

Zusammenfassung der wissenschaftlichen Ergebnisse
Zur Dissertation

**Synthesis of Phosphonate Analogues of the
Antibiotic Moenomycin A₁₂**

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eingereicht von

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The moenomycin-type compounds are known to inhibit selectively the enzyme *penicillin binding protein 1b* (PBP 1b) that catalyses the transglycosylation reaction in the biosynthesis of bacterial cell wall peptidoglycan. The moenomycins (see moenomycin ₁₂) have been shown to interfere with this biosynthetic step interacting with the enzyme(s).

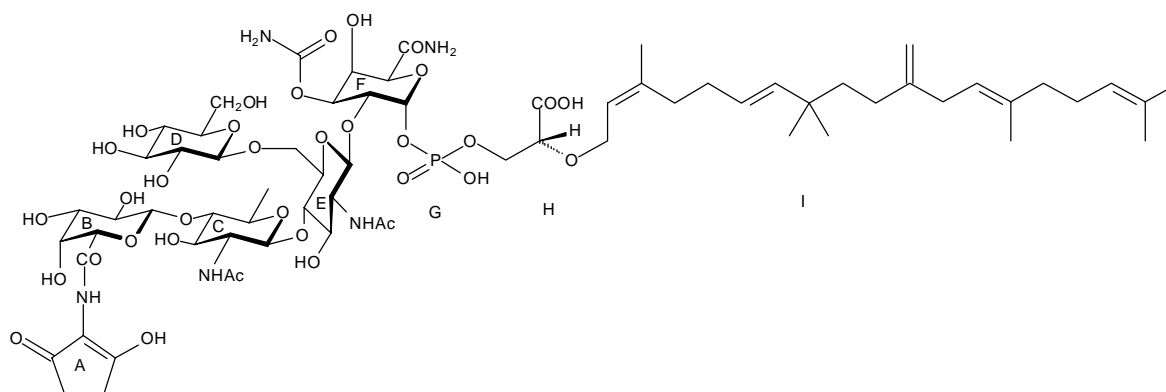


Figure 1: Moenomycin A₁₂

The moenomycins do not induce resistance readily. A weak point in this respect may, however, be the phosphate bond to unit F. Its cleavage by a yet poorly characterized enzyme is the only enzymatic degradation reaction of the moenomycins that is known to -date. With this in mind we started a programme aimed at synthesizing trisaccharide analogues of moenomycin A₁₂ in which the phosphate oxygen at -1 of unit F is replaced by a CH₂ group.

It seemed important to retain all other functional groups in ring F as present in moenomycin since they are known to be of major importance as far as antibiotic activity is concerned.

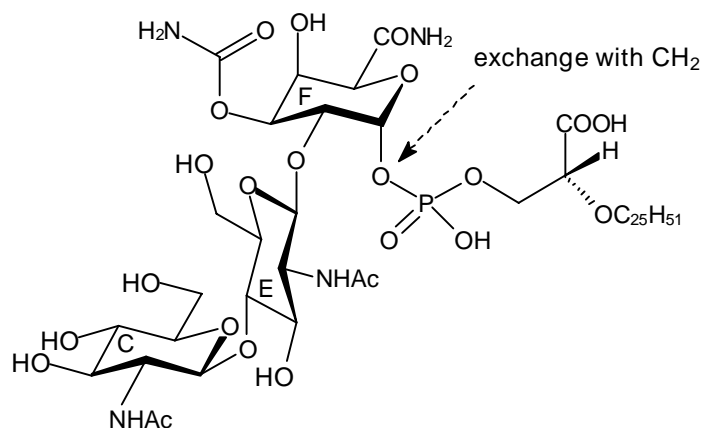
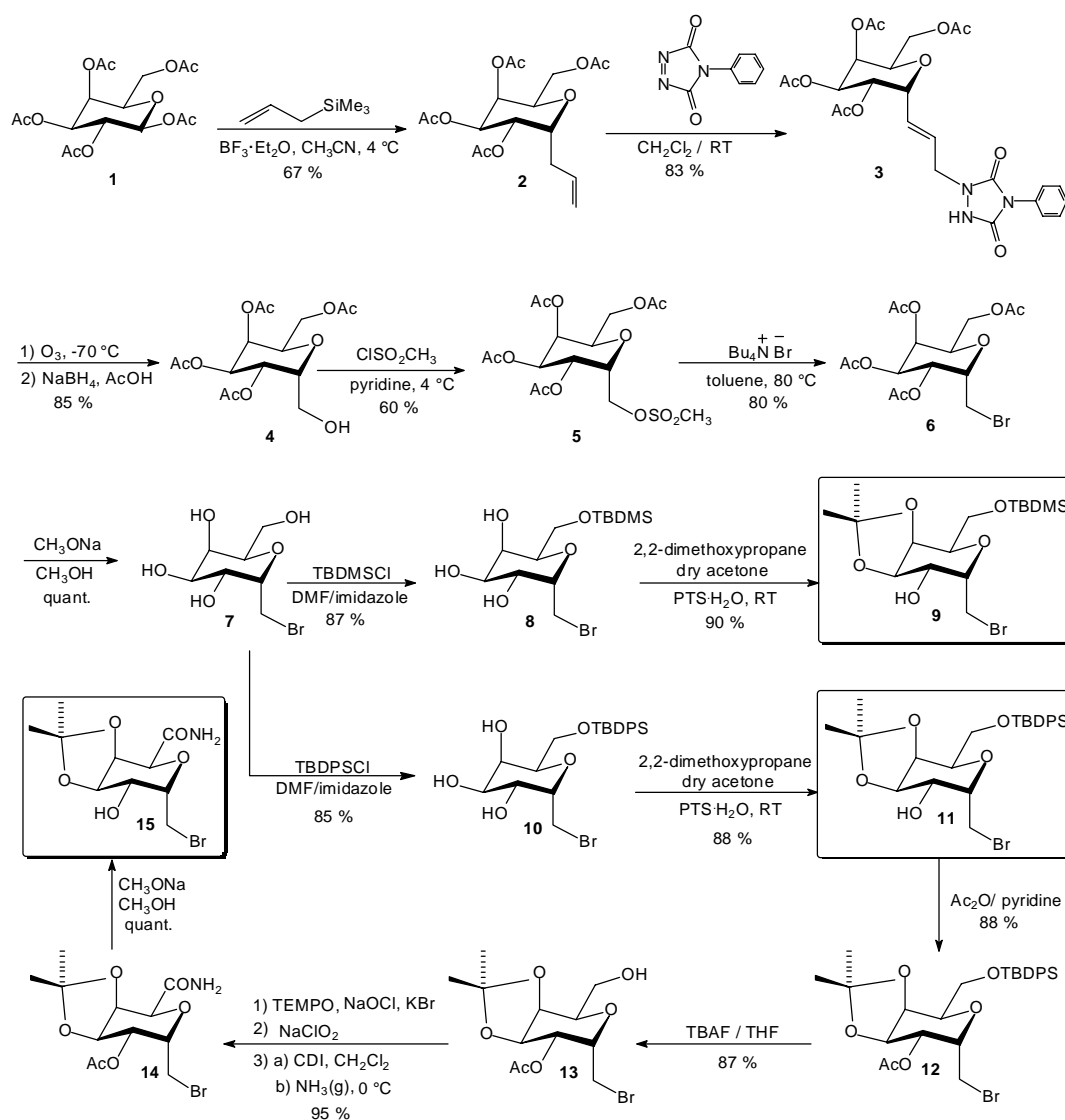


Figure 2: Target molecule

It appeared that the commercially available and cheap β -D-galactose-pentaacetate **1** would be an interesting starting material for this synthesis. The synthesis began with the introduction of the C-glycoside appendage at position 1 according to *Giannis et al.*, thus forming the allyl C-galactopyranoside **2**, a substance that represents the first C-glycosyl backbone for the synthesis of the glycosyl acceptors. The total synthesis of the glycosyl acceptors is shown in Scheme 1. Ene reaction of **2** with 4-phenyltriazolin-3,5-dione in CH_2Cl_2 provided **3** in 83 % yield. Ozonolysis of this alkene ($-70\text{ }^\circ\text{C}$, $\text{MeOH}-\text{CH}_2\text{Cl}_2$) and subsequent quenching with dimethyl sulfide, followed by reduction of the crude aldehyde with sodium acetoxyborohydride (prepared from NaBH_4 and AcOH in THF) furnished the primary alcohol **4** (85 %). This alcohol was converted into the mesylate **5** (60 %), and this in turn into the bromide **6** (80 %) by heating it at $80\text{ }^\circ\text{C}$ with tetrabutylammonium bromide in toluene. The acetate groups were hydrolysed using *Zemplén* conditions to furnish **7** quantitatively. The primary hydroxyl group in **7** was protected as a ${}^t\text{BuMe}_2\text{Si}$ ether **8** (87 %) on reaction with ${}^t\text{BuMe}_2\text{SiCl}$ in *N,N'*-dimethylformamide (DMF) at $0\text{ }^\circ\text{C}$ and as a ${}^t\text{BuPh}_2\text{Si}$ ether **10** (85 %) on reaction with ${}^t\text{BuPh}_2\text{SiCl}$ in DMF at $0\text{ }^\circ\text{C}$ in the presence of imidazole. 4-toluenesulfonic acid-catalysed isopropylideneation of the 3,4-diols **8** and **10** with 2,2-dimethoxypropane in dry acetone gave the 3,4-*O*-acetonide derivatives **9** (88 %) and **11** (90 %), respectively.

The glycosyl acceptor **15** was obtained from the glycosyl acceptor **11** in the following sequence. The free hydroxyl group in compound **11** was protected as an acetate group on reaction with acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine (DMAP) giving **12** (88 %). The silyl ether in **12** was cleaved with a molar solution of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) affording compound **13** in 87

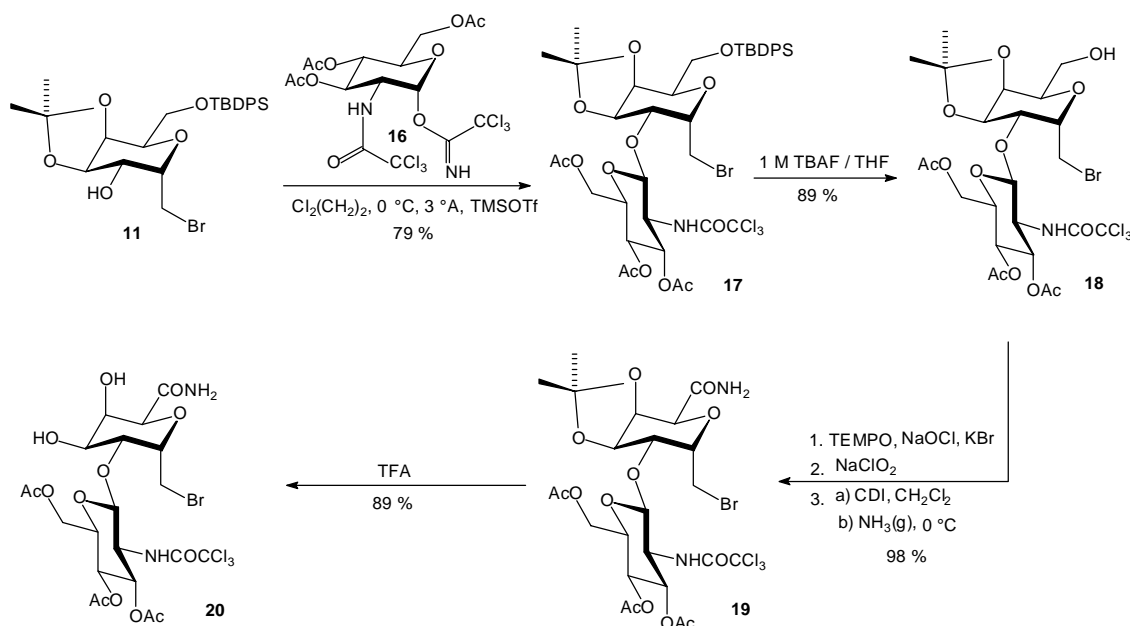
% yield. The free hydroxyl group in **13** was then subjected to an oxidation using the 2,2,6,6-tetramethyl-1-piperidinyloxy-radical (TEMPO) method affording the aldehyde which was in turn oxidised with sodium chlorite to the corresponding acid. The acid was converted to the amide **14**, making use of *Staab's* method, in which the acid was activated with *N,N'*-carbonyldiimidazole (CDI) in dichloromethane to give the imidazolidine, which upon reaction with ammonia furnished the amide **14** in an overall yield of 95 %. The required glycosyl acceptor **15** was obtained in quantitative yield by cleavage of the ester bond at position 5 under *Zemplén* conditions.



Scheme 1: Synthesis of the glycosyl acceptors

Disaccharide formation was achieved employing the *Jacquinet* and *Blatter* method, which involves the use of glycosyl donor **16** and trimethylsilyl triflate (TMSOTf). No reaction was observed between this donor and acceptor **15**, which may reflect the low nucleophilicity of the acceptor. On the contrary, glycosylation with acceptor **11** gave **17** (79 %). Deprotection of the

silyl group in the disaccharide **17** was easily accomplished on treatment with a molar solution of TBAF in THF at room temperature (RT) affording **18** (89 %). Synthesis of the uronamide **19** was achieved after three major steps, in an overall yield of 98 %. Oxidation of the primary hydroxyl group in unit F of **18** to the corresponding aldehyde was accomplished with sodium hypochlorite and TEMPO. Oxidation of the crude aldehyde to the carboxylic acid with sodium chlorite followed by amide formation according to *Staab* gave **19**. Removal of the isopropylidene group from **19** with trifluoroacetic acid (TFA) at RT furnished the diol **20** (89 %).

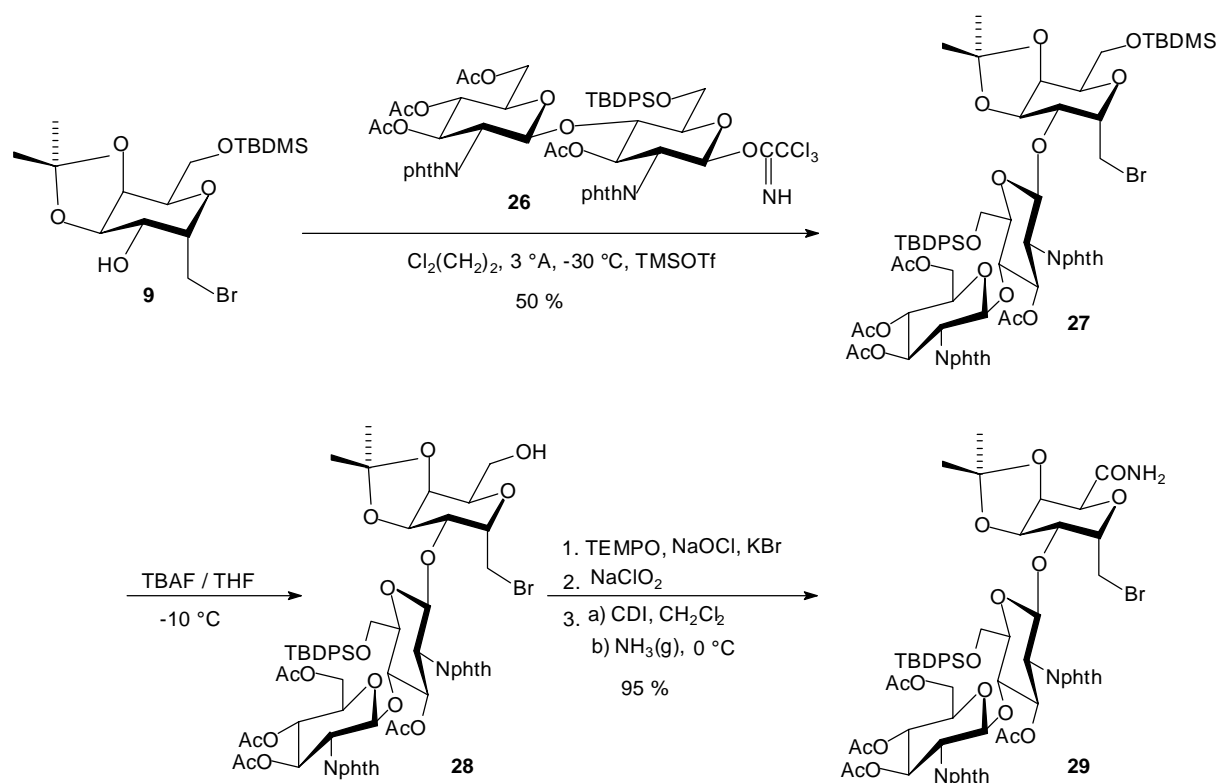


Scheme 2: Synthesis of disaccharide **20**

Introduction of the carbamoyl group at -4^F position was not easy (Scheme 3). It was achieved in two steps. Conversion of the diol **20** into the cyclic carbonate **21** with CDI into the CH_2Cl_2 (84 %) and subsequent ring opening of this carbonate by bubbling a stream of gaseous ammonia in CH_2Cl_2 solution at $0\text{ }^\circ\text{C}$ gave **22** (62 %) as well as its isomer (21 %).

Dehalogenation of the N-trichloroacetyl group was intensively studied, but interactions of other functional groups in the studied substances could not be avoided. The base-labile carbonate in **21** and the carbamoyl group in urethane **22** were cleaved under the reaction conditions. Hydrolysis of **22** with 0.5 M LiOH in MeOH-THF (1:1) followed by acetylation gave **24** (73 %), while its reduction with NaBH_4 in ethanol followed by acetylation gave **23** ($60\text{ }^\circ\text{C}$, 85 %; RT, 83 %). On the other hand, reduction of **22** with NaBH_4 in ethanol at $60\text{ }^\circ\text{C}$ followed by acetylation gave **23** (78 %), while performing the reduction step at $5\text{ }^\circ\text{C}$ (THF - MeOH 4:1) or at RT (ethanol or isopropanol) gave **24** in an average yield of 65 %. The reaction between the N-trichloroacetyl group and NaBH_3CN was also fruitless. The phosphonate grouping was installed making use of *Arbuzov* reaction furnishing **25** (70 %).

Trisaccharides could not be obtained from the recently synthesized donor **26** and the acceptor **15**. However, trisaccharide formation was achieved through the glycosylation reaction of donor **26** and acceptor **9** in 50 % yield (-30 °C, 1,2 -dichloroethane, 3 Å, TMSOTf - triethylamine). Selective deprotection of the ^tBuMe₂Si group in compound **27** was accomplished at -10 °C with 1 eq of a molar solution of TBAF in THF. The free hydroxyl group of **28** was subjected to an oxidation using the TEMPO method affording the aldehyde. After oxidation of the aldehyde with sodium chlorite, the resulting carboxylic acid was converted according to *Staab's* method into the amide **29** in an overall yield of 95 % (based on **27**). There were difficulties in converting the N-phthalimido group in **29** to the N-acetyl group which is necessary for biological activity of moenomycin-type compounds, since the reactions were accompanied by elimination of HBr.



Scheme 4: Trisaccharide synthesis

In conclusion, the synthetic methods employed in this work allow to prepare the di- and trisaccharides C-phosphonate analogues of moenomycin A₁₂.