H, 6.79. Found: C, 68.89 ; H, 6.47.

7.4.11 *R*-(+)-5-Benzyloxymethyl-5*H*-furan-2-one (**1**) from **61** *via* Tf_2O

To a stirred solution of **61** (100mg, 0.28mmol) in 4ml of anhydrous dichloromethane, at 0 °C under argon, pyridine (45μl, 0.56mmol, 2eq) was added. Then, Tf_2O (95μl, 0.56mmol, 2eq) was added dropwise and the resulting mixture stirred for 3h at rt. Then, the mixture was transferred to a separatory funnel and the organic layer washed consecutively with a 1% HCl aqueous solution, water and brine. The organic phase was dried over anhydrous Na_2SO_4 and after removal of the solvent, the crude product was purified by column chromatography on silica gel using as eluent Et_2O/*n*-hexane (2/1)→Et_2O. **1** was isolated in 65% yield (37mg) as colorless oil.

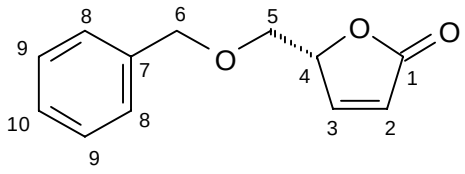


1

All spectroscopic data were identical with those already reported above (paragraph 7.3.7).

7.4.12 *R*-(+)-5-Benzyloxymethyl-5*H*-furan-2-one (**1**) from **61** *via* DCC/CuCl

In a 10ml round bottomed flask equipped with magnetic stirrer and condenser, **61** (200mg, 0.56mml) was dissolved in 3ml of 1,4-dioxane. Then, DCC (139mg, 0.67mmol, 1.2eq) and CuCl (catalytic ammounts, a few mg's) were successively added and the resulting mixture was stirred for 3 days at 50 °C. After this time the solvent was removed and the crude product redissolved in 5ml of dry toluene. To this solution at rt solid $ClCH_2CO_2H$ (64mg, 0.67mmol, 1.2eq) was added in one portion. The mixture was refluxed for 24h, allowed to cool at rt, and after removal of the solvent the crude product was purified by column chromatography on silica gel using as eluent Et_2O/*n*-hexane (2/1)→Et_2O. **1** was isolated in 40% yield (55mg) as a colorless oil.



1

All spectroscopic data were identical with those already reported above (paragraph 7.3.7).

7.4.13 (3*S*,4*S*,5*S*)-(-)-5-Benzyloxymethyl-3,4-dihydroxy-dihydro-furan-2-one (**65**)

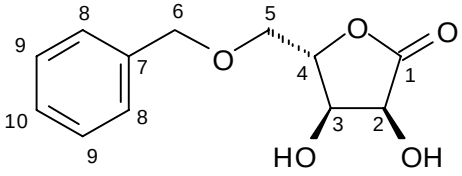
Method A:

To a vigorously stirred solution of *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**, 500mg, 2.45mmol) and dicyclohexano-18-crown-6 (91.2mg, 0.24mmol, 0.1eq) in 15ml of dry dichloromethane, under argon, at –42 °C (CH_3CN/CO_2 bath) $KMnO_4$ (465mg, 2.94mmol, 1.2eq) was added in several portions over 30min. The mixture was stirred for 2h at that temperature and then transferred to a separatory funnel. 2g of solid Na_2SO_3 were added, followed by the dropwise addition of 1M H_2SO_4 under shaking until complete decolorization was observed. The mixture was filtered by suction to remove excess solids and the aqueous phase was extracted with dichloromethane (2x20ml). The collected organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel using as eluent AcOEt/*n*-hexane (2/1). The diol **65** (291mg) was obtained in 60% yield by taking into account the recovered starting material **1** (85mg). Recrystallization from AcOEt/*n*-hexane gave **65** in form of white needles.

Method B:

R-(+)-5-benzyloxymethyl-5*H*-furan-2-one (**1**, 500mg, 2.45mmol) was dissolved in 10ml acetone/H_2O 9:1 (*v/v*) to which at -5 °C, $KMnO_4$ (465mg, 2.94mmol, 1.2eq) was added in several portions, thereby maintaining the temperature below 0 °C. The mixture was stirred

for 2h at that temperature, and if required additional $KMnO_4$ was added to the mixture until complete disappearance of the starting material (T.l.c.). The solution was then heated to 50 °C for 10min, filtered by suction and transferred to a separatory funnel. 2g of solid Na_2SO_3 were added followed by the dropwise addition of 1M H_2SO_4 under shaking until complete decolorization was observed. The mixture was diluted with AcOEt and extracted with water and brine. The organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel using as eluent AcOEt/*n*-hexane (2/1). The diol **65** was obtained in only 27% yield (158mg) and no starting material could be recovered.



65

m.p. 106-107 °C (from AcOEt/*n*-hexane).

R_f : 0.25 AcOEt/*n*-hexane (2/1)

$[\alpha]_D^{20}$ = -22.7 (*c* 0.91, acetone).

^{1}H NMR (acetone-d_6):

δ 7.36-7.23 (m, 5H, Ph), 4.62 (br, 2OH), 4.59 (d, *J*=5.59 Hz, 1H, C-2), 4.52 (s, 2H, C-6), 4.46 (t, *J*=3.05 Hz, 1H, C-4), 4.36 (d, *J*=5.59 Hz, 1H, C-3), 3.75 (dd, *J*=11.08 Hz, *J*=3.05 Hz, 1H, C-5), 3.71 (dd, *J*=10.92 Hz, *J*=3.12 Hz, 1H, C-5').

^{13}C NMR (acetone-d_6):

δ 177.02 (C-1), 139.57 (C-7), 129.85 (C_{ar}), 129.14 (C_{ar}), 129.05 (C_{ar}), 84.99 (C-4), 74.65 (C-6), 71.64 (C-2), 70.93 (C-5), 70.44 (C-3).

IR (KBr, cm^{-1}):

3474 (OH), 3298 (OH), 2923 ($-CH_2-_{asym}$), 2864 ($-CH_2-_{sym}$), 1756 (C=O).

MS *m/z*:

238 (M^+), 107 ($PhCH_2O^+$), 91 (tropyllium ion).

Elemental Analysis:

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.14; H, 5.45.

7.4.14 (3*S*,4*S*,5*S*)-(+)-5-Benzyloxymethyl-4-hydroxy-3-(4-methylbenzenesulfonate)-dihydro-furan-2-one (**78**)

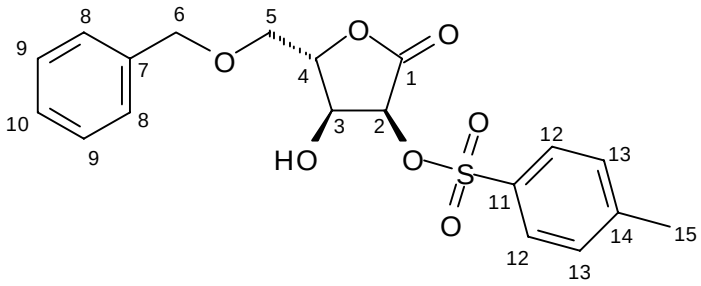
Method A:

280mg of (3*S*,4*S*,5*S*)-(-)-5-benzyloxymethyl-3,4-dihydroxy-dihydro-furan-2-one (**65**, 1.17mmol) were dissolved in 10ml of dry dichloromethane. To this stirred solution, at 0 °C was added Et_3N (248µl, 1.76mmol, 1.5eq) followed by the addition of solid *p*-TsCl (224mg, 1.17mmol, 1eq) in one portion. The mixture was allowed to stand in a freezer at –20 °C without stirring for 18h and was then diluted with dichloromethane (10ml). The organic layer was consecutively washed with aqueous 1N HCl and brine and then dried

over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel using as eluent AcOEt/*n*-hexane (1/1) and **78** was isolated as pale yellow oil in 82% yield (363mg).

Method B:

100mg of (3*S*,4*S*,5*S*)-(-)-5-benzyloxymethyl-3,4-dihydroxy-dihydro-furan-2-one (**65**, 0.42mmol) were dissolved in 1ml of pyridine. Then, *p*-TsCl (80mg, 0.42mmol, 1eq), dissolved in 1ml acetone was added slowly and dropwise within 5min *via* a syringe and the resulting mixture stirred over night at 0 °C. Then, the mixture was transferred to a separatory funnel, diluted with 10ml AcOEt, and extracted with a 5% aqueous solution of HCl (2x5ml). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the crude product was purified by column chromatography on silica gel using as eluent AcOEt/*n*-hexane (1/1). **78** was isolated as pale yellow oil in 50% yield (82mg).



78

R_f : 0.38 AcOEt/*n*-hexane (1/1)

$[\alpha]_D^{20} = +37.2$ (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$):

δ 7.80 (d, *J*=8.14 Hz, 2H, C-12), 7.40-7.22 (m, 7H, C-8–C10, C-13), 5.34 (d, *J*=5.09 Hz, 1H, C-2), 4.62 (d, *J*=5.09 Hz, 1H, C-3), 4.59 (m, C-4), 4.53 (d, *J*=11.69 Hz, 1H, C-6), 4.48 (d, *J*=11.69 Hz, 1H, C-6'), 3.73 (t, *J*=2.03 Hz, 2H, C-5), 2.56 (br, 1OH), 2.45 (s, 3H, C-15).

^{13}C NMR ($CDCl_3$):

δ 169.27 (C-1), 145.88 (C-14), 136.79 (C-7), 131.56 (C_{ar}), 130.01 (C_{ar}), 128.62 (C_{ar}), 128.28 (C_{ar}), 127.97 (C_{ar}), 127.70 (C_{ar}), 83.61 (C-4), 74.30 (C-2), 73.85 (C-6), 70.15 (C-3), 68.86 (C-5), 21.70 (C-15).

IR (film, cm^{-1}):

3508 (OH), 2924 ($-CH_2-_{asym}$), 2870 ($-CH_2-_{sym}$), 1797 (C=O), 1370 ($-SO_3-$).

MS *m/z*:

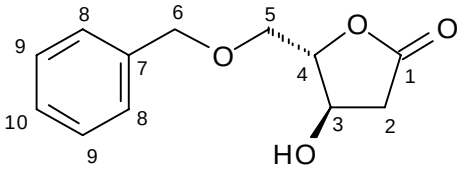
392 (M^+), 237 (M+ - $CH_3PhSO_2^-$), 220 ($C_{12}H_{12}O_4^+$), 155 ($CH_3PhSO_2^+$), 107 ($PhCH_2O^+$), 91 (tropyllium ion).

Elemental Analysis:

Anal. Calcd for $C_{19}H_{20}O_7S$: C, 58.15; H, 5.14; S, 8.17. Found: C, 58.01; H, 5.07; S, 8.05.

7.4.15 (4*R*,5*S*)-(-)-5-Benzyloxymethyl-4-hydroxy-dihydro-furan-2-one (**48**) from **78**

To a stirred solution of (3*S*,4*S*,5*S*)-(+)-5-Benzyloxymethyl-4-hydroxy-3-(4-methylbenzene sulfonate)-dihydro-furan-2-one (**78**, 300mg, 0.79mmol) in 5ml of THF at 0 °C, hydrazine (80% aq. solution, 370µl, 3.96mmol, 5eq) was added and the mixture stirred for 30min at rt. Then at 0°C, Br_2 (304µl, 5.92mmol, 7.5eq) was added dropwise until no more N_2 evolution was observed. The organic solvent was removed under vacuum and the crude aqueous solution diluted with 10ml of water. The pH was adjusted to pH ≅7 and the aqueous phase was extracted with dichloromethane (3x10ml). After removal of the solvent, chromatographic purification on silica gel using as eluent *n*-hexane/AcOEt (1/1) yielded 132mg of **48** (75%) as a colorless oil. R_f: 0.26 hexane/AcOEt (1/1). $[\alpha]_D^{20}$ = -5.0 (*c* 1.44, $CHCl_3$).



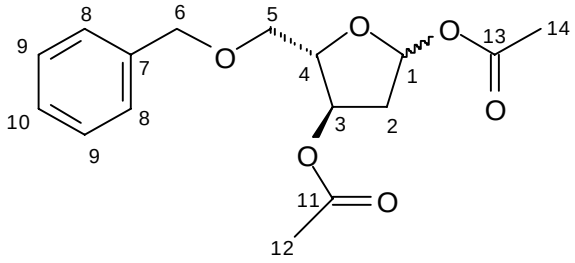
48

All spectroscopic data were consistent with those already reported above (paragraph 7.4.5).

7.5 2-Deoxy-L-nucleosides

7.5.1 α,β-(-)-Di-*O*-Acetyl-5-*O*-benzyl-2-deoxy-ribofuranose (**79**)

To a stirred solution of α,β-(4*R*,5*S*)-(-)-5-benzyloxymethyl-tetrahydro-furan-2,4-diol (**47**, 735mg, 3.27mmol) in 10ml of dry THF, under argon, at 0 °C pyridine (1.6ml, 19.66mmol, 6eq) and Ac_2O (8.1ml, 85.21mmol, 26eq) were added and the reaction mixture was stirred for 18h at rt. Then, the mixture was poured unto ice/H_2O (50ml) and stirred for 30min. The solution was then extracted with dichloromethane (2x100ml) and the organic layer dried over Na_2SO_4. The crude product was purified by column chromatography on silica gel using as eluent *n*-hexane/AcOEt (2/1). **79** was isolated as colorless oil in 95% yield (950mg) as anomeric mixture (α/β ≅ 1/1, ^{1}H-NMR).



79

R_f : 0.28 *n*-hexane/AcOEt (2/1)

$[\alpha]_D^{20}$ = -20.8 (*c* 1.38, $CHCl_3$).

^{1}H NMR ($CDCl_3$):

δ 7.37-7.25 (m, 10H, 2Ph), 6.38 (m, 2H, 2C-1), 5.32 (m, 1H, C-3), 5.23 (m, 1H, C-3), 4.57 (s, 2H, C-6), 4.54 (d, *J*=4.57 Hz, 2H, C-6), 4.37 (m, 1H, C-4), 4.28 (m, 1H, C-4), 3.68 (dd, *J*=10.68 Hz, *J*=3.56 Hz, 1H, C-5), 3.62 (m, 3H, C-5), 2.49 (m, 2H, C-2), 2.27 (m, 2H, C-2), 2.07 + 2.07 + 2.06 + 2.05 (4s, 12H, 2C-12 + 2C-14).

^{13}C NMR ($CDCl_3$):

δ 170.73 + 170.44 + 170.26 + 169.99 (2C-11 + 2C-13), 137.93 + 137.83 (2C-7), 128.33 (C_{ar}), 128.28 (C_{ar}), 127.62 (C_{ar}), 127.57 (C_{ar}), 127.47 (C_{ar}), 127.46 (C_{ar}), 98.69 (C-1), 98.30 (C-1), 85.03 (C-4), 83.85 (C-4), 74.35 (C-3), 74.28 (C-3), 73.56 (C-6), 73.32 (C-6), 70.48 (C-5), 69.90 (C-5), 38.52 (C-2), 38.34 (C-2), 21.18 + 21.08 + 20.95 + 20.85 (2C-12 + 2C-14)

IR (film, cm^{-1}):

2936 ($-CH_2-_{asym}$), 2856 ($-CH_2-_{sym}$),, 1739 (C=O), 1232.

MS *m/z*:

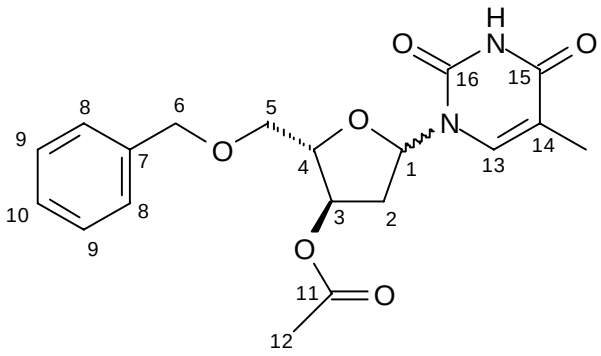
248 (M^+ - $CH_3CO_2^{\cdot}$), 91 (tropyllium ion).

Elemental Analysis:

Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.21; H, 6.40.

7.5.2 α,β-(+)-3'-Acetyl-5'-benzyl-L-thymidine (**80**)

Thymine (410mg, 3.24mmol, 2eq) was suspended in 20ml hexamethyldisilazane (HMDS) together with a catalytic amount of $(NH_4)_2SO_4$ and heated at 150 °C until a clear solution was formed (3-5 hours). Then, the solvent was removed *via* short path distillation at 30 °C under high vacuum. The crude product containing the thus silylated thymine was dissolved in 5 ml of dry CH_3CN. To this solution **79** (400mg, 1.29mmol), dissolved in 10ml of dry CH_3CN was added. The mixture was cooled to –30 °C and under argon TMS-triflate (256µl, 1.42mmol, 1.1eq) was added dropwise. The temperature was allowed to reach 0 °C and the mixture was stirred for a further 30min. T.l.c analysis showed complete conversion. Dichloromethane was then added (25ml) and the entire mixture poured unto ice/water (50ml) and stirred for a few minutes. Then, 70ml of a saturated solution of $NaHCO_3$ were added and the separated aqueous layer extracted with dichloromethane (2x100ml). The collected organic layers were washed with brine and dried over anhydrous Na_2SO_4. Purification was accomplished by column chromatography on silica gel using as eluent AcOEt/*n*-hexane (2/1) to afford **80** as amorphous solid in 73% yield (355mg) as a 1:2 mixture of the α and β anomers (^{1}H-NMR analysis).



80

R_f : 0.26 AcOEt/*n*-hexane (2/1)

$[\alpha]_D^{20}$ = +13.7 (*c* 0.93, $CHCl_3$).

^{1}H NMR ($CDCl_3$):

β-anomer: δ 9.03 (br, 1NH), 7.55 (s, 1H, C-13), 7.40-7.28 (m, 5H, Ph), 6.44 (dd, *J*=9.15 Hz, *J*=5.59 Hz, 1H, C-1), 5.37 (d, *J*=5.08 Hz, 1H, C-3), 4.58 (m, 2H, C-6), 4.18 (m, 1H, C-4), 3.81 (m, 1H, C-5), 3.62 (m, 1H, C-5'), 2.38 (dd, *J*=14.24 Hz, *J*=5.59 Hz, 1H, C-2), 2.26 (m, 1H, C-2'), 2.10 (s, 3H, C-12), 1.62 (s, 3H, C-17).

^{1}H NMR ($CDCl_3$):

α-anomer: δ 8.94 (br, 1NH), 7.40-7.28 (m, 6H, Ph + C-13), 6.32 (dd, *J*=7.12 Hz, *J*=2.03 Hz, 1H, C-1), 5.29 (d, *J*=6.10 Hz, 1H, C-3), 4.58 (m, 3H, C-6 + C-4), 3.81 (m, 1H, C-5), 3.62 (m, 1H, C-5'), 2.87 (m, 1H, C-2), 2.15 (m, 1H, C-2'), 2.03 (s, 3H, C-12), 1.94 (s, 3H, C-17).

^{13}C NMR ($CDCl_3$):

δ 170.54 + 169.90 (2C-11), 163.86 + 163.60 (2C-15), 150.49 + 150.30 (2C-16), 137.43 + 137.28 (2C-7), 135.55 + 135.42 (2C-13), 128.62 + 128.50 + 128.09 + 127.87 + 127.57 + 127.45 (4C-8 + 4C-9 + 2C-10), 111.35 + 110.06 (2C-14), 86.89 (α-anomer, C-1), 86.02 (α-anomer, C-4), 84.69 (β-anomer, C-1), 84.00 (β-anomer, C-4), 75.69 (β-anomer, C-3), 75.19 (α-anomer, C-3), 73.75 + 73.70 (2C-6), 70.52 + 70.48 (2C-5), 38.92 (α-anomer, C-2), 37.73 (β-anomer, C-2), 20.94 + 20.89 (2C-12), 12.59 +12.09 (2C-17).

IR (film, cm^{-1}):

3160 (C=C), 3040, 1690 (COO + CO-NH-CO), 1460 .

MS *m/z*:

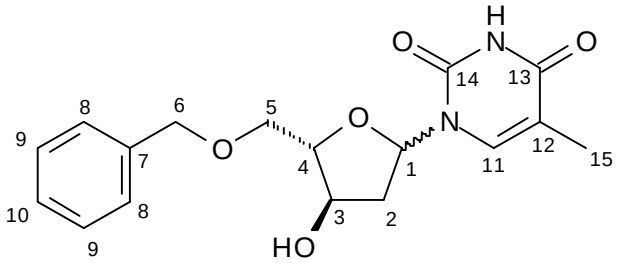
374 (M^+), 249 (M^+ -thymine), 189 ($C_{12}H_{14}O_2^+$), 159 ($C_7H_{10}O_4^+$), 121, 91 (tropyllium ion)

Elemental Analysis:

Anal. Calcd for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.11; H, 5.23; N, 7.08.

7.5.3 α,β-(+)-5'-Benzyl-L-thymidine (**81**)

To a stirred solution of **80** (240mg, 0.64mmol) in 3ml of MeOH, 1ml of *n*-butylamine was added and the mixture stirred for 3h at rt. A clear solution was obtained. Then, the solvent and excess *n*-$BuNH_2$ were removed under vacuum and the crude product purified by column chromatography on silica gel using as eluent AcOEt. **81** was isolated in 90% yield (212mg) as colorless oil as anomeric mixture (α/β ≅ 1/2, ^{1}H-NMR).



81

R_f : 0.30 AcOEt

$[\alpha]_D^{20}$ = +4.46 (*c* 0.94, $CHCl_3$).

^{1}H NMR ($CDCl_3$):

δ 9.14 (NH), 9.00 (NH), 7.56 (d, *J*=1.01 Hz, 1H, C-11), 7.50 (d, *J*=1.01 Hz, 1H, C-11), 7.39-7.26 (m, 10H, 2Ph), 6.40 (dd, *J*=7.62 Hz, *J*=6.10 Hz, 1H, C-1), 6.12 (dd, *J*=7.62 Hz, *J*=2.54 Hz, 1H, C-1), 4.59 (s, 2H; C-6), 4.55 (d, *J*=4.00 Hz, 2H, C-6), 4.46 (m, 1H, C-4), 4.43 (m, 1H, C-4), 4.12 (m, 2H, 2C-3), 3.79 (dd, *J*=10.17 Hz, *J*=2.54 Hz, 1H, C-5), 3.68 (dd, *J*=10.68 Hz, *J*=3.05 Hz, 1H, C-5), 3.56 (m, 2H, C-5), 3.23 (m, 1H, C-2), 2.73 (m, 1H, C-2), 2.35 (m, 1H, C-2), 2.20 (m, 1H, C-2), 1.89 (s, 3H, C-15), 1.64 (s, 3H, C-15).

^{13}C NMR ($CDCl_3$):

δ 164.49 + 164.10 (2C-13), 150.68 (2C-14), 137.63 (C-7), 137.49 (C-11), 137.46 (C-11), 136.00 (C-7), 128.93 (C_{ar}), 128.51 (C_{ar}), 128.40 (C_{ar}), 128.13 (C_{ar}), 127.91 (C_{ar}), 127.74 (C_{ar}), 127.55 (C_{ar}), 127.43 (C_{ar}), 110.89 + 109.77 (2C-12), 87.93 (C-1 +C-4), 86.03 (C-4), 84.97 (C-1), 73.54 (C-6), 73.49 (C-6), 72.36 (C-3), 72.23 (C-3), 70.59 (C-5), 70.26 C-5), 40.76 (C-2), 39.53 (C-2), (C-15), 12.06 (C-15).

IR (film, cm^{-1}):

3361 (OH), 3195 (C=C), 2929 ($-CH_2-_{asym}$), 2863 ($-CH_2-_{sym}$), 1693 (CO-NH-CO), 1472.

MS *m/z*:

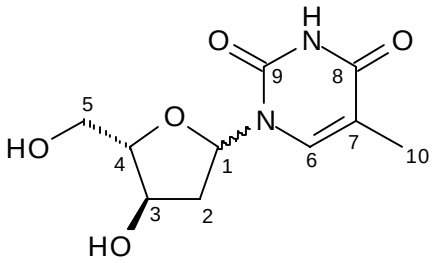
332 (M^+), 207 (M^+ - thymine), 99, 91 (tropyllium ion).

Elemental Analysis:

Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.35; H, 6.01; N, 8.21.

7.5.4 α,β-(-)-L-Thymidine (**82**)

In a 50ml Schlenk flask equipped with amagnetic stirrer, 10ml of MeOH were degassed for a few minutes by connecting the flask to an aspirator. Then, 10% Pd/C (20mg) was carefully added and the solution degassed again for a few minutes. After this, the plug valve was closed thereby taking care to avoid any entry of air and the flask was then connected under vacuum with a hydrogen source *via* a rubber hose. The suspension was vigorously stirred for 15min and after this period **81** (186mg, 0.55mmol), dissolved in 2ml degassed MeOH was added and the resulting mixture stirred for 1h at rt. Removal of the catalyst by filtration and evaporation of the solvent afforded a crude product which was purified by column chromatography on silica gel using as eluent AcOEt/MeOH 9/1. The anomeric mixture of **82** was obtained in 76% yield (102mg) as white solid as anomeric mixture (α/β ≅ 1/2, ^{1}H-NMR). The anomeric ratio was also confirmed *via* HPLC using as reference natural β-D-thymidine (column LiChroCART 250-4, LiChroSPHER 100, RP-8 (5μm), UV 262, eluent: methanol - phosphate buffer pH 4.4 – water (0.1:5:94.9), flow rate 1ml/min).



82

m.p. 162 - 163 °C (from AcOEt/MeOH 9/1).

R_f : 0.35 AcOEt/MeOH 9/1.

$[\alpha]_D^{20}$ = -19.2 (*c* 1.0, MeOH).

^{1}H NMR ($CDCl_3$):

β-anomer: δ 7.70 (s, 1H, C-6), 6.13 (m, 1H, C-1), 4.42 (m, 1H, C-3), 4.35 (m, 1H, C-4), 3.67 (dd, *J*=17.80 Hz, *J*=5.59 Hz, 1H, C-5), 3.58 (dd, *J*=12.20 Hz, *J*=5.08 Hz, 1H, C-5'), 2.68 (m, 1H, C-2), 2.12 (m, 1H, C-2'), 1.86 (s, 3H, C-10).

^{13}C NMR ($CDCl_3$)

β-anomer: δ 168.93 (C-8), 153.85 (C-9), 140.28 (C-6), 112.85 (C-7), 90.77 (C-4), 89.14 (C-1), 72.91 (C-3), 63.75 (C-5), 41.71 (C-2), 13.81 (C-10).

^{1}H NMR ($CDCl_3$):

α-anomer: δ 7.59 (s, 1H, C-6), 6.23 (t, *J*=6.74 Hz, 1H, C-1), 4.42 (m, 1H, C-3), 3.97 (m, 1H, C-4), 3.80 (dd, *J*=12.20 Hz, *J*=3.56 Hz, 1H, C-5), 3.71 (dd, *J*=12.71 Hz, *J*=5.08 Hz, 1H, C-5'), 2.32 (m, 2H, C-2), 1.84 (s, 3H, C-10).

^{13}C NMR ($CDCl_3$):

α-anomer: δ 168.68 (C-8), 153.90 (C-9), 139.72 (C-6), 113.65 (C-7), 88.75 (C-4), 87.31 (C-1), 72.70 (C-3), 63.44 (C-5), 40.77 (C-2), 13.75 (C-10).

IR (Kbr, cm^{-1}):

3311 (OH), 3156 (C=C), 3025 (CO-NH), 2975 ($-CH_{2-asym}$), 2836 ($-CH_{2-sym}$), 1700 (C=O), 1658 (C=O),

MS *m/z*

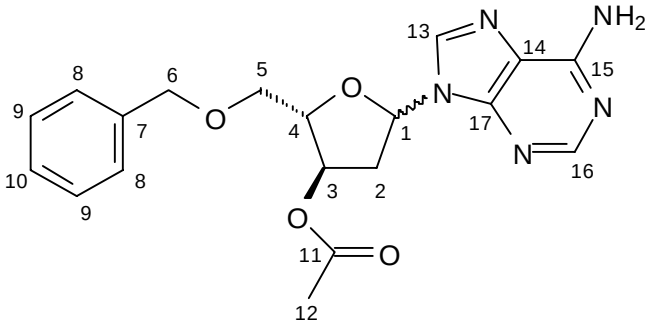
242 (M^+), 126 (thymine), 117 (M^+ - thymine).

Elemental Analysis:

Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.56. Found: C, 49.41; H, 5.60; N, 11.44.

7.5.5 α,β-(-)-3'-Acetyl-5'-benzyl-2'-deoxy-L-adenosine (**83**)

Adenine (201mg, 1.49mmol, 1eq) was suspended in 5ml hexamethyldisilazane (HMDS) together with a few mg's of $(NH_4)_2SO_4$ and heated at 150 °C until formation of a clear solution (3-5 hours). Then, the solvent was removed *via* short path distillation at 30 °C under high vacuum. The crude product containing the silylated adenine was dissolved in 14ml of toluene/CH_3CN (1/1 *v/v*) and to this solution α,β-(-)-Di-*O*-Acetyl-5-*O*-benzyl-2-deoxy-ribofuranose (**79**, 460mg, 1.49mmol) was added together with KI (247mg, 1.49mmol, 1eq) and dibenzo-18-crown-6 (107mg, 0.29mmol, 0.2eq). The resulting mixture was refluxed for 4h, allowed to cool at rt and then transferred to a separatory funnel. The organic phase was washed successively with H_2O and brine and then dried over anhydrous Na_2SO_4. Evaporation of the solvents under reduced pressure afforded a crude product which was purified by column chromatography on silica gel using as eluent AcOEt/MeOH (9/1 *v/v*). **83** was isolated in 56% yield (320mg) as a pale yellow solid as anomeric mixture (α/β ≅ 2/1, ^{1}H-NMR).



83

m.p.: 56 – 57 °C (form AcOEt/MeOH).

R_f : 0.46 AcOEt/MeOH 9/1.

$[\alpha]_D^{20}$ = -9.2 (*c* 0.6, MeOH).

^{1}H NMR ($CDCl_3$):

α anomer: δ 8.34 (s, 1H, C-16), 8.09 (s, 1H, C-13), 7.36-7.27 (m, 5H, Ph), 6.55 (dd, *J*=7.62 Hz, *J*=2.03 Hz, 1H, C-1), 6.34 (s, NH_2), 5.39 (m, 1H, C-3), 4.56 (m, 3H, 2C-6 + C-4), 3.70 (dd, *J*=10.68 Hz, *J*=3.56 Hz, 1H, C-5), 3.65 (dd, *J*=10.68 Hz, *J*=3.56 Hz, 1H, C-5'), 2.97 (m, 1H, C-2), 2.61 (d, *J*=14.75 Hz, 1H, C-2'), 1.95 (s, 3H, C-12)

^{13}C NMR ($CDCl_3$):

α anomer: δ 170.11 (C-11), 155.62 (C-15), 152.91 (C-16), 149.38 (C-17), 138.37 (C-13), 137.51 (C-7), 128.38 (C_{ar}), 127.74 (C_{ar}), 127.47 (C_{ar}), 119.71 (C-14), 85.63 (C-4), 85.38 (C-1), 75.22 (C-3), 73.64 (C-6), 70.32 (C-5), 38.65 (C-2), 20.79 (C-12).

^{1}H NMR ($CDCl_3$):

β anomer: δ 8.31 (s, 1H, C-16), 8.09 (s, 1H, C-13), 7.36-7.27 (m, 5H, Ph), 6.52 (dd, *J*=8.64 Hz, *J*=6.10 Hz, 1H, C-1), 6.39 (s, NH_2), 5.45 (m, 1H, C-3), 4.56 (m, 2H, 2C-6), 4.28 (m, C-4), 3.75 (d, *J*=3.05 Hz, 2H, C-5), 2.75 (m, 1H, C-2), 2.55 (ddd, *J*=14.24 Hz, *J*=6.10 Hz, *J*=1.52 Hz 1H, C-2'), 2.09 (s, 3H, C-12).

^{13}C NMR ($CDCl_3$):

β anomer: δ 170.33 (C-11), 155.67 (C-15), 152.96 (C-16), 149.64 (C-17), 138.43 (C-13), 137.26 (C-7), 128.47 (C_{ar}), 127.92 (C_{ar}), 127.70 (C_{ar}), 119.52 (C-14), 84.17 (C-4), 83.96 (C-1), 75.72 (C-3), 73.69 (C-6), 70.26 (C-5), 38.54 (C-2), 20.87 (C-12).

IR (Kbr, cm^{-1}):

3323 + 3172 (d, N-H_{str}), 1740 (C=O), 1647 + 1597 (d, N-$H_{def.}$).

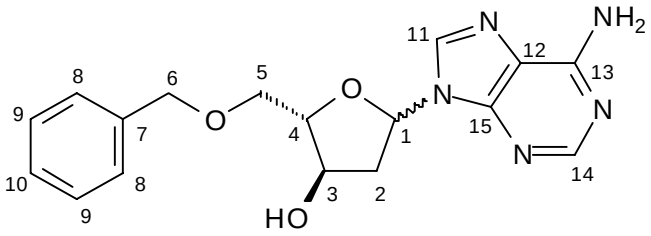
MS *m/z*

383 (M^+), 292 (M^+ - $PhCH_2^{\cdot}$), 277 ($C_{11}H_{11}N_5O_4^+$), 218 ($C_{10}H_{11}N_5O^+$), 164, 135 (adenine).

7.5.6 α,β-(-)-5'-Benzyl-2-deoxy-L-adenosine (**84**)

To a stirred solution of α,β-(-)-3'-Acetyl-5'-benzyl-2'-deoxy-L-adenosine (**83**, 238mg, 0.62mmol) in 3ml of MeOH, 1ml of *n*-butylamine was added and the mixture stirred for 1h at rt. Then, the solvent and excess *n*-$BuNH_2$ were removed under vacuum and the crude product purified by column chromatography on silica gel using as eluent AcOEt/MeOH

9/1. **84** was isolated in 88% yield (185mg) as a white solid as anomeric mixture (α/β ≅ 2/1, ^{1}H-NMR).



84

m.p.: 59 – 60 °C (from AcOEt/MeOH)

R_f : 0.33 (AcOEt/MeOH 9/1).

$[\alpha]_D^{20}$ = -8.3 (*c* 0.7, MeOH).

^{1}H NMR ($CDCl_3$):

α anomer: δ 8.36 (s, 1H, C-14), 8.17 (s, 1H, C-11), 7.35-7.21 (Ph, 5H), 6.39 (dd, *J*=7.62 Hz, *J*=2.03 Hz, 1H, C-1), 4.53 (d, *J*=1.01 Hz, 2H, C-6), 4.43 (m, 1H, C-3), 4.39 (m, 1H, C-4), 3.58 (d, *J*=4.06 Hz, 2H, C-5), 2.89 (m, 1H, C-2), 2.38 (m, 1H, C-2).

^{13}C NMR ($CDCl_3$):

α anomer: δ 157.39 (C-13), 153.49 (C-11), 149.80 (C-15), 141.93 (C-14), 139.48 (C-7), 129.42 (C_{ar}), 128.81 (C_{ar}), 128.82 (C_{ar}), 120.46 (C-12), 89.37 (C-4), 86.78 (C-1), 74.58 (C-6), 74.50 (C-3), 71.90 (C-5), 41.62 (C-2).

^{1}H NMR ($CDCl_3$):

β anomer: δ 8,23 (s, 1H, C-14), 8.15 (s, 1H, C-11), 7.35-7.21 (Ph, 5H), 6.43 (t, *J*=6.61 Hz, 1H, C-1), 4.57 (m, 1H, C-3), 4.52 (s, 2H, C-6), 4.11 (m, 1H, C-3), 3.73 (dd, *J*=10.68 Hz, *J*=3.56 Hz, 1H, C-5), 3.66 (dd, *J*=10.68 Hz, *J*=4.06 Hz, 1H, C-5'), 2.71 (m, 1H, C-2), 2.44 (m, 1H, C-2').

^{13}C NMR ($CDCl_3$):

β anomer: δ 157.25 (C-13), 153.80 (C-11), 150.31 (C-15), 140.76 (C-14), 139.30 (C-7), 129.45 (C_{ar}), 128.91 (C_{ar}), 128.75 (C_{ar}), 120.26 (C-12), 87.87 (C-4), 85.76 (C-1), 74.50 (C-6), 72.92 (C-3), 71.32 (C-5), 41.59 (C-2).

IR (Kbr, cm^{-1}):

3323 + 3170 (d, N-H_{str}), 3300 (OH), 1650 + 1600(d, N-$H_{def.}$).

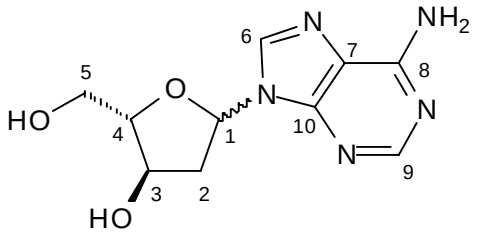
MS *m/z*

341 (M^+), 250 (M^+ - $Bn^{\cdot}$),135 (adenine), 108 (BnO^+) 91 (tropyllium ion).

7.5.7 α,β-(-)-2-Deoxy-L-adenosine (**85**)

84 (63mg, 0.18mmol) was dissolved in 4ml EtOH and 2ml cyclohexene. To this solution 50mg of $Pd(OH)_2/C$ were added and the resulting suspension stirred for 2h at reflux. Then the cooled mixture was filtered to remove the catalyst and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography on

silica gel using as eluent MeOH/AcOEt 2/1. **85** was isolated in 65% yield (30mg) as a white solid. Anomeric mixture ($\alpha/\beta \cong 2/1$, ^{1}H-NMR)



85

m.p.: 158 – 160 °C (from AcOEt/MeOH).

R_f : 0.46 (MeOH/AcOEt 2/1).

$[\alpha]_D^{20}$ = -27 (*c* 1, MeOH).

^{1}H NMR ($CDCl_3$):

α anomer: δ 8.38 (s, 1H, C-9), 8.18 (s, 1H, C-6), 6.40 (m, 1H, C-1), 4.43 (m, 1H, C-3), 4.28 (m, 1H, C-4), 3.64 (dd, *J*=11.69 Hz, *J*=4.06 Hz, 1H, C-5), 3.59 (dd, *J*=12.20 Hz, *J*=4.57 Hz, 1H, C-5'), 2.86 (m, 1H, C-2), 2.43 (m, 1H, C-2').

^{13}C NMR ($CDCl_3$):

α anomer: δ 157.52 (C-8), 153.49 (C-6), 149.91 (C-10), 141.86 (C-9), 120.45 (C-7), 90.83 (C-4), 86.65 (C-1), 72.95 (C-3), 63.46 (C-5), 41.63 (C-2).

^{1}H NMR ($CDCl_3$):

β anomer: δ 8.28 (s, 1H, C-9), 8.15 (s, 1H, C-6), 6.40 (m, 1H, C-1), 4.55 (m, 1H, C-3), 4.04 (m, 1H, C-4), 3.82 (dd, *J*=12.20 Hz, *J*=3.05 Hz, 1H, C-5), 3.71 (dd, *J*=12.20 Hz, *J*=3.56 Hz, 1H, C-5'), 2.78 (m, 1H, C-2), 2.37 (m, 1H, C-2').

^{13}C NMR ($CDCl_3$):

β anomer: δ 157.49 (C-8), 153.49 (C-6), 149.96 (C-10), 141.50 (C-9), 120.86 (C-7), 89.88 (C-4), 87.09 (C-1), 73.01 (C-3), 63.62 (C-5), 41.54 (C-2).

IR (Kbr, cm^{-1}):

3320 + 3180 (d, N-H_{str}), 3200 (OH), 1640 + 1605(d, N-$H_{def.}$).

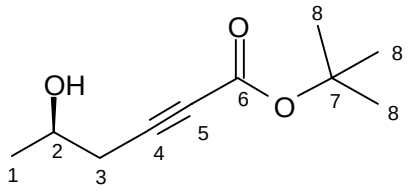
MS *m/z*:

251 (M^+), 162 ($C_7H_7N_5$), 100 ($C_5H_8O_2$).

7.6 δ-lactones

7.6.1 *R*-(-)-5-Hydroxy-hex-2-ynoic acid *tert*-butyl ester (**88**)

To a stirred solution of *tert*-butyl propiolate (23.5ml, 0.17mol, 1.2eq) in 1L of dry THF, under argon, at –78 °C, *n*-butyllithium (15% in *n*-hexane, 104.4ml, 0.17mol, 1.2eq) was added dropwise. After stirring for 30 min. *R*-(+)-2-methyl-oxirane (10ml, 0.14mol) in 30ml of dry THF and BF_3-Et_2O (17.9ml, 0.14mol, 1eq) were added and the reaction mixture was stirred for 2.5 hours. Subsequently the temperature was increased to –10 °C and the reaction was quenched with 50ml of a saturated aqueous solution of NH_4Cl. Water and AcOEt were added to favor phase separation and the separated aqueous phase was extracted twice with AcOEt. The collected organic layers were washed with brine and then dried over anhydrous Na_2SO_4. After filtration and removal of the solvents under reduced pressure on a rotavapor, the crude product mixture containing also the impurities derived from the hydrolysis of BF_3-Et_2O (boronates) was either directly purified by column chromatography on silica gel using as eluent *n*-hexane/AcOEt (3/1) or stored in the freezer over night. (**88** had been observed to be instable in the crude mixture at rt). After chromatography **88** was isolated in 87% yield (22.8g) as a pale yellow oil.



88

R_f : 0.23 (*n*-hexane/AcOEt 3/1).

$[\alpha]_D^{20}$ = -11.9 (*c* 1.7, $CHCl_3$);

^{1}H NMR ($CDCl_3$):

δ 4.02 (m, 1H, C-2), 2.48 (br, 1OH), 2.42 (d, *J*=5.95, 2H, C-3), 1.44 (s, 9H, C-8), 1.24 (d, *J*=6.21, 3H, C-1).

^{13}C NMR ($CDCl_3$):

δ 152.74 (C-6), 83.41 (C-4), 83.23 (C-5), 76.23 (C-2), 65.78 (C-7), 29.02 (C-3), 27.91 (C-8), 22.48 (C-1).

IR (film, cm^{-1}):

3390 (OH), 2945 ($-CH_3$), 2900 ($-CH_2-_{asym}$), 2215 (-C≡C-), 1690 (C=O).

MS *m/z*:

140 ($C_8H_{11}O_2^+$), 128 (M^+ - *t*-Bu^-), 111 (M^+ - *t*-BuO^-), 101 (*t*-$BuOC{=}O^+$), 84 ($C_5H_7O^+$), 67 ($C_4H_2O^+$), 56, 41.

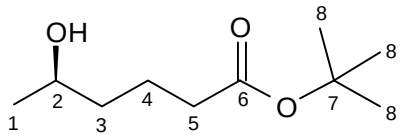
Elemental Analysis:

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.13; H, 8.68. Found: C, 64.32; H, 8.71.

7.6.2 *R*-(-)-5-Hydroxy-hexanoic acid *tert*-butyl ester (**89**)

2 g of 5% Pd/C were placed in a 500ml Schlenk round bottom flask equipped with magnetic stirrer and a septum to which 200ml of AcOEt (HPLC grade) were added. The

resulting suspension was degassed under stirring for 5min by applying vacuum using an aspirator. After this, the plug valve was closed thereby taken great care to avoid any entry of air and the flask under vacuum was connected under vacuum with a hydrogen source *via* a rubber hose. The resulting suspension was vigorously stirred for 30min to allow absorption of H_2 onto the metal surface. After this time the solution was cooled to –20 °C and **88** (20.1 g, 0.11mol) dissolved in 20ml of AcOEt was added. The mixture was stirred for 6 hours at –20 °C while the reaction progress was monitored *via* GC analysis of drawn samples. The samples were drawn as follows: with a syringe connected to a long needle a few drops of the suspension were taken from the flask, filtered in a micro chromatography column consisting of a Pasteur pipette filled with about 3cm silica gel in order to remove the catalyst. To elute the products HPLC grade AcOEt was used and the resulting eluate injected into the gas chromatograph. When the starting material was completely consumed (6h), the suspension was filtered using a double filter in order to avoid the presence of any traces of catalyst and the organic solvent removed under reduced pressure. Without further purification **89** was isolated in quantitative yield (20.5 g) and 97% purity (GC analysis) as a colorless oil.



89

R_f : 0.20 (*n*-hexane/AcOEt 3/1).

$[\alpha]_D^{20}$ = -6.3 (*c* 1.8, $CHCl_3$);

^{1}H NMR ($CDCl_3$):

δ 3.76 (m, 1H, C-2), 2.21 (t, *J*=7.54, 2H, C-5), 1.63 (m, 2H, C-3 + 1OH), 1.42 (m, 2H, C-4), 1.41 (s, 9H, C-8), 1.16 (d, *J*=6.14, 3H, C-1);

^{13}C NMR ($CDCl_3$):

δ 173.14 (C-6), 80.16 (C-2), 67.49 (C-7), 38.60 (C-3), 35.30 (C-5), 28.08 (C-8), 23.42 (C-1), 21.11 (C-4);

IR (film, cm^{-1}):

3420 (OH), 2960 ($-CH_3$), 2920 ($-CH_2-_{asym}$), 1715 (C=O).

MS *m/z*:

115 (M^+ - *t*-BuO^-), 97 ($C_6H_{10}O^+$), 88, 73 (*t*-BuO^+), 69, 57 (*t*-Bu^+), 45, 41;

Elemental Analysis:

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.74; H, 10.62. Found: C, 62.97; H, 10.34.

7.6.3 *R*-(+)-6-Methyl-tetrahydro-pyran-2-one (**87**) from **89**

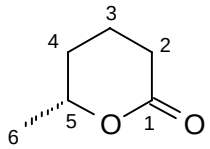
Method A:

To a stirred solution of **89** (19.6 g, 0.104mol) in 500ml of anhydrous dichloromethane, under argon atmosphere, at rt, 0.7ml of trifluoroacetic acid were added dropwise and the resulting mixture stirred for a period of 24h. The course of the reaction was monitored *via* GC by taking aliquots from the solution with a capillary and diluting the probe with HPLC grade AcOEt. The resulting solution could be directly injected in the gas chromatograph for analysis. After completion of the reaction the entire solution was transferred to a separatory funnel and the organic phase was extracted twice with a saturated aqueous

solution of Na_2CO_3 (2x100ml). Particularly attention must be addressed to this operation. Vigorous shaking during the extractions is essential in order to completely remove all TFA into the aqueous phase (see chapter 5 for discussion). The separated organic layer was then washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting crude product purified by column chromatography on silica gel using as eluent Et_2O/*n*-hexane 2/1. After removal of the solvents again under removed pressure, a short path distillation (Kugelrohr, 70 °C, 10^{-3} mbar) afforded 4.1g of **87** (35% yield) as white crystals.

Method B:

30ml of toluene and 30ml of water were placed into a separatory funnel and shaken well. The water saturated organic phase was then separated and transferred into a 100ml Schlenk flask containing **89** (2.9g, 15.55mmol). To this stirred solution solid *p*-toluenesulfonic acid (296mg, 1.55mmol, 0.1eq) was added and the resulting mixture refluxed for 1.30h. After this period, the solution was allowed to cool to rt and the solvent was removed under reduced pressure. Without any additional work-up, the crude product (containing also *p*-TsOH) was purified by column chromatography on silica gel using as eluent Et_2O/*n*-hexane 2/1. After removal of the solvents, a short path distillation (Kugelrohr, 70 °C, 10^{-3} mbar) afforded 1.2g of **87** (70% yield) as white crystals.



87

m.p. 31 °C.

R_f : 0.32 (*n*-hexane/AcOEt 2/1)

$[\alpha]_D^{20}$ = +36 (*c* 0.7, $CHCl_3$);

^{1}H NMR ($CDCl_3$):

δ 4.39 (m, 1H, C-5), 2.44 (m, 2H, C-2), 1.84 (m, 3H, 2H(C-3) + 1H(C-4)), 1.47 (m, 1H, C-4), 1.32 (d, *J*=6.10, 3H, C-6);

^{13}C NMR ($CDCl_3$):

δ 171.67 (C-1), 76.76 (C-5), 29.47 (C-2), 29.09 (C-4), 21.56 (C-3), 18.40 (C-6).

IR (film, cm^{-1}):

2945 ($-CH_3$), 1720 (C=O).

MS *m/z*:

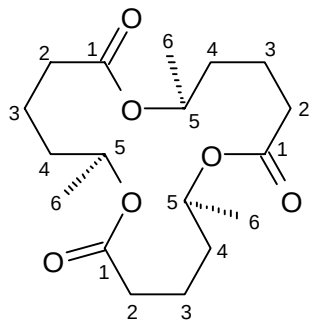
114 (M^+), 99 ($M^+ - {}^{\cdot}CH_3$), 70 ($C_4H_6O^+$), 55, 42 ($C_3H_6^+$), 39.

Elemental Analysis:

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.52; H, 8.57.

7.6.4 (6*R*,12*R*,18*R*)-(-)-6,12,18-Trimethyl-1,7,3-trioxa-cyclooctadecane-2,8,14-trione (**90**)

Trifluoroacetic acid (0.043mmol, 3.3µl, 0.01eq) was added to 500mg of neat **87** and the mixture was homogenized by gently heating the mixture to 40 °C until complete melting was observed and then stored at 20 °C. NMR spectra (^{1}H and ^{13}C) were taken every 7 days in order to establish the rate of formation of trimer **90**. After 5 weeks an equilibrium was reached between the monomer **87** and the trimer **90**. This mixture was dissolved in 10ml of dichloromethane and the resulting solution washed twice with 5ml of a saturated aqueous solution of Na_2CO_3. The separated organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum. **87** could be removed from the mixture by short path distillation (Kugelrohr, 100 °C, 10^{-3}mBar) to afford pure **90** in 50% (250mg) yield as highly viscous colorless oil.



90

$[\alpha]_D^{20}$ = -8 (*c* 0.6, $CHCl_3$);

^{1}H NMR ($CDCl_3$):

δ 4.90 (m, 3H), 2.29 (m, 6H), 1.61 (m, 12H), 1.21 (d, *J*=6.10, 9H);

^{13}C NMR ($CDCl_3$):

δ 172.84 (C-1), 70.37 (C-5), 35.23 (C-2), 34.18 (C-4), 20.81 (C-3), 19.87 (C-6).

IR (film, cm^{-1}):

2921 ($-CH_3$), 1701 (C=O).

Elemental Analysis:

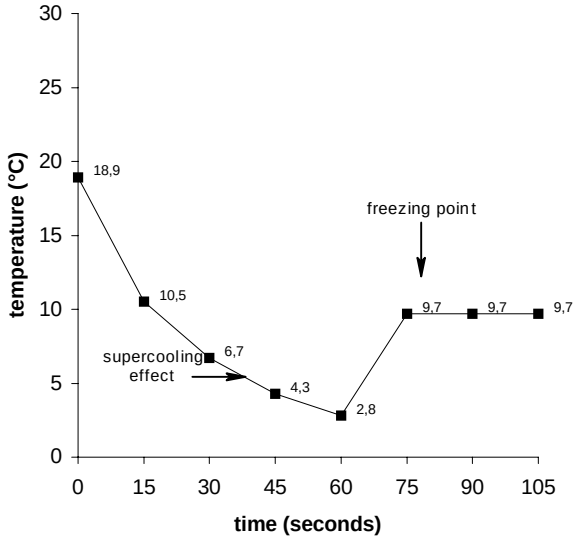
Anal. Calcd for $C_{18}H_{30}O_6$: C, 63.14; H, 8.83. Found: C, 62.62; H, 8.59.

7.6.5 *R*-(+)-6-Methyl-tetrahydro-pyran-2-one (**87**) from **90**

The trimer **90** (5.0 g, 14.60mmol) was dissolved in THF (200ml) and at 0 °C 2N NaOH (50ml) was slowly added. After stirring at rt for 30 min, the pH was adjusted to pH=1-2 with concentrated aqueous HCl. The solvents were removed under reduced pressure and the crude product containing NaCl was dried over night in a vacuum-desiccator containing P_2O_5. The so obtained δ-hydroxy acid **91** was suspended in anhydrous dichloromethane (100ml) and trifluoroacetic acid (500µl) was then added under argon. The mixture was stirred over night at rt, the organic layer was washed with a saturated aqueous solution of Na_2CO_3, water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified by column chromatography on silica gel using as eluent Et_2O/*n*-hexane 2/1. The collected fractions were evaporated and after short path distillation on a Kugelrohr (10^{-3}mBar, 70 °C), **87** was obtained in 35% overall yield (1.7g).

7.6.6 Determination of molecular weight of **90** by freezing point depression

1.27 g of 1,4-dioxane was placed into a test tube (13cm x 1.3cm) containing a small magnetic stirrer. The test tube was closed with a septum which was previously pierced in order to allow the insertion of a metal contact thermometer with electronic display (0.1 °C scale). This apparatus was immersed into a cooling bath maintained at 0 °C and the solution was stirred. Every 15 seconds the temperature was recorded until it became constant for ca. 30 seconds. This value (10.6 °C) was taken as freezing point of pure 1,4-dioxane (a supercooling effect was observed). Then **90** (91 mg) was added carefully to the test tube thereby avoiding any loss of solvent until a homogeneous solution was obtained and the experiment was repeated as above recording the data. The thus obtained freezing point of the solution was +9.7 °C.



Applying the formula for the calculation of the molecular weight *via* the freezing point depression of a substance we found:

$$MW = \frac{(K_f)\,(g_{\,solute})}{\Delta T_f\,(Kg_{\,solvent})} = \frac{-\,4.63 \times 0.091}{-\,0.9 \times (1.27 \times 10^{-3})} = 367.16 \quad \text{(theor. 342.43)}$$

K_f is the cryoscopic constant (-4.63 for 1,4-dioxane) and $\Delta T_f = T_{f\ solution} - T_{f\ solvent}$ is the difference of the freezing points between pure 1,4-dioxane and the above described solution of **90** in the same solvent. The error thus was 7.2%.

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