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Potential Intermediates for Antiviral and Antitumor Agents

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$[\alpha]_D^{22}$	specific rotation with an index of temperature and sodium D-lines
°C	degree Celsius
Ac	acetyl
AIBN	N,N'-Azobisisobutyronitril
aq	aqueous
B	boron
c	concentration
calcd	calculated
cat.	catalytic
COSY	correlated spectroscopy
DMF	dimethylformamide
EtOAc	ethyl acetate
ESI	elektrosprayionisation
Et	ethyl
g	gram
h	hour(s)
HRMS	high resolution mass spectrometry
Hz	hertz
M	mol/l
Me	methyl
mg	milligram
MHz	megahertz
min	minute(s)
ml	milliliter
mmol	millimol
mp	melting point
Ms	mesyl/methansulfonyl
m/Q	mass-to-charge ratio
MS	mass spectrometry
NEt_3	triethylamine
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Enhancement and Exchange Spectroscopy
PE	petroleum ether

R_f	retention factor
rt	ambient temperature
THF	Tetrahydrofuran
TLC	thin layer chromatography
Tol	toluene
${}^{x}J_{y,z}$	coupling via x-bonds between the atoms y and z
δ	chemical shift

„Carbohydrates, even nowadays, form a typical field for discovering new knowledge“

Thisbe K. Lindhorst

Abstract

In this work, potential intermediates for antiviral and antitumor agents were successfully synthesized. Because of the advantages and enormous biologic activity of the glycosides/nucleosides and metal-based drugs, according to the previous research, the combination of both types was investigated. Hence, this thesis is focused on the development of the 2-deoxy-D-ribofuranose analogues, due to the similarity with DNA building blocks, with diamine moieties that should be able to form metal complexes similar to cisplatin. This thesis deals with the synthesis and characterization of *C*-nucleoside analogues of D-ribose. By optimizing the reaction conditions, the synthesis of the *β*-allyl-*C*-glycoside of the 2-deoxy-D-ribofuranose were improved and, as a result, excellent yields were achieved. The regioselectivety and correct stereochemistry of the *C*-allyl residue introduced, have been analytically investigated and confirmed. In addition, we have succeeded in obtaining several 2-deoxy-D-ribofuranose derivatives with ethylenediamine group on a spacer with one or three carbon atoms to the sugar moiety. Preliminary tests for the synthesis of carbohydrate-metal-complexes were done. Furthermore, several potentially biologically active compounds were obtained. The compounds are at present widely investigated as ligands for *cis*-platinum complexes and for other metal complexes.

1 Introduction

1.1 Carbohydrates

Carbohydrates are one of the four most important classes of biomolecules, besides proteins, nucleic acids and lipids. The monosaccharides form the fundamental building blocks for polysaccharides, according to the number of their subunits divided into mono-, oligo- and polysaccharides. It is estimated that over 10^{11} tons of carbon dioxide are absorbed by photosynthesis each year. This carbon dioxide is reduced by light energy to form carbohydrates. The greatest part of naturally occurring carbohydrates are not free monosaccharides, but their condensation products. One of the most common condensed products is starch, accumulating in chloroplasts during day light and is then used by the plant during the night as an energy source. Likewise, for humans and animals carbohydrates are the important energy sources, which also serve for the storage of energy (glycogen, ADP/ATP, NAD^+/NADH).[1] In the human body, simple sugar such as sucrose and glucose are easily absorbed and metabolized to give energy and CO_2. Composite carbohydrates can not be easily absorbed, either they are partly biodegraded by enzymatic processes.[2] Furthermore, carbohydrates are essential components of nucleosides of DNA and RNA and as building blocks of it. By covalent linking of oligomers or polymeric carbohydrates with lipids or proteins glycolipids and glycoproteins form. They are found for example in cell membranes, where they are involved in many cellular processes such as cell-cell recognition, cellular transport and cell adhesion.[3]

1.2 C-glycosides

The replacement of the anomeric oxygen of a sugar by a carbon atom of some heterocycle, results in a *C*-glycoside. A nucleoside is a specific form of glycosides, where the heterocycle is one of the nucleobase and a sugar is a ribofuranose or 2-deoxy-ribofuranose. The *C*-glycosides have specific chemical reactivities, like absent anomeric effect and stability to the acid hydrolysis and enzymatic attacks. Furthermore, in tumor cells, virus host cells and bacteria, a rapid metabolism is observed, modified carbohydrates, like glycoside or nucleoside analogues, can greatly influence the DNA transcription and metabolic processes as interfering factors, leading to cell necrosis. In recent years, several naturally occurring *C*-glycosides (**Figure 1**) with significant biological potentials such as antibacterial, antiviral, anti-HIV and anti-tumor effects have been isolated.[4]

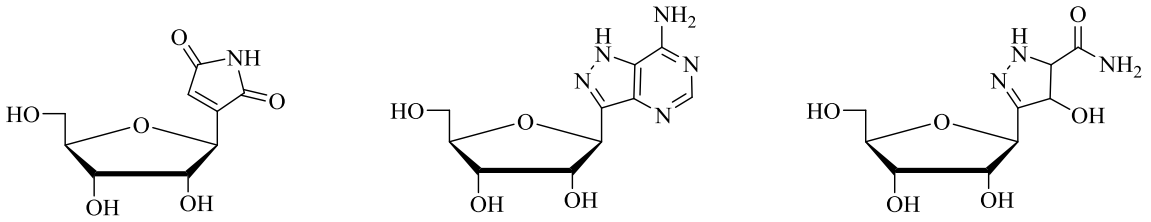


Figure 1. Naturally occurring *C*-glycosides.

The broad spectrum of biological activities of naturally occurring glycosides and nucleoside analogues is one of the reasons why these substances have been used as the lead structures for the synthesis of drugs with antibacterial, antiviral, cancerostatical and fungicidal properties.[5],[6] Some known synthetic compounds with important biological properties and medical relevance are shown in **Figure 2**.

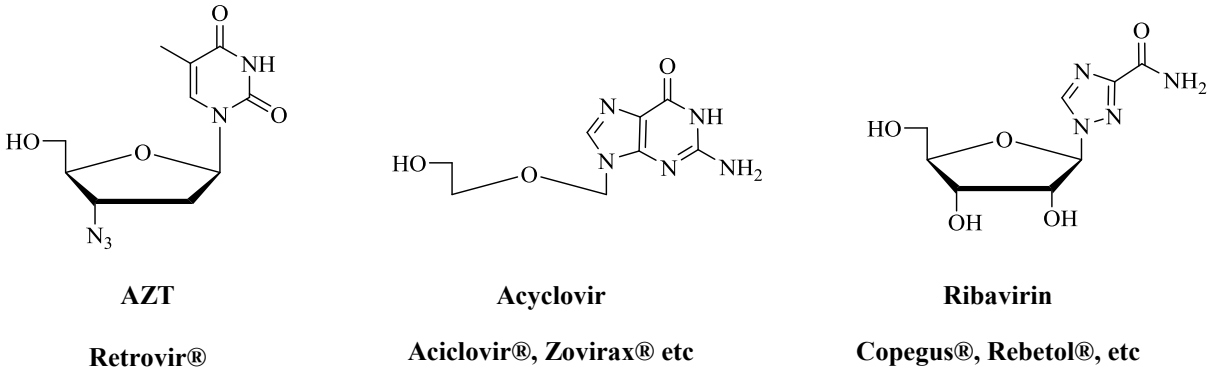


Figure 2. Synthetic nucleoside analogues with important medical relevance.

The AZT or 3ˈ-azido -3ˈ-deoxythymidine is one of the most applied drugs to treat HIV.[7] Acyclovir and its derivatives are used as a drug against most species of the herpes virus family.[8] Ribavirin has a broad spectrum of applications and is used against DNA and RNA viruses such as hepatitis C virus, herpes virus, influenza virus and viral hemorrhagic fevers.[9] Three different strategies are known to synthesize glycosides and nucleoside analogues. The first variant is the modification of the naturally occurring glycosides and nucleosides; the second variant is the modification of already existing synthetically produced molecules. The third variant envisages a total synthesis of simple molecules, in which carbohydrates are generally not used.[10] The glycosides or nucleosides analogs can be accomplished by rearrangement of the heterocycle or carbohydrate moiety, as well as by modification of the linkage between the monosaccharide and the heterocycle. The third variant involves a structural change by the incorporation of a methylene group or an alkylidene chain. These structures are referred to homo-*C*-glycoside analogs or bridged-/(spacer)-*C*-glycoside analogs.[11]

1.3 Medical relevant drugs, containing transition metals

The use of metal-based drugs in medicine has a long history. However, the most important and known metal containing drug is the cisplatin. In 1964, B. Rosenberg, a professor of biophysics at Michigan State University, measured the influence of electric fields on *Escherichia coli* cell growth. In this experiment, as shown in **Figure 3**, platinum electrodes and a nutrient medium of glucose, $MgCl_2$ and NH_4Cl were used.

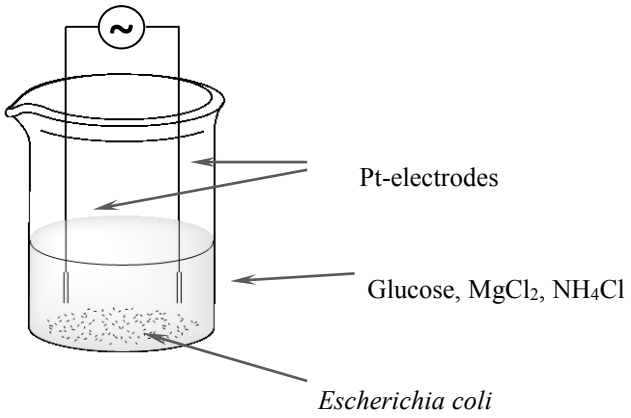


Figure 3. The experiment of professor Rosenberg.

This experiment has showed that the cell division of *E. coli* was inhibited, resulting the formation of the long filamentous bacterial cells.[12] Over the following years, it was proved that the use of platinum electrodes and NH_4Cl has led to the electrochemical synthesis of platinum compounds, such as the *cis*-diamminetetrachloridoplatin(IV), *cis*-$(NH_3)_2PtCl_4$, and the *cis*-diamminedichloridoplatinum(II), *cis*-$(NH_3)_2PtCl_2$, also known as cisplatin, having the growth inhibitory effect. The most effective *cis*-$(NH_3)_2PtCl_2$ species is a square-planar Pt^{2+} complex containing two chlorido and two ammonia ligands in *cis* position (**Figure 4**), giving the compound its trivial name.

***cis*-$(NH_3)_2PtCl_2$**
„Cisplatin“

***cis*-$(NH_3)_2PtCl_4$**

Figure 4. Platinum compounds, inhibiting the growth of bacteria.

The biological activity of cisplatin is not limited just to bacteria. Generally, strong cytostatic properties against many other cells were observed. From a medical point of view, this phenomenon is of particular interest for fighting rapidly growing tumor cells. After successful

application of cisplatin on animals,[13] medical studies on humans were done, showing the effectivity against the variety of the cell lines of cancer.[14]

Table 1. Clinical activity of the cisplatin as single agent against various human tumors.[14]

tumor type	number of responders related to the total of treated patients
genito-urinary tumors	
testicular tumors	58%
prostatic carcinomas	30%
penile carcinomas	53%
carcinomas of the head and neck	44%
skin tumors	24%
brain tumors	40%
bronchogenic tumors	15%
gastrointestinal tumors	
gastric carcinomas	21%
esophageal carcinomas	20%
lymphomas	28%

The actual anti-tumor effect mechanism could only be explored by comparing many similar platinum complexes. The mechanism of action of cis-platinum has been much speculated and various mechanisms proposed. The most likely variant was the covalent binding of cis-platinum to the DNA in the nucleus. Several types of DNA-platinum-adducts are proposed to be formed. The most stable binding results were found between platinum and the N-7 positions of two guanine moieties in the DNA, both interstrand and intrastrand. Nevertheless, the interaction between cisplatin with a single guanine base, between cisplatin and guanine proteine crosslink and in some cases the cisplatin-adenine-guanine-intrastrand crosslink were observed. Which type of adduct is most responsible for the cytotoxic effect of cisplatin has never been fully established. This interaction between platinum and DNA leads to inhibition of the DNA replication, resulting cell death, especially of rapidly dividing cells, like the tumor cells.[15]

The discovery of a second and third generation of cisplatin complexes has helped to reduce some side effects and to achieve better pharmacokinetic properties. The second and third generation of cisplatin drugs are platinum complexes with further ligands,[16] where, for example, the dichloro ligands were replaced by a 1,1-cyclobutadiene carboxylate group (car-

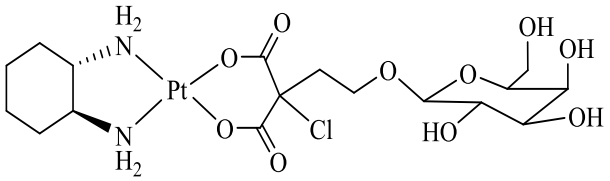
boplatin). Carboplatin, compared to cisplatin can be applied in higher doses with lower toxicity. In case of oxaliplatin, the two ammonia groups on the platinum atom were replaced by a 1,2-diaminocyclohexane group, resulting in lower reactivity and thereby reducing toxicity (**Figure 5**).[17]

Oxaliplatin **Carboplatin**

Figure 5. Second generation of cisplatin complexes.

In the following years, other transition metals (palladium, rhodium, iridium, ruthenium, etc) were investigated for their biological activities and cytostatic properties.[18] The other potent metal complexes with high cytostatic properties are the ruthenium-based drugs.[19]

Moreover, increasing research on metal-carbohydrate complexes over the last 20 years shows their enormous importance in many bioorganic processes in different organisms. For example, platinum-carbohydrate complexes with excellent cytostatic activity.



Galactose-Pt(II) complex

Figure 6. Galactose-Pt(II) complex with significant tumor cytotoxicity.

In the **Figure 6**, one of the biologically active platinum-carbohydrate complexes is shown. The galactose-Pt(II) complex has showed an increased therapeutic index by over 30-fold, compared to cisplatin and oxaliplatin, offering improved cytotoxicity against human colon and lung cancer cell lines.[20]

1.4 The aim of the thesis

The rapidly increasing number of new diseases and tumor lines in modern society requires increased research in this field. Therefore, the aim of this work was to achieve potential intermediates for antiviral and antitumor agents. Because of the advantages and enormous biological activity of glycoside and metal-based drugs, according to previous research, the combination of both types was desirable. Moreover, the combination of carbohydrate moieties and metal complexes are supposed to be more effective and less toxic, than the particular one. Hence, we focused on the development of 2-deoxy-D-ribofuranose analogues, due to the similarity with the DNA building blocks, with diamine moieties that should be able to form the metal complexes similar to cisplatin.

For the present work, the strategy of synthesis of the *β*-allyl-*C*-glycoside of the 2-deoxy-D-ribofuranose were used, previously mentioned by Dr. Heike Otero Martinez (née Wächtler) in her dissertation 2008 [21], Dr. Dilver Pena Fũentes in his dissertation 2012 [22] and in the following publications [23], [24]. The first step was to combine the preliminary research for the synthesis of the *β*-allyl-*C*-glycoside of the 2-deoxy-D-ribofuranose, as well as the optimization, validation and verification of the synthetic pathway.

The next step was to convert the double bond of the allyl group into a diamino group. Furthermore, we wanted to examine the possibilities to arrange the platinum at different distances to the furan ring, achieving in this way more flexibility of the molecule.

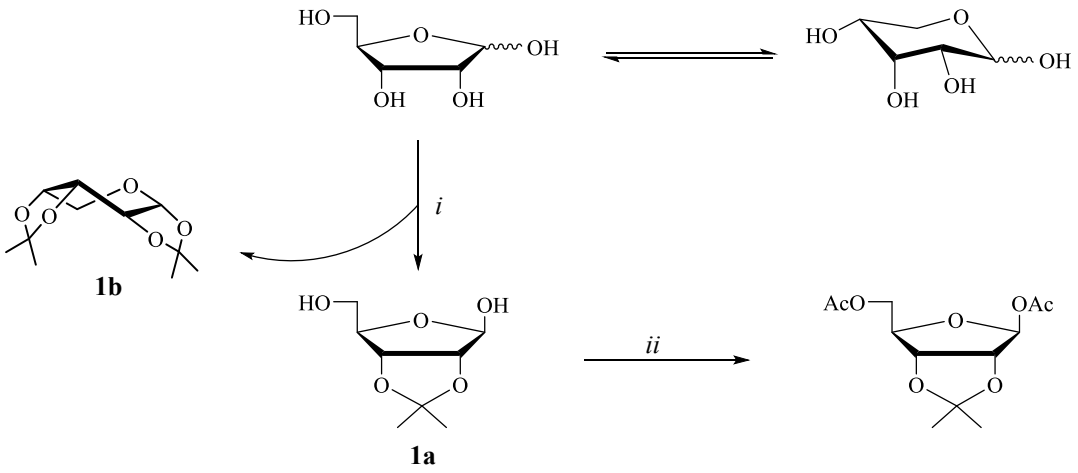
The preliminary verification of the reaction of the 2-deoxy-D-ribofuranose analogues with diamine moieties with platinum was also required. Thus, applying the cis-platinum-glycoside analogue complex could lead not only to better cytostatic results, but the combination of an active metal complex with a ligand, which has its own biological activity, could also lead to entirely new pharmacological effects.

2 Results & Discussion

2.1 Synthesis of the β-C-allylglucoside of the 2-deoxy-D-ribofuranose

2.1.1 Synthesis of the D-ribofuranose derivative 2 suitable for the preparation of the *C*-allylglucoside

Starting with commercially available D-ribose, the first aim was to synthesize the β-*C*-glycoside in kinetically preferred form of the D-ribofuranose. In aqueous solution, D-ribose exists as a isomers mixture: α- and β-ribopyranose as a six-membered ring and α- and β-ribofuranose as a five-membered ring and in less than 0.1% in two acyclic form (hydrate and aldehyde).[25] Therefore, simple acetylation of D-ribose gave a mixture of different acetylated products, preferentially with the ribopyranose as a thermodynamically stable product.[26] Making the purification and isolation of the desired β-ribofuranose from this mixture highly sophisticated. That's why, the synthesis pathway presented in this work, to achieve the 2-deoxy-D-ribofuranose, simplified the whole procedure already from the first step.



i: dry acetone, cat. H_2SO_4, 2 h, rt; ii: dry pyridine, Ac_2O, 15 h, rt.

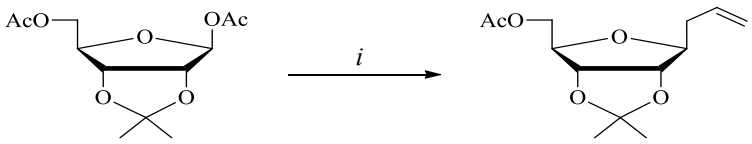
Scheme 1. Synthesis of compound 2.

Regarding the **Scheme 1**, the D-ribose reacted with dry acetone in the presence of catalytic amounts of sulfuric acid as an activator to give compound **1**.[27] The quality of the acetone was found to be crucial.[28] The addition of the activated acetone to the hydroxyl groups forms the hemiacetal firstly, which reacts with the vicinal hydroxyl group to form the five-membered ring.[29] The isopropylidene protective group on the carbon atoms C-2' and C-3' of the sugar ring[1] fixed the D-ribose in its furanose form. The yield of compound **1a** amounts

[1] The atom numbering of carbon and hydrogen atoms of the ribofuranose ring refers to the standard numbering of pentoses and may differ from the IUPAC numbering used in naming of the molecule. The atom numbering used here is obviously shown in the experimental section for each compound respectively.

to 87%. To achieve a good yield, it is significant to add 1% v/v triethylamine to the eluent by the chromatographical purification. Furthermore, the pyranose form derivative **1b**, containing two isopropylidene groups on the carbon atoms C-1' and C-2', together with C-3' and C-4', was isolated by flash chromatography and characterized, yielding 0.4%.[30],[31] In the next step, the acetylation was done. Therefore, the purified compound **1a** was treated with dry pyridine and freshly distilled acetic anhydride at 0 °C.[32] We have found, that the usage of the freshly distilled acetic anhydride could increase the yield considerably. The reaction mixture was stirred over night at room temperature. Next addition of methanol removed excess of Ac_2O from the reaction mixture. After work up and flash chromatography, product **2** was achieved in 93% yield as a colorless syrup. In ^{1}H-NMR, four characteristic signals of the methyl groups were found: for two methyl groups of the isopropylidene group at 1.34 ppm and 1.50 ppm and for two methyl groups of the acetyl groups at 2.06 ppm and 2.09 ppm, which indicates together with other analyses the desired diacetylated compound **2**.

2.1.2 Synthesis of the *C*-allylglucoside of D-ribofuranose



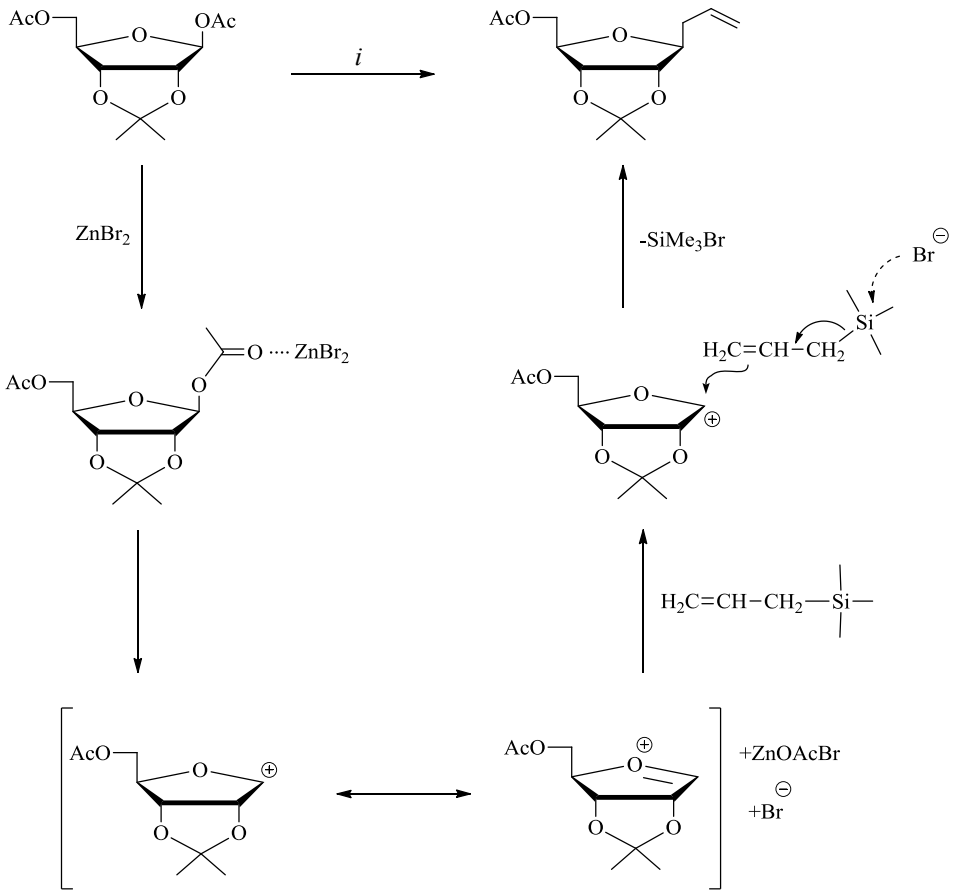
2 **3**

i: $ZnBr_2$, AllTMS, $MeNO_2$, 0 °C → rt, under an argon atmosphere.

Scheme 2. Synthesis of compound 3.

Diacetate **2** was converted into the *C*-furanosyl compound **3** by treatment with zinc bromide and allyltrimethylsilane (AllTMS) [33] in $MeNO_2$ as a solvent [23],[24]. After several experiments we have found that the freshness and dryness of the $ZnBr_2$ together with a quick addition of $ZnBr_2$ to the reaction mixture, played the main role in achieving a good yield.[34] The work up of this reaction was also very tricky, while the extraction, the intense shaking could led to the emulsion, which was difficult to separate, causing the yield loss. To prevent an emulsion layer the vigorously shaking of the mixture must be avoided and the ratio of the organic and aqueously phase should be complied!

In this reaction, zinc bromide has acted as a lewis acid, activating the acetyl group at the anomeric center, increasing its aptitude the readiness of the acetyl group to leave its position (**Scheme 3**). This allowed the nucleophilic addition of the allyltrimethylsilane at the anomeric center of the furane ring. The silyl group was attacked by the free bromide ion and removed, forming the terminal double bond on the carbon chain.



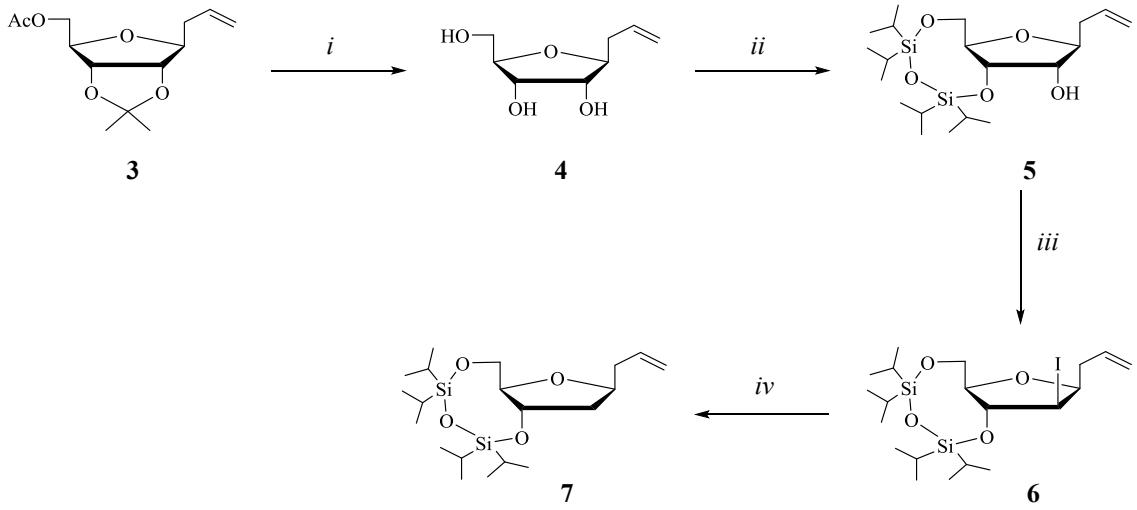
i: $ZnBr_2$, AllTMS, $MeNO_2$, 0 °C → rt, under an argon atmosphere.

Scheme 3. Proposed reaction mechanism of the synthesis of *C*-allylglucoside 3.

The advantageous location of one of the methyl groups of isopropylidene caused by steric hindrance, benefiting the formation of the β-product and preventing attack of the nucleophile at the α-position, giving compound **3** with a α/β ratio of 1:6. After appropriate purification, the desired pure β-*C*-allylribofuranose **3** was isolated as colorless syrup by flash chromatography in a yield of 78%. The structure of β-compound was confirmed via NMR, especially, nuclear overhauser enhancement and exchange spectroscopy (NOESY).

2.1.3 Synthesis of the 2-deoxy-D-ribofuranose derivative 7

The synthesis pathway to produce the 2-deoxy-D-ribofuranose derivative **7** is shown in the **Scheme 4**.



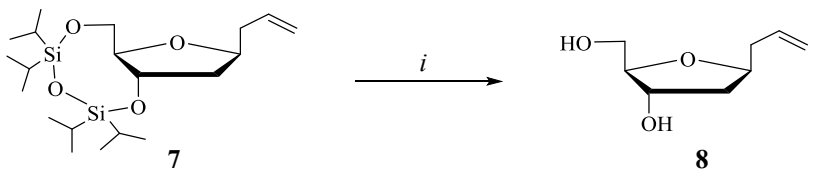
i: 1.0 M HCl, ethanol, 2 d, rt, ii: TIPDSCl, imidazole, DMF, 1 h, 0 °C, iii: I_2, Ph_3P, imidazole, dry toluene, 2x5 h, reflux, iv: Bu_3SnH, AIBN, dry toluene, 4 h, reflux.

Scheme 4. Synthesis of the 2-deoxy-D-ribofuranose derivative 7.

Because of the two different kinds of protecting groups of the compound **3**, there are some possibilities for further syntheses of various intermediates. However, for our purposes, all protecting groups except the allyl group must be cleaved. It is well known, that the acetals are hydrolysed by dilute aqueous acid. [29] Treatment of compound **3** with hydrogen chloride 1 M in ethanol for 2 d at room temperature hydrolysed advantageously not only the isopropylidene group, but also the acetyl group, giving the unprotected species **4** in a yield of 85% as a colorless syrup. After storage of the syrup in refrigerator, a colorless amorphous solid was formed. Unfortunately, the crystallisation of compound **4** for X-ray crystallographic analysis was unsuccessful. Nevertheless, the varied analytical data confirmed the structure of the unprotected species with a very high probability.

The crucial challenge of the next step was simultaneous protection of the 3'- and 5'-positions of the ribofuranose ring. This problem was previously solved by *Markiewicz*, working with tetraisopropyldisiloxane.[36] For our purpose, the tetraisopropyldisiloxane group was also absolutely appropriate. The treatment of deprotected compound **4** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TIPDSCl) and imidazole, as an acid scavenger, in dry DMF [37] at 0°C avoided regioisomers and afforded compound **5** in a yield of 85%.

Previous experiments for deoxygenation of carbohydrate-type compounds were done under noxious conditions (phosgene). They were not chemospecific for the 2'-position and rendered byproducts.[38],[39] A general procedure for the efficient deoxygenation of secondary alcohols at ribonucleosides was developed by *M. J. Bobins, J. S. Wilson and F. Hansske* [40] using phenoxythiocarbonyl for further radical-based reduction. The iodination procedure in carbohydrates for converting a hydroxyl group into an iodo group was developed by *Garegg et al.* [41]. The inversion of the substituents on the 2'-position of the ring is due to the redox-mediated nucleophilic S_N2-reaction (mukaiyama redox condensation), where the carbon C-2' containing the hydroxyl group had the (*S)*-configuration and with the iodine became (*R)*-configured. Triphenylphosphine oxide resulting from the procedure of iodination was completely removed from the system by flash chromatography with relatively nonpolar eluent (petroleum ether – EtOAc 100:1) giving **6** in 95% yield. That allowed the optimal radical-based reduction under standard free-radical conditions with tri-*n*-butyltin hydride, catalysed by azobisisobutyronitrile (AIBN) previously applied by *Gimisis et al.*[42] It is well known, that the reactions, using tri-*n*-butyltin hydride as a reactant, are leading to the formation of tin salts as byproducts, which are hard to remove. Therefore, for the removal of the tin species from the reaction mixture, the work of *P. Kocienski* and *C. Pant* was applied.[43] In this processing variant, the highly insoluble tin salts were achieved by treatment of the reaction mixture with aqueous 10% potassium fluoride solution and removed by aqueous work up, followed by flash chromatography. The use of this work up procedure has led to the easy isolation of product **7** in a yield of 89% as a colorless syrup. The deoxygenation of the position 2' was confirmed via elemental analysis and mass spectra. The ^{1}H-NMR showed two signals, each with one proton for the H-2'a at 1.78–1.89 ppm and for the H-2'b at 1.97–2.07 ppm, instead of a multiplet at 4.24–4.28 ppm, presented one proton of the H-2' of compound **6**. Treatment of compound **7** with tetrabutylammonium fluoride trihydrate (TBAF) in dry acetone [44] provided compound **8** in a good yield (**Scheme 5**). The total yield of the complete reaction pathway was markedly improved to 54%, compared to the previously reported 34%.[23],[34],[35]



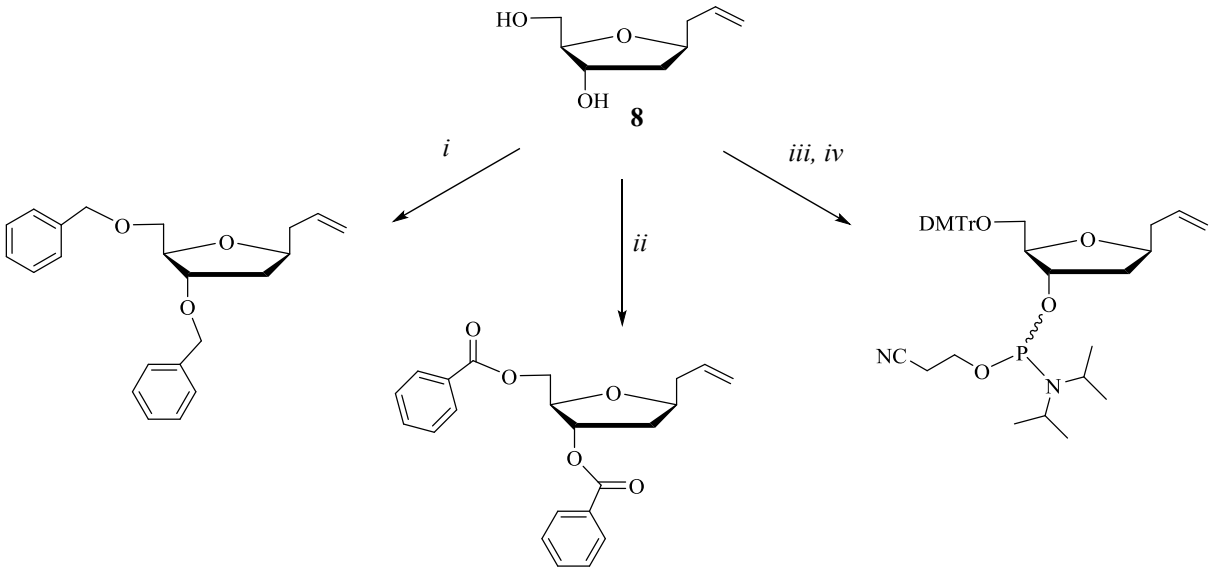
7 **8**

i: TBAF, dry acetone, 1.5 h, rt.

Scheme 5. Cleavage of the silyl protecting group.

Furthermore, it was confirmed that the protocol for the synthesis of compounds **1**–**8** also could be used for large-scale work. The synthetic pathway for improved synthesis of all previous compounds until the 2-deoxy-D-ribofuranose derivates **7** and **8** was evaluated and verified by a few renowed scientists and it was successfully published in the book *Carbohydrate Chemistry: Proven Synthetic Methods*, Vol. 4.[34],[35]

The hydroxyl groups of compound **8** in positions C-3' and C-5' can be easily used for further transformation, some of them are shown in the **Scheme 6**.



i: Benzyl bromide, NaH 60% in oil, dry DMF, 6 h, rt, ii: Benzoyl chloride, DMAP, pyridine, 15 h, rt, iii: 4,4'-dimethoxytrityl chloride, NEt_3, dry DMF, 24 h, rt, iv: 2-cyanoethyl N,N-diisopropyl-chlorophosphoramidite, diisopropylethylamine, dry CH_2Cl_2, 3 h, rt.

Scheme 6. Some possible further protections of positions C-3' and C-5'.

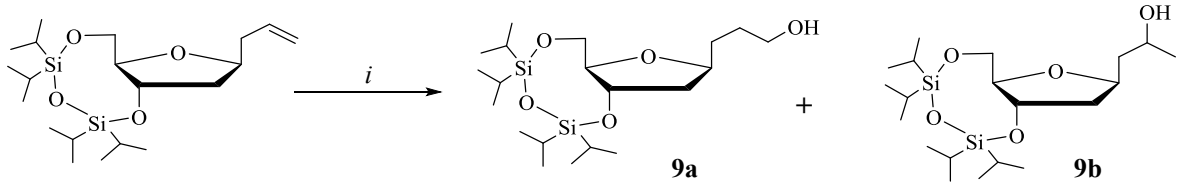
The preliminary experiments, to confirm this statement, showed that an ether, for example Benzyl,[22] or an ester group, like Benzoyl (unpublished)[2], or 4,4'-dimethoxytrityl group on 3' and phosphoramidite derivative an 5', which will be mentioned later, and other substituents can be introduced on this positions. Different protecting groups could be chosen, depending on the further reaction requirements, with high acid or base lability or even with the different reactivity on both positions.

[2] We introduced benzoyl groups the same way as by the introduction of pivaloyl. The work-up procedure was not enough for the benzoyl, so the spectra of NMR showed residues of benzoyl chloride together with the desired product. So an improved work up procedure is required.

2.2 Synthesis of the β- allyl-C-glucoside of the 2-desoxy-D-ribofuranose with ethylenediamine moieties

2.2.1 Synthesis of the primary alcohol via hydroboration-oxidation reaction

Here, we converted the allyl group of compound **7** into a primary alcohol as an intermediate stage (**Scheme 7**). For our purpose, the hydroxyl group was very stable. Hence, it was transformed into mesyl compound **10**, which reacted smoothly in the following steps.



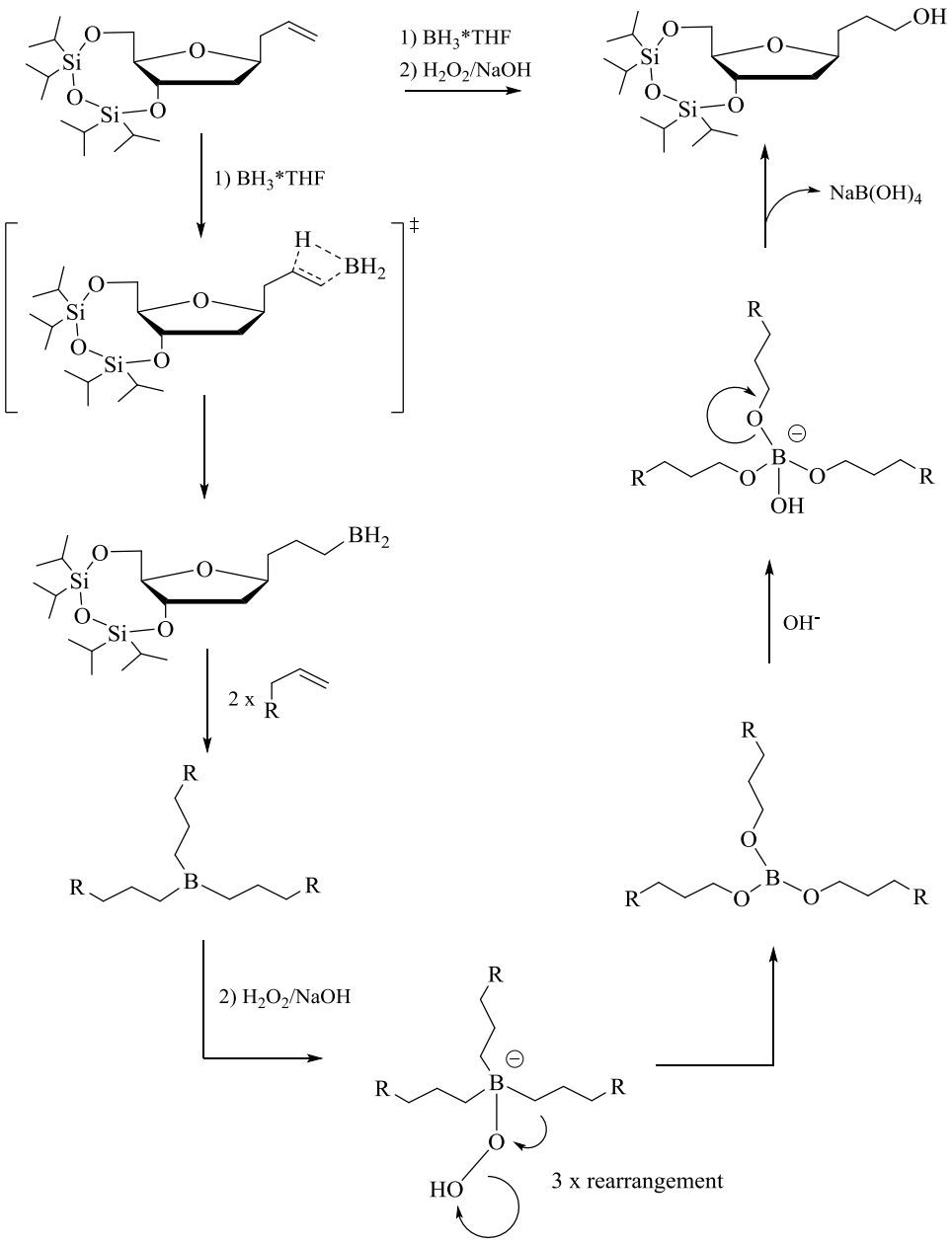
9a **9b**

***anti*-Markovnikov product** **Markovnikov product**

*i: BH_3*THF, dry THF, 3 h, 0 °C.*

Scheme 7. Synthesis of the primary alcohol 9a.

The transformation of the allyl group of the 2-deoxy-D-ribofuranose derivates **7** into the terminal alcohol **9a** occurred over a hydroboration–oxidation reaction. Therefore, olefin **7** was treated with a 1.0 M borane tetrahydrofuran complex solution in dry THF and the mixture was stirred intensively for 3 h at 0 °C.[45] The BH_3 bound regioselectively to the less hindered carbon atom of the olefin. A 4-electron-4-center transition state with a following addition of the B-H fragment on the double bond was formed via *syn*-addition (**Scheme 8**). This process was repeated twice more, until the triple substituted borane is formed. After that, the mixture of aqueously sodium hydroxide solution 3 M and 30% hydrogen peroxide was very cautiously added to the stirred reaction mixture. The electron poor boron atom was attacked by the electron rich hydroperoxide ion by formation of the peroxydic boranate with very weak O-O bond. The following rearrangement causes the elimination of a hydroxide ion by retention of the configuration. This process was repeated until all three substituents have migrated to the oxygen atoms and a boric-acid ester was formed. The boric-acid ester was hydrolysed with a base, forming mostly the *anti*-Markovnikov product - primary alcohol **9a**.[46] We have also isolated the Markovnikov product **9b** in a yield of approx. 5%. By varying reaction conditions the Markovnikov product could be obtained in a yield up to 19%. The byproduct **9b** was easily separated by column chromatography.

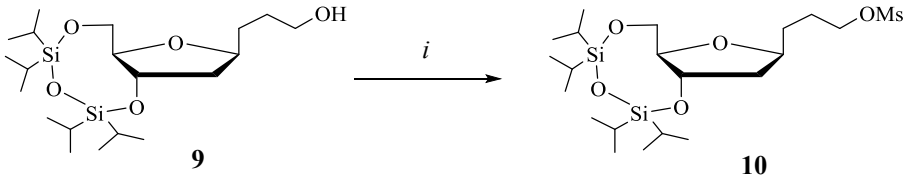


Scheme 8. Proposed mechanism of hydroboration-oxidation reaction.

2.2.2 Synthesis of the important intermediate 10 and further reactions

Related to the general knowledge about the stability of primary hydroxyl groups for substitution reactions, the primary alcohol is relatively stable, so another leaving group was necessary. Mesylation of the primary alcohol led to a convenient leaving group for further nucleophilic substitution reactions. For this purpose, the variant of *Kornilov et al.* was applied [47] to achieve intermediate **10**. Therefore compound **9** was treated with methansulfonyl chloride (MsCl) in dry CH_2Cl_2 with addition of triethylamine. Thus, after a short reaction time

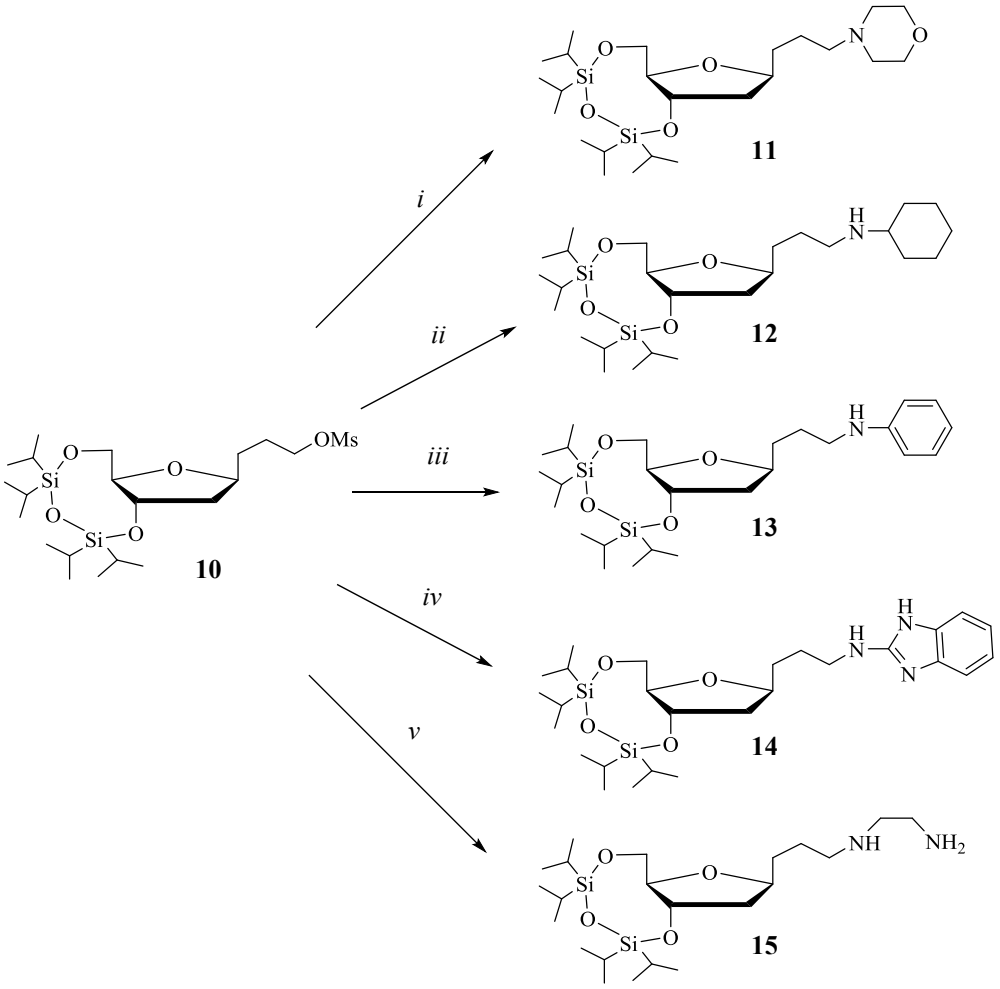
of 20 min and after the corresponding work up, the mesylated compound **10** was obtained in an excellent yield of 93% (**Scheme 9**).



i: MsCl, NEt_3, dry CH_2Cl_2, 20 min, 0 °C.

Scheme 9. Synthesis of the mesylated compound 10.

In the following step, we have made a series of attempts, treating the intermediate **10** with several nucleophiles to obtain compounds **11-15** (**Scheme 10**).

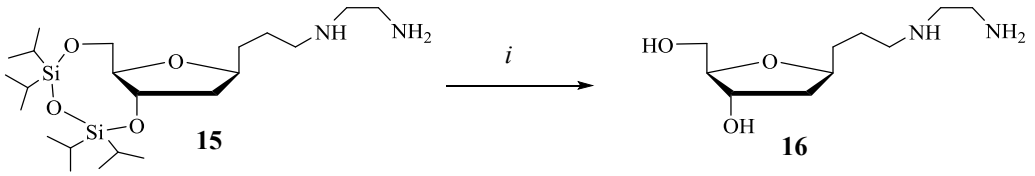


i: Morpholine, dry methanol, 6 d, rt; ii: Cyclohexylamine, dry methanol, 6 d, rt; iii: Aniline, dry methanol, 5 d, rt; iv: 2-Aminobenzimidazole, dry methanol, 10 d, rt;
v: Ethane-1,2-diamine, dry methanol, 22 h, rt.

Scheme 10. Synthesis of compounds 11-15.

The substitution reactions of mesylate **10**, leading to products **11-15** were carried out in dry methanol for different reaction times, until the reactions were completed. All experiments were carried out at room temperature. The differences in the reaction time, 22 h to 10 d, can be explained by the different solubility of the reactants in dry methanol. Probably, the choice of other solvents or a reaction temperature could make the substitution faster, but it was not the purpose of this work. The reactants were selected due to their reported biological activities. For example, morpholines have showed anaesthetic, antifungal [48] and antiviral [49] properties, even DNA protein kinase inhibitory activity.[50] *Bhakta et al.* scanned the activity of several substituted pyrroles against *mycobacterium tuberculosis*. Cyclohexanamine substituted pyrrole showed low eukaryotic cell toxicity with highly antitubercular activity on *M. smegmatis, M. bovis* and *M. aurum* mycobacterial strains and against multidrug-resistant clinical isolates.[51] Aniline derivatives were tested as highly potent and nontoxic inhibitors of breast cancer resistance protein (ABCG2).[52] The substituted ethylenediamines were thoroughly investigated in their effects. Acting as classic bidentate ligand, ethylenediamine are well known in catalysis. Also, the medical effect of ethylenediamine substituted molecules is very eclectic. For example, *Tiwari et al.* have found that substituted ethylenediamine showed very good performance against filariasis[3].[53] Therefore, important ligand **15** was prepared by dissolving compound **10** in dry methanol and reacted it with ethane-1,2-diamine at room temperature. After stirring for 22 h, product **15** was isolated as a light-yellow syrup in an excellent yield of 95% and it was characterized analytically. The absence of sulfur and the presence of nitrogen was confirmed by elemental analysis.

To deprotect **15**, this compound was dissolved in dry acetone and treated with tetra-*n*-butylammonium fluoride trihydrate (TBAF) in dry acetone.[44] The chromatographic purification of compound **16** was very laborious because of its high polarity. The use of a very short chromatographical column and the eluent, which contained 1% triethylamine, is highly recommended for the purification. In ^{1}H NMR and ^{13}C NMR spectra, there were no peaks of the tetradiisopropyldisiloxane detected, indicating a complete elimination of the silyl protecting group. Product **16** was isolated in an excellent yield of 90% and characterized exhaustively (**Scheme 11**).



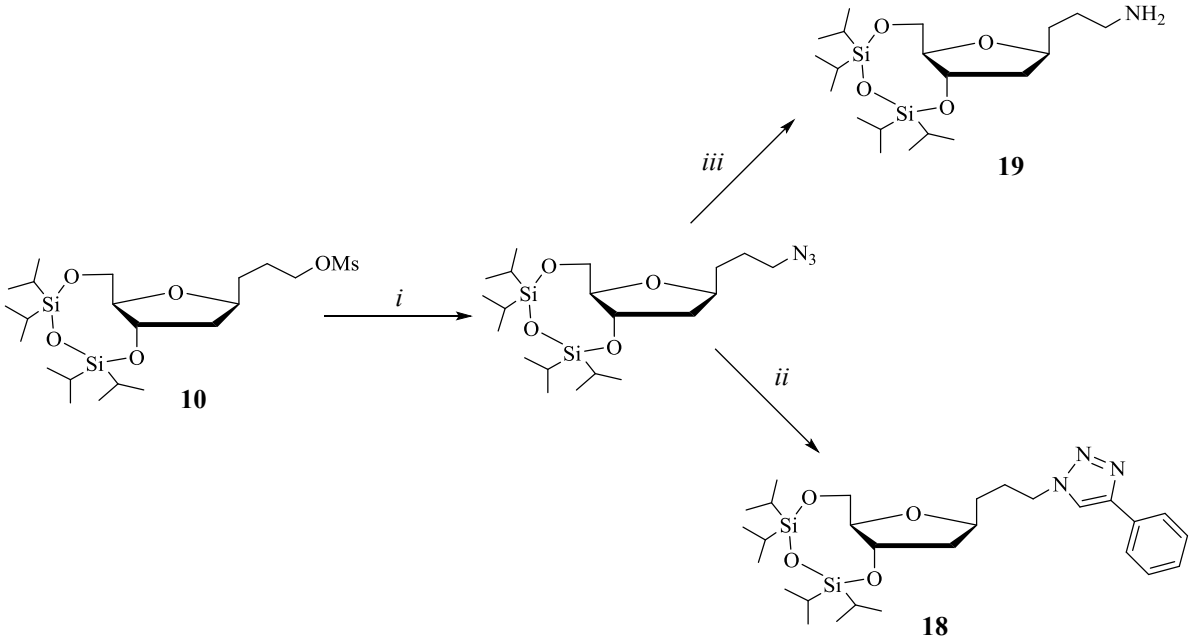
i: TBAF, dry acetone, 1.5 h, rt.

Scheme 11. Deprotection of compound 15.

[3] Filariasis is a parasitic disease transmitted by mosquitoes. It is caused by filarial worms living almost exclusively in humans, lodged in the lymphatic system.

2.2.3 Synthesis of the primary amine and Schiff base

The primary amines give the great opportunity for further reactions, even acting as a leaving group for the preparation of *N*-nucleosides.[54],[21] The mesyl group gave an excellent opportunity for the transformation into the primary amine. We have modified the pathway used by *Kornilov et al.* to achieve amine **19** (**Scheme 12**).



i: TBAF, dry acetone, 1.5 h, rt; ii: Phenylacetylene, $CuSO_4$, L(+)-ascorbic acid, water/DMF, 63 h, 75 °C; iii: Pd/C, dry methanol, 24 h, rt, H_2.

Scheme 12. Synthesis of the primary amine 19.

The mesylated compound **10** was stirred with sodium azide in dry DMF for 24 h at ambient temperature giving compound **17** in excellent yield of 96%. In addition to the elemental analysis that showed the absence of sulfur with the simultaneous presence of nitrogen and IR spectra, showing the typical peak of azido groups on $\nu = 2092$ cm^{-1} (**Figure 7**), the cyclisation **18** was applied for the confirmation of the structure **17**. Glycoside **18** was obtained in 83% yield by 1,3-cycloaddition of azido compound **17** with phenylacetylene [55]. Finally, catalytic hydrogenation of **17** with Pd/C under hydrogen atmosphere led to the primary amine **19**. In ^{1}H NMR the peak of the protons of the C-1 of the side chain in close vicinity to the amine was shifted to 2.71 ppm, previously showed 3.24–3.37 ppm by azido compound **17**. Moreover, no peak of the azido group in IR spectra of the **19** was detected (**Figure 7**). Together with elemental analysis and mass spectrometry, the proposed structure of the **19** was supported.

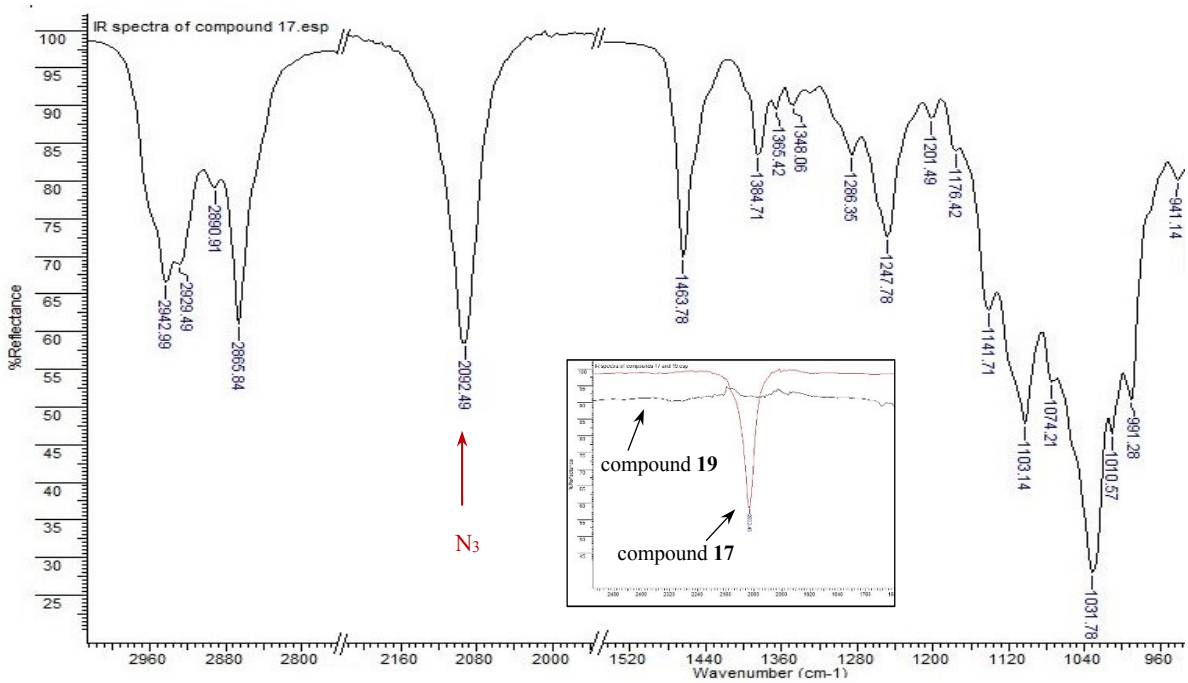
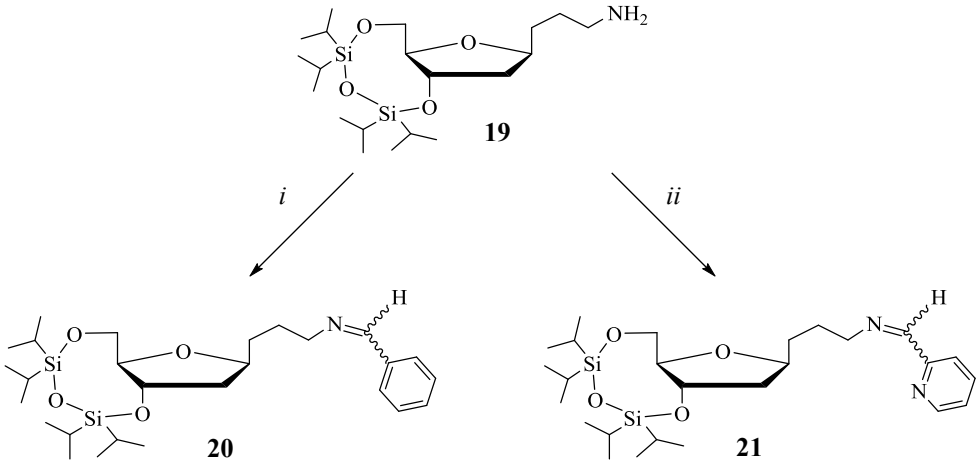


Figure 7. IR spectra of compound 17.

To confirm the structure of **19** chemically, it was treated with benzaldehyde and pyridine-2-carbaldehyde in dry methanol leading to imines (-CH=N-) **20** and **21** (**Scheme 13**).



i: Benzaldehyde, molecular sieve powder, dry methanol, 40 h, rt; ii: Pyridine-2-carbaldehyde, molecular sieve powder, dry methanol, 40 h, rt.

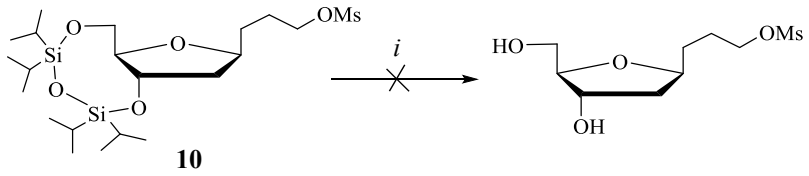
Scheme 13. Synthesis of the Schiff bases.

The rate of the reaction is dependent on the purity of the reagents. So it is highly recommended, to use a fresh batch or at least freshly distilled benzaldehyde and pyridine-2-carbaldehyde. The purity of the starting materials is also significant for the purity of the imine. The purification and work up could lead to byproducts or even destruction of the Schiff base. In ^{1}H and ^{13}C NMR spectra peaks indicating aromatic groups were found. In addition, the typical peaks for -C*H*=N- were localized at 8.28 ppm for compound **20** and at 8.37 ppm for compound **21**. In the literature, complexes of ruthenium with iminopyridine ligands were

found to have a remarkable activity for the *anti*-Markovnikov reductive hydrogenation of alkynes.[56] *Cucciolito et al.* have also mentioned glucose containing platinum(II)-Schiff base complexes with anticancer activity, showing better water-solubility and minor toxicity side effects with respect to other widely used platinum drugs.[57] Furthermore, all the Schiff base transition metal complexes derived from cephalexin containing sugars (D-Glucose and D-Xylose) and metals such as Fe(II), Co(II), Ni(II) showed more antibacterial activities as compared to the pure cephalexin. [58] Such sugar-containing antibiotic complexes could be the new step to solve the problem of drug resistance. The increased activity of the drugs, especially antibiotics, after its coordination on metal was already studied by *Chohan et al*. [59]

2.2.4 Synthesis of the 2-deoxy-D-ribofuranose derivatives with pivaloyl groups

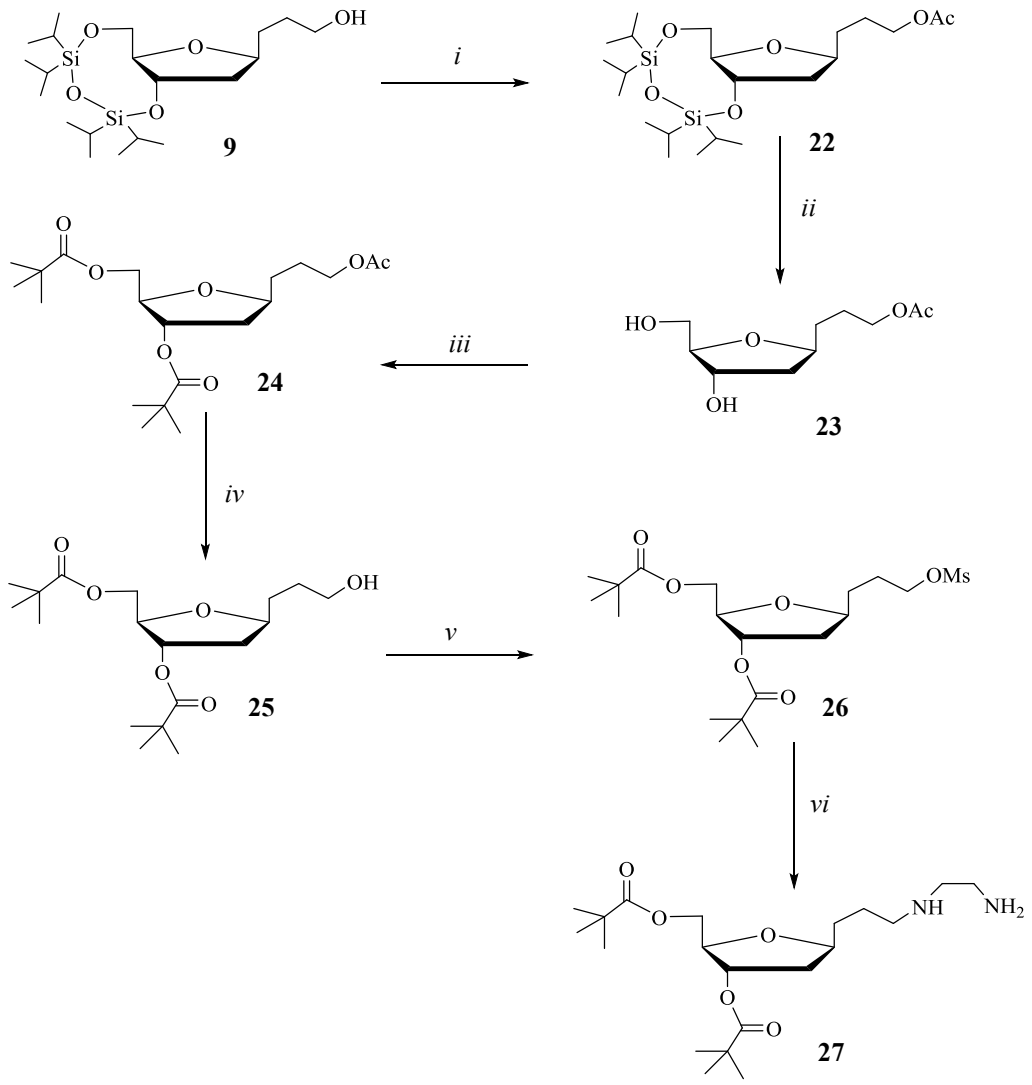
Further, we want to investigate, if other protecting groups besides silyl group on the 3'- and 5'-positions of the furane ring are possible and if it could lead us to crystalline compounds. Until now, all derivatives were syrupy or amorphous, so no X-ray analysis could be performed. We have found that the cleavage of the silyl group of mesylated compound **10** with TBAF has resulted in cleavage of mesyl and silyl groups simultaneously, so no subsequent reaction to introduce the ethylenediamine was possible (**Scheme 14**).



i: TBAF, dry acetone, 1.5 h, rt.

Scheme 14. The reaction of mesylated compound 15 with TBAF.

Hence, we went a step in return and transformed the primary alcohol **9** into an acetate **22**, which was stable to TBAF under the applied conditions (**Scheme 15**). This reaction was carried out according to the classical procedure for acetylation, mentioned previously in chapter 2.1.1. The cleavage of the silyl group was performed with TBAF, similarly as prior. Thus, compound **23** was achieved in an excellent yield of 96%. For the insertion of pivaloyl groups on the 3'- and 5'-positions of compound **23**, it was treated with pivaloyl chloride [60] in dry DMF. The addition of the 4-(dimethylamino)pyridine (DMAP) as catalyst made the reaction 5 x faster at room temperature and increased the yield from 20% to 95%. The peaks of the pivaloyl groups on the 3'- and 5'-positions of the furane ring were found in ^{1}H NMR at 1.20 ppm and 1.21 ppm, not overlapping with protons of acetyl group at 2.04 ppm. After the introduction of pivaloyl groups the acetyl group was converted into a primary alcohol **25**, thereafter into mesylate **26** and transfer into ethylenediamine **27**. The cleavage of acetyl



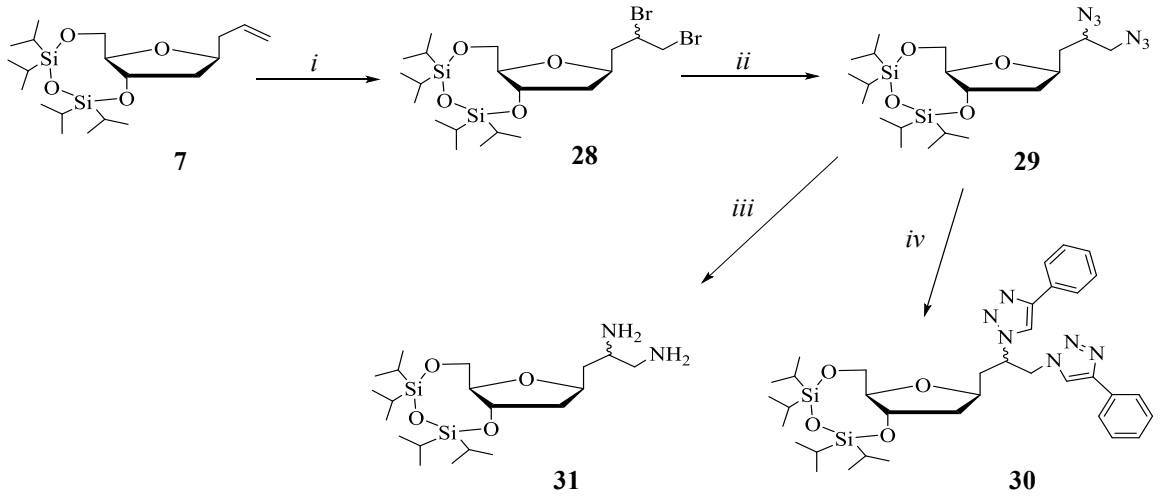
i: Ac_2O, dry pyridine, 15 h, rt; ii: TBAF, dry acetone, 1.5 h, rt; iii: Pivaloyl chloride, DMAP, dry DMF, 4 h, rt; iv: Acetyl chloride, dry methanol, 4 h, rt; v: MsCl, NEt_3, dry CH_2Cl_2, 20 min, 0 °C; vi: ethane-1,2-diamine, dry methanol, 20 h, rt.

Scheme 15. The synthesis of ethylenediamine derivative with pivaloyl groups.

group in presence of pivaloyl group is sophisticated because of it's similar reactivity. The ancient, well-known and often used procedure of G. Zemplén for the cleavage of acetyl group on carbohydrates with NaOMe [61][62] was tested at first. The various concentrations from 0.025 M to 1 M and various temperatures from 0 °C to ambient temperature and reaction times from 10 min to 1 h resulted in simultaneous cleavage of the acetyl and one or both of the pivaloyl groups. However, the selective deprotection of acetyl in presence of pivaloyl was successfully obtained with 0.28 M methanolic HCl solution in dry methanol. To avoid the possible migration of pivaloyl groups on the primary alcohol, the deacetylated compound **25** was used for subsequent reaction without further purification. Following mesylation **26** and transition into ethylenediamine **27** was carried out according to the procedures mentioned before (**Scheme 15**).

2.2.5 Synthesis of 2-deoxy-D-ribofuranose derivates with an ethylenediamine group via bromination of the allyl group

We have also investigated another synthetic route for ethylenediamine derivatives starting from the 2-deoxy-D-ribofuranose **7**. Bromination led to dibromide **28**. A subsequent nucleophilic substitution gave diazido compound **29**, which was hydrogenated to diamine **31**.



i: $C_2H_5NHBr_3$, dry CH_2Cl_2, 40 min, rt; ii: NaN_3, dry DMF, 2.5 h, 70 °C; iii: Pd/C, dry methanol, H_2, 24 h, rt; iv: Phenylacetylene, $CuSO_4$, L(+)-ascorbic acid, water/DMF, 60 h, 75 °C.

Scheme 16. Synthesis of the diamino compound 31.

First, a classical bromination with elemental bromine was tested. Due to the high reactivity of the bromine, not only addition to the double bond but also partial destruction of the molecule was observed. Therefore, milder conditions were used, which only allow the selective addition of bromine to the double bond of the allyl group. In the variant of *Inaba et al.* the pyridinium tribromide as a mild brominating reagent with subsequent conversion into the diazido compound with sodium azide in dry DMF were used.[63] The brominated compound **28** was used in the next reaction step without further purification since it has started to decompose. The dibromination caused an asymmetric center on C-2 of the side chain. The following reactions were carried out using the diastereomeric mixture. To obtain the diazido compound **29**, the brominated compound **28** was treated with sodium azide in dry DMF. The reaction was carried out at 70 °C for 2.5 h to give **29** as a colorless syrup. The identity of diazido compound **29** was confirmed by analytical data. The IR spectra showed the typical azido peaks on the $\nu = 2100$ cm^{-1} (**Figure 9**). Cycloaddition of phenylacetylene to diazide **29** leading to bistriazole **30** was carried out in order to chemically confirm the structure of com-

pound **29**. The bis(4-phynyl-1*H*-1,2,3-triazole) **30** was synthesized according to the procedure for the 1,3-cycloaddition of the azide with phenylacetylene, mentioned previously. The fair yield of 55% indicates that further improvements of the reaction procedure are desired.

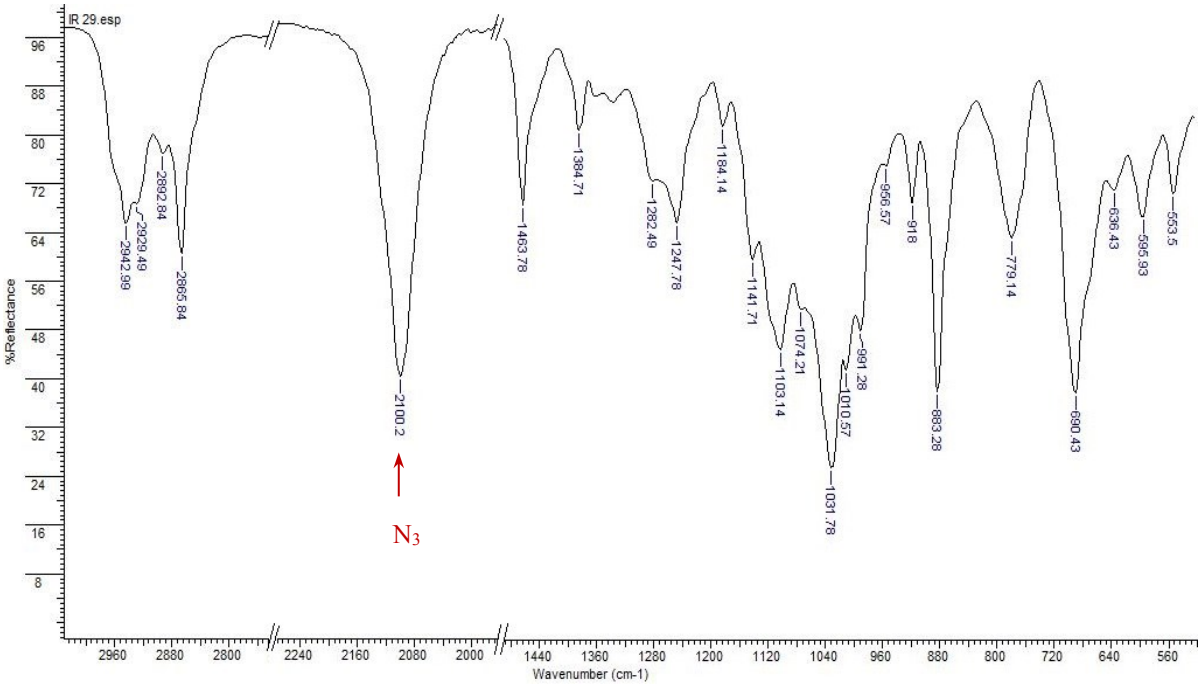
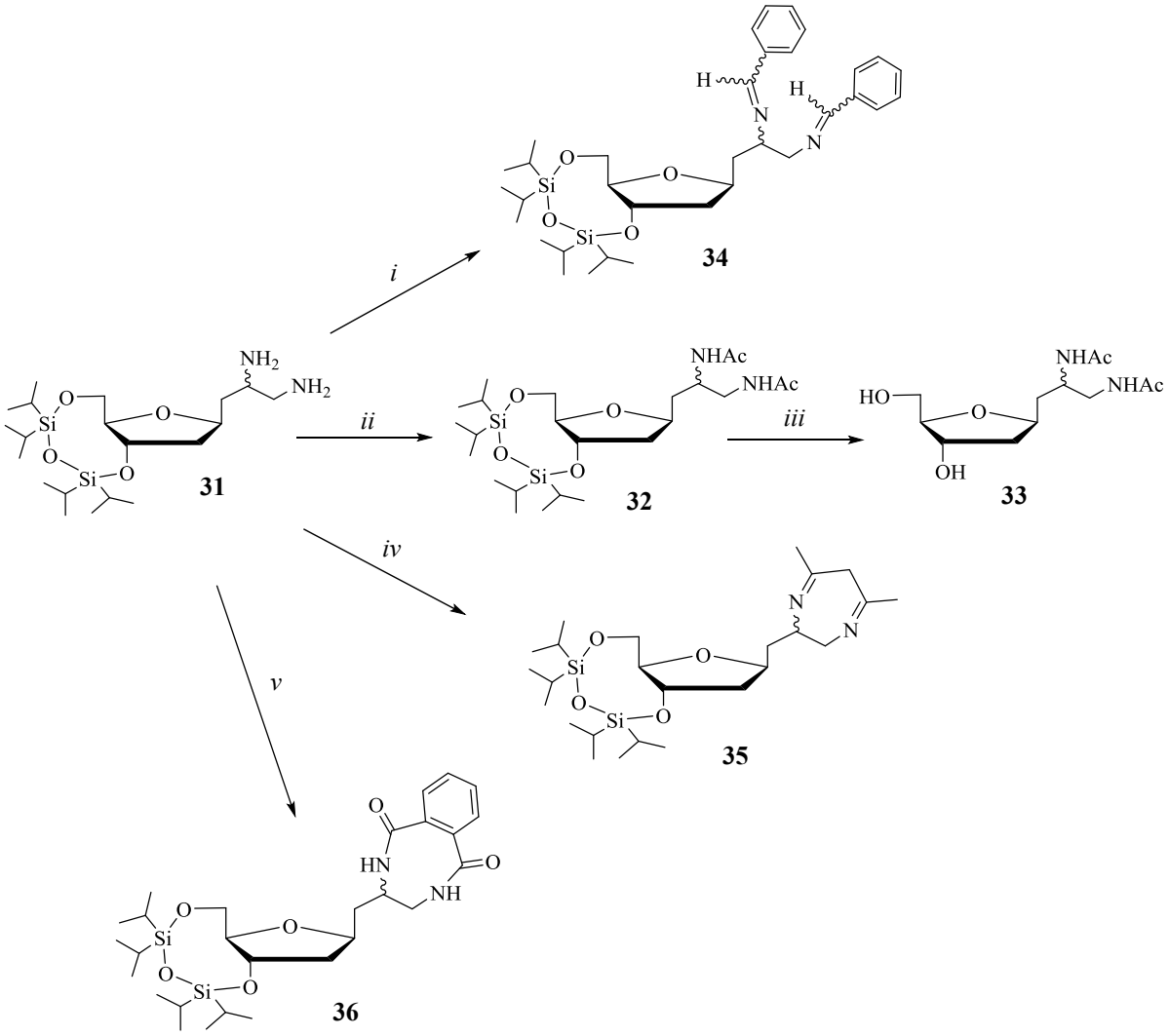


Figure 8. IR spectra of the diazido compound 29.

For the reduction of an azido group to the corresponding amine, various variants are known. A principal method is to use a catalyst such as platinum compounds[63] or palladium on carbon[64] in the presence of hydrogen. The platinum compounds could also cause the cleavage of the silyl protecting group due to the high reactivity, which is undesirable in this case because the silyl group is intended to prevent interfering interactions with the hydroxy groups during the coordinative bonding with the platinum. Therefore, reduction of the diazido groups to amines with Pd/C was pursued. The reaction was carried out according to the classical procedure for the reduction with Pd/C [64] The diamino product **31** was extensively analyzed. In addition, elemental analysis confirmed the decrease in the percentage content of nitrogen from the azide to the amine.We have also studied the transfer of an azido group into an amine via Staudinger reaction. Unexpectedly, the desired diamine product **31** was contaminated with dimers of itself. Changes in the reaction conditions did not suppress dimerisation. We suggest that the formation of dimers could be explained with the 4-membered-ring transition state,[65], [66] which in our case most probably occurs intermolecularly.

As a chemical verification for the diamino compound **31** (**Scheme 17**), it was acetylized to give the less polar compound **32**. The ^{1}H NMR showed two additional singlets of acetyl groups at 1.95 ppm and 1.97 ppm together with the two peaks of N*H*Ac. Regarding the X-ray analysis, until now, we could not achieve any crystalline products. On that account, the cleavage of silyl group was studied to give compound **33**, unfortunately, as a colorless syrup.

Nevertheless, compound **33** represent a great opportunity for the protection of positions C-3' and C-5' with subsequent protecting groups.



i: Benzaldehyde, molecular sieve powder, dry methanol, 36 h, rt; ii: Ac_2O, dry pyridine, 15 h, rt; iii: TBAF, dry acetone, 1.5 h, rt; iv: Acetylacetone, dry ethanol, 24 h, rt; v: Phthaloyl chloride, dry pyridine, 5 d, rt.

Scheme 17. The subsequent reactions of the diamine compound 31.

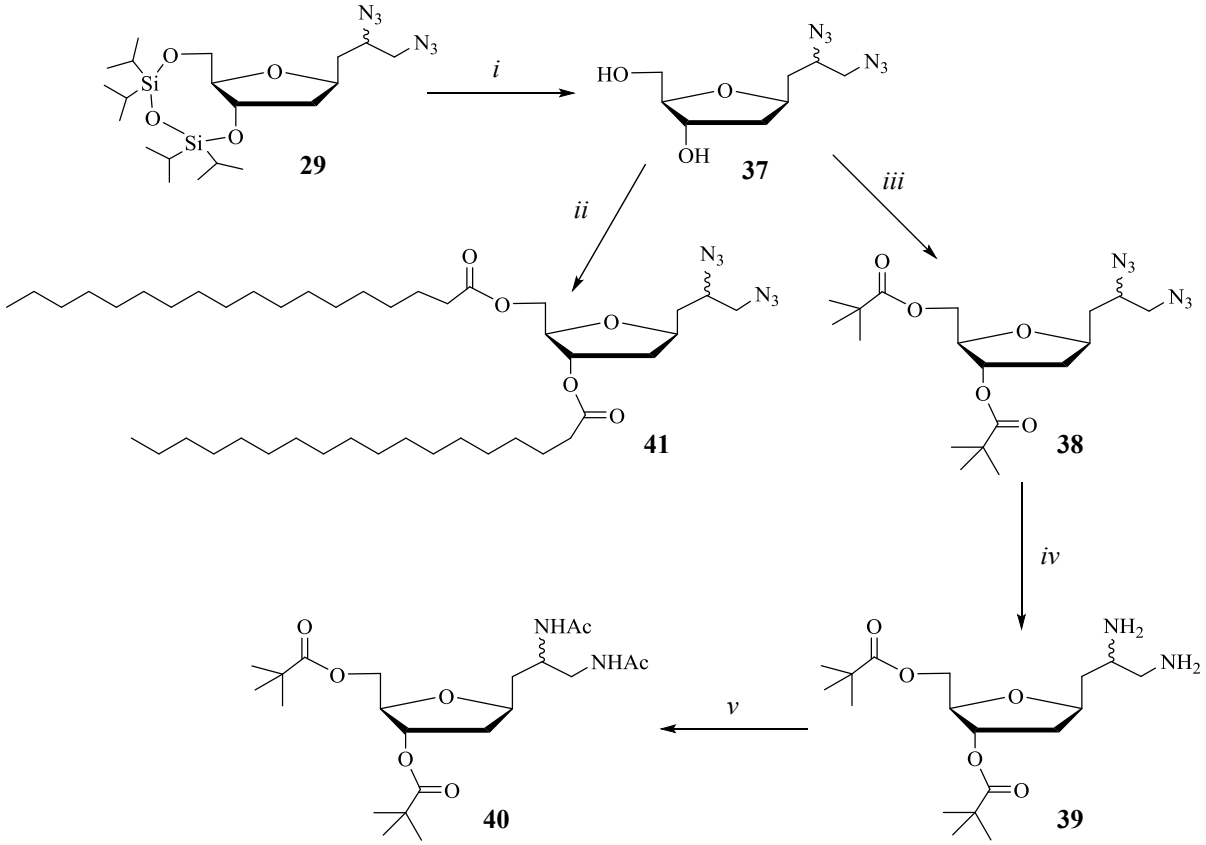
The identity of diamino compound **31** was further verified via transformation into diamino compound **34**. This chemical reaction was carried out with benzaldehyde, molecular sieve powder in dry methanol to give diimino compound **34** as a brown-yellow syrup in a very good yield. In NMR, ten protons of phenyl and three peaks of NC*H* (diastereomeric C-2 protons of the side chain are splitted) were found. Furthermore, we investigated the building of cyclic species. Amines are known to react readily as nucleophiles with halide compounds and carboxylic derivatives as well as undergo condensation reactions with aldehydes and ketones, giving imines. Considering the stability of the ring and the velocity of reaction, 5- to 8-membered rings were the optimum. Therefore, species, which contained one to four

carbon atoms, were possible for our purpose. As a one-carbon compound, formic acid was appropriate. Unfortunately, the treatment of diamine compound **31** with formic acid in triethyl orthoformate for 4 h at 100 °C [67] led to the formation of side products, so that desired compound could not be purified for further analysis. As two-carbon chain compounds, oxaldehyde [68], oxalyl chloride and oxalic acid were tested but all with unsatisfactory results. The chain with three carbon atoms provided the first positive result. Therefore compound **31** was treated with acetylacetone in dry ethanol and the reaction mixture was stirred for 24 h at ambient temperature to give compound **35** as a brown syrup. In ^{1}H NMR both methyl groups and CH_2 of the acetylacetone chain was found. The ^{1}H, ^{13}C NMR correlation spectra (HMBC) showed the correlation between C-1 of the side chain and CH_2 of the acetylacetone. Interestingly, the correlation between diastereomeric C-2 of the side chain and CH_2 of the acetylacetone in HMBC was not observed, most probably, the weak signal of one diastereomeric proton was not detectable above the base line noise. Moreover, we assume that the probable dynamic effects of the new cyclic diimine structure could also have an effect on the correlation intensity in NMR. Ensuing, we want to verify if this effect takes place on the other cyclic species. Considering that, the reaction of diamine **31** with diethyl malonate, the other 3 carbon atoms species, was tested. Perfectly, the reaction of diamine with diethyl malonate in dry ethanol is supposed to be byproduct-free, because the ethanol is the only byproduct of the reaction and acts simultaneously as a solvent. But the lactam-lactim tautomerie of the isolated product was very vigorous, causing very wide signals in the ^{1}H NMR, which could not be analyzed or allocated. Finally, we have tested the cyclization of diamine **31** with phthaloyl chloride. This reagent, contributing with 4 carbon atoms to the ring, has also a potentially stabilizing phenyl moiety between both lactams. Reagent **31** was treated with phthaloyl chloride in dry pyridine to give compound **36** as a brown syrup. As we have predicted, the phenyl moiety stabilized the ring, so that characterization of the product was successfully achieved. The ^{1}H and ^{13}C NMR exhibited the typical phenyl signals. Supportively, ^{1}H, ^{13}C NMR correlation spectra (HMBC) showed the correlation between C-1 of the side chain and phenyl. Here, the correlation of C-2 of the side chain and phenyl was also not observed, supporting our presumption mentioned previously. Retrospectively, we could say, that two amines are included in diamine compound **31** and are available for the further reactions.

2.2.6 Synthesis of ethylenediamine derivates with pivaloyl protecting groups

After the verification of the diamino structure, we studied the removal of the silyl group and further introduction of other protecting groups on the C-3' and C-5' positions of the pseudosugar ring (**Scheme 18**). Because of the high polarity of the diamino compound, the cleavage of the silyl group occurred according to the standard procedure with TBAF starting with diazo compound **29**. The reaction mixture was stirred for 2 h to give unprotected diazo compound **37** as a light-yellow syrup in a very good yield. In the ^{1}H NMR no signal from the

silyl group was observed, additionally elemental analysis confirmed the calculated amount of nitrogen.



i: TBAF, dry acetone, 2 h, rt; ii: Stearoyl chloride, DMAP, dry pyridine, 2 h, rt; iii: Pivaloyl chloride, DMAP, dry pyridine, 2.5 h, rt; iv: Pd/C, dry methanol, 24 h, rt, H_2; v: Ac_2O, dry pyridine, 15 h, rt.

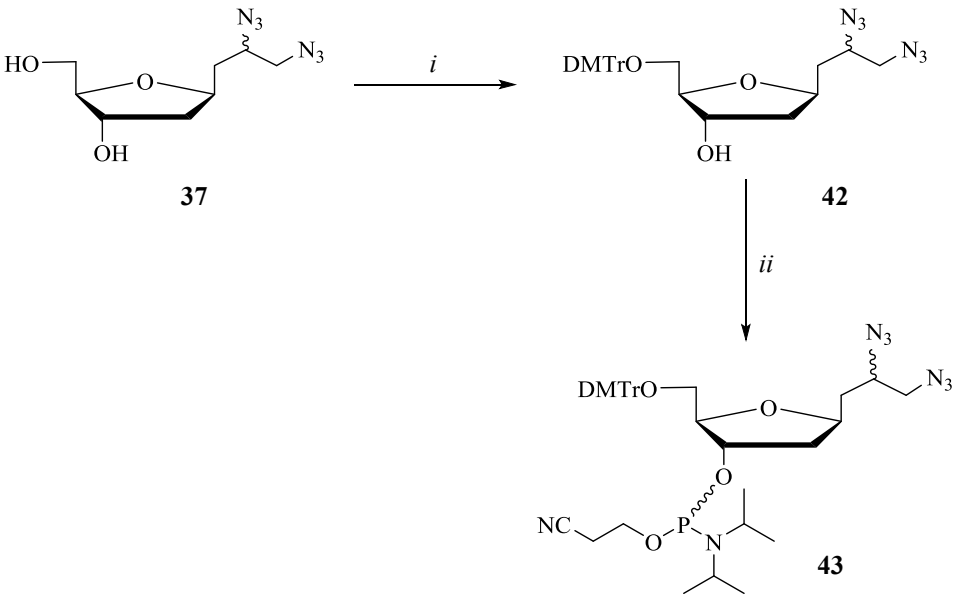
Scheme 18. Synthesis of the compounds with pivaloyl and stearoyl groups.

The protection of hydroxyl groups on C-3' and C-5'with the benzoyl group was also studied. NMR spectra showed residues of benzoyl chloride together with the desired product. Hence, the insertion of pivaloyl groups brought satisfactory results. For the reaction of diol **37** with pivaloyl chloride, similar reaction conditions were used. Here, addition of the 4-(dimethylamino)pyridine (DMAP) also led to an increase of the reaction rate giving the desired protected product **38** after 2.5 h. The subsequent reduction of diazo compound **38** to diamine **39** was achieved via reduction using palladium on carbon. The diamino compound **39** was confirmed analytically. Nevertheless, acetylation leading to diamide **40** was accomplished. Beside the protons of the pivaloyl groups in ^{1}H NMR the signals for the acetyl groups were found, giving the multiplet together with protons on C-3 and C-2'. Supportively, the ^{1}H, ^{13}C NMR correlation spectra (HMBC) showed unambiguously that the positions C-3' and C-5' of the pseudo-sugar ring are protected with pivaloyl moieties. Further, the stearoyl chloride, derivative of stearic acid (18:0) one of the most common saturated fatty acids found in nature, was also studied as a structural element and further building block of the biomembrane.

The reaction of **37** with stearoyl chloride and DMAP in dry pyridine achieved the formation of diazo compound **41** with two stearoyl groups on C-3' and C-5'. The white amorphous solid was exhaustively characterized. Unfortunately, further reduction of the diazo groups was not successful. The classical solvent (methanol) for reduction with Pd/C did not completely dissolve the starting compound **41**. To dissolve the substrat some amount of chloroform was needed, causing difficulties to remove Pd/C by filtration.

2.2.7 Synthesis of 2-deoxy-D-ribofuranose derivates with phosphoramidite

In this chapter, the synthesis of a phosphoramidite derivative is presented. Starting with deprotected derivative **37**, suitable building blocks for use in automated oligonucleotide synthesis were achieved (**Scheme 19**).



i: DMTrCl, DMAP, dry DMF, 24 h, rt; ii: 2-cyanoethyl N,N-diisopropylchlorophosphoramidite, diisopropylethylamine, dry CH_2Cl_2, 3 h, rt.

Scheme 19. Synthesis of the phosphoramidite derivative.

To achieve the building blocks for the use in automated oligonucleotide synthesis, the 5'-hydroxyl group should be temporary protected to avoid undesired by-products. The following introduction of the phosphoramidite group to the 3'-position gives the desired building blocks for the solid phase synthesis. The 4,4'-dimethoxytrityl group (DMTr or DMT) was established as a standard for the protection of 5'-position. Advantageously, DMTr is removable under mild acidic conditions and the measurement of absorption in the range of 498 nm according to the DMTr cation gave indirect response about the yield of the solid phase synthesis. [69], [70] The reaction with 4,4'-dimethoxytrityl is well known. Therefore, alcohol **37** was treated with 4,4'-dimethoxytrityl chloride, DMAP and triethylamine in dry DMF.[71] The reaction mixture was stirred for 24 h at ambient temperature to give **42** as a yellow syrup

in a good yield. In ^{1}H and ^{13}C NMR spectra, the typical signals of the 4,4'-dimethoxytrityl group together with the hydroxyl group on C-3' position were observed. Additionally, the ^{1}H, ^{13}C NMR correlation spectra (HMBC) showed the correlation between the 5'-position and the 4,4'-dimethoxytrityl group. Together with further spectra, everything points to the given structure **42**. Reporting the activity of modified dinucleotides against an enzyme produced by a retrovirus (such as HIV), *Y. Aubert et al.* published the classical procedure for the introduction of phosphoramidites.[72] We used Aubert's approach to synthesize phosphoramidite derivative **43**. Compound **42** was dried by co-evaporation with dry pyridine and left under vacuum overnight. Using commercially available phosphitilating reagent 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite, the reaction was found to occur after stirring the mixture of the phosphitilating reagent, compound **42** and diisopropylethylamine in dry CH_2Cl_2. The 1% v/v of the triethylamine was added to the eluent by the flash chromatography to protect the 4,4'-dimethoxytrityl group from the cleavage via slight acidic silica gel. Product **43** was obtained as a mixture of diastereomers in a yield of 60% as a yellow syrup. All analytic data confirm the structure **43**. In ^{1}H and ^{13}C NMR spectra the new signals for the cyanoethyl and diisopropyl group were observed. Using COSY, HSQC and HMBC experiments all signals could be assigned. The elemental analysis and HRMS were in accordance with expected values. Both isomers could be used without separation in the oligonucleotide solid phase synthesis. The stereochemical information at the phosphorus atom is lost by the oxidation of the coupled nucleosides to phosphatesters. Hence, tedious separation of the diastereomers can be omitted.

2.3 Research application

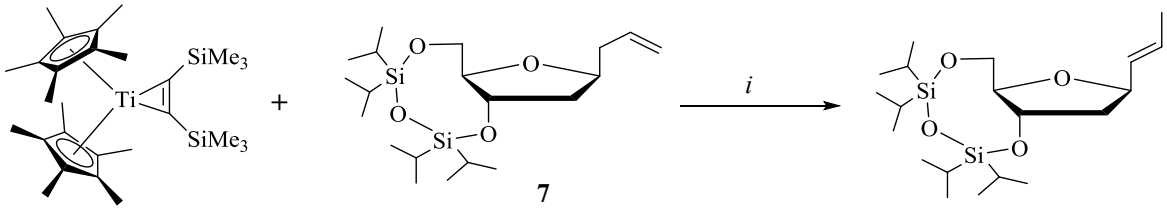
The purpose of this work was to synthesize potential intermediates for antiviral and antitumor reagents. Therefore, we want to test some compounds for it's further application as potential biologic active reagents.

2.3.1 Reaction of the β-allyl-*C*-glucoside of the 2-desoxy-D-ribofuranose with titanocene

Exo-glycals are important intermediates in natural product synthesis and could be conjugated into the spiro-compound, having one carbon atom as a part of the glucose scaffold and simultaneously as a part of the heterocycle. For example, the microwave irradiation assisted 1,3-dipolar cycloaddition of *exo*-glucals with aryl nitrones was found to be stereoselective for the synthesis of the spiro-isoxazolidine glycosides by *X. Li et al*. Furthermore, the spiro-isoxazolidine glycosides were found to have an inhibitor activity against α-Amylase, α- and

β-Glucosidase, and even antitumor activity against Hela cell lines[4].[73] The deprotected spiro-isoxalines were evaluated as inhibitors of muscle glycogen phosphorylase b (GPb), acting as a potential agent in improving glycemic control in type 2 diabetes.[74] Besides the excellent biological activity as an enzyme inhibitor, the synthesis of the *exo*-glucals is sophisticated, requiring rough reaction conditions and multiple steps procedure.[75] Nevertheless, the *exo*-glucals can be also obtained via a iridium(I) catalysed stereoselective isomerisation reaction of the *C*-allyl glycosides giving *(E)*-*C*-vinyl glycosides and *(Z)*-*exo*-glycals.[76] Subsequently, the olefin isomerisation reactions to the *(E)*- and *(Z)*-products via metal catalysts like iron [77], cobalt [78], nickel [79], rhodium [80], ruthenium [81], palladium [82], [83] and iridium [84] are known. There are also numerous titanocene compounds known as a catalysts for the isomerisation of olefins.[85]

Here, we chose to examine the reaction of β-*C*-allylglucoside of the 2-desoxy-D-ribofuranose **7** with titanocene species. This work was done in cooperation with Leibniz Institute for Catalysis by Dr. Melanie Reiß.[5] The β-*C*-allylglucoside **7** was treated with equimolar amount of titanocene in dry toluene and the reaction mixture was stirred for 4 d at 60 °C. After aqueous work up the tinane species was separated via flash chromatography with 1:1 EtOAc/*n*-Hexane eluent. The NMR spectra carried out at a 500 MHz device confirming the structure in **Scheme 20**. Unfortunately, the titanocene was found to isomerize the allyl group selectively giving just the *(E)*-*C*-vinyl glycosides and no reaction to the *(Z)*-*exo*-glycals was observed.



i: dry toluene, 4 d, 60 °C.

Scheme 20. Reaction of the β-C-allylglucoside with titanocene.

However, it is still unclear if the titanocene has acted as a promoter or the reaction proceeded catalytically. Nevertheless, the *(E)*-*C*-vinyl glycosides could be further developed into the diamine species with shorter carbon chain or even into heterocycles. In this way, advanced potential antiviral and antitumor intermediates of the glycosides could be obtained.

[4] The human cervical cancer cells

[5] Leibniz Institute for Catalysis, Albert-Einstein-Str. 29a, 18059 Rostock, Germany

2.3.2 Reaction of the diamine of the 2-deoxy-D-ribofuranose with K_2PtCl_4

Beside the interest in new metal ions for cancer chemotherapy, platinum based drugs, especially cisplatin (*cis*-$Pt(NH_3)_2Cl_2$), are still the most used. The design of cisplatin analogues plays the key role to find more potent antitumor drugs with the same efficiency, simultaneously, to overcome the disadvantages of clinically used platinum based drugs. Therefore, we have tested some of the compounds to investigate their reactivity with platinum. For this purpose, the four 2-deoxy-D-ribofuranose diamine compounds, showing in **Figure 9**, were studied.

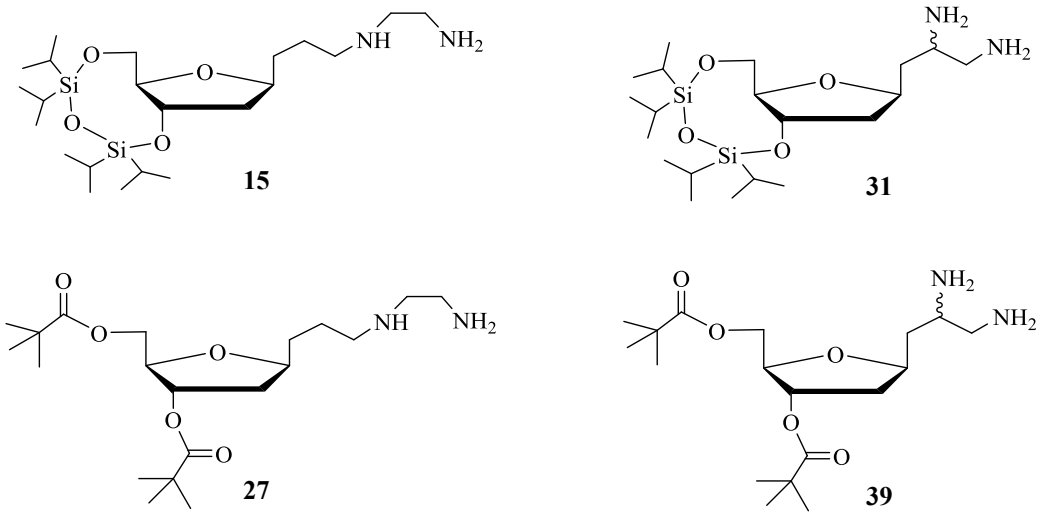
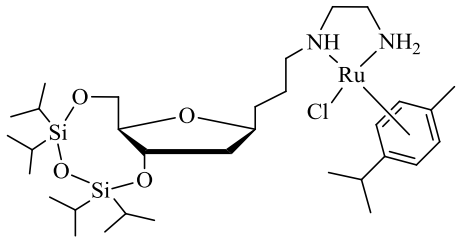


Figure 9. The diamine compounds for platinum complexes.

The preliminary experiments were accomplished by the working group of Prof. Dr. Wolfram Seidel.[6] It was investigated whether the coupling of the carbohydrate ligand **15** with the metals was possible. The ruthenium-sugar complex starting from compound **15** was successfully obtained (**Figure 10**). Moreover, the similar *cis*-ruthenium complexes but without a monosaccharide unit are known from the literature and have been characterized as highly soluble in water and effective against various types of tumors.[86]



***cis*-ruthenium-carbohydrate complex with compound 15.**

Figure 10. The ruthenium-sugar complex.

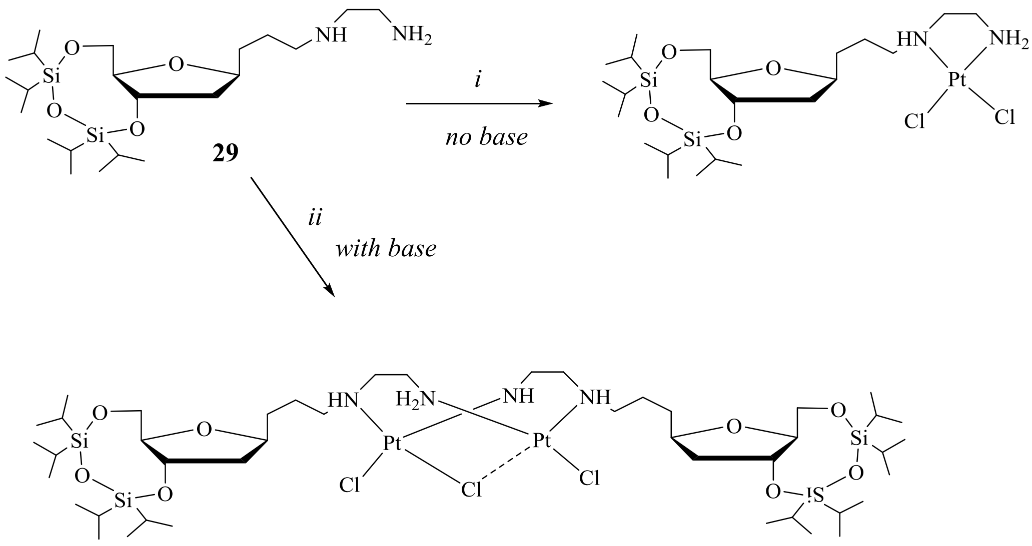
[6] University of Rostock, department of anorganic chemistry, Albert-Einstein-Straße 3a, 18059 Rostock, Germany

Further, we have investigated the synthesis of the complexes with platinum. There are a few approachs to synthesize the platinum complexes, to differ in starting platinum compounds and the reaction conditions. *Gianini et al.* have prepared the platinum complexes starting with $Pt(SEt_2)_2Cl_2$ in THF as a solvent for 1.5 h at -70 °C → 0 °C in a "Schlenk" flask under argon.[87] *Hanessian et al.* have reported the coordination of K_2PtCl_4 in aqueous solution setting for 2 h at the ambient temperature.[64] The same reaction conditions were also known from *Mikata et al.* In his work, the eight carbohydrate-pendant platinum(II) complexes, containing the unprotected pyranose derivatives of D-/L-glucose, D-mannose, D-galactose and D-xylose were prepared. The sugar containing platinum(II) complexes have promising anticancer activity and reduced the toxicity inherent with platinum(II) complexes.[88] The other glucose containing platinum(II)- Schiff base complexes were published by *Cucciolito et al.* These platinum(II) complexes were obtained from $PtCl_2(DMSO)_2$ in dioxane for 0.5 h at 25 °C.[57] In our case, the starting diamine were well soluble in methanol, so the method of *Palmer et al.* was found to be the best course of action. Here, the synthesis of platinum(II) complexes was proceeded with K_2PtCl_4 and $NaHCO_3$ in methanol/water at ambient temperature for 2.5 h. The further stirring of the reaction mixture with 5% aqueous KCl has associated the precipitation of the desired complexes.[89] We used slightly a varied Palmer's approach to prepare the platinum(II) complexes.

For the synthesis of the platinum(II) complexes, the four 2-deoxy-D-ribofuranose diamine compounds **15**, **27**, **31** and **39** were dissolved in water/methanol 1.5:1 and treated with equimolar amounts of K_2PtCl_4 and 1.5 eq $NaHCO_3$ dissolved in a small amount of water. After stirring for 3 h at room temperature in the dark, aq 5% KCl solution was added and the reaction mixture was stirred for further 2.5 h at ambient temperature. After that, the yellow precipitant was filtered and washed twice with water. The product was obtained as a yellow powder. A variety of crystallisation procedures were examined. Unfortunately, no crystals could be isolated.

The NMR showed a slight shift of protons close to platinum. The ^{195}Pt NMR showed no sharp signal for platinum, but a very broad signal was found in the expected shift region. However, electrospray ionization ion trap mass spectrometry (ESI-ITMS) unveiled an unexpected result.

We have found, that the usage of $NaHCO_3$ led to the desired platinum(II) complexes, but in the form of dimers (**Scheme 21**). The reaction without $NaHCO_3$ produced only the monomeric complex. Interestingly, this phenomenon was applicable only while using sugar as a ligand. Experiments with phenylenediamine produced monomeric complexes in both cases, with base and without base, under the same reaction conditions. Due to the amorphous nature of the complex, X-ray analysis was not possible. Hence, the exact structure of the dimer could not be determined.



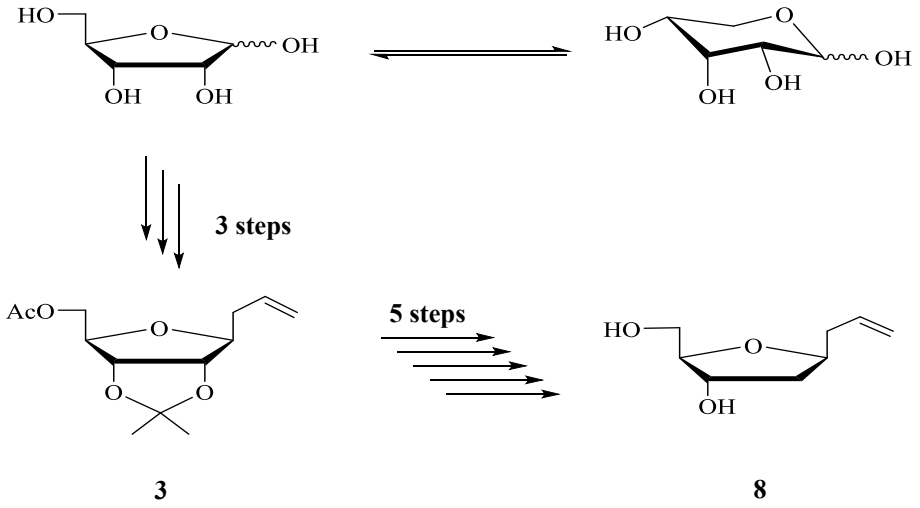
i:1) K_2PtCl_4, 3 h, rt, 2) aq 5% KCl, 2.5 h, rt; ii: 1) K_2PtCl_4, $NaHCO_3$, 3 h, rt, 2) aq 5% KCl, 2.5 h, rt.

Scheme 21. Synthesis and proposed structure of the platinum(II) glucoside complexes.

3 Summary

The aim of this work was to achieve potential intermediates for antiviral and antitumor agents. Hence, we focused on the development of the 2-deoxy-D-ribofuranose analogues with diamine moieties that should be able to form metal complexes similar to cisplatin.

In the first part, a β-allyl-*C*-glycoside was prepared. Starting with the D-ribofuranose via 2-deoxy-D-ribofuranose using the allyl group on the furan ring as a spacer unit for attachment of the ethylenediamine group. First, the D-ribose was fixed by an isopropylidene protecting group on carbon atoms C-2' and C-3' in their furanose form in a yield of 87% (**1a**), whereby the formation of the protected pyranose as byproduct was resulted (**1b**). Next, the acetylation of the free hydroxyl groups was performed in a yield of 95% (**2**). The subsequent introduction of the allyl group having a double bond at the terminal end was targeted at the anomeric center of the furan ring (**3**). Due to the steric hindrance of the α-side by a methyl group of the isopropylidene protecting group, the introduction of the allyl group in the desired β-position was achieved in a yield of 78%. We have succeeded in carrying out the removal of all protecting groups to form compound **4** in a yield of 85%. The optimized reaction conditions of the silylation resulted in a fixation of the 3'- and 5'-positions of the furane ring (**5**). The remaining free hydroxyl group of compound **5** was reductively removed after exchange with iodine (**6**). Thus, the 2-deoxy-D-ribofuranose derivative **7** was obtained in a yield of 89%. The cleavage of the silyl group led to the unprotected β-allyl-*C*-glycoside of the 2-deoxy-D-ribofuranose (**8**). The complete reaction pathway of compounds **1**-**8** was verified and the total yield was markedly improved by 54% (**Scheme 22**).



Scheme 22. Synthesis of the unprotected 2-deoxy-D-ribofuranose derivative 8 via important intermediate 3.

Then, starting from compound **7**, two different methods were developed to get differently long spacer chains of the *C*-glycoside. The first variant involved oxidative hydroboration **9**, subsequent mesylation rendered **10** as a substrate for the formation of ethylenediamine **15**.

Moreover, the further reaction of the mesylated compound **10** with subsequent nucleophiles gained products **11**-**14**. Mesylate **10** was further converted into azide **17**, which was verified by transformation into triazole **18.** A following reduction of azide **17** gave the primary amine **19**. The subsequent reaction of primary amine **19** to imines **20** and **21** confirmed its proposed structure. Diamine **15** was tested, for the introduction of further protecting groups on the C-3' and C-5' positions of the furane ring. Due to the lability of the mesyl group upon treatment with TBAF, another synthetic pathway was developed. Here, the primary alcohol **9** was converted into acetate **22**, which was successfully deprotected, giving diol **23**. Following allocation of the 3'- and 5'-positions of the furane ring gave pivalate **24**. Acidic transesterification gave alcohol **25**, which upon mesylation gave compound **26**. Nucleophilic substitution of the mesylate gave diamino compound **27** in a yield of 80%.

The second pathway starting from compound **7** involves bromination of the allyl double bond, giving dibromide **28**. Nucleophilic substitution with NaN_3 led to diazide **29**. A subsequent reduction gave diamine **31**. Through this route, the other target substance bearing a diamine moiety **31** was obtained in a yield of 93%. The diamine structure (**31**) was confirmed via acetylation to the corresponding amide **32**, conversion into diimine **34**, as well as cyclisation of the diamine giving **35** and **36**. Starting with diazido compound **29**, the silyl group was cleaved via TBAF, gave diol **37**. Introduction of pivaloyl groups on the 3'- and 5'-positions (**38**) and a following reduction gave diamine **39** in a yield of 90%. The unprotected diazido compound **37** was found to be optimal for the introduction of further protecting groups, like stearoyl (product **41**) or even the DMTr (product **42**) together with phosphoramidite derivative **43**, achieving the potential building blocks for the automated oligonucleotide synthesis.

Thus, we have succeeded in obtaining several 2-deoxy-D-ribofuranose derivatives with an ethylenediamine group on a spacer with one or three carbon atoms to the sugar moiety (**Figure 11**).

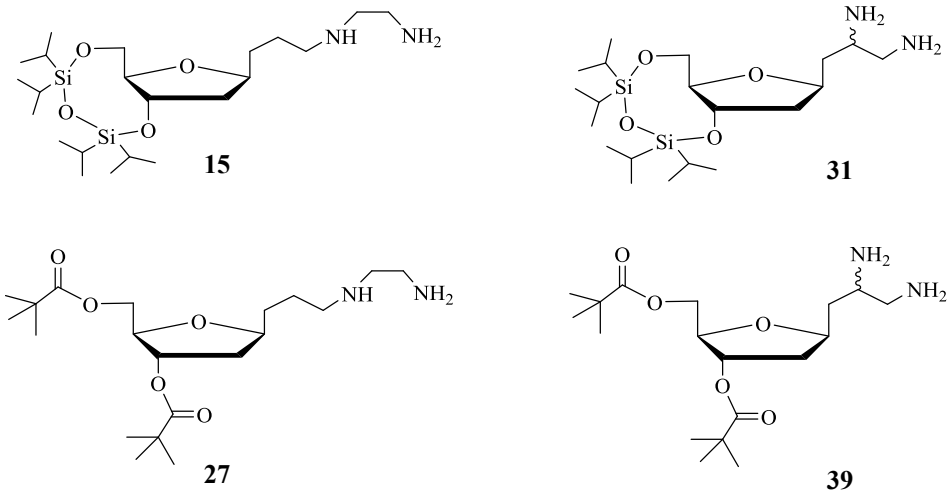


Figure 11. Several 2-deoxy-d-ribofuranose derivatives with an ethylenediamine group.

Subsequently, in cooperation with the working group of Prof. W. Seidel, it was investigated whether coordination of sugar ligand **15** to a metal, was possible. And indeed, a ruthenium-sugar complex was successfully prepared (**Figure 10**).

Considering the cooperation with Dr. Melanie Reiß from the Leibniz Institute for Catalysis, we could mention, that the use of carbohydrate-based species, as well as carbohydrate-based diamine complexes does not only have to be limited to medical aspects. It provides a previously unexplored field of investigation in catalysis (for example as a catalysts for direct aldol reactions [90] or as catalyst for non-enzymatic hydrolysis of RNA [91]), for the synthesis of molecular recognition structures,[92] and as a functional group in the synthesis of macrocycles [92], [93] and polymers [94].

4 Experimental Section

4.1 General

4.1.1 Reagents and materials

All solvents and reagents were purified and dried according to standard procedures [95].

Washing solutions used here, like saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl solution, saturated aqueous $Na_2S_2O_3$ solution and 15% aqueous $NaHSO_4$ solution, were cooled to~4 °C.

Thin-layer chromatography (TLC) to monitor the reactions were performed using silica gel on aluminum foil (silica gel 60, F_{254}, layer thickness 0.2 mm, MERCK). The detection of products with amino groups was pursued by UV-absorption on 254 nm and by charring with ethanolic 10% H_2SO_4 solution. For other compounds the detection was pursued by UV-absorption on 254 nm and by charring with a mixture of ethanol, concentrated H_2SO_4 and 3-methoxyphenol (1000:10:1 v/v). The colors may range from deep violet to light pink or brown, even greenish, blueish or greyish spots were observed.

Flash chromatography was performed on slurry-packed silica gel 60 (63-200 µm, MERCK). The solvent systems are described in the experimental section for each compound separately. The mixing ratios of the solvent systems are volume ratios. The eluents were distilled before their use. Petroleum ether was used as a 60 °C – 80 °C fraction.

Solutions in organic solvents were dried over $MgSO_4$ and concentrated under reduced pressure (rotary evaporator).

4.1.2 Analytics

Melting points were determined with a Boetius micro-heating plate BHMK 05 (Rapido, Dresden) and were not corrected. Optical rotation was measured with a digital polarimeter GYROMAT (Dr. Kernchen GmbH) for solutions in dry $CHCl_3$, dry CH_2Cl_2 and dry methanol using a 2 cm cuvette.

^1H NMR spectra (250.13, 300.13 and 500.13 MHz) and ^{13}C NMR spectra (62.89, 75.47 and 125.76 MHz) were recorded on BRUKER AC 250, ARX 300 and AVANCE 500. The calibration of spectra was carried out on solvent signals ($CDCl_3$: δ ^1H = 7.27 ppm, δ ^{13}C = 77.00 ppm; MeOH-d_4: δ ^1H = 3.31 ppm, δ ^{13}C = 49.15 ppm). The following abbreviations were applied characterizing the signal splitting: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublet, t = triplet, q= quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet. The ^1H and ^{13}C NMR signals were assigned by distortionless enhancement by polarization transfer (DEPT), two-dimensional ^1H, ^1H homonuclear

correlation spectroscopy (COSY), nuclear overhauser enhancement and exchange spectroscopy (NOESY), ^{1}H, ^{13}C correlation spectra (HMBC) and heteronuclear single quantum coherence (HSQC).

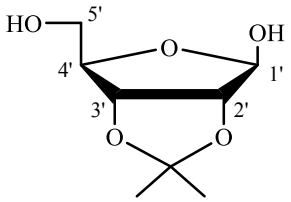
Elemental analysis was recorded on a CHNS Flash EA 1112 (Thermoquest)**.** The mass spectra were performed on an AMD 402/3 spectrometer (AMD Intectra GmbH) and the HR-MS (ESI) analysis, on a LTQ Thermo Finnigan spectrometer.

4.2 Synthesis of the multistep compounds

4.2.1 Introduction of the isopropylidene protecting group

Concentrated sulphuric acid (0.34 ml) was added dropwise to a vigorously stirred suspension of D-ribose (15.0 g, 100 mmol) in dry acetone (150 ml). After stirring for 2 h at ambient temperature (monitored by TLC in petroleum ether – EtOAc 1:2 with 1% NEt_3), the clear light-yellow solution was cautiously neutralized (ice bath) by addition of solid calcium hydroxide. After filtration using a glass sintered-filter funnel equipped with a layer of silica gel, the solids were washed with acetone (3 × 30 ml) and the combined filtrates were concentrated. Chromatography (petroleum ether – EtOAc 1:2 with 1% NEt_3) gave first 1,2:3,4-di-*O*-isopropylidene-α-D-ribopyranose (**1b**). Eluated next was the desired compound 2,3-*O*-Isopropylidene-β-D-ribofuranose (**1a**).

4.2.1.1 ((3a*R*,4*R*,6*S*,6a*R*)-6-acetoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl acetate (1a)



Yield: 16.5 g (87%), light-yellow syrup

$[\alpha]_D^{24}$: –24.5 (*c* 1.0, $CHCl_3$)

R*f*: 0.37 (PE:EtOAc 1:2 with 1% NEt_3)

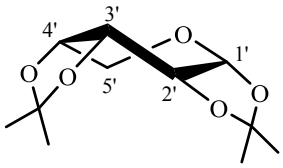
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.33, 1.49 [2 x s, 6H, 2 x $C(CH_3)_2$], 3.62–3.79 (m, 3H, H-5', OH), 4.40–4.42 (m, 1H, H-4'), 4.58 (d, 1H, $^{3}J_{2',3'}$ = 6.0 Hz, H-2'), 4.83 (dd, 1H, $^{3}J_{2',3'}$ = 5.9 Hz, $^{3}J_{3',4'}$ = 1.0 Hz, H-3'), 5.03 (br s, 1H, OH), 5.41 (s, 1H, H-1').

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 24.74, 26.38 [2 x C(CH_3)$_2$], 63.62 (C-5'), 81.63(C-3'), 86.77 (C-2'), 87.72 (C-4'), 102.91 (C-1'), 112.10 [C(CH_3)$_2$].

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_8H_{14}O_5$ $[M+Na]^+$: 213.07334, found 213.07329.

$C_8H_{14}O_5$ (190.19)	calcd:	C 50.52	H 7.42
	found:	C 50.31	H 7.41

4.2.1.2 (3a*R*,5a*R*,8a*R*)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran (1b)



Yield: 99.7 mg (0.4%), colorless crystals

$[\alpha]_D^{24}$: –39.4 (*c* 1.0, $CHCl_3$)

mp: 63–64 °C

R_f: 0.32 (PE:EtOAc 2:1 with 1% NEt_3)

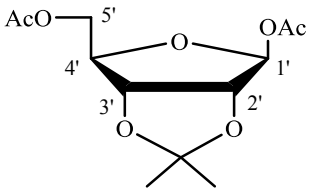
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.35, 1.38, 1.55, 1.60 [4 x s, 12H, 2 x C(CH_3)$_2$], 3.81–3.89, 4.01 (m, 2H, H-5'), 4.25 (m, 1H, H-3'), 4.41–4.52 (m, 2H, H-2', H-4'), 5.44 (d, 1H, $^3J_{1,2}$ = 2.5 Hz, H-1').

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 25.02, 25.28, 26.09, 26.36 [2 x C(CH_3)$_2$], 61.24 (C-5'), 69.60, 72.04, 72.06 (C-2', C-3', C-4'), 96.49 (C-1'), 109.45, 110.84 [2 x C(CH_3)$_2$].

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{11}H_{18}O_5$ $[M+Na]^+$: 253.10464, found 253.10463

$C_{11}H_{18}O_5$ (230.26)	calcd:	C 57.38	H 7.88
	found:	C 57.36	H 7.97

4.2.2 ((3a*R*,4*R*,6*S*,6a*R*)-6-acetoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl acetate (2)



Freshly distilled Ac_2O (15 ml) was added (dropwise at 0 °C) to a vigorously stirred solution of **1a** (5.0 g, 26 mmol) in dry pyridine (30 ml). The mixture was allowed to attain ambient temperature and stirring was continued overnight. TLC (petroleum ether – EtOAc 2:1 with 1% NEt_3) showed then that the reaction was complete. Excess of Ac_2O was then destroyed by addition of methanol (10 ml) at 0 °C and stirring was continued for additional 30 min. The mixture was poured into iced water and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic phases were successively washed with aq 15% $NaHSO_4$ (3 × 50 ml), ice water (70 ml), and sat aq $NaHCO_3$ solution (2 × 50 ml), then dried and concentrated. Chromatography (petroleum ether – EtOAc 2:1 with 1% NEt_3) gave the compound **2**.

Yield: 6.7 g (93%), colorless syrup

$[\alpha]_D^{23}$: –61.0 (*c* 1.0, $CHCl_3$)

R_f: 0.30 (PE:EtOAc 2:1 with 1% NEt_3)

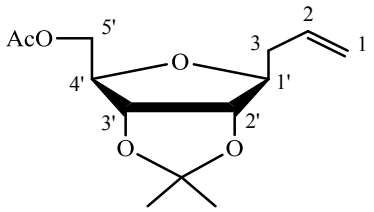
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.34, 1.50 [2 x s, 6H, C(C*H*$_3$)$_2$], 2.06, 2.09 (2 x s, 6H, 2 x COC*H*$_3$), 4.12 (d, 1H, $^2J_{5'a,5b}$ = 2.6 Hz, H-5'a), 4.14 (d, 1H, $^2J_{5'a,5'b}$ = 2.6 Hz, H-5'b), 4.47 (dd, 1H, $^3J_{4',5a'}$ = 7.1 Hz, $^3J_{4',5b'}$ = 6.5 Hz, H-4'), 4.72 (s, 2H, H-2', H-3'), 6.22 (s, 1H, H-1').

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 20.76, 21.13 (2 x CO*C*H$_3$), 25.04, 26.41 [2 x C(*C*H$_3$)$_2$], 64.04 (C-5'), 81.54 (C-3'), 85.09 (C-2'), 85.33 (C-4'), 102.12 (C-1'), 113.22 (*C*(CH$_3$)$_2$), 169.24, 170.45 (2 x *C*OCH$_3$).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{12}H_{18}O_7$ $[M+Na]^+$: 297.09447, found 297.09478.

$C_{12}H_{18}O_7$ (274.27)	calcd:	C 52.55	H 6.62
	found:	C 52.41	H 6.45

4.2.3 ((3a*R*,4*R*,6*S*,6a*S*)-6-allyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl acetate (3)



$ZnBr_2$ (6.5 g, 29 mmol; fresh batch, avoid any contact with air and moisture!) was added to a stirred solution of **2** (3.0 g, 11 mmol) in dry freshly distilled $MeNO_2$ (50 ml; 4 h boiled over CaH_2 for drying) at 0 °C under argon atmosphere. Allyltrimethylsilane (8.3 ml, 52 mmol) was added during 30 min at 0 °C, and stirring was continued for additional 90 min at ambient temperature under argon atmosphere (monitored by TLC in petroleum ether – EtOAc 6:1 with 1% NEt_3). Sat aq $NaHCO_3$ (150 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 ml). To prevent an emulsion layer, both the ratio between the organic phase and water should be adhered, and vigorously shaking of the mixture must be avoided. The combined organic phases were dried and concentrated. Chromatography (petroleum ether – EtOAc 6:1 with 1% NEt_3) provided compound **3**.

Yield: 2.2 g (78%), colorless syrup

$[\alpha]_D^{22}$: +12.2 (*c* 1.0, $CHCl_3$)

R_f: 0.3 (PE:EtOAc 6:1 with 1% NEt_3)

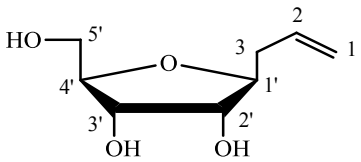
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.34, 1.50 [2 x s, 6H, C(CH_3)$_2$], 2.10 (s, 3H, COCH_3), 2.35–2.41 (m, 2H, H-3), 3.97–4.03 (m, 1H, H-1'), 4.08–4.14 (m, 2H, H-5'a, H-4'), 4.24–4.31 (m, 1H, H-5'b), 4.39 (dd, 1H, $^3J_{2',3'}$ = 6.9 Hz, $^3J_{1',2'}$ = 4.4 Hz, H-2'), 4.49 (dd, 1H, $^3J_{2',3'}$ = 6.9 Hz, $^3J_{3',4'}$ = 4.4 Hz, H-3'), 5.10–5.20 (m, 2H, H-1), 5.75– 5.91 (m, 1H, H-2).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 20.82 (CO*C*H$_3$), 25.50, 27.37 [2 x C(*C*H$_3$)$_2$], 37.74 (C-3), 64.36 (C-5'), 81.62 (C-4'), 81.90 (C-3'), 83.73 (C-1'), 83.89 (C-2'), 114.67 [*C*(CH$_3$)$_2$], 117.94 (C-1), 133.24 (C-2), 170.68 (*C*OCH$_3$).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{13}H_{20}O_5$ $[M+H]^+$: 257.13835, found 257.13851.

$C_{13}H_{20}O_5$ (256.29)	calcd:	C 60.92	H 7.87
	found:	C 60.72	H 7.65

4.2.4 (2*S*,3*R*,4*S*,5*R*)-2-allyl-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (4)



1.0 M aq HCl (19.3 ml) was added to a solution of **3** (8.0 g, 31 mmol) in ethanol (15 ml), and the mixture was stirred for 2 d at ambient temperature (monitored by TLC in petroleum ether – EtOAc 11:1). The mixture was neutralized with solid $NaHCO_3$, filtered, a small amount of silica gel (ca. 8 g, suitable for flash chromatography) was added, and the mixture was concentrated. Chromatography (EtOAc–MeOH 11:1) gave compound **4**.

Yield: 4.6 g (85%), amorphous solid

mp: 41–43 °C

R*f*: 0.36 (EtOAc:MeOH 11:1)

$[\alpha]_D^{22}$: –4.6 (*c* 1.0, MeOH)

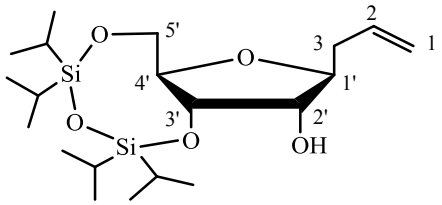
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.28–2.52 (m, 2H, H-3), 2.52–2.67 (m, 1H, OH-5'), 3.10–3.22 (m, 1H, OH-2'), 3.32–3.56 (m, 1H, OH-3'), 3.61–3.75 (m, 1H, H-5'a), 3.77– 3.91 (m, 4H, H-1', H-2', H-4', H-5'b), 4.00–4.06 (m, 1H, H-3'), 5.09–5.21 (m, 2H, H-1), 5.77–5.92 (m, 1H, H-2).

^{13}C NMR (62.90 MHz, $CDCl_3$): δ 37.57 (C-3), 62.53 (C-5'), 71.38 (C-3'), 74.25 (C-2'), 82.72 (C-1'), 83.34 (C-4'), 117.98 (C-1), 133.66 (C-2).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_8H_{14}O_4$ $[M+Na]^+$: 197.07843, found 197.07869.

$C_8H_{14}O_4$ (174.19)	ber.: C 55.16	H 8.10
	gef.: C 55.08	H 7.98

4.2.5 (6a*R*,8*S*,9*S*,9a*S*)-8-allyl-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-9-ol (5)



1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (2.4 ml, 7.4 mmol) and imidazole (2.1 g, 31 mmol) were added at 0 °C to a solution of **4** (1.2 g, 7 mmol) in dry DMF (17 ml). After stirring at 0 °C for 1 h (monitored by TLC in petroleum ether – EtOAc 5:1), the mixture was poured into iced water (150 ml). The aqueous phase was extracted with CH_2Cl_2 (4 × 70 ml), and the combined organic phases were washed with sat aq $NaHCO_3$ (60 ml), dried, and concentrated. Chromatography (petroleum ether – EtOAc 11:1) afforded compound **5**.

Yield: 2.5 g (85%), colorless syrup

R_f: 0.39 (PE:EtOAc 11:1)

$[\alpha]_D^{22}$: –16.0 (*c* 1.0, $CHCl_3$)

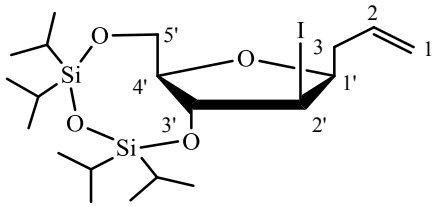
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.96–1.14 [m, 28H, 4 x C*H*(CH_3)$_2$], 2.28–2.44 (m, 2H, H-3), 2.83 (d, 1H, $^3J_{OH,H\text{-}2'}$ = 3.7 Hz, OH-2'), 3.77–3.92 (m, 4H, H-1', H-2', H-4', H-5'a), 4.02 (dd, 1H, $^2J_{5'a,5'b}$ = 12.0 Hz, $^3J_{4',5'b}$ = 3.2 Hz, H-5'b), 4.20 (t, 1H, $^3J_{2',3'} = {}^3J_{3',4'}$ = 6.5 Hz, H-3'), 5.07–5.18 (m, 2H, H-1), 5.81–5.94 (m, 1H, H-2).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 12.64, 12.78, 13.18, 13.36 [4 x *C*H(CH_3)$_2$], 16.93, 17.00, 17.03, 17.15, 17.28, 17.31 (2), 17.42 [4 x CH(*C*H_3)$_2$], 37.74 (C-3), 62.70 (C-5'), 72.22 (C-2'), 73.81 (C-3'), 82.17 (C-4'), 83.36 (C-1'), 117.46 (C-1), 133.87 (C-2).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{20}H_{40}O_5Si_2$ $[M+H]^+$: 417.24870, found 417.24938.

$C_{20}H_{40}O_5Si_2$ (416.70)	calcd:	C 57.65	H 9.68
	found:	C 57.51	H 9.73

4.2.6 (6a*R*,8*S*,9*R*,9a*R*)-8-allyl-9-iodo-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin (6)



A mixture of **5** (2.0 g, 5 mmol), triphenylphosphane (3.3 g, 12.6 mmol), imidazole (885 mg, 13 mmol), and iodine (1.9 g, 7.5 mmol) in dry toluene (60 ml) was heated under reflux for 4–6 h (monitored by TLC in petroleum ether – EtOAc 50:1). The reaction mixture was cooled down to room temperature, sat aq $NaHCO_3$ solution (50 ml) was added, and the mixture was stirred for 5 h. The toluene phase was then separated and concentrated. Chromatography (petroleum ether – EtOAc 100:1) of residue provided compound **6**.

Yield: 2.4 g (95%), colorless syrup

R_f: 0.32 (PE:EtOAc 50:1)

$[\alpha]_D^{21}$: –58.6 (*c* 1.0, $CHCl_3$)

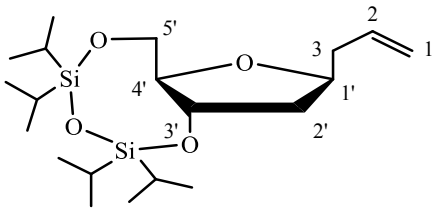
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.94–1.13 [m, 28H, 4 x C*H*(CH_3)$_2$], 2.28–2.55 (m, 2H, H-3), 3.20 (dt, 1H, $^3J_{1',3}$ = 6.6 Hz, $^3J_{1',2'}$ = 3.8 Hz, H-1'), 3.80 (dt, 1H, $^3J_{4',5'a}$ = 9.7 Hz, $^3J_{4',5'b}$ = 4.0 Hz, $^3J_{3',4'}$ = 3.6 Hz, H-4'), 3.91–3.99 (m, 1H, H-5'a), 4.15–4.22 (m, 1H, H-5'b), 4.24–4.28 (m, 1H, H-2'), 4.94 (dd, 1H, $^3J_{3',4'}$ = 3.7 Hz, $^3J_{2',3'}$ = 1.6 Hz, H-3'), 5.11–5.28 (m, 2H, H-1), 5.74–5.89 (m, 1H, H-2).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 12.44, 13.11, 13.44, 13.61 [4 x *C*H(CH_3)$_2$], 16.86, 16.96, 17.04, 17.23, 17.39 (2), 17.47, 17.54, [4 x CH(*C*H_3)$_2$], 38.59 (C-2'), 41.17 (C-3), 65.57 (C-5'), 78.90 (C-1'), 84.44 (C-3'), 87.35 (C-4'), 118.02 (C-1), 133.36 (C-2).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{20}H_{39}IO_4Si_2$ $[M+Na]^+$: 549.13238, found 549.13240.

$C_{20}H_{39}IO_4Si_2$ (526.60)	calcd: C 45.62	H 7.46
	found: C 45.53	H 7.15

4.2.7 (6a*R*,8*S*,9a*S*)-8-allyl-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4] trioxadisilocin (7)



A mixture of compound **6** (1.3 g, 2.5 mmol), tri-*n*-butyltin hydride (1.3 ml, 4.8 mmol), and azobisisobutyronitrile (AIBN, 98 mg, 0.6 mmol) in dry toluene (30 ml) was stirred under reflux for 4 h (monitored by TLC in petroleum ether – EtOAc 50:1)). The solution was filtered and concentrated. The crude product was dissolved in Et_2O (40 ml) and washed with aq 10% KF solution (15 ml), the organic phase was dried and concentrated. Chromatography (petroleum ether – EtOAc 80:1) afforded compound **7**.

Yield: 0.88 g (89%), colorless syrup

$[\alpha]_D^{21}$: –12.6 (*c* 1.0, CH_2Cl_2)

R_f: 0.27 (PE:EtOAc 80:1)

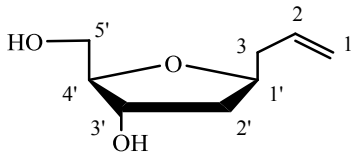
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.94–1.13 [m, 28H, 4 x C*H*(C*H*$_3$)$_2$], 1.78–1.89 (m, 1H, H-2'a), 1.97–2.07 (m, 1H, H-2'b), 2.19–2.40 (m, 2H, H-3), 3.69–3.78 (m, 2H, H-4', H-5'a), 3.99–4.09 (m, 1H, H-5'b), 4.09–4.19 (m, 1H, H-1'), 4.38 (dt, 1H, $^3J_{2'a,3'}$ = 7.9 Hz, $^3J_{2'b,3'}$ = $^3J_{3',4'}$ = 4.5 Hz, H-3'), 5.04–5.14 (m, 2H, H-1), 5.74–5.89 (m, 1H, H-2).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 12.55, 12.94, 13.38, 13.49 [4 x *C*H(CH$_3$)$_2$], 16.96, 17.02, 17.12, 17.28, 17.38, 17.41 (2) 17.55 [4 x CH(*C*H$_3$)$_2$], 39.72 (C-3), 39.82 (C-2'), 63.82 (C-5'), 73.49 (C-3'), 76.94 (C-1'), 85.92 (C-4'), 117.16 (C-1), 134.33 (C-2).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{20}H_{40}O_4Si_2$ $[M+H]^+$: 401.25314, found 401.25314; calcd for $C_{20}H_{40}O_4Si_2$ $[M+Na]^+$: 423.23573, found 423.23597.

$C_{20}H_{40}O_4Si_2$ (400.70)	calcd:	C 59.95 H 10.06
	found:	C 60.03 H 9.88

4.2.8 (2*R*,3*S*,5*S*)-5-allyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (8)



A solution of tetra-*n*-butylammonium fluoride trihydrate (316 mg, 1.2 mmol) in dry acetone (1 ml) was added dropwise at ambient temperature to a solution of **7** (0.2 g, 0.5 mmol) in dry acetone (5 ml). The reaction mixture was stirred for 1.5 h (monitored by TLC in petroleum ether – EtOAc 11:1) and then concentrated. Chromatography (EtOAc-MeOH 15:1) afforded compound **8**.

Yield: 0.59 g (75%), colorless syrup

$[\alpha]_D^{23}$: +35.3 (*c* 1.0, $CHCl_3$)

R_f: 0.27 (EtOAc-MeOH 15:1)

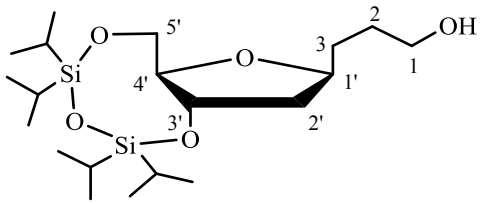
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.73 (ddd, 1H, $^2J_{2'a,2'b}$ = 13.2 Hz, $^3J_{1',2'a}$ = 9.5 Hz, $^3J_{2'a,3'}$ = 6.6 Hz, H-2'a), 1.91 (ddd, 1H, $^2J_{2'a,2'b}$ = 13.2 Hz, $^3J_{1',2'b}$ = 5.7 Hz, $^3J_{2'b,3'}$ = 2.5 Hz, H-2'b), 2.30 (m, 2H, H-3), 3.12 (t, 1H, $^3J_{5',OH}$ = 5.7 Hz, OH-5'), 3.43 (d, 1H, $^3J_{3',OH}$ = 3.6 Hz, OH-3'), 3.59 (m, 2H, H-5'), 3.78 (dt, 1H, $^3J_{4',5'}$ = 4.9 Hz, $^3J_{3',4'}$ = 3.4 Hz, H-4'), 4.15–4.25 (m, 2H, H-1', H-3'), 5.04–5.13 (m, 2H, H-1), 5.81 (m, 1H, H-2).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 39.52 (C-3), 39.82 (C-2'), 63.12 (C-5'), 73.09 (C-3'), 77.74 (C-1'), 86.72 (C-4'), 117.44 (C-1), 134.13 (C-2).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_8H_{14}O_3$ $[M+Na]^+$: 181.08352, found 181.08326.

$C_8H_{14}O_3$ (158.20)	calcd:	C 60.74 H 8.92
	found:	C 60.48 H 8.89

4.2.9 3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]-trioxadisilocin-8-yl)propan-1-ol (9)



Borane tetrahydrofuran complex solution (43.8 ml, 1.0 M in THF) was added during 30 min at 0 °C to a stirred solution of **7** (5.0 g, 12.5 mmol) in dry THF (45 ml) and stirring was continued for additional 3 h at 0 °C. A mixture of aq sodium hydroxide (180 ml, 3 N) and hydrogen peroxide (180 ml, 30%) was cautiously added at 0 °C to the reaction solution. The reaction mixture was warmed up to 15 °C and was stirred for another 1.5 h (monitored by TLC petroleum ether – EtOAc 4:1). The mixture was poured into iced water (100 ml) and the aqueous phase was extracted with CH_2Cl_2 (4 × 150 ml). The combined organic phases were washed with sat aq NaCl (100 ml), dried and concentrated. Chromatography (petroleum ether – EtOAc 4:1) afforded compound **9**.

Yield: 3.81 g (73%), colorless syrup

$[\alpha]_D^{21}$: – 22.0 (*c* 1.0, CH_2Cl_2)

R_f: 0.24 (PE:EtOAc 4:1)

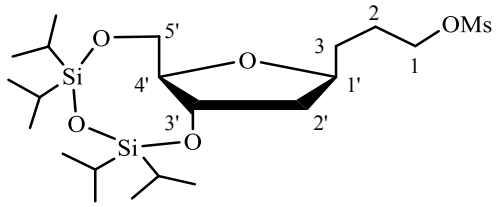
^{1}H NMR (500.13 MHz, $CDCl_3$): δ 0.96–1.13 [m, 28H, 4 x C*H*(C*H*$_3$)$_2$], 1.55–1.70 (m, 4H, H-2, H-3), 1.81 (m, 1H, H-2'a), 2.04 (m, 1H, H-2'b), 2.11 (br s, 1H, OH-1), 3.61–3.70 (m, 2H, H-1), 3.70–3.77 (m, 2H, H-5'a, H-4'), 3.98–4.05 (m, 1H, H-5'b), 4.05–4.13 (m, 1H, H-1'), 4.36–4.43 (m, 1H, H-3').

^{13}C NMR (62.89 MHz, $CDCl_3$): δ 12.54, 12.95, 13.36, 13.48 [4 x *C*H(CH$_3$)$_2$], 16.95, 17.03, 17.11, 17.26, 17.36, 17.40 (2), 17.54 [4 x CH(*C*H$_3$)$_2$], 29.42, 32.28 (C-2, C-3), 40.65 (C-2'), 62.77 (C-1), 63.85 (C-5'), 73.68 (C-3'), 77.84 (C-1'), 86.19 (C-4').

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{20}H_{42}O_5Si_2$ $[M+H]^+$: 419.26435, found 419.26415; calcd for $C_{20}H_{42}O_5Si_2$ $[M+Na]^+$: 441.24630, found 441.24613.

$C_{20}H_{42}O_5Si_2$ (418.72)	calcd:	C 57.37	H 10.11
	found:	C 57.03	H 9.97

4.2.10 3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]-trioxadisilocin-8-yl)propyl methanesulfonate (10)



Methanesulfonyl chloride (0.22 ml, 2.8 mmol) was added dropwise at 0 °C to a stirred solution of **9** (0.5 g, 1.2 mmol) and trimethylamine (0.9 ml, 6.5 mmol) in dry CH_2Cl_2 (7 ml). After stirring for 20 min (monitored by TLC in petroleum ether – EtOAc 1:1), the mixture was diluted with CH_2Cl_2 (40 ml). The organic phase was washed with iced water (2 x 30 ml), sat aq $NaHCO_3$ (30 ml), and sat aq NaCl (30 ml) dried, and concentrated. Chromatography (petroleum ether – EtOAc 4:1) afforded compound **10**.

Yield: 0.55 g (93%), colorless syrup

$[\alpha]_D^{25}$: –15.7 (*c* 1.0, $CHCl_3$)

R_f: 0.3 (PE:EtOAc 3:1)

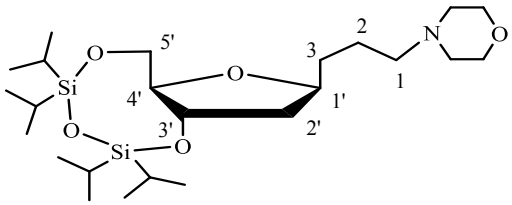
^{1}H NMR (500.13 MHz, $CDCl_3$): δ 0.88–1.12 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.56–1.95 (m, 5H, H-2'a, H-2, H-3), 2.00–2.09 (m, 1H, H-2'b), 3.01 (s, 3H, SO_2CH_3), 3.69–3.75 (m, 2H, H-4', H-5'a), 3.99–4.04 (m, 1H, H-5'b), 4.04–4.12 (m, 1H, H-1'), 4.22–4.30 (m, 2H, H-1), 4.34–4.42 (m, 1H, H-3').

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 12.54, 12.93, 13.35, 13.49 [4 x *C*H(CH_3)$_2$], 16.95, 17.02, 17.11, 17.27, 17.37, 17.40 (2), 17.54 [4 x CH(*C*H_3)$_2$], 25.75, 31.32 (C-2, C-3), 37.37 (SO_2CH_3), 40.44 (C-2'), 63.77 (C-5'), 69.94 (C-1), 73.53 (C-3'), 76.93 (C-1'), 86.09 (C-4').

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{21}H_{44}O_7SSi_2$ $[M+H]^+$: 497.24190, found 497.24204; calcd for $C_{21}H_{44}O_7SSi_2$ $[M+Na]^+$: 519.22385, found 519.22362.

$C_{21}H_{44}O_7SSi_2$ (496.81)	calcd:	C 50.77	H 8.93	S 6.45
	found:	C 50.60	H 9.04	S 6.53

4.2.11 4-(3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4] trioxadisilocin-8-yl)propyl)morpholine (11)



Morpholine (44 µl, 0.5 mmol) was added dropwise at 0 °C to a stirred solution of **10** (40 mg, 0.08 mmol) in dry methanol (1 ml). After stirring for 6 d at ambient temperature (monitored by TLC in petroleum ether – EtOAc 1:1), the mixture was concentrated. The residue was diluted with CH_2Cl_2 (7 ml) and the organic phase was washed with sat aq $NaHCO_3$ (4 ml), and water (4 ml), dried and concentrated. Chromatography (petroleum ether – EtOAc 1:1) afforded compound **11**.

Yield: 37.7 mg (96%), colorless syrup

$[\alpha]_D^{23}$: –16.6 (*c* 1.0, $CHCl_3$)

R*f*: 0.15 (PE:EtOAc 1:1)

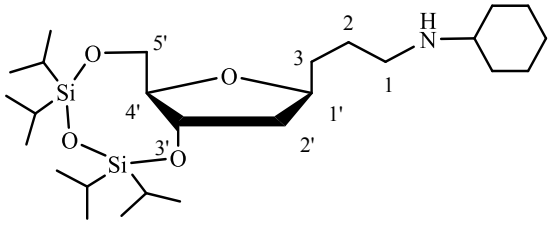
^{1}H NMR (500.13 MHz, $CDCl_3$): δ 0.88–1.10 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.45–1.63 (m, 4H, H-2, H-3), 1.74–1.81 (m, 1H, H-2'a), 1.99–2.04 (m, 1H, H-2'b), 2.34 (t, 2H, $^3J_{1,2}$ = 7.11 Hz, H-1), 2.42 (br. s., 4H, CH_2NCH_2), 3.69–3.73 (m, 6H, H-5'a, H-4', CH_2OCH_2), 3.97–4.07 (m, 2H, H-5'b, H-1'), 4.35–4.38 (m, 1H, H-3').

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 12.56, 12.94, 13.37, 13.49 [4 x *C*H(CH_3)$_2$], 16.96, 17.03, 17.12, 17.27, 17.37, 17.40, 17.42, 17.54 [4 x CH(*C*H_3)$_2$], 22.87, 33.34 (C-2, C-3), 40.56 (C-2'), 53.69 (2) (*C*H_2N*C*H_2), 58.85 (C-1), 64.06 (C-5'), 66.99 (2) (*C*H_2O*C*H_2), 73.86 (C-3'), 77.59 (C-1'), 85.96 (C-4').

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{24}H_{49}NO_5Si_2$ $[M+H]^+$: 488.3222, found 488.32199.

$C_{24}H_{49}NO_5Si_2$ (487.83)	calcd:	C 59.09	H 10.12	N 2.87
	found:	C 58.87	H 10.05	N 2.76

4.2.12 *N*-(3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)propyl)cyclohexanamine (12)



Cyclohexylamine (325.2 µl, 2.82 mmol) was added dropwise at 0 °C to a stirred solution of **10** (70 mg, 0.14 mmol) in dry methanol (1 ml). After stirring for 6 d at ambient temperature (monitored by TLC in petroleum ether – EtOAc 3:1), the mixture was concentrated. The residue was diluted with CH_2Cl_2 (7 ml) and the organic phase was washed with sat aq $NaHCO_3$ (4 ml), and water (4 ml), dried, and concentrated. Chromatography (EtOAc – MeOH 10:1) afforded compound **12**.

Yield: 58 mg (83%), colorless syrup

$[\alpha]_D^{25}$: –17.1 (*c* 1.0, $CHCl_3$)

R*f*: 0.11 (EtOAc:MeOH 10:1)

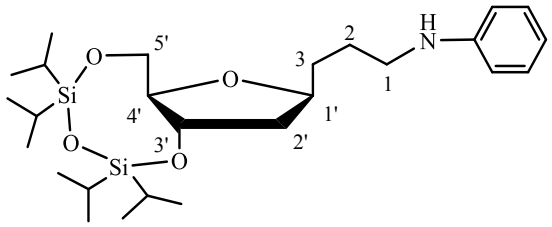
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.84–1.32 [m, 34H, 4 x C*H*(C*H*$_3$)$_2$, 3 x C*H*$_{2\text{Cyclohexyl}}$], 1.40–1.66 (m, 4H, H-2, H-3), 1.66–1.81 (m, 3H, H-2'a, C*H*$_{2\text{Cyclohexyl}}$), 1.82–1.94 (m, 2H, C*H*$_{2\text{Cyclohexyl}}$) 1.95–2.13 (m, 1H, H-2'b), 2.32–2.54 (m, 1H, C*H*$_{\text{Cyclohexyl}}$), 2.55–2.72 (m, 2H, H-1), 3.64–3.78 (m, 2H, H-5'a, H-4'), 3.92–4.10 (m, 2H, H-5'b, H-1'), 4.31–4.41 (m, 1H, H-3').

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 12.52, 12.91, 13.34, 13.45 [4 x *C*H(CH$_3$)$_2$], 16.93, 17.01, 17.09, 17.25, 17.37 (3), 17.51 [4 x CH(*C*H$_3$)$_2$], 25.02 (2) (2 x *C*H$_{2\text{Cyclohexyl}}$), 26.43, 33.32 (C-2, C-3), 33.32 (2) (2 x *C*H$_{2\text{Cyclohexyl}}$), 40.46 (C-2'), 46.72 (C-1), 56.77 (*C*H$_{\text{Cyclohexyl}}$) 63.98 (C-5'), 73.77 (C-3'), 77.61 (C-1'), 85.92 (C-4').

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{26}H_{53}NO_4Si_2$ $[M+H]^+$: 500.35859, found 500.35869.

$C_{26}H_{53}NO_4Si_2$ (499.88)	calcd:	C 62.47	H 10.69	N 2.80
	found:	C 62.37	H 10.72	N 2.78

4.2.13 *N*-(3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4] trioxadisilocin-8-yl)propyl)aniline (13)



Aniline (202 µl, 2.2 mmol) was added dropwise at 0 °C to a stirred solution of **10** (73 mg, 0.15 mmol) in dry methanol (1 ml). After stirring for 5 d at ambient temperature (monitored by TLC in petroleum ether – EtOAc 3:1), the mixture was concentrated. The residue was diluted with CH_2Cl_2 (7 ml) and the organic phase was washed with sat aq $NaHCO_3$ (4 ml), and water (4 ml) dried, and concentrated. Chromatography (petroleum ether – EtOAc 10:1) afforded compound **13**.

Yield: 54 mg (75%), light-yellow syrup

$[\alpha]_D^{23}$: –23.2 (*c* 1.0, $CHCl_3$)

R*f*: 0.46 (PE:EtOAc 10:1)

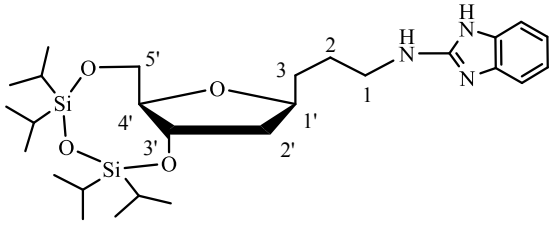
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.82–1.19 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.54–1.86 (m, 5H, H-2, H-3, H-2'a), 1.99–2.10 (m, 1H, H-2'b), 3.15 (t, 2H, $^3J_{1,2}$ = 6.61 Hz, H-1), 3.61–3.88 (m, 2H, H-4', H-5'a), 3.96–4.16 (m, 2H, H-1', H-5'b), 4.35–4.46 (m, 1H, H-3'), 6.58–6.73 (m, 3H, 3 x H_{Phenyl}), 7.12–7.23 (m, 2H, 2 x H_{Phenyl}).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 12.54, 12.94, 13.37, 13.48 [4 x *C*H(CH_3)$_2$], 16.96, 17.03, 17.12, 17.28, 17.38, 17.41(2), 17.54 [4 x CH(*C*H_3)$_2$], 25.83, 33.02 (C-2, C-3), 40.58 (C-2'), 43.86 (C-1), 63.94 (C-5'), 73.72 (C-3'), 77.47 (C-1'), 86.03 (C-4'), 112.70(2), 117.12, 129.19 (2) (5 x C_{Phenyl}), 148.38 ($C_{quartPhenyl}$).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{26}H_{47}NO_4Si_2$ $[M+H]^+$: 494.30728, found 494.30719.

$C_{26}H_{47}NO_4Si_2$ (493.84)	calcd:	C 63.24	H 9.59	N 2.84
	found:	C 63.35	H 9.42	N 2.72

4.2.14 *N*-(3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)propyl)-1*H*-benzo[d]imidazol-2-amine (14)



2-Aminobenzimidazole (474 mg, 0.14 mmol) was added in few portions at 0 °C to a stirred solution of **10** (71 mg, 0.15 mmol) in dry methanol (2 ml). After stirring for 10 d at ambient temperature (monitored by TLC in petroleum ether – EtOAc 3:1), the mixture was concentrated. The residue was diluted with CH_2Cl_2 (7 ml) and the organic phase was washed with sat aq $NaHCO_3$ (4 ml), and water (4 ml) dried and concentrated. Chromatography (EtOAc – MeOH 7:1) afforded **14**.

Yield: 54 mg (75%), light-yellow syrup

$[\alpha]_D^{24}$: –35.6 (*c* 1.0, $CHCl_3$)

R*f*: 0.41 (EtOAc:MeOH 10:1)

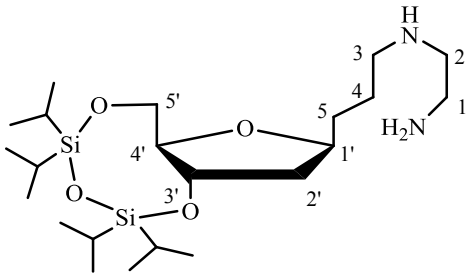
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.84–1.10 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.44–1.69 (m, 2H, H-3), 1.76–1.97 (m, 2H, H-2a, H-2'a), 1.99–2.10 (m, 2H, H-2b, H-2'b), 3.73–3.88 (m, 2H, H-5'a, H-4'), 3.97–4.13 (m, 2H, H-5'b, H-1), 4.12–4.22 (m, 1H, H-1'), 4.35–4.43 (m, 1H, H-3'), 6.99–7.18, 7.41–7.44 (m, 4H, 4 x H_{Aryl}).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 12.49, 12.97, 13.27, 13.46 [4 x *C*H(CH_3)$_2$], 16.91, 17.01, 17.06, 17.20, 17.36, 17.39, 17.42, 17.54 [4 x CH(*C*H_3)$_2$], 26.36 (C-2), 30.75 (C-3), 40.35 (C-2'), 42.21 (C-1), 62.81 (C-5'), 72.38 (C-3'), 79.05 (C-1'), 86.35 (C-4'), 107.57, 116.19, 119.47, 121.33 (4 x *C*H_{Aryl}), 134.03, 141.99 (2 x $C_{quartAryl}$), 154.08 (HN*C*NNH).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{27}H_{47}N_3O_4Si_2$ $[M+H]^+$: 534.31779, found 534.31761.

$C_{27}H_{47}N_3O_4Si_2$ (533.86)	calcd:	C 60.75	H 8.87	N 7.87
	found:	C 60.35	H 8.42	N 7.53

4.2.15 N^1-(3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4] trioxadisilocin-8-yl)propyl)ethan-1,2-diamine (15)



Ethane-1,2-diamine (20 ml, 0.3 mmol) was added dropwise at 0 °C to a stirred solution of **10** (2.8 g, 5.6 mmol) in dry methanol (30 ml). After stirring for 22 h at ambient temperature (monitored by TLC in EtOAc – MeOH 5:1 with 1% NEt_3), the mixture was concentrated. The residue was diluted with CH_2Cl_2 (7 ml) and the organic phase was washed with sat aq $NaHCO_3$ (4 ml), and water (4 ml) dried and concentrated. Chromatography (EtOAc – MeOH 3:1 with 1% NEt_3) afforded **15**.

Yield: 2.5 g (95%), light-yellow syrup

$[\alpha]_D^{25}$: –14.5 (*c* 1.0, CH_2Cl_2)

R*f*: 0.15 (EtOAc:MeOH 3:1 with 1% NEt_3)

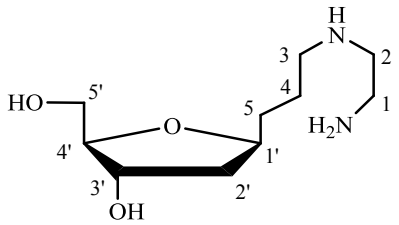
^{1}H NMR (500.13 MHz, $CDCl_3$): δ 0.88–1.12 [m, 28H, 4 x C*H*(C*H*$_3$)$_2$], 1.27 (br s, 3H, NH, NH_2), 1.41–1.53 (m, 2H, H-5), 1.47–1.53 (m, 2H, H-4), 1.65–1.72 (m, 1H, H-2'a), 1.91–1.96 (m, 1H, H-2'b), 2.52–2.58 (m, 2H, H-3), 2.56–2.59 (m, 2H, H-2), 2.76– 2.82 (m, 2H, H-1), 3.60-3.65 (m, 2H, H-5'a, H-4'), 3.92-3.99 (m, 2H, H-5'b, H-1'), 4.26-4.31 (m, 1H, H-3').

^{13}C NMR (125.76 MHz, $CDCl_3$): δ 12.54, 12.94, 13.36, 13.48 [4 x *C*H(CH$_3$)$_2$], 16.95, 17.02, 17.11, 17.27, 17.37, 17.39, 17.40, 17.53 [4 x CH(*C*H$_3$)$_2$], 26.41 (C-4), 33.24 (C-5), 40.56 (C-2'), 41.75 (C-1), 49.72 (C-3), 52.49 (C-2), 64.05 (C-5'), 73.85 (C-3'), 77.65 (C-1'), 85.97 (C-4').

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{22}H_{48}N_2O_4Si_2$ $[M+H]^+$: 461.32254, found 461.32271; calcd for $C_{22}H_{48}N_2O_4Si_2$ $[M+Na]^+$: 483.30448, found 483.30472.

$C_{22}H_{48}N_2O_4Si_2$ (460.80)	calcd:	C 57.34	H 10.50	N 6.08
	found:	C 56.75	H 10.40	N 5.93

4.2.16 (2*R*,3*S*,5*S*)-5-(3-((2-aminoethyl)amino)propyl)-2-(hydroxymethyl)tetra-hydro-furan-3-ol (16)



A solution of tetra-*n*-butylammonium fluoride trihydrate (0.5 g, 2 mmol) in dry acetone (2 ml) was added dropwise at ambient temperature to a solution of **15** (0.6 g, 1.3 mmol) in dry acetone (5 ml). The reaction mixture was stirred for 1.5 h (monitored by TLC in EtOAc – MeOH 5:2 with 1% NEt_3) and then concentrated. Chromatography (EtOAc – MeOH 1:1 with 1% NEt_3) afforded compound **16**.

Yield: 0.2 g (90%), light-yellow syrup

$[\alpha]_D^{24}$: –24.5 (*c* 1.0, $CHCl_3$)

R_f: 0.0 (EtOAc:MeOH 3:1 with 1% NEt_3)

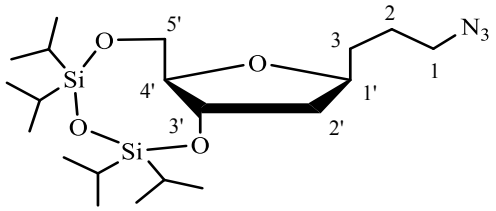
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.43–1.63 (m, 2H, H-3), 1.47–1.65 (m, 2H, H-4), 1.65–1.76 (m, 1H, H-2'a), 1.88–1.99 (m, 1H, H-2'b), 2.55–2.66 (m, 4H, H-5, H-2), 2.71–2.79 (m, 2H, $^3J_{1ab,2ab}$ = 5.77 Hz, $^3J_{1ab,2ab}$ = 5.93 Hz, H-1), 3.47 (dd, 1H, $^2J_{5'a,5'b}$ = 11.14 Hz, H-5'a), 3.64 (d´t`, 1H, $^3J_{4',5'}$ = 4.15 Hz, $^2J_{5'a,5'b}$ = 11.14 Hz, H-5'b), 3.75 (d´t`, 1H, $^3J_{4',5'b}$ = 4.15 Hz, $^3J_{3',4'}$ = $^3J_{4',5'a}$ = 7.2 Hz, H-4'), 3.99–4.12 (m, 1H, H-1'), 4.25 (dt, 1H, $^3J_{3',4'}$ = 7.2 Hz, H-3').

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 26.45 (C-4), 33.41 (C-3), 40.37 (C-2'), 41.33 (C-1), 49.51 (C-5), 52.14 (C-2), 63.44 (C-5'), 73.30 (C-3'), 77.84 (C-1'), 87.11 (C-4').

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{10}H_{22}N_2O_3$ $[M+H]^+$: 219.16728, found 219.16721.

$C_{10}H_{22}N_2O_3$ (218.30)	calcd:	C 55.02	H 10.16	N 12.83
	found:	C 54.78	H 10.29	N 12.96

4.2.17 (6a*R*,8*S*,9a*S*)-8-(3-azidopropyl)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocine (17)



Sodium azide (3.4 g, 52.3 mmol) was added at ambient temperature to a solution of **10** (2.35 g, 4.7 mmol) in dry DMF (25 ml). The reaction mixture was stirred for 24 h (monitored by TLC in petroleum ether – EtOAc 20:1) and then the mixture was diluted with EtOAc (30 ml). The organic phase was washed with iced water (2 x 30 ml), dried and concentrated. Chromatography (petroleum ether – EtOAc 50:1) afforded compound **17**.

Yield: 2.02 g (96%), colorless syrup

$[\alpha]_D^{23}$: –38.8 (*c* 1.0, $CHCl_3$)

R_f: 0.32 (PE:EtOAc 50:1)

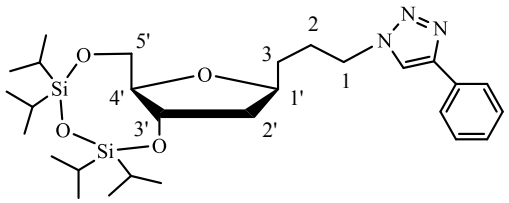
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.87–1.16 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.55–1.74 (m, 4H, H-2, H-3), 1.74–1.83 (m, 1H, H-2'a), 2.00–2.08 (m, 1H, H-2'b), 3.24–3.37 (m, 2H, H-1), 3.68–3.76 (m, 2H, H-5'a, H-4'), 3.99–4.11 (m, 2H, H-5'b, H-1'), 4.35–4.41 (m, 1H, H-3').

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 12.55, 12.95, 13.38, 13.49 [4 x *C*H(CH_3)$_2$], 16.96, 17.04, 17.12, 17.28, 17.38, 17.41(2), 17.55 [4 x CH(*C*H_3)$_2$], 25.40 (C-2), 32.56 (C-3), 40.55 (C-2'), 51.40 (C-1), 63.93 (C-5'), 73.70 (C-3'), 77.12 (C-1'), 86.08 (C-4').

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{20}H_{41}N_3O_4Si_2$ $[M+H]^+$: 444.27084, found 444.27107; calcd for $C_{20}H_{41}N_3O_4Si_2$ $[M+Na]^+$: 466.25278, found 466.25291.

$C_{20}H_{41}N_3O_4Si_2$ (443.74)	calcd:	C 54.14	H 9.31	N 9.47
	found:	C 54.18	H 9.19	N 9.12

4.2.18 4-phenyl-1-(3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)propyl)-1*H*-1,2,3-triazole (18)



A mixture of compound **17** (0.1 g, 0.23 mmol), copper(II) sulfate pentahydrate (2 mg, 0.08 mmol), L(+)-ascorbic acid (10 mg, 0.06 mmol) and phenylacetylene (50 µl, 0.46 mmol) in water/DMF (1.5 ml/0.5 ml) was stirred for 63 h at 75 °C (monitored by TLC in petroleum ether – EtOAc 20:1). The solution was filtered and concentrated. Chromatography (petroleum ether – EtOAc 3:1) afforded compound **18**.

Yield: 102 mg (83%), light-yellow syrup

$[\alpha]_D^{23}$: –17.9 (*c* 1.0, $CHCl_3$)

R_f: 0.42 (PE:EtOAc 3:1)

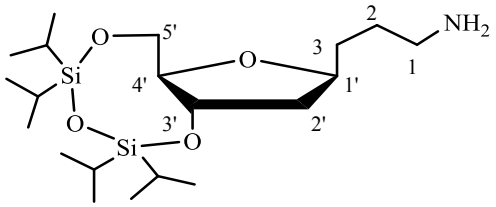
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.84–1.12 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.53–1.63 (m, 2H, H-3), 1.73–1.82 (m, 1H, H-2'a), 2.00–2.18 (m, 3H, H-2, H-2'b), 3.69–3.78 (m, 2H, H-5'a, H-4'), 3.99–4.16 (m, 2H, H-5'b, H-1'), 4.34–4.40 (m, 1H, H-3'), 4.42–4.53 (m, 2H, H-1), 7.30–7.46 (m, 3H, 3 x H_{Phenyl}), 7.77 (s, 1H, C*H*=C), 7.81–7.85 (m, 2H, 2 x H_{Phenyl}).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 12.52, 12.89, 13.34, 13.46 [4 x *C*H(CH_3)$_2$], 16.94, 17.02, 17.09, 17.25, 17.34, 17.38, 17.39, 17.53 [4 x CH(*C*H_3)$_2$], 26.97 (C-2), 32.21 (C-3), 40.41 (C-2'), 50.22 (C-1), 63.68 (C-5'), 73.36 (C-3'), 77.03 (C-1'), 86.10 (C-4'), 119.55 (*C*H=C), 125.67 (2), 128.05, 128.79 (2) (C_{Phenyl}), 130.71 ($C_{quartPhenyl}$), 147.70 (CH=*C*).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{28}H_{47}N_3O_4Si_2$ $[M+H]^+$: 546.31779, found 546.31738; calcd for $C_{28}H_{47}N_3O_4Si_2$ $[M+Na]^+$: 568.29973, found 568.29927.

$C_{28}H_{47}N_3O_4Si_2$ (545.87)	calcd:	C 61.61	H 8.68	N 7.70
	found:	C 61.49	H 8.78	N 7.59

4.2.19 3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4] trioxadisilocin-8-yl)propan-1-amine (19)



Palladium on carbon 10 wt. % (0.4 g, 3.8 mmol) was added to a stirred solution of **17** (1.7 g, 3.8 mmol) in dry methanol (20 ml). After stirring for 24 h at ambient temperature (monitored by TLC in EtOAc – MeOH 1:1 with 1% NEt_3), The solution was filtered and concentrated. Chromatography (EtOAc – MeOH 1:1 with 1% NEt_3) afforded compound **19**.

Yield: 0.9 g (56%), brown-yellow syrup

$[\alpha]_D^{22}$: –17.1 (*c* 1.0, MeOH)

R_f: 0.26 (EtOAc:MeOH 1:1 with 1% NEt_3)

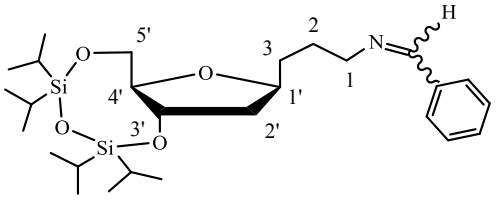
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.81–1.13 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.41–1.63 (m, 4H, H-2, H-3), 1.65–1.89 (m, 1H, H-2'a), 1.94–2.05 (m, 1H, H-2'b), 2.71 (br s, 2H, H-1), 3.67–3.78 (m, 2H, H-5'a, H-4'), 3.98–4.08 (m, 2H, H-5'b, H-1'), 4.33–4.39 (m, 1H, H-3').

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 12.51, 12.91, 13.34, 13.46 [4 x *C*H(CH_3)$_2$], 16.93, 17.00, 17.09, 17.24, 17.35, 17.38 (2), 17.51 [4 x CH(*C*H_3)$_2$], 29.83 (C-2), 32.78 (C-3), 40.53 (C-2'), 42.03 (C-1), 63.95 (C-5'), 73.74 (C-3'), 77.57 (C-1'), 85.95 (C-4').

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{20}H_{43}NO_4Si_2$ $[M+H]^+$: 418.28034, found 418.28017; calcd for $C_{20}H_{43}NO_4Si_2$ $[M+Na]^+$: 440.26228, found 440.26176.

$C_{20}H_{43}NO_4Si_2$ (417.74)	calcd:	C 57.51	H 10.38	N 3.35
	found:	C 58.04	H 10.28	N 3.19

4.2.20 1-phenyl-*N*-(3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)propyl)methanimine (20)



A mixture of compound **19** (0.1 g, 0.24 mmol), benzaldehyde (25 µl, 0.25 mmol), molecular sieve powder (20 mg, A3 and A4) in dry methanol (1 ml) was stirred for 40 h at ambient temperature. The solution was filtered and concentrated without further purification to give compound **20**.

Yield: 115 mg (95%), brown-yellow syrup

$[\alpha]_D^{24}$: –13.1 (*c* 1.0, $CHCl_3$)

R_f: 0.38 (PE:EtOAc 5:1)

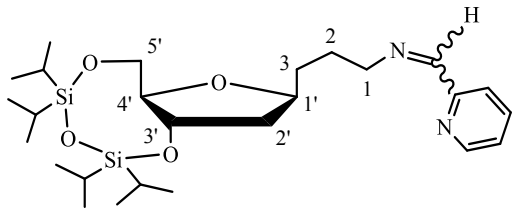
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 0.83–1.19 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.43–1.92 (m, 5H, H-2, H-3, H-2'a), 1.96–2.11 (m, 1H, H-2'b) 3.55–3.66 (m, 2H, H-1), 3.67–3.79 (m, 2H, H-4', H-5'a), 3.95–4.19 (m, 2H, H-1', H-5'b), 4.30–4.43 (m, 1H, H-3'), 7.32–7.50, 7.66–7.74 (m, 5H, 5 x H_{Phenyl}), 8.28 (s, 1H, NC*H*).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ 12.55, 12.93, 13.38, 13.49 [4 x *C*H(CH_3)$_2$], 16.97, 17.04, 17.13, 17.28, 17.38, 17.41 (2), 17.55 [4 x CH(*C*H_3)$_2$], 27.09 (C-2), 33.24 (C-3), 40.52 (C-2'), 61.49 (C-1), 64.04 (C-5'), 73.85 (C-3'), 77.63 (C-1'), 85.93 (C-4'), 128.02 (2), 128.54 (2), 130.47 (5 x C_{Phenyl}), 136.28 ($C_{quartPhenyl}$), 161.01 (N*C*H).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{27}H_{47}NO_4Si_2$ $[M+H]^+$: 506.31164, found 506.31112.

$C_{27}H_{47}NO_4Si_2$ (505.85)	calcd:	C 64.11	H 9.37	N 2.77
	found:	C 64.42	H 9.08	N 2.73

4.2.21 1-(pyridin-2-yl)-*N*-(3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo [3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)propyl)methanimine (21)



Compound **19** (0.1 g, 0.24 mmol), pyridine-2-carbaldehyde (25 µl, 0.25 mmol) and molecular sieve powder (20 mg, A3 and A4) in dry methanol (1 ml) was stirred for 40 h at ambient temperature. The solution was filtered and concentrated without further purification to give compound **21**.

Yield: 109 mg (90%), brown-yellow syrup

$[\alpha]_D^{24}$: –12.5 (*c* 1.0, $CHCl_3$)

R_f: 0.35 (PE:EtOAc 3:1)

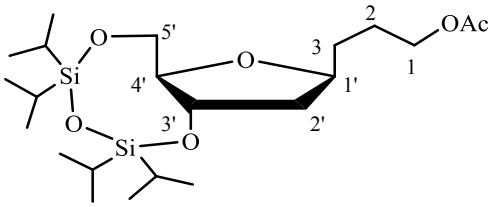
^{1}H NMR (250.13 MHz, $CDCl_3$): δ 0.79–1.19 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.20–2.09 (m, 6H, H-2, H-3, H-2'), 3.45–3.80 (m, 4H, H-1, H-4', H-5'a), 3.84–4.15 (m, 2H, H-1', H-5'b), 4.15–4.53 (m, 1H, H-3'), 7.06–8.01 (m, 3H, 3 x $H_{Pyridine}$), 8.37 (s, 1H, NC*H*), 8.46–8.68 (m, 1H, $H_{Pyridine}$).

^{13}C NMR (62.89 MHz, $CDCl_3$): δ 12.53, 12.92, 13.36, 13.47 [4 x *C*H(CH_3)$_2$], 16.95, 17.02, 17.11, 17.26, 17.39 (3), 17.53 [4 x CH(*C*H_3)$_2$], 26.90, 33.19 (C-2, C-3), 40.51 (C-2'), 61.26 (C-1), 64.02 (C-5'), 73.83 (C-3'), 77.20 (C-1'), 85.94 (C-4'), 121.18, 124.61, 136.49, 149.37 (4 x $C_{Pyridine}$), 154.56 ($C_{quartPyridine}$), 161.95 (N*C*H).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{26}H_{46}N_2O_4Si_2$ $[M+H]^+$: 507.30689, found 507.30739.

$C_{26}H_{46}N_2O_4Si_2$ (506.83)	calcd:	C 61.62	H 9.15	N 5.53
	found:	C 61.15	H 8.99	N 5.35

4.2.22 3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4] trioxadisilocin-8-yl)propyl acetate (22)



Freshly distilled Ac_2O (7.5 ml) was added dropwise at 0 °C to a vigorously stirred solution of **9** (2.3 g, 5.5 mmol) in dry pyridine (15 ml). The mixture was allowed to attain ambient temperature and stirring was continued overnight. TLC (in petroleum ether – EtOAc 5:1 with 1% NEt_3) showed then that the reaction was complete. Excess of Ac_2O was then destroyed by addition of methanol (5 ml) at 0 °C and stirring was continued for additional 30 min. The mixture was poured into iced water and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 ml). The combined organic phases were successively washed with aq 15% $NaHSO_4$ (3 × 40 ml), ice water (40 ml), and sat aq $NaHCO_3$ solution (2 × 40 ml), then dried and concentrated. Chromatography (petroleum ether – EtOAc 5:1) gave the compound **22**.

Yield: 2.18 g (86%), colorless syrup

$[\alpha]_D^{22}$: –20.5 (*c* 1.0, CH_2Cl_2)

R_f: 0.57 (PE:EtOAc 5:1)

^{1}H NMR (250.13 MHz, $CDCl_3$): δ 0.97–1.13 (m, 28H, 4 x C*H*(C*H*$_3$)$_2$), 1.54–1.80 (m, 5H, H-3, H-2, H-2'a), 1.99–2.08 (m, 1H, H-2'b), 2.04 (s, 3H, COC*H*$_3$), 3.67–3.76 (m, 2H, H-5'a, H-4'), 3.98–4.12 (m, 4H, H-1', H-5'b, H-1), 4.38 (ddd, 1H, $^3J_{3',4'}$ = 4.1 Hz, $^3J_{3',2'b}$ = 4.3 Hz, $^3J_{3',2'a}$ = 8.1 Hz, H-3').

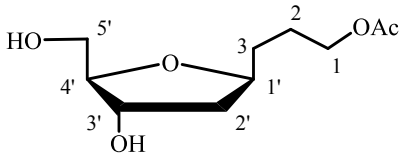
^{13}C NMR (62.89 MHz, $CDCl_3$): δ 12.54, 12.94, 13.38, 13.49 [4 x *C*H(CH$_3$)$_2$], 16.96, 17.03, 17.12, 17.28, 17.38, 17.41 (2), 17.54 [4 x CH(*C*H$_3$)$_2$], 20.94 (CO*C*H$_3$), 25.05 (C-2), 31.89 (C-3), 40.49 (C-2'), 63.93 (C-5'), 64.36 (C-1) 73.72 (C-3'), 77.21 (C-1'), 86.03 (C-4'), 171.12 (*C*OCH$_3$).

^{29}Si NMR (99.35 MHz, $CDCl_3$): δ –12.8, –15.5.

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{22}H_{44}O_6Si_2$ $[M+H]^+$: 461.27492, found 461.27531; calcd for $C_{22}H_{44}O_6Si_2$ $[M+Na]^+$: 483.25686, found 483.25706.

$C_{22}H_{44}O_6Si_2$ (460.76)	calcd:	C 57.35	H 9.63
	found:	C 57.31	H 9.45

4.2.23 3-((2*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)propyl acetate (23)



A solution of tetra-*n*-butylammonium fluoride trihydrate (1.5 g, 5.7 mmol) in dry acetone (5 ml) was added dropwise at ambient temperature to a solution of **22** (1.5 g, 3.3 mmol) in dry acetone (25 ml). The reaction mixture was stirred for 1.5 h at ambient temperature (monitored by TLC in EtOAc) and then concentrated. Chromatography (EtOAc – MeOH 15:1) afforded compound **23**.

Yield: 683 mg (96%), colorless syrup

$[\alpha]_D^{22}$: +18.5 (*c* 1.0, MeOH)

R_f: 0.43 (EtOAc:MeOH 15:1)

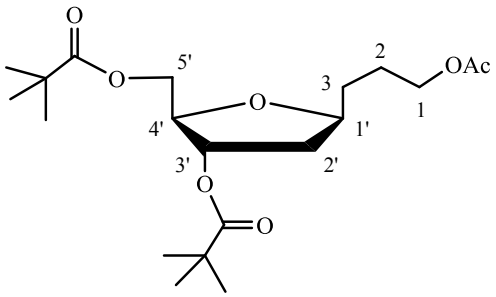
^{1}H NMR (250.13 MHz, $CDCl_3$): δ 1.56–1.77 (m, 5H, H-2, H-3, H-2'a), 1.92–1.99 (m, 1H, H-2'b), 2.05 (s, 3H, COC*H*$_3$), 2.38 (br s, 1H, OH-5'), 2.47 (br s, 1H, OH-3'), 3.58–3.68 (m, 2H, H-5'), 3.79–3.84 (m, 1H, H-4'), 4.06–4.13 (m, 2H, H-1), 4.13–4.21 (m, 1H, H-1'), 4.29 (m, 1H, H-3').

^{13}C NMR (62.89 MHz, $CDCl_3$): δ 20.96 (CO*C*H$_3$), 25.25 (C-2), 31.64 (C-3), 41.35 (C-2'), 63.19 (C-5'), 64.30 (C-1) 73.37 (C-3'), 78.11 (C-1'), 86.78 (C-4'), 171.33 (*C*OCH$_3$).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{10}H_{18}O_5$ $[M+Na]^+$: 241.10464, found 241.10499.

$C_{10}H_{18}O_5$ (218.25)	calcd:	C 55.03	H 8.31
	found:	C 52.60	H 8.28

4.2.24 (2*R*,3*S*,5*S*)-5-(3-acetoxypropyl)-2-((pivaloyloxy)methyl)tetrahydrofuran-3-yl pivalate (24)



Pivaloyl chloride (10 ml, 0.08 mmol) and 4-(dimethylamino)pyridine (20 mg, 0.16 mmol) was added to a solution of **23** (1.0 g, 4.6 mmol) in dry DMF (25 ml). The reaction mixture was stirred for 4 h (monitored by TLC in Tol – EtOAc 3:1) and then the mixture was concentrated and finally diluted with sat aq $NaHCO_3$ solution (30 ml). The aqueous phase was extracted with CH_2Cl_2 (4 x 50 ml), dried and concentrated. Chromatography (petroleum ether – EtOAc 10:1) afforded compound **24**.

Yield: 1.7 g (95%), colorless syrup

$[\alpha]_D^{22}$: +17.3 (*c* 1.0, CH_2Cl_2)

R_f: 0.57 (Tol:EtOAc 3:1)

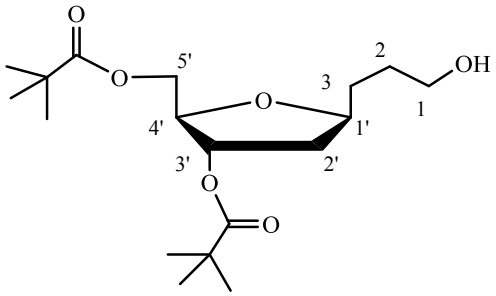
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.20, 1.21 [2 x s, 18H, 2 x C(CH_3)$_3$], 1.60–1.79 (m, 5H, H-3, H-2, H-2'a), 1.97–2.04 (m, 1H, H-2'b), 2.04 (s, 3H, COCH_3), 4.00–4.05 (m, 1H, H-4'), 4.07–4.13 (m, 3H, H-1, H-1'), 4.14–4.19 (m, 2H, H-5'), 5.07–5.13 (m, 1H, H-3').

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 20.91 (COCH_3), 25.24 (C-2), 26.99, 27.20 [2 x COC(CH_3)$_3$], 31.43 (C-3), 38.47 (C-2'), 38.54, 38.75 [2 x COC(CH_3)$_3$], 64.23 (C-1), 64.32 (C-5'), 76.33 (C-3'), 78.55 (C-1'), 82.37 (C-4'), 171.07 (COCH_3), 178.01, 178.05 [2 x COC(CH_3)$_3$].

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{20}H_{34}O_7$ $[M+Na]^+$: 409.21967, found 409.21949.

$C_{20}H_{34}O_7$ (386.49)	calcd:	C 62.16	H 8.87
	found:	C 61.87	H 8.86

4.2.25 (2*R*,3*S*,5*S*)-5-(3-hydroxypropyl)-2-((pivaloyloxy)methyl)tetrahydrofuran-3-yl pivalate (25)



Acetyl chloride (0.82 ml, 11.5 mmol) was added dropwise at 0 °C to a vigorously stirred dry methanol (40 ml). To that methanolic HCl-solution, compound **24** (0.57 g, 1.5 mmol) was added. The mixture was allowed to attain ambient temperature and stirring was continued for 4 h (monitored by TLC in Tol – EtOAc 1:1). The reaction solution was cautiously neutralized by addition of ion-exchange resins OH^-, filtered and concentrated. To avoid any side reaction, the desired compound **25** was used for subsequent reaction without further purification. Chromatography (Tol – EtOAc 1:1) afforded an analytical sample.

Yield: approx. 483 mg (95%), colorless syrup

$[\alpha]_D^{22}$: +35.5 (*c* 1.0, CH_2Cl_2)

R_f: 0.57 (Tol:EtOAc 1:1)

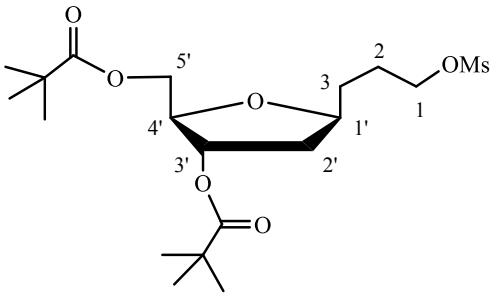
^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.20, 1.21 [2 x s, 18H, 2 x C(C*H*$_3$)$_3$], 1.56–1.86 (m, 5H, H-3, H-2, H-2'a), 2.02 (m, 1H, H-2'b), 2.18 (br s, 1H, OH), 3.61–3.74 (m, 2H, H-1), 4.03–4.07 (m, 1H, H-4'), 4.09–4.15 (m, 1H, H-1'), 4.17–4.23 (m, 2H, H-5'), 5.07–5.12 (m, 1H, H-3').

^{13}C NMR (75.46 MHz, $CDCl_3$): δ 27.01, 27.20 [2 x COC(*C*H$_3$)$_3$], 29.67 (C-2), 31.87 (C-3), 38.71 (C-2'), 38.56, 38.78 [2 x CO*C*(CH$_3$)$_3$], 62.65 (C-1), 64.34 (C-5'), 76.21 (C-3'), 79.25 (C-1'), 82.58 (C-4'), 178.05, 178.13 [2 x *C*OC(CH$_3$)$_3$].

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{18}H_{32}O_6$ $[M+Na]^+$: 367.20911, found 367.20945.

$C_{18}H_{32}O_6$ (344.45)	calcd:	C 62.77	H 9.36
	found:	C 61.79	H 9.45

4.2.26 (2*R*,3*S*,5*S*)-5-(3-((methylsulfonyl)oxy)propyl)-2-((pivaloyloxy)methyl) tetrahydrofuran-3-yl pivalate (26)



Methanesulfonyl chloride (0.22 ml, 2.8 mmol) was added dropwise at 0 °C to a stirred solution of **25** (0.5 g, 1.5 mmol) and trimethylamine (0.9 ml, 6.5 mmol) in dry CH_2Cl_2 (10 ml). After stirring for 20 min at ambient temperature (monitored by TLC in petroleum ether – EtOAc 1:1), the mixture was diluted with CH_2Cl_2 (20 ml). The organic phase was washed with sat aq $NaHCO_3$ (10 ml), and sat aq NaCl (10 ml) dried, and concentrated. Chromatography (petroleum ether – EtOAc 3:1) afforded compound **26**.

Yield: 567 mg (91%), colorless syrup

$[\alpha]_D^{22}$: +22.7 (*c* 1.0, $CHCl_3$)

R_f: 0.57 (Tol:EtOAc 1:1)

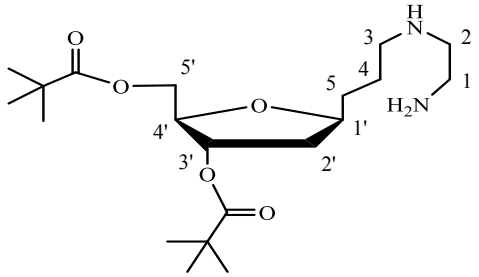
^{1}H NMR (250.13 MHz, $CDCl_3$): δ 1.20, 1.21 [2 x s, 18H, 6 x C(C*H*$_3$)], 1.60–1.75 (m, 2H, H-3), 1.76–1.84 (m, 1H, H-2'a), 1.84–1.95 (m, 2H, H-2), 1.96–2.04 (m, 1H, H-2'b), 3.01 (s, 3H, SO_2CH_3), 4.01–4.04 (m, 1H, H-4'), 4.03–4.12 (m, 1H, H-1'), 4.14–4.20 (m, 2H, H-5'), 4.23–4.35 (m, 2H, H-1), 5.09–5.11 (m, 1H, H-3').

^{13}C NMR (62.89 MHz, $CDCl_3$): δ 26.05 (C-2), 27.01, 27.21 [2 x COC(*C*H$_3$)], 30.83 (C-3), 37.38 (SO_2CH_3), 38.53 (C-2'), 38.56, 38.77 [2 x CO*C*(CH$_3$)], 64.26 (C-5'), 69.79 (C-1), 76.20 (C-3'), 78.33 (C-1'), 82.53 (C-4'), 178.02, 178.06 [2 x *C*OC(CH$_3$)].

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{19}H_{34}O_8S$ $[M+Na]^+$: 445.18666, found 445.18686.

$C_{19}H_{34}O_8S$ (422.53)	calcd:	C 54.01	H 8.11	S 7.59
	found:	C 54.00	H 8.02	S 7.60

4.2.27 (2*R*,3*S*,5*S*)-5-(3-((2-aminoethyl)amino)propyl)-2-((pivaloyloxy)methyl) tetrahydrofuran-3-yl pivalate (27)



Ethane-1,2-diamine (0.1 ml, 1.5 mmol) was added dropwise at 0 °C to a stirred solution of **26** (0.12 g, 0.3 mmol) in dry methanol (1.5 ml). After stirring for 20 h at ambient temperature (monitored by TLC in EtOAc – MeOH 10:1 with 1% NEt_3), the mixture was concentrated. The residue was diluted with CH_2Cl_2 (10 ml) and the organic phase was washed with sat aq $NaHCO_3$ (7 ml), and water (7 ml) dried and concentrated. Chromatography (EtOAc – MeOH 1:1 with 1% NEt_3) afforded **27**.

Yield: 88 mg (80%), light-yellow syrup

$[\alpha]_D^{22}$: –17.6 (*c* 1.0, $CHCl_3$)

R_f: 0.12 (EtOAc:MeOH 1:1 with 1% NEt_3)

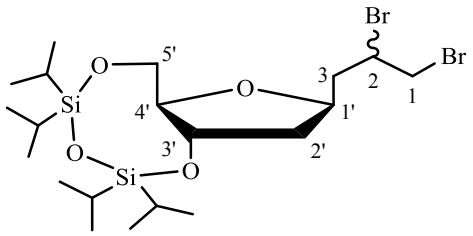
^{1}H NMR (500.13 MHz, MeOD): δ 1.20, 1.21 [2 x s, 18H, 2 x C(C*H*$_3$)$_3$], 1.55–1.77 (m, 4H, H-4, H-5), 1.78–1.87 (m, 1H, H-2'a), 2.03–2.10 (m, 1H, H-2'b), 2.82–2.91 (m, 2H, H-3), 2.98–3.07 (m, 4H, H-2, H-1), 3.98–4.01 (m, 1H, H-4'), 4.06–4.20 (m, 3H, H-1', H-5'), 5.10–5.12 (m, 1H, H-3').

^{13}C NMR (125.76 MHz, MeOD): δ 25.98 (C-4), 27.37, 27.60 [2 x COC(*C*H$_3$)$_3$], 33.36 (C-5), 39.26 (C-1), 39.49 (C-2'), 39.55, 39.84 [2 x CO*C*(CH$_3$)$_3$], 48.12 (C-2), 49.69 (C-3), 65.40 (C-5'), 77.62 (C-3'), 80.19 (C-1'), 83.94 (C-4'), 179.41, 179.67 [2 x *C*OC(CH$_3$)$_3$].

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{20}H_{38}N_2O_5$ $[M+Na]^+$: 409.26729, found 409.26733.

$C_{20}H_{38}N_2O_5$ (386.53)	calcd:	C 62.15	H 9.91	N 7.25
	found:	C 61.83	H 9.29	N 7.03

4.2.28 (6a*R*,8*R*,9a*S*)-8-(2,3-dibromopropyl)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo [3,2-*f*][1,3,5,2,4]trioxadisilocine (28)

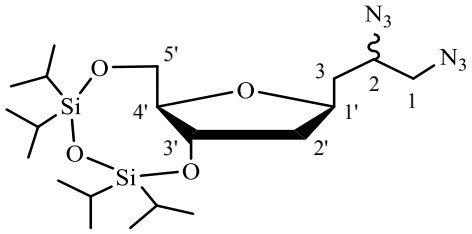


Pyridinium tribromide (6 g, 18.8 mmol) was added in few portions to a stirred solution of **7** (5 g, 12.5 mmol) in dry CH_2Cl_2 (200 ml). After stirring for 40 min at ambient temperature (monitored by TLC in Tol), the mixture was diluted with aq $Na_2S_2O_3$ (50 ml, 1 M) and stirring was continued until the brown solution was decolorized. The mixture was extracted with Et_2O (3 × 100 ml). The organic phase was washed with sat aq $NaHCO_3$ (100 ml), water (100 ml) and sat aq NaCl (100 ml) dried and concentrated. Chromatography (petroleum ether – EtOAc 3:1) afforded compound **28**. To avoid any side reaction, the desired compound **28** was used for subsequent reaction without further purification.

Yield: approx. 6.64 g (95%), brown-yellow syrup

R*f*: 0.67 (Tol)

4.2.29 (6a*R*,8*S*,9a*S*)-8-(2,3-diazidopropyl)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocine (29)



Sodium azide (9 g, 0.1 mol) was added at ambient temperature to a solution of **28** (7 g, 12.5 mmol) in dry DMF (60 ml). The reaction mixture was stirred for 2.5 h at 70 °C (monitored by TLC in Tol) and then the mixture was diluted with EtOAc (100 ml). The organic phase was washed with iced water (60 ml) and sat aq NaCl (60 ml), dried and concentrated. Chromatography (Tol) afforded compound **29**.

Yield: 4.5 g (75%), colorless syrup

$[\alpha]_D^{25}$: –27.6 (*c* 1.0, CH_2Cl_2)[7]

R_f: 0.44 (Tol)

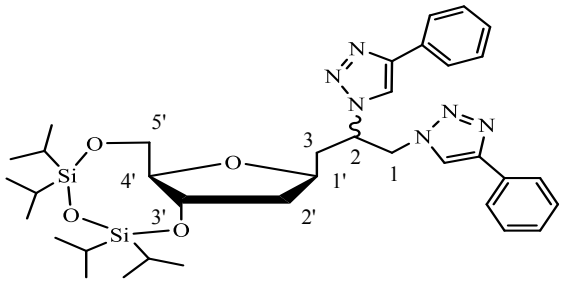
^{1}H NMR (300.13 MHz, $CDCl_3$) 2 diastereomers: δ 0.88–1.12 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.56–1.62 (m, 1H, H-3a), 1.67–1.72 (m, 1H, H-3b), 1.77–1.86 (m, 1H, H-2'a), 2.07–2.12 (m, 1H, H-2'b), 3.30–3.46 (m, 1H, H-1a), 3.46– 3.51 (m, 1H, H-1b), 3.66-3.74 (m, 1H, H-5'a), 3.74 (m, 1H, H-4'), 3.75-3.79 (m, 1H, H-2), 4.01-4.03 (m, 1H, H-5'b), 4.12-4.23 (m, 1H, H-1'), 4.37-4.41 (m, 1H, H-3').

^{13}C NMR (75.47 MHz, $CDCl_3$) 2 diastereomers: δ 12.54, 12.97, 13.34, 13.47 [4 x *C*H(CH_3)$_2$], 16.94, 17.02, 17.10, 17.25, 17.37, 17.39 (2), 17.53 [4 x CH(*C*H_3)$_2$], 36.94, 38.13 (C-3), 40.77, 40.82 (C-2'), 54.28, 55.35 (C-1), 59.02, 59.42 (C-2), 63.70, 63.81 (C-5'), 73.40, 73.54 (C-3'), 73.94, 74.05 (C-1'), 86.21, 86.41 (C-4').

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{20}H_{40}N_6O_4Si_2$ $[M+Na]^+$: 507.25418, found 507.25408.

$C_{20}H_{40}N_6O_4Si_2$ (484.74)	calcd:	C 49.56	H 8.32	N 17.34
	found:	C 49.27	H 8.55	N 17.11

4.2.30 1,1'-(3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)propane-1,2-diyl)bis(4-phenyl-1*H*-1,2,3-triazole) (30)



A mixture of compound **29** (0.1 g, 0.21 mmol), copper(II) sulfate pentahydrate (4 mg, 0.16 mmol), L(+)-ascorbic acid (25 mg, 0.15 mmol) and phenylacetylene (100 µl, 0.92 mmol) in water/DMF (1.5 ml/1.5 ml) was stirred for 60 h at 75 °C (monitored by TLC in Tol). The solution was filtered and concentrated. Chromatography (petroleum ether – EtOAc 1:1) afforded compound **30**.

Yield: 78 mg (55%), white amorphous solid

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[7] Optical rotation was determined although compound 29 implies a mixture of diastereomers. The same applies all the other diastereomers too.

$[\alpha]_D^{23}$: –25.6 (*c* 1.0, $CHCl_3$)

R_f: 0.81 (PE:EtOAc 1:1)

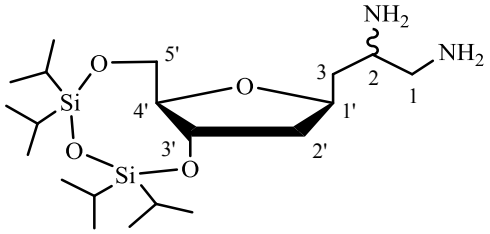
^{1}H NMR (500.13 MHz, $CDCl_3$) 2 diastereomers: δ 0.74–1.15 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.74–1.88 (m, 1H, H-2'a), 1.98–2.12 (m, 1H, H-2'b), 2.13–2.63 (m, 2H, H-3), 3.69–3.83 (m, 2H, H-5'a, H-4'), 3.98–4.06 (m, 1H, H-5'b), 3.62–3.69, 4.23–4.33 (m, 1H, H-1'), 4.34–4.45 (m, 1H, H-3'), 4.95–5.14 (m, 2H, H-1), 5.22–5.35 (m, 1H, H-2), 7.24–7.77 (m, 12H, 10 x H_{Phenyl}, 2 x C*H*=C).

^{13}C NMR (125.76 MHz, $CDCl_3$) 2 diastereomers: δ 12.51, 12.90, 13.28, 13.42 [4 x *C*H(CH_3)$_2$], 16.86, 16.91, 16.99, 17.05, 17.21, 17.36 (2), 17.49 [4 x CH(*C*H_3)$_2$], 38.38, 38.92 (C-3), 40.32, 40.45 (C-2'), 52.89, 53.72 (C-1), 58.96, 59.31 (C-2), 63.44, 63.51 (C-5'), 72.98, 73.11 (C-3'), 77.19, 73.57 (C-1'), 86.09, 86.26 (C-4'), 120.42, 120.66, 120.86, 121.67 (2 x *C*H=C), 125.71 (3), 125.75, 128.20, 128.29, 128.72 (2), 128.77 (2) (2 x 5 C_{Phenyl}), 130.02 (2) (2 x $C_{quartPhenyl}$), 147.48, 147.64, 147.83 (2 x CH=*C*).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{36}H_{52}N_6O_4Si_2$ $[M+H]^+$: 689.36728, found 689.36699.

$C_{36}H_{52}N_6O_4Si_2$ (689.02)	calcd:	C 62.76	H 7.61	N 12.20
	found:	C 62.16	H 7.35	N 12.06

4.2.31 3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]-trioxadisilocin-8-yl)propan-1,2-diamine (31)



Palladium on carbon 10 wt. % (0.2 g, 0.2 mmol was added to a stirred solution of **29** (0.5 g, 1 mmol) in dry methanol (7 ml). After stirring for 24 h at ambient temperature (monitored by TLC in EtOAc – MeOH 5:1 with 1% NEt_3). The solution was filtered and concentrated. Analytical sample of **31** was achieved by chromatography (EtOAc – MeOH 1:1 with 1% NEt_3).

Yield: 415 mg (93%), yellow syrup

$[\alpha]_D^{23}$: –17.5 (*c* 1.0, CH_2Cl_2)

R_f: 0.0 (EtOAc:MeOH 1:1 with 1% NEt_3)

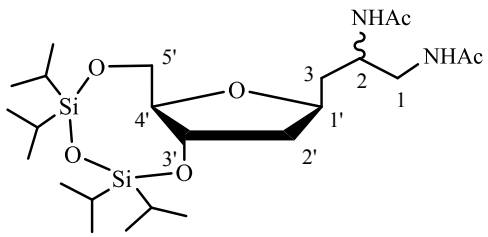
^{1}H NMR (500.13 MHz, MeOD) 2 diastereomers: δ 0.97–1.12 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.44–1.73 (m, 1H, H-3), 1.82–1.91 (m, 1H, H-2'a), 2.02–2.10 (m, 1H, H-2'b), 2.50–2.56 (m, 1H, H-1a), 2.67–2.75 (m, 1H, H-1b), 2.88–2.93 (m, 1H, H-2), 3.67–3.78 (m, 2H, H-5'a, H-4') 3.98–4.04 (m, 1H, H-5'b), 4.16–4.26 (m, 1H, H-1'), 4.38–4.44 (m, 1H, H-3').

^{13}C NMR (125.76 MHz, MeOD) 2 diastereomers: δ 14.01, 14.35, 14.74, 14.86 [4 x *C*H(CH_3)$_2$], 17.62, 17.67, 17.74, 17.90, 18.03 (2), 18.16 [4 x CH(*C*H_3)$_2$], 41.23, 41.51 (C-3), 42.22, 42.52 (C-2'), 48.38, 48.68 (C-1), 51.81, 53.14 (C-2), 65.28, 65.48 (C-5'), 75.40, 75.49 (C-3'), 76.48, 78.07 (C-1'), 87.76, 88.03 (C-4').

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{20}H_{44}N_2O_4Si_2$ $[M+H]^+$: 433.29124, found 433.29152.

$C_{20}H_{44}N_2O_4Si_2$ (432.75)	calcd:	C 55.51	H 10.25	N 6.47
	found:	C 54.36	H 10.22	N 6.32

4.2.32 *N,N*'-(3-((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)propane-1,2-diyl)diacetamide (32)



Freshly distilled Ac_2O (1.5 ml) was added dropwise at 0 °C to a vigorously stirred solution of **31** (0.1 g, 0.23 mmol) in dry pyridine (3 ml). The mixture was allowed to attain ambient temperature and stirring was continued overnight. TLC (in EtOAc – MeOH 5:1 with 1% NEt_3) showed then that the reaction was complete. Excess of Ac_2O was then destroyed by addition of methanol (50 µl) at 0 °C and stirring was continued for additional 30 min. The mixture was poured into iced water and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic phases were dried and concentrated. Chromatography (EtOAc – MeOH 10:1) gave the compound **32**.

Yield: 87 mg (73%), white amorphous solid

$[\alpha]_D^{23}$: +37.3 (*c* 1.0, $CHCl_3$)

mp: 149–156 °C

R_f: 0.34 (EtOAc:MeOH 10:1)

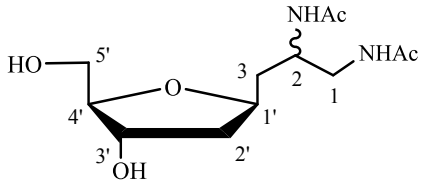
^{1}H NMR (250.13 MHz, $CDCl_3$) 2 diastereomers: δ 0.86–1.10 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.52–1.72 (m, 1H, H-3a), 1.76–1.92 (m, 2H, H-3b, H-2'a), 1.95, 1.97 (2 x s, 6H, 2 x COC*H*$_3$) 2.04–2.20 (m, 1H, H-2'b), 3.24–3.55 (m, 1H, H-1), 3.64–3.71 (m, 1H, H-4'), 3.69–3.83 (m, 1H, H-5'a) 3.94–4.08 (m, 2H, H-5'b, H-2), 4.08–4.30 (m, 1H, H-1'), 4.32–4.42 (m, 1H, H-3'), 6.39, 7.02 (2 x d, 1H, N*H*-2), 6.54–6.67 (m, 1H, N*H*-1).

^{13}C NMR (62.89 MHz, $CDCl_3$) 2 diastereomers: δ 12.50, 12.53, 12.76, 12.92, 13.24, 13.28, 13.44, 13.48 [4 x *C*H(CH_3)$_2$], 16.92, 17.00, 17.06, 17.21, 17.34, 17.36, 17.45, 17.52 [4 x CH(*C*H$_3$)$_2$], 23.15, 23.19, 23.44 (2 x CO*C*H$_3$), 37.64 (2) (C-3), 40.30, 40.62 (C-2'), 44.20, 45.25 (C-1), 49.35, 49.39 (C-2), 62.44, 63.44 (C-5'), 71.33, 72.82 (C-3'), 74.88, 75.60 (C-1'), 85.78, 86.22 (C-4'), 170.79, 171.03, 171.47 (2 x *C*OCH$_3$).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{24}H_{48}N_2O_6Si_2$ $[M+H]^+$: 517.31237, found 517.31269; calcd for $C_{24}H_{48}N_2O_6Si_2$ $[M+Na]^+$: 539.29431, found 539.29417.

$C_{24}H_{48}N_2O_6Si_2$ (516.83)	calcd:	C 55.78	H 9.36	N 5.42
	found:	C 55.72	H 9.21	N 5.29

4.2.33 *N,N'*-(3-((2*S*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl) propane-1,2-diyl)diacetamide (33)



A solution of tetra-*n*-butylammonium fluoride trihydrate (70 mg, 0.27 mmol) in dry acetone (1 ml) was added dropwise at ambient temperature to a solution of **32** (0.1 g, 0.2 mmol) in dry acetone (10 ml). The reaction mixture was stirred for 1.5 h at ambient temperature (monitored by TLC in EtOAc – MeOH 5:1) and then concentrated. Chromatography (EtOAc – MeOH 1:1) afforded compound **33**.

Yield: 46 mg (87%), colorless syrup

$[\alpha]_D^{23}$: +12.6 (*c* 1.0, MeOH)

R_f: 0.3 (EtOAc:MeOH 1:1)

^{1}H NMR (500.13 MHz, MeOD, 2 diastereomers): δ 1.68–1.83 (m, 3H, H-3, H-2'a), 1.92–2.02 (m, 1H, H-2'b), 1.98 (s, 6H,2 x COC*H*$_3$) 3.18–3.26, 3.38–3.45 (m, 2H, H-1), 3.53–3.62

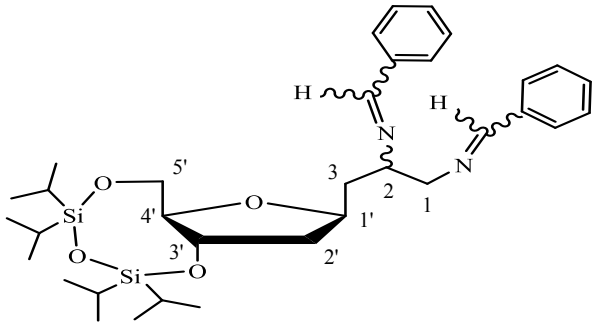
(m, 2H, H-5') 3.77–3.81 (m, 1H, H-4'), 4.05–4.17 (m, 1H, H-2), 4.18–4.24 (m, 2H, H-1', H-3').

^{13}C NMR (125.76 MHz, MeOD, 2 diastereomers): δ 22.73, 22.75, 22.95, 23.00 (2 x CO*C*H$_3$), 38.75, 38.89 (C-3), 42.23, 42.39 (C-2'), 44.33, 44.50 (C-1), 48.91, 49.09 (C-2), 64.12 (2) (C-5'), 74.07, 74.15 (C-3'), 76.91, 77.30 (C-1'), 88.79, 88.88 (C-4'), 173.36, 173.38, 173.81, 173.82 (2 x *C*OCH$_3$).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{12}H_{22}N_2O_5$ $[M+H]^+$: 275.15728, found 275.15706.

$C_{12}H_{22}N_2O_5$ (274.32)	calcd:	C 52.54	H 8.08	N 10.21
	found:	C 50.11	H 8.67	N 9.98

4.2.34 N,N'-(3-((6aR,8S,9aS)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5, 2,4] tri oxadisilocin-8-yl)propane-1,2-diyl)bis(1-phenylmethanimine) (34)



A mixture of compound **31** (70 mg, 0.16 mmol), benzaldehyde (31 µl, 0.3 mmol), molecular sieve powder (15 mg, A3 and A4) in dry methanol (0.7 ml) was stirred for 36 h at ambient temperature. The solution was filtered and concentrated without further purification to give compound **34**.

Yield: 80 mg (81%), brown-yellow syrup

$[\alpha]_D^{24}$: –13.9 (*c* 1.0, $CHCl_3$)

R$_f$: 0.31 (PE:EtOAc 10:1)

^{1}H NMR (300.13 MHz, CDCl$_3$) 2 diastereomers: δ 0.84–1.21 [m, 28H, 4 x C*H*(C*H*$_3$)$_2$], 1.43–2.36 (m, 4H, H-3, H-2'), 3.53–4.28 (m, 7H, H-1, H-1', H-2, H-5', H-4'), 4.28–4.50 (m, 1H, H-3'), 6.62–7.95 (m, 10H, 10 x H$_{Phenyl}$), 8.20, 8.24, 8.29 (3 x s, 3H, 2 x NC*H*).

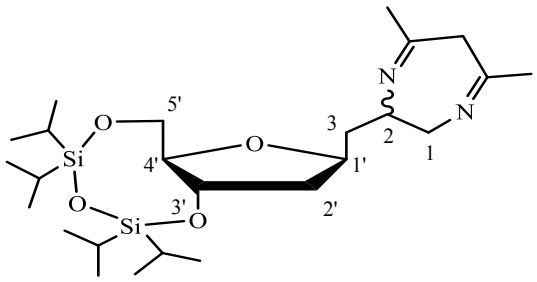
^{13}C NMR (75.47 MHz, CDCl$_3$) 2 diastereomers: δ 12.53, 12.89, 13.32, 13.42, [4 x *C*H(CH$_3$)$_2$], 16.93, 16.99, 17.10, 17.25, 17.38 (2), 17.52 [4 x CH(*C*H$_3$)$_2$], 39.92, 40.39 (C-3), 40.49, 41.14 (C-2'), 64.12, 64.20 (C-5'), 66.16, 66.72 (C-1), 68.08, 68.25 (C-2), 73.98 (2)

(C-3'), 74.78, 75.18 (C-1'), 85.58, 85.60 (C-4'), 128.01, 128.03, 128.10, 128.43 (10 x C_{Phenyl}), 130.41, 130.46 (2), 130.50 (2 x $C_{quartPhenyl}$), 161.37, 162.07, 162.53, 162.80 (2 x N*C*H).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{34}H_{52}N_2O_4Si_2$ $[M+H]^+$: 609.35384, found 609.35413.

$C_{34}H_{52}N_2O_4Si_2$ (608.97)	calcd:	C 67.06	H 8.61	N 4.60
	found:	C 65.70	H 7.96	N 4.46

4.2.35 5,7-dimethyl-2-(((6aR,8S,9aS)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)methyl)-3,6-dihydro-2*H*-1,4-diazepine (35)



A mixture of compound **31** (50 mg, 0.12 mmol) and acetylacetone (12.3 µl, 0.12 mmol) in dry ethanol (1 ml) was stirred for 24 h at ambient temperature (monitored by TLC in EtOAc – MeOH 1:1 with 1% NEt_3). The solution was filtered and concentrated without other purification to give compound **35**.

Yield: 52 mg (91%), brown syrup

$[\alpha]_D^{24}$: –22.4 (*c* 1.0, $CHCl_3$)

R_f: 0.85 (EtOAc:MeOH 1:1)

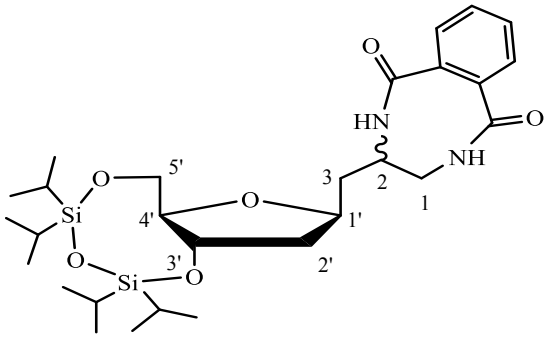
^{1}H NMR (500.13 MHz, $CDCl_3$) 2 diastereomers: δ 0.86–1.14 [m, 28H, 4 x C*H*(CH_3)$_2$], 1.15–2.61 (m, 10H, H-3, H-2', 2 x CH_3), 3.01–4.20 (m, 7H, H-1, H-2, H-1', H-4', H-5'), 4.25–4.48 (m, 1H, H-3'), 4.90–5.04 (m, 2H, $CH_3CCH_2CCH_3$).

^{13}C NMR (75.47 MHz, $CDCl_3$) 2 diastereomers: δ 12.52 (2), 12.96, 13.45 [4 x *C*H(CH_3)$_2$], 16.94, 17.01, 17.09, 17.25, 17.36 (3), 17.54 [4 x CH(*C*H_3)$_2$], 18.68, 18.94, 28.77, 28.85 (2 x CH_3), 39.37, 40.07 (C-3), 40.54, 40.88 (C-2'), 48.87, 50.14 (C-1), 51.62, 51.75 (C-2), 63.75, 64.30 (C-5'), 73.47, 73.92 (C-3'), 76.69, 77.20 (C-1'), 85.75, 86.73 (C-4'), 95.65, 95.90, 95.00 ($CH_3CCH_2CCH_3$), 162.46, 162.94, 163.11, 163.24, 163.54 ($CH_3CCH_2CCH_3$).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{25}H_{48}N_2O_4Si_2$ $[M+H]^+$: 497.32254, found 497.32250.

$C_{25}H_{48}N_2O_4Si_2$ (496.84)	calcd:	C 60.44	H 9.74	N 5.64
	found:	C 60.32	H 9.78	N 5.41

4.2.36 3-(((6a*R*,8*S*,9a*S*)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)methyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]diazocine-1,6-dione (36)



Phthaloyl chloride (30 µl, 0.21 mmol) was added at 0 °C to a stirred solution of **31** (68 mg, 0.16 mmol) in dry pyridine (2 ml). After stirring for 5 d at ambient temperature (monitored by TLC in EtOAc – MeOH 2:1) methanol (50 µl) was added and stirring was continued for additional 5 min. The mixture was poured into iced water and the aqueous phase was extracted with CH_2Cl_2 (5 × 10 ml). The combined organic phases were successively washed with aq 15% $NaHSO_4$ (10 ml), ice water (10 ml), and sat aq $NaHCO_3$ solution (10 ml), then dried and concentrated. Chromatography (EtOAc – MeOH 2:1) gave the compound **36**.

Yield: 50 mg (57%), brown syrup

$[\alpha]_D^{24}$: –16.2 (*c* 1.0, $CHCl_3$)

R_f: 0.9 (EtOAc:MeOH 2:1)

^{1}H NMR (500.13 MHz, $CDCl_3$) 2 diastereomers: δ 0.72–1.18 [m, 28H, 4 x C*H*(C*H*$_3$)$_2$], 1.19–2.50 (m, 4H, H-3, H-2'), 3.05–5.06 (m, 8H, H-1, H-2, H-1', H-3', H-4', H-5'), 7.27–8.04 (m, 4H, 4 x H_{Phenyl}).

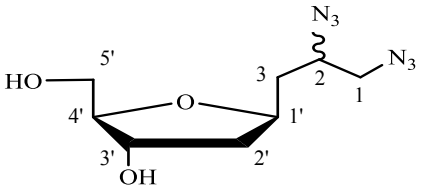
^{13}C NMR (125.76 MHz, $CDCl_3$) 2 diastereomers: δ 12.57, 12.97, 13.40, 13.50 [4 x *C*H(CH$_3$)$_2$], 14.15 (2) (C-2), 16.97, 17.05, 17.14, 17.30, 17.38, 17.42 (2), 17.55 [4 x CH(*C*H$_3$)$_2$], 19.06 (2) (C-1), 37.74 (2) (C-3), 40.62 (2) (C-2'), 64.18 (2) (C-5'), 74.01 (2) (C-3'), 77.69 (2) (C-1'), 85.95 (2) (C-4'), 123.30, 132.03, 132.30, 133.93 (4 x C_{Phenyl}), 168.70, 168.92 (2 x $C_{quartPhenyl}$).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{28}H_{46}N_2O_6Si_2$ $[M+H]^+$: 563.29672, found

563.29682; calcd for $C_{28}H_{46}N_2O_6Si_2$ $[M+Na]^+$: 585.27866, found 585.27825.

$C_{28}H_{46}N_2O_6Si_2$ (562.85)	calcd:	C 59.75	H 8.24	N 4.98
	found:	C 59.59	H 8.13	N 5.06

4.2.37 (2*R*,3*S*,5*S*)-5-(2,3-diazidopropyl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (37)



A solution of tetra-*n*-butylammonium fluoride trihydrate (0.6 g, 2 mmol) in dry acetone (10 ml) was added dropwise at ambient temperature to a solution of **29** (1 g, 2.1 mmol) in dry acetone (10 ml). The reaction mixture was stirred for 2 h at ambient temperature (monitored by TLC in EtOAc – Tol 1:1) and then concentrated. Chromatography (EtOAc) afforded compound **37**.

Yield: 430 mg (86%), light-yellow syrup

$[\alpha]_D^{24}$: –14.9 (*c* 1.0, $CHCl_3$)

R_f: 0.3 (EtOAc)

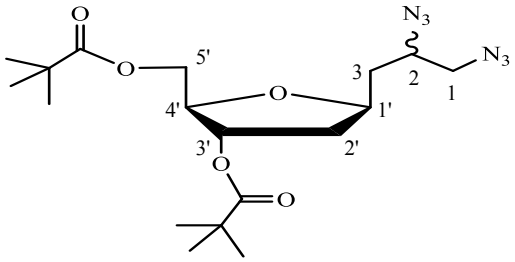
^{1}H NMR (300.13 MHz, $CDCl_3$, 2 diastereomers): δ 1.62–1.87 (m, 3H, H-3, H-2'a), 1.99–2.06 (m, 1H, H-2'b), 2.11 (br. s, 1H, OH-5'), 2.16 (br. s, 1H, OH-3'), 3.37–3.54 (m, 2H, H-1), 3.61–3.80 (m, 3H, H-2, H-5'), 3.82–3.89 (m, 1H, H-4'), 4.19–4.36 (m, 2H, H-1', H-3').

^{13}C NMR (75.47 MHz, $CDCl_3$, 2 diastereomers): δ 36.9, 37.6 (C-3), 41.9 (2) (C-2'), 54.3, 55.1 (C-1), 59.4, 59.6 (C-2) 63.1 (2) (C-5'), 73.2, 73.3 (C-3'), 75.1 (2) (C-1'), 87.0, 87.2 (C-4').

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_8H_{14}N_6O_3$ $[M+Na]^+$: 265.10196, found 265.10229.

$C_8H_{14}N_6O_3$ (242.24)	calcd:	C 39.67	H 5.83	N 34.69
	found:	C 39.60	H 6.03	N 34.21

4.2.38 (2*R*,3*S*,5*S*)-5-(2,3-diazidopropyl)-2-((pivaloyloxy)methyl)tetrahydrofuran-3-yl pivalate (38)



Pivaloyl chloride (2.5 ml, 0.02 mmol) and 4-(dimethylamino)pyridine (20 mg, 0.16 mmol) was added to a solution of **37** (90 mg, 0.4 mmol) in dry pyridine (5 ml). The reaction mixture was stirred for 2.5 h at ambient temperature (monitored by TLC in Tol – EtOAc 3:1) and then the mixture was concentrated and finally diluted with sat aq $NaHCO_3$ solution (10 ml). The aqueous phase was extracted with CH_2Cl_2 (4 x 20 ml), dried and concentrated. Chromatography (petroleum ether – EtOAc 9:1) afforded compound **38**.

Yield: 138 mg (90%), colorless syrup

$[\alpha]_D^{22}$: +26.3 (*c* 1.0, CH_2Cl_2)

R_f: 0.35 (PE:EtOAc 9:1)

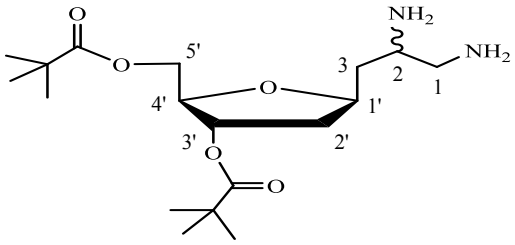
^{1}H NMR (300.13 MHz, $CDCl_3$, 2 diastereomers): δ 1.20, 1.21 [m, 18H, 2 x C(C*H*$_3$)$_3$], 1.57–1.95 (m, 3H, H-3, H-2'a), 2.04–2.10 (m, 1H, H-2'b), 3.32–3.55 (m, 2H, H-1), 3.67–3.80 (m, 1H, H-2), 4.03–4.07 (m, 1H, H-4'), 4.11–4.25 (m, 3H, H-1', H-5'), 5.10–5.12 (m, 1H, H-3').

^{13}C NMR (75.47 MHz, $CDCl_3$, 2 diastereomers): δ 27.0, 27.2 [2 x COC(*C*H$_3$)$_3$], 36.6, 37.7 (C-3), 38.6, 38.8 [2 x CO*C*(CH$_3$)$_3$], 38.9, 38.9 (C-2'), 54.3, 55.3 (C-1), 59.2, 59.7 (C-2) 64.2 (2) (C-5'), 75.3, 75.5 (C-1'), 75.9, 76.1 (C-3'), 82.7, 82.8 (C-4'), 178.0, 178.1 [2 x *C*OC(CH$_3$)$_3$].

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{18}H_{30}N_6O_5$ $[M+Na]^+$: 433.21699, found 433.21673.

$C_{18}H_{30}N_6O_5$ (410.48)	calcd:	C 52.67	H 7.37	N 20.47
	found:	C 52.70	H 7.42	N 20.39

4.2.39 (2*R*,3*S*,5*S*)-5-(2,3-diaminopropyl)-2-((pivaloyloxy)methyl)tetrahydrofuran-3-yl pivalate (39)



Palladium on carbon 10 wt. % (160 mg, 1.5 mmol was added to a stirred solution of **38** (0.5 g, 1.2 mmol) in dry methanol (7 ml). After stirring for 24 h at ambient temperature (monitored by TLC in EtOAc – MeOH 10:1 with 1% NEt_3). The solution was filtered and concentrated. Analytical sample of **39** was achieved by chromatography (EtOAc – MeOH 1:1 with 1% NEt_3).

Yield: 393 mg (90%), light-yellow syrup

$[\alpha]_D^{23}$: +8.43 (*c* 1.0, MeOH)

R_f: 0.1 (EtOAc:MeOH 3:1)

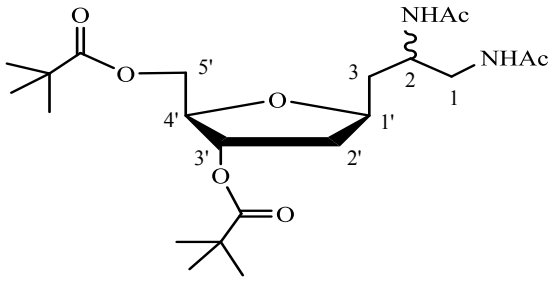
^{1}H NMR (500.13 MHz, MeOD, 2 diastereomers): δ 1.20, 1.21 [2 x s, 18H, 2 x C(C*H*$_3$)$_3$], 1.49–1.89 (m, 3H, H-3, H-2'a), 2.05–2.12 (m, 1H, H-2'b), 2.53–2.60 (m, 1H, H-1a), 2.69–2.77 (m, 1H, H-1b), 2.92–2.96 (m, 1H, H-2), 3.99–4.03 (m, 1H, H-4'), 4.14–4.28 (m, 3H, H-1', H-5'), 5.07–5.10 (m, 1H, H-3').

^{13}C NMR (125.76 MHz, MeOD, 2 diastereomers): δ 27.54, 27.76 [2 x COC(*C*H$_3$)$_3$], 39.73, 40.00 [2 x CO*C*(CH$_3$)$_3$], 40.03, 40.22 (C-2'), 40.77, 41.05 (C-3), 48.33, 48.60 (C-1), 51.94, 53.28 (C-2), 65.62, 65.69 (C-5'), 77.43, 77.67 (C-3'), 77.81, 79.47 (C-1'), 84.28, 84.49 (C-4'), 179.65, 179.82 [2 x *C*OC(CH$_3$)$_3$].

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{18}H_{34}N_2O_5$ $[M+H]^+$: 359.25405, found 359.25421; calcd for $C_{18}H_{34}N_2O_5$ $[M+Na]^+$: 381.23599, found 381.23623.

$C_{18}H_{34}N_2O_5$ (358.48)	calcd:	C 60.31	H 9.56	N 7.81
	found:	C 59.87	H 9.50	N 7.93

4.2.40 (2*R*,3*S*,5*S*)-5-(2,3-diacetamidopropyl)-2-((pivaloyloxy)methyl)tetrahydrofuran-3-yl pivalate (40)



Freshly distilled Ac_2O (1.5 ml) was added dropwise at 0 °C to a vigorously stirred solution of **31** (140 mg, 0.3 mmol) in dry pyridine (3 ml). The mixture was allowed to attain ambient temperature and stirring was continued overnight (monitored by TLC in EtOAc – MeOH 5:1 with 1% NEt_3). Excess of Ac_2O was then destroyed by addition of methanol (50 µl) at 0 °C and stirring was continued for additional 30 min at that temperature. The mixture was poured into iced water and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic phases were dried and concentrated. Chromatography (EtOAc – MeOH 10:1) gave the compound **40**.

Yield: 108 mg (63%), colorless solid

$[\alpha]_D^{23}$: + 59.3 (*c* 1.0, $CHCl_3$)

R*f*: 0.32 (EtOAc:MeOH 10:1)

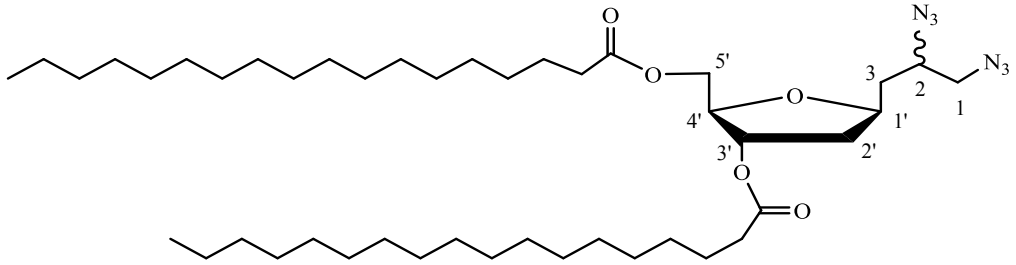
^{1}H NMR (500.13 MHz, $CDCl_3$, 2 diastereomers): δ 1.20, 1.21 [2 x s, 18H, 2 x C(C*H*$_3$)$_3$], 1.41–2.15 (m, 10H, H-3, H-2', 2 x COC*H*$_3$), 3.27–3.36, 3.58–3.67 (m, 2H, H-1), 3.91–4.03 (m, 2H, H-2, H-4'), 4.07–4.67 (m, 3H, H-1', H-5'), 5.06–5.09 (m, 1H, H-3'), 6.40–6.42, 7.35–7.36 (2 x d, 1H, N*H*-2), 6.63–6.70 (m, 1H, N*H*-1).

^{13}C NMR (125.76 MHz, $CDCl_3$, 2 diastereomers): δ 22.87, 23.14, 23.41 (2) [2 x CO(*C*H$_3$)], 26.99, 27.00, 27.22, 27.31 [2 x CO(*C*H$_3$)$_3$], 32.62, 36.85 (C-3), 38.55, 38.80 [2 x C_{quart}] 38.90, 39.62 (C-2'), 43.49, 45.04 (C-1), 49.68, 50.60 (C-2), 63.50, 64.10 (C-5'), 75.44, 75.52 (C-3'), 77.16, 77.20 (C-1'), 83.34, 84.45 (C-4'), 170.64, 171.10, 171.46, 172.65 [2 x CO*C*(CH$_3$)], 178.08, 178.23, 178.38, 178.66 [2 x *C*OC(CH$_3$)$_3$].

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{22}H_{38}N_2O_7$ $[M+H]^+$: 443.27518, found 443.27547; calcd for $C_{22}H_{38}N_2O_7$ $[M+Na]^+$: 465.25712, found 465.25714.

$C_{22}H_{38}N_2O_7$ (442.55)	calcd:	C 59.71	H 8.66	N 6.33
	found:	C 58.83	H 8.78	N 6.10

4.2.41 (2*R*,3*S*,5*S*)-5-(2,3-diazidopropyl)-2-((nonadecanoyloxy)methyl)tetrahydro furan-3-yl nonadecanoate (41)



Stearoyl chloride (3 g, 10 mmol) and 4-(dimethylamino)pyridine (20 mg, 0.16 mmol) was added to a solution of **37** (160 mg, 0.66 mmol) in dry pyridine (20 ml). The reaction mixture was stirred for 2 h at ambient temperature (monitored by TLC in EtOAc) and then the mixture was concentrated and finally diluted with sat aq $NaHCO_3$ solution (10 ml). The aqueous phase was extracted with CH_2Cl_2 (5 x 20 ml), dried and concentrated. Chromatography (Tol – EtOAc 25:1) afforded compound **41**.

Yield: 426 mg (80%), white amorphous solid

$[\alpha]_D^{22}$: –2.6 (*c* 1.0, $CHCl_3$)

R_f: 0.25 (Tol:EtOAc 50:1)

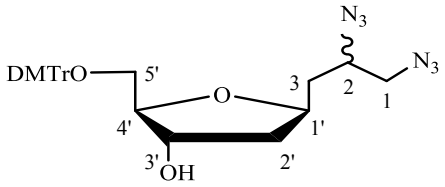
^{1}H NMR (250.13 MHz, $CDCl_3$, 2 diastereomers): δ 0.86–0.91 [m, 6H, 2 x $CH_2CH_2(CH_2)_{14}CH_3$], 1.26 [br s, 56H, 2 x $CH_2CH_2(CH_2)_{14}CH_3$], 1.58–1.69 [m, 4H, 2 x $CH_2CH_2(CH_2)_{14}CH_3$], 1.75–1.92 (m, 3H, H-3, H-2'a), 2.09 (dd, 1H, $^2J_{2'a,2'b}$ =13.48 Hz, $^3J_{2'b,3'}$ = 4.81 Hz, H-2'b), 2.29–2.37 [m, 4H, 2 x $CH_2CH_2(CH_2)_{14}CH_3$], 3.31–3.55 (m, 2H, H-1), 3.66–3.81 (m, 1H, H-2), 4.03–4.11 (m, 1H, H-4'), 4.11–4.25 (m, 3H, H-1', H-5'), 5.9–5.13 (m, 1H, H-3').

^{13}C NMR (62.89 MHz, $CDCl_3$, 2 diastereomers): δ 14.1 (2) [2 x $CH_2CH_2(CH_2)_{14}CH_3$], 22.7, 24.9, 24.9, 29.1, 29.1, 29.2, 29.3, 29.34, 29.5, 29.6, 29.7, 29.7 (2), 31.9, 34.2, 34.3 [2 x $CH_2CH_2(CH_2)_{14}CH_3$], 36.5, 37.7 (C-3), 38.6, 38.8 (C-2'), 54.3, 55.3 (C-1), 59.1, 59.6 (C-2) 64.0 (2) (C-5'), 75.3, 75.5 (C-1'), 75.9, 76.0 (C-3'), 82.5, 82.6 (C-4'), 173.3, 173.4 [2 x $COOCH_2CH_2(CH_2)_{14}CH_3$].

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{46}H_{86}N_6O_5$ $[M+Na]^+$: 797.62389, found 797.62363.

$C_{46}H_{86}N_6O_5$ (803.23)	calcd:	C 68.79	H 10.79	N 10.46
	found:	C 68.94	H 10.16	N 10.71

4.2.42 (2*R*,3*S*,5*S*)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5-(2,3-diazido propyl)tetrahydrofuran-3-ol (42)



4,4′-Dimethoxytrityl chloride (850 mg, 2.5 mmol), 4-(dimethylamino)pyridine (30 mg, 0.25 mmol) and triethylamine (0.51 ml, 4 mmol) was added to a solution of **37** (0.5 g, 2.1 mmol) in dry DMF (15 ml). The reaction mixture was stirred for 24 h at ambient temperature (monitored by TLC in petroleum ether – EtOAc 1:1) and then was diluted with CH_2Cl_2 (15 ml). The solution was washed with iced water (10 ml) and sat aq NaCl (10 ml) dried, and concentrated.. Chromatography (petroleum ether – EtOAc 1:1) afforded compound **42**.

Yield: 0.9 g (80%), yellow syrup

$[\alpha]_D^{22}$: –13.1 (*c* 1.0, $CHCl_3$)

R_f: 0.25 (Tol:EtOAc 50:1)

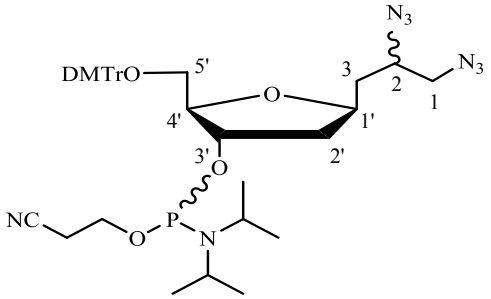
^{1}H NMR (500.13 MHz, $CDCl_3$, 2 diastereomers): δ 1.53–1.71 [m, 1H, 3'-OH], 1.73–1.92 (m, 3H, H-3, H-2'a), 1.97–2.04 (m, 1H, H-2'b), 3.10–3.13 (m, 1H, H-5'a), 3.23–3.26 (m, 1H, H-5'b), 3.39–3.53 (m, 2H, H-1), 3.67–3.75 (m, 1H, H-2), 3.80 (s, 6H, C*H*$_3$-O), 3.89–3.92 (m, 1H, H-4'), 4.21–4.31 (m, 1H, H-1'), 4.32–4.36 (m, 1H, H-3'), 6.83–6.85, 7.16–7.25, 7.28-7.34, 7.43–7.46 (m, 13H, *Aryl*-DMTr).

^{13}C NMR (125.76 MHz, $CDCl_3$, 2 diastereomers): δ 31.1 (C-3), 41.1 (C-2'), 54.3 (C-1), 55.2 (2 x *C*H$_3$-O), 59.4 (C-2) 64.5 (C-5'), 74.4 (C-3'), 74.6 (C-1'), 86.1 (C-4'), 86.2 (*C*(Ph)$_3$), 113.1, 126.8, 127.8, 128.1, 129.1, 130.0, 136.0, 144.8, 158.5 (*Aryl*-DMTr).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{29}H_{32}N_6O_5$ $[M+Na]^+$: 567.23264, found 567.23318.

$C_{29}H_{32}N_6O_5$ (544.61)	calcd:	C 63.96	H 5.92	N 15.43
	found:	C 68.94	H 10.16	N 10.71

4.2.43 ((2*R*,3*S*,5*S*)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5-(2,3-diazido propyl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite (43)



Compound **42** (125 mg, 0.23 mmol) was dried by co-evaporation with dry pyridine (3 x 5 ml) and left under vacuum overnight. The residue was dissolved with dry CH_2Cl_2 (5 ml). 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite (77 µl, 0.35 mmol) and diisopropylethylamine (0.16 ml, 0.12 g, 0.92 mmol) were added under stirring. After stirring for 3 h at ambient temperature (monitored by TLC in petroleum ether – EtOAc 1:1 with 1% NEt_3) the reaction mixture was diluted with CH_2Cl_2 (5 ml) and washed with sat aq $NaHCO_3$ (6 ml) and sat aq NaCl (6 ml) dried and concentrated. Chromatography (petroleum ether – EtOAc 2:1 with 1% NEt_3) afforded compound **43**.

Yield: 103 mg (60%), yellow syrup

$[\alpha]_D^{23}$: +7.3 (*c* 1.0, $CHCl_3$)

R_f: 0.1 (PE:EtOAc 2:1 with 1% NEt_3)

^{1}H NMR (500.13 MHz, $CDCl_3$, 2 diastereomers): δ 0.91–1.58 [m, 12H, 2 x CH(CH_3)$_2$], 1.61–1.95 (m, 3H, H-3, H-2'a), 2.08–2.42 (m, 1H, H-2'b), 2.47–2.97 (m, 2H, CH_2CN), 3.00–3.25 (m, 2H, H-5'), 3.26–3.67 (m, 4H, H-1, 2 x C*H*(CH_3)$_2$), 3.68–3.83 (m, 6H, CH_3-O), 3.85–4.46 (m, 5H, H-1', H-4', H-2, CH_2OP),4.70–4.97 (m, 1H, H-3'), 6.71–6.85, 7.10–7.54, 8.04–8.10 (m, 13H, *Aryl*-DMTr).

^{13}C NMR (125.76 MHz, $CDCl_3$, 2 diastereomers): δ 20.03, 20.14 (*C*H_2CN), 22.41, 22.58, 22.85, 22.89, 22.94, 22.97 (2 x CH(*C*H_3)$_2$), 37.01 (C-3), 40.28 (C-2'), 45.25, 45.34 (2 x *C*H(CH_3)$_2$), 54.34 (C-1), 55.17 (2) (2 x *C*H_3-O), 58.07, 58.16 (*C*H_2OP), 59.44 (C-2) 64.15 (C-5'), 77.20, 77.79 (C-3', C-1'), 86.06 (C-4'), 86.07 (*C*(Ph)$_3$), 113.07 (*Aryl*-DMTr), 116.85 (CN) 126.75, 127.75, 128.17, 129.17, 130.07 (2), 135.94, 136.14 (*Aryl*-DMTr).

HRMS, ESI-TOF/MS positive (*m/Q*): calcd for $C_{38}H_{49}N_8O_6P$ $[M+H]^+$: 745.35728, found 745.35713.

$C_{38}H_{49}N_8O_6P$ (744.83)	calcd:	C 61.28	H 6.63	N 15.04
	found:	C 60.79	H 6.35	N 15.22

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Statement

Hereby, I declare that I have prepared this thesis independently. Only the sources and resources explicitly mentioned in the work were used. In fact, I have marked literally or analogously accepted ideas distinctly.

Rostock, 01.02.2018	Helena Apelt
Place, Date	Signature