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Macrocyclic nitrogen-containing receptors with sucrose unit: synthesis and complexing properties

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"Sugars as raw materials in the synthesis of products with high added value".

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I would like to thank all the colleagues from Group IV IChO PAS for help and great working atmosphere.

Summary

Glossary

ANS -	8-anilino-1-naphthalene sulfonate
BAIB –	(bisacetoxyiodo)benzene
BOP reagent –	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
CTP –	cytidine-5’-triphosphate
dAMP –	2’-deoxyadenosine-5’-monophosphate
DEPC –	diethyl phosphoryl cyanide, diethyl cyanophosphonate
dGMP –	2’-deoxyguanosine-5’-monophosphate
DIC –	*N*,*N'*-diisopropylcarbodiimide
DMA –	dimethylacetamide
EDC (EDAC or EDCI) –	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Fmoc –	Fluorenylmethyloxycarbonyl
HAPyU –	1-(1-pyrrolidinyl-1H-1,2,3-triazolo[4,5-b]pyridinylmethylene)-pyrrolidinium hexafluorophosphate-3-oxide
HATU –	*O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate
HOAt –	1-hydroxy-7-azabenzotriazole
HOBt –	hydroxybenzotriazole
IIDQ –	1-(isobutoxycarbonyl)-2-isobutoxy-1,2-dihydroquinoline
Mtr –	4-methoxy-2,3,6-trimethylbenzenesulfonyl
NMM –	N-Methylmorpholine
SAA –	sugar amino acid
SAC –	sugar-aza-crown
Pd2,6ST –	*Photobacterium damsela* α-2,6-sialyltransferase
PTC -	phase-transfer catalysis
RCAM –	Ring-closing alkyne metathesis
TBTU –	2-(1*H*benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TEMPO –	2,2,6,6-tetramethyl-1-piperidinyloxyl
TPP -	triphenylphosphine

1 Introduction

Nitrogen-containing macrocyclic compounds (amines, amides, *N*-heterocyclic derivatives), because of their complexing abilities, are very important targets in supramolecular chemistry.[1] No wonder, therefore, that development of novel, chiral, macrocyclic receptors is of great interest in this field of research. One of the main problems is connected with the search for useful precursors of these receptors.

In this context, carbohydrates, because of their properties (biological activity, chirality, poly-functionality, solubility *etc*.) and economic factors (relatively low price), are perspective synthetic building blocks. Combination of the carbohydrate scaffold and nitrogen-containing functional groups in macrocyclic molecules should, therefore, open a convenient way to chiral receptors with interesting properties.

Surprisingly, despite the large potential of macrocyclic structures with incorporated carbohydrate unit(s), application of the cheapest carbohydrate: sucrose is not well investigated.

The aim of the research presented in this dissertation is to explore the use of sucrose scaffold as a building block in the synthesis of nitrogen-containing macrocycles.

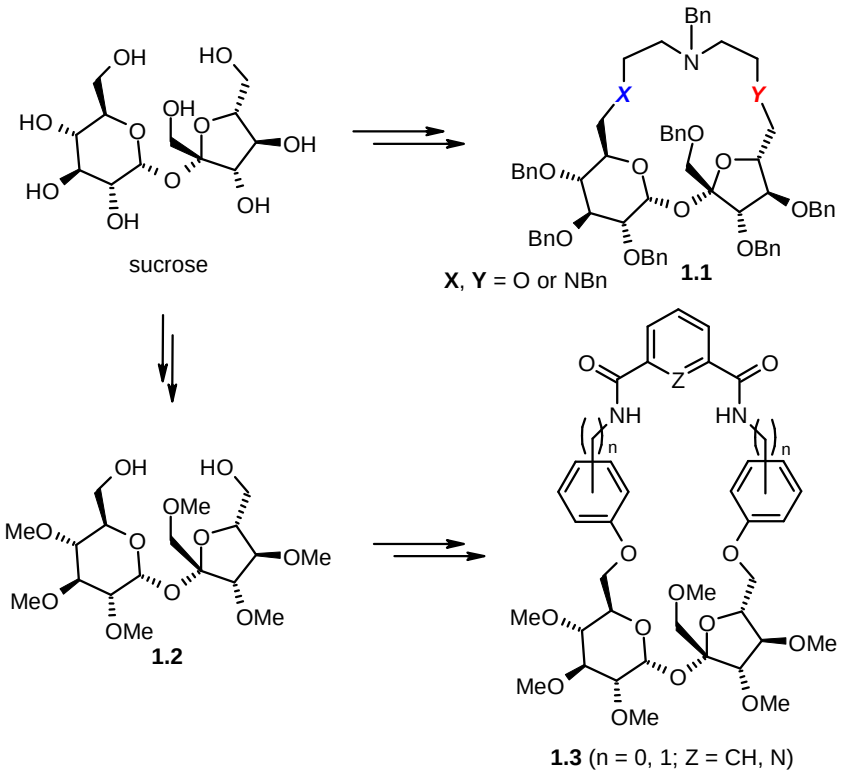
In the previous study of Jarosz group, a series of per-oxygen sucrose-based crown ethers were presented (Mach's[2] and Listkowski's[3] PhD disertations). Several aza-crown ethers were also studied (Lewandowski's PhD dissertation[4]). This research showed that the receptors containing nitrogen functionalities have more interesting complexing properties than the per-oxygen analogs. I have decided, therefore, to investigate in more detail the nitrogen-containing sucrose-based receptors.

In the first part of my research, I have planned to perform the synthesis of novel mono- and di-aza-crown ethers **1.1** (Scheme 1.1). Next step would require an extensive study of their complexing properties; especially the enantioselectivity of the complexation of chiral, natural products (such as aminoacid derivatives). One of the important problems which could arise during the study is: how these properties would depend on a number of the nitrogen atoms, as well as, their position(s) in the macrocyclic ring.

Another part of the proposed research would deal with the synthesis of macrocyclic amides with sucrose scaffold. As is already proven, presence of the amide functionalities in

the macrocyclic molecules greatly enhance their complexing abilities; moreover, sucrose unit should provide significant contribution to enatioselective recognition of the guests.

I decided, therefore, to develop an efficient approach to sucrose-containing dilactams **1.3** (Scheme 1.1).



Scheme 1.1 Macrocyclic nitrogen-containing compounds with sucrose units.

To my opinion, the sucrose-based macrocyclic derivatives (planned in my PhD work) are very promising hosts which should exhibit interesting complexing properties, especially towards chiral natural compounds (like aminoacids). Elaboration of a convenient synthesis of such compounds should give us an easy access to large assortment of the artificial receptors based on the sucrose platform. I hope that it may also give an insight to better understanding of enantioselective complexation.

2 Literature review

Carbohydrates (saccharides) are natural, biologically important compounds that, together with nucleic acids, proteins, and lipids, are components of cells and constitute a large and diverse class of compounds present in various materials and have major roles in applications in chemistry, biology, material science, and related fields.[5,6]

In synthetic aspect, carbohydrates are polyhydroxy molecules that, because their natural genesis, optical purity, as well as, excellent water solubility are useful building blocks in preparation of many essential drugs.[7] Our attention was drawn to macrocyclic compounds containing the carbohydrate units. In this overview, we categorized the carbohydrate based macrocycles, demonstrated the common approaches to the synthesis of these macrocycles and showed their most important use.

2.1 Aza-crown ethers containing the carbohydrate subunit

Crown ethers are primary supramolecular receptors[8] which play a crucial role in the formation of host-guest complexes.[1] Cation-complexing ability of these macrocycles is widely used in catalysis (including phase transfer catalysis: PTC),[9] transport of metal cations through membranes,[10] as well as, in the synthesis of catenenes[11] and rotaxanes.[12] Chiral crown ethers and their analogs[13] are often used as catalysts in asymmetric synthesis[9] and/or as synthetic receptors in chiral analysis and separation.[14] The design of these receptors is based on common enatiomerically pure starting plaforms such as *e.g.*: amino acids,[15–18] binaphtyl,[19–21] salen,[21] terpenes,[22] or sugars.[23,24]

Carbohydrates, cheap and renewable raw materials, available in optically pure form, are particularly useful in planning and executing the synthesis of such chiral hosts. Presence of the 1,2-diol grouping with different arrangement, depending on the configuration of the sugar, which may be incorporated directly into the target macrocycle, makes these compounds convenient chiral synthetic analogs of the polyethylene glycol (PEG) reagents.[25]

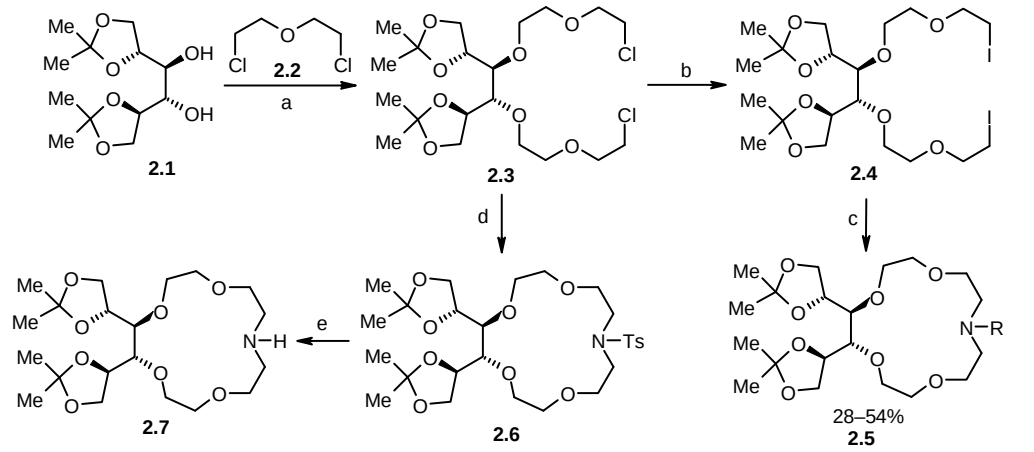
Crown ethers in which one (or more) oxygen atoms is replaced by an amino functional group are known as aza-crown ethers. They are intermediates between the per-oxygen crown compounds and per-aza analogs, also named cyclens. The advantage of aza-crown ethers (over the ‘normal crowns’ compounds containing only oxygen atoms) is their better complexing ability for ammonium cations and for transition-metal ions which results from the

fact that the nitrogen atom is more electronegative element than oxygen. Also, they are useful precursors of the lariat aza-crown ethers. Di-aza-crown macrocycles are also important intermediates for the synthesis of cryptands.[26]

The most common synthetic strategy for the preparation of sugar-aza-crown ethers (SAC) is based on the application of carbohydrate units with unprotected only two hydroxyl groups, as substrate.

In particular, Bakó and co-workers used carbohydrate 1,2-diols as starting materials for the preparation of the mono-aza-crown ethers. Such compounds are chiral synthetic equivalents of four-atomic O-C-C-O synthons.

One of the most available and useful carbohydrate 1,2-diols is 1,2:5,6-di-*O*-isopropylidene-**D**-mannitol (**2.1**).[27,28] Hydroxyl groups at the C3 and C4 carbon atoms of mannitol derivative **2.1** were alkylated with bis(2-chloro-ethyl)ether (**2.2**) in a liquid-liquid two-phase reaction [bis(2-chloro-ethyl)ether **2.2** was used as solvent and reagent with tetra-butylammonium hydrogensulphate as a phase-transfer catalyst] to provide the bis-chloro podand **2.3**.[29] Treatment of this product with NaI in acetone afforded more reactive bis-iodide **2.4**. A double alkylation of different primary amines with bis-iodo podand **2.4** in acetonitrile in the presence of anhydrous Na_2CO_3 led to macrocyclization and formation of the required 15-membered mono-aza-crown ethers **2.5** in 28–54% yields. *N*-Tosylated aza-macrocycle **2.6** was obtained after realization of alkylation reaction of compound **2.3** with tosylamine. Cleavage of the tosyl group by sodium amalgam gave secondary amine **2.7** (Scheme 2.1).[30]

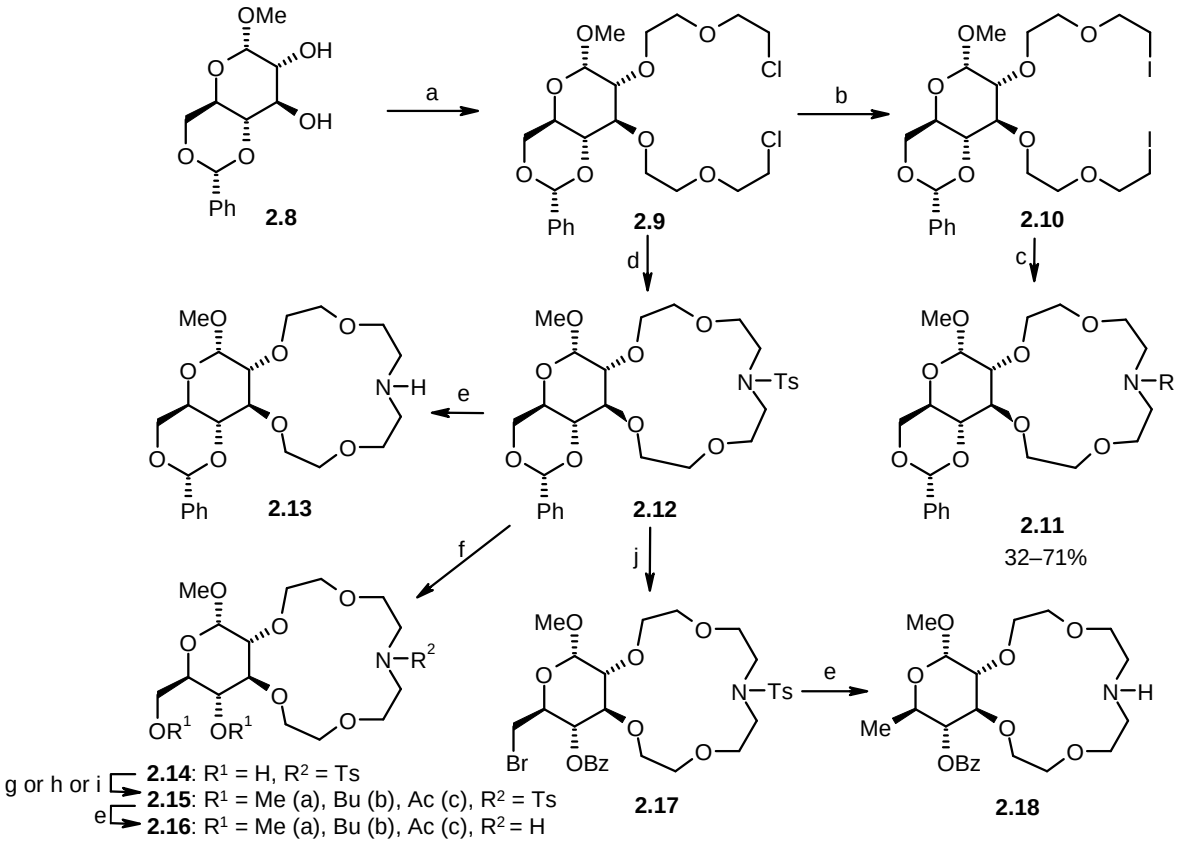


(a) 50% aq. NaOH, Bu_4NHSO_4, 14h, 20 °C, 90%; (b) NaI, acetone, reflux, 24h, 90%; (c) RNH_2, Na_2CO_3, MeCN, reflux; (d) $TsNH_2$, K_2CO_3, DMF, reflux, 46%; (e) 4% Na/Hg_x, Na_2HPO_4, MeOH, reflux, 87%
R = *n*-Bu, C_6H_{11}, Bn, $(CH_2)_2Ph$, $(CH_2)_3OH$, $(CH_2)_4OH$, $(CH_2)_2OMe$, $(CH_2)_3OMe$

Scheme 2.1 Synthesis of aza-crown ethers **2.5**, **2.6** and **2.7**.

Similar strategy was used by these authors for the preparation of SACs, based on glucopyranose. Thus, reaction of methyl-4,6-*O*-benzylidene-α-**D**-glucopyranoside (**2.8**)[31] with bis-

(2-chloro-ethyl)ether (**2.2**) provided the bis-chloro podand **2.9**, which was converted into the appropriate di-iodo derivative **2.10**. The ring closing reaction of "*half-crown*" **2.10** with various aliphatic and aromatic amines resulted in formation of the glucopyranoside-based macrocycles **2.11** in 32–71% yield.[32–38] Dichloro derivative **2.9** was also converted into the *N*-tosyl aza-macrocycle **2.12** *via* reaction with tosylamide in the presence of K_2CO_3. Treatment of this compound with sodium amalgam provided the unprotected product **2.13**. Removal of the benzylidene group in compound **2.12** with acetic acid gave di-hydroxy compound **2.14**, which – upon alkylation or acylation – furnished the products **2.15a–c**. Finally, removal of the protecting tosyl group from **2.15a–c** furnished the crown amines **16a–c**. On the other hand, reaction of compound **2.12** with NBS led to the bromo derivative **2.17** which – upon treatment with sodium amalgam – was converted into secondary amines **2.18** (Scheme 2.2).[39]



(a) **2**, 50% aq. NaOH, Bu_4NHSO_4, 14h, rt, 80%; (b) NaI, acetone, reflux, 24h, 92%; (c) RNH_2, Na_2CO_3, MeCN, reflux; (d) $TsNH_2$, K_2CO_3, DMF, reflux, 42%; (e) 4% Na/Hg_x, Na_2HPO_4, MeOH, reflux, 92% for **2.13**; 78% for **2.16a**; 58% for **2.16b**; 75% for **2.16c**; 90% for **2.18**; (f) AcOH, reflux, 92%; (g) MeI, DMF, 8h, rt; (h) BuBr, NaH, DMF, 40h, 40°C; (i) Ac_2O, Py, rt; (j) NBS, $BaCO_3$, $(PhCO_2)_2$, 88%

R = *n*-Bu, C_6H_{11}, $(CH_2)_9CH_3$, Ph, Bn, $(CH_2)_2Ph$, $(CH_2)_2Py$, 1-naphtyl, $(CH_2)_2OH$, $(CH_2)_3OH$, $(CH_2)_2OMe$, $(CH_2)_3OMe$, CH_2CO_2Me, $(CH_2)_nP(O)(Ph)_2$, $(CH_2)_nP(O)(OEt)_2$ (n = 1-5)

Scheme 2.2 Synthesis of pyranoside containing macrocycles **2.11–2.18**.

The methyl 4,6-di-*O*-butyl-*α*-**D**-glucopyranoside-based macrocycles of type **2.19** were prepared in an analogous way.[40] Furthermore, Bakó *et al.* also synthesized a series of aza-crown ethers based on phenyl *β*-**D**-glucopyranoside (**2.20**),[41,42] methyl *α*-**D**-galactopyranoside (**2.21**),[34] and methyl α-**D**-mannopyranoside (**2.22**)[37,43] (Figure 2.1).

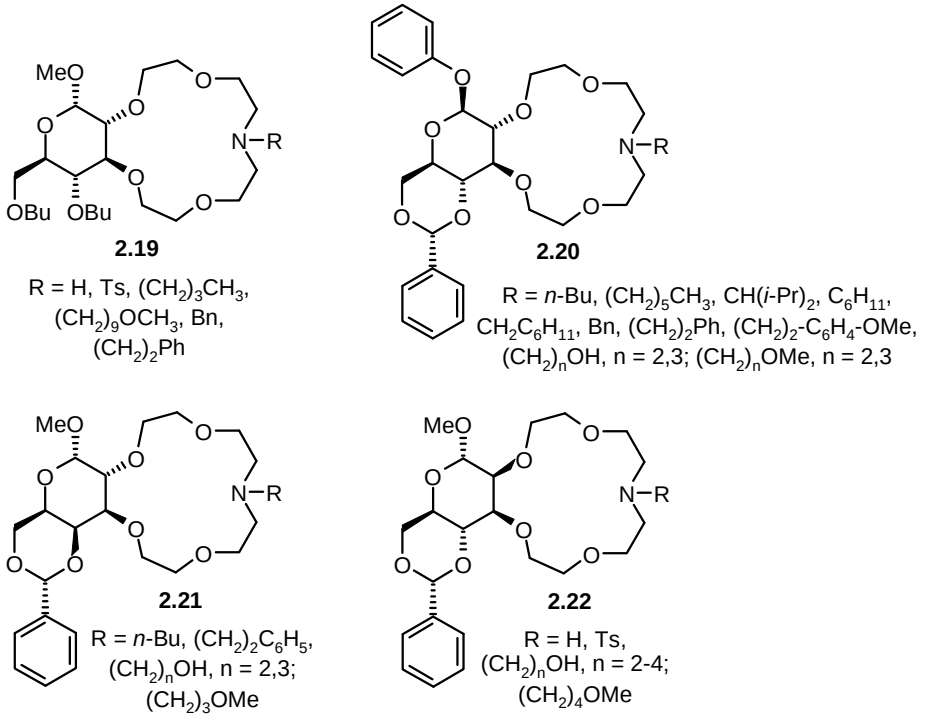
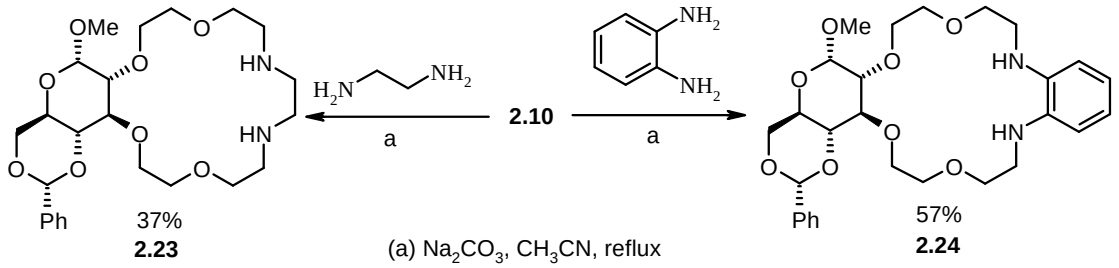


Figure 2.1 Aza-crown ethers **2.19–2.22**.

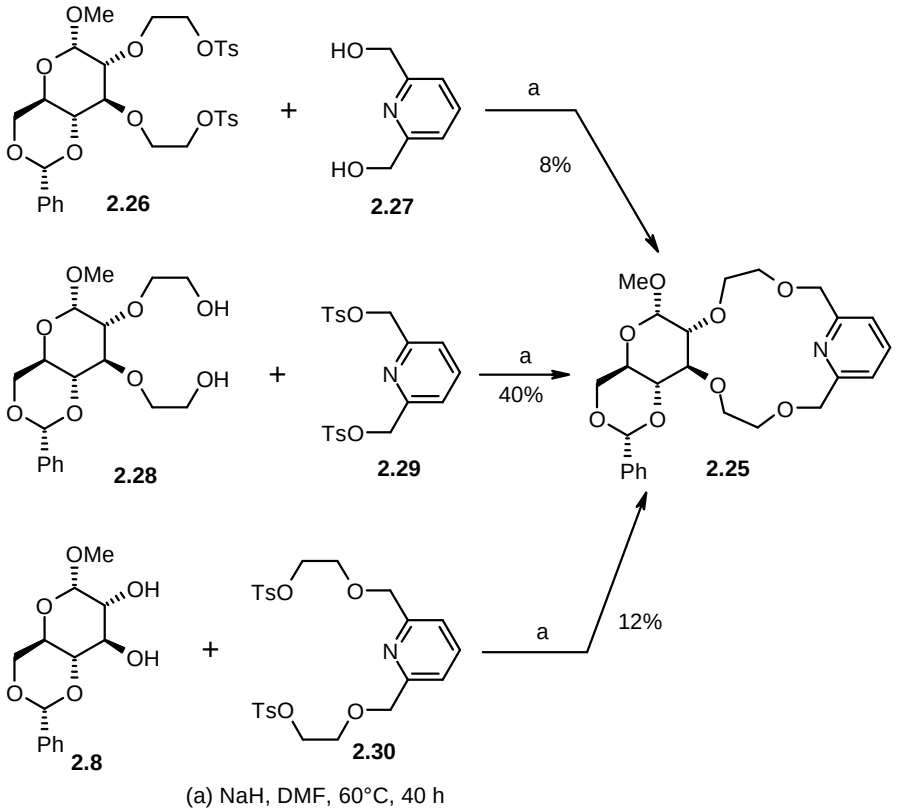
These authors also obtained the 18-membered di-aza-crown ethers: **2.23** and **2.24** by reaction of the *α*-**D**-glucose-based bis-iodo podand **2.10** with ethylenediamine or *o*-phenylene-diamine (Scheme 2.3).[32]



Scheme 2.3 Synthesis of the 18-membered di-aza-crown ethers **2.23** and **2.24**.

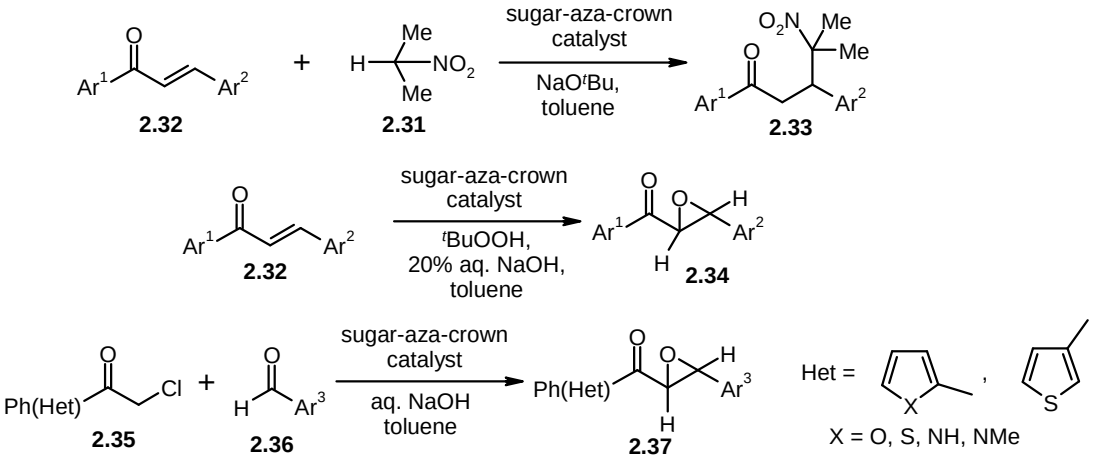
Another example of sugar-aza-crown ethers is represented by an analogous glucopyranoside-based macrocycle, incorporating a pyridine unit. The synthesis of aza-crown ether **2.25** was realized on three different cyclization pathways using various coupling partners, as shown in Scheme 2.4. The ring forming reaction of glucopyranoside-based diol-ditosylate

2.26 and 2,6-bis(hydroxymethyl)pyridine **2.27** in the presence sodium hydride was not really efficient since the yield of aza-crown ether **2.25** was only 8%. On the other hand, the double alkylation of glucopyranoside-based diol **2.28** with 2,6-pyridinedimethyl ditosylate **2.29** provided the product **2.25** in 40% yield, whereas the ring closing reaction of methyl-4,6-*O*-benzylidene-α-**D**-glucopyranoside (**2.8**) with ditosylate derivative **2.30** afforded compound **2.25** in only 12% yield.[44]



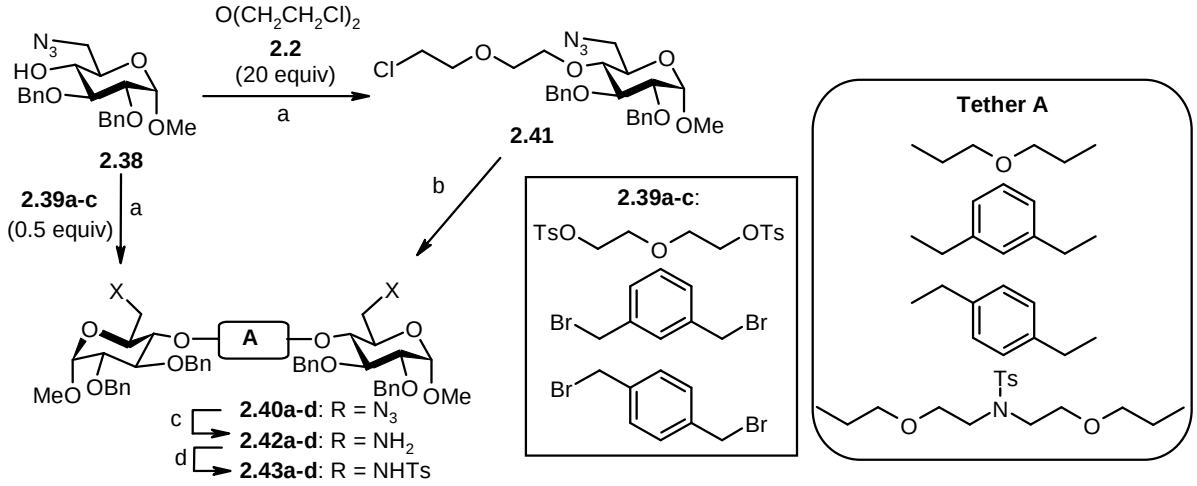
Scheme 2.4 Synthesis of the pyridine containing aza-crown ether **2.25**.

The study of the phase transfer properties (in a liquid-liquid system) of the 15-membered mono-aza-crown ethers **2.5**, **2.11**, **2.19–2.22**, and **2.25** indicated the high binding affinity towards the sodium cation. Therefore, this library of aza-carbohydrate coronands was investigated as ligands in asymmetric catalysis. In particular, these macrocycles are particularly useful as very efficient chiral phase transfer catalysts which allow to perform the Michael addition of 2-nitropropane (**2.31**) to chalcones **2.32** with asymmetric induction; products **2.33** were obtained with the enantiomeric excess (ee) to 95%.[30,33–36,39–52] These SAC ethers were also used in asymmetric epoxidation of chalcones (to 99% ee)[37,43,50–56] and the Darzens condensation of 2-chloro-1-phenyl(hetaryl)ethanones (**2.35**) with aryl aldehydes (**2.36**) (to 86% ee)[34,41–43,49–53,57] (Scheme 2.5).



Scheme 2.5 The use of sugar-aza-crown ethers as catalysts in asymmetric synthesis.

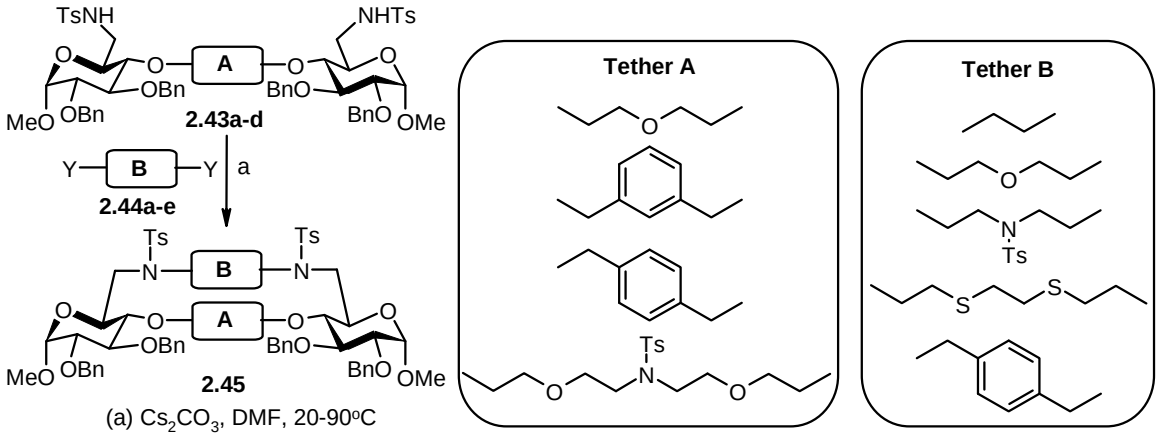
Rathjens and Thiem recently received symmetrical, nitrogen containing, structures with two or four glucose units.[58] They used methyl 6-azido-6-deoxy-2,3-di-*O*-benzyl-α-**D**-gluco-pyranoside (**2.38**)[59] as a suitable monosaccharide building unit. The phase-transfer catalyzed alkylation of the hydroxyl group of compound **2.38** with 0.5 equiv. of diethylene glycol ditosylate (**2.39a**) or α,α'-dibromo-*m*-xylene (**2.39b**), or α,α'-dibromo-*p*-xylene (**2.39c**) led to formation of disaccharide products **2.40a-c**. Alternatively, the corresponding reaction of the alcohol **2.38** with 20 equiv. of bis(2-chloro-ethyl)ether (**2.2**) gave glucose derivative **2.41** which – upon reaction with 0.5 equiv. of *p*-tosylamide and cesium carbonate – was converted into the product **2.40d** having a bridged 3,9-oxa-6-*N*-tosyl-aza-undecane chain. Afterwards the azido functional groups were transformed into the amino and further into the tosylamide functions (compounds **2.42a-d** and **2.43a-d** respectively)[58] (Scheme 2.6).



(a) 50% NaOH, TBAB, toluene; (b) $TsNH_2$, Cs_2CO_3, DMF, 50°C; (c) Pd/C, H_2, MeOH; (d) TsCl, Py, -20°C

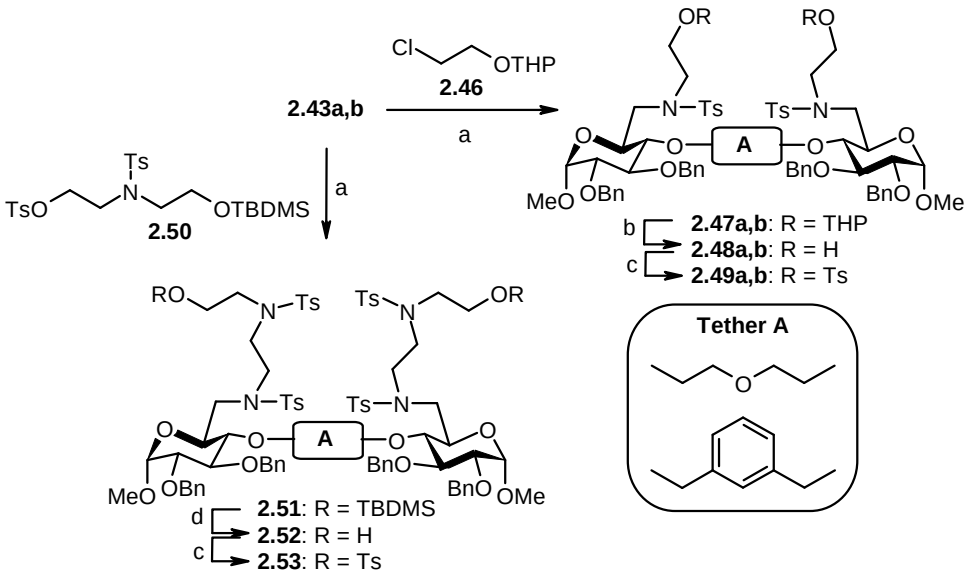
Scheme 2.6 Synthesis of ditosylamides **2.43a-d**.

Richman–Atkins cyclisation of ditosylamides **2.43a-d** with various alkyl tosylates [ethylene glycol ditosylate (**2.44a**), diethylene glycol ditosylate (**2.44b**), diethanol amine tritosylate (**2.44c**), and 1,8-bis-*p*-toluene sulfonyloxy-3,6-dithia-octane (**2.44d**)] as well as α,α'-dibromo-*p*-xylene (**2.44e**) gave of the carbohydrate coronands **2.45** containing oxygen, nitrogen and sulphur donors as shown in Scheme 2.7.



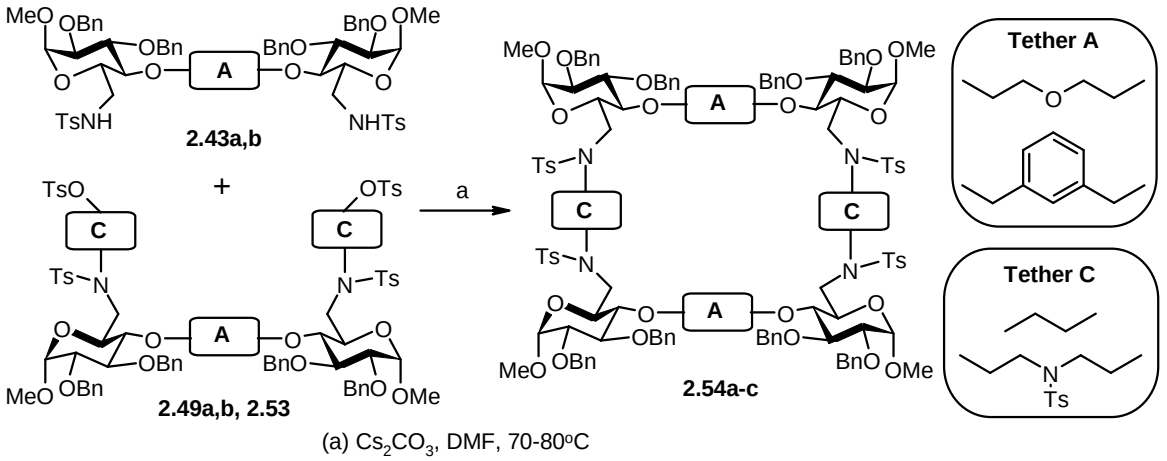
Scheme 2.7 Synthesis of the carbohydrate coronands **2.45**.

Treatment of the precursors **2.43a,b** with an excess of 2-(2-chloroethoxy)-tetra-hydropyran (**2.46**) and subsequent acidic hydrolysis of the THP-groups, gave compounds **2.47a,b** and **2.48a,b**, respectively. Both free hydroxyl groups in diols **2.48a,b** were activated as tosyl esters (compounds **2.49a,b**). Similarly, using the mono-silylated diethanoloamine ditosylate **2.50** and precursors **2.43a**, the di-glucose derivatives: **2.51**, **2.52** and **2.53** were obtained (Scheme 2.8). Compounds **2.49a,b** and **2.53** are ideally suited for further reactions to be used as electrophilic components in Richman–Atkins cyclizations.[58]



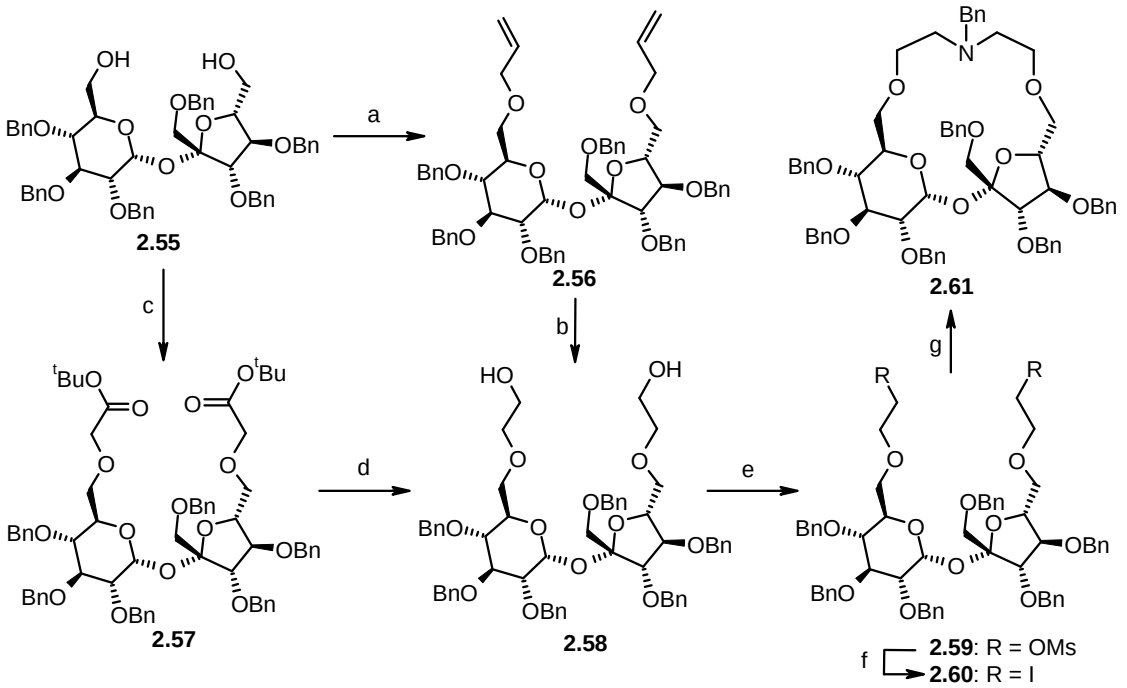
Scheme 2.8 Synthesis of of ditosylamides **2.49a,b** and **2.53**.

Ring closing reactions of ditosylamides **2.43a,b** with 6,6'-extended derivatives **2.49a,b** and **2.53** were implemented in formation of the disaccharide analogs (as the previously described). Tetrasaccharide aza-crown macrocycles **2.54a-c** were obtained in ~ 50% yield (Scheme 2.9).[58]



Scheme 2.9 Synthesis of the macrocyclic derivatives **2.54a–c**.

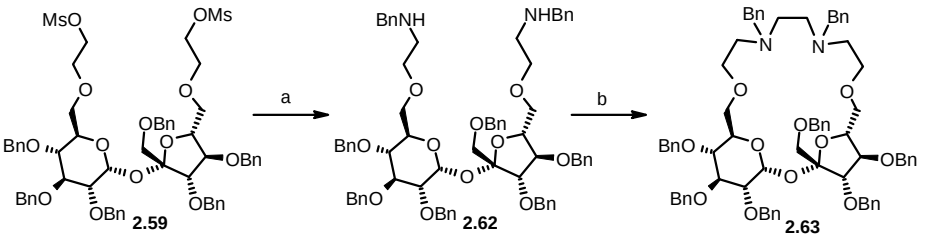
As mentioned above (see Introduction), in the previous study of Jarosz group, aza-crown ethers analogs containing sucrose scaffold were presented.[4] Double alkylation of 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**2.55**) with allyl bromide or *tert*-butyl bromoacetate furnished the corresponding products **2.56** and **2.57** which were further converted into the 6,6'-extended diol **2.58** as shown in Scheme 2.10. Reaction of the di-alcohol **2.58** with the excess of methanesulfonyl chloride and subsequent substitution with iodide gave compounds **2.59** and **2.60**, respectively. Treatment of di-iodide **2.60** with 0.5 equiv. of benzylamine in the presence of sodium carbonate produced the sucrose coronand **2.61** in 73% yield (Scheme 2.10).[60]



(a) AllBr, NaH, DMF, 3 h, rt, 95%; (b) OsO_4, $NaIO_4$, THF/H_2O (1:1) then $NaBH_4$, 52%; (c) $BrCH_2CO_2{}^tBu$, 50% NaOH, toluene, TBAB, 69%; (d) $LiAlH_4$, THF, 95%; (e) MsCl, Et_3N, DMAP, CH_2Cl_2; (f) NaI, acetone, reflux, 6 h, 69% (over two steps); (g) $BnNH_2$ (0.5 eqiuv), Na_2CO_3, MeCN, 50 h, reflux, 73%

Scheme 2.10 Synthesis of the sucrose-based aza-crown ether **2.61**.

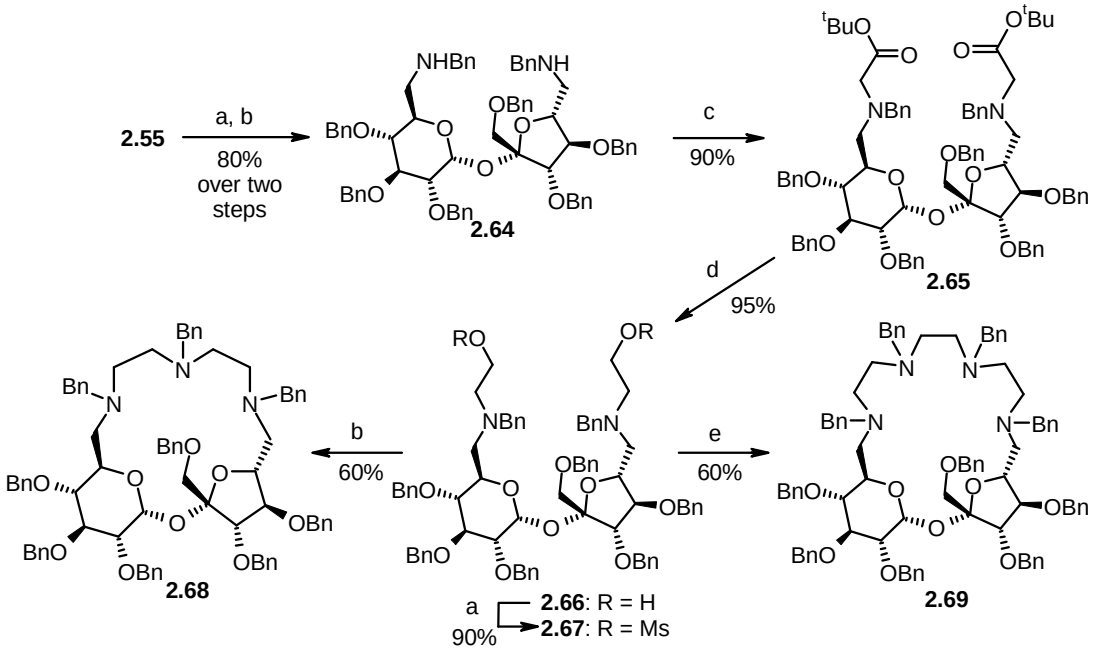
Treatment of the dimesylate **2.59** with excess of benzylamine gave the diamine **2.62**, which – in ring closing reaction with ethylene glycol ditosylate – led to sucrose di-aza-crown derivative **2.63** in 55% yield (Scheme 2.11).[61]



(a) $BnNH_2$, Na_2CO_3, MeCN, 70%; (b) $TsOCH_2CH_2OTs$, Na_2CO_3, MeCN, 55%

Scheme 2.11 Synthesis of the sucrose-based di-aza-coronand **2.63**.

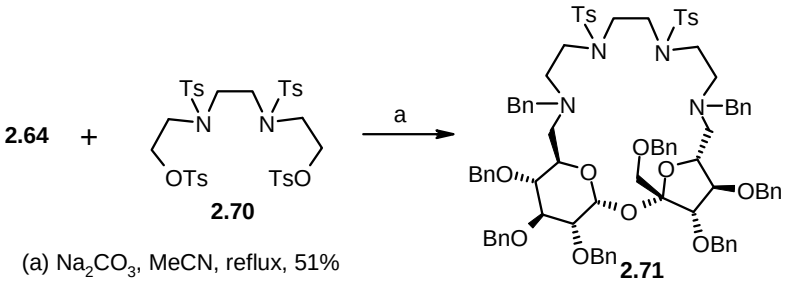
For the preparation of sucrose aza-coronands with three and four nitrogen atoms the diol **2.55** was transformed into the corresponding diamine **2.64**. Using a similar (to previously described) strategy the diester **2.65**, dialcohol **2.66** and dimesylate **2.67** were obtained. Reaction of compound **2.67** with 1.2 equiv. of benzylamine led to sucrose-tri-aza-coronand **2.68** in good yield.[61] Analogous process with *N*,*N*'-dibenzylethylenediamine gave tetra-aza-coronand **2.69** in 60% yield[62] (Scheme 2.12).



(a) MsCl, DMAP, Et_3N, CH_2Cl_2; (b) $BnNH_2$, Na_2CO_3, 80°C, MeCN; (c) $BrCH_2CO_2{}^tBu$, K_2CO_3,toluene; (d) $LiAlH_4$, THF; (e) $BnNH(CH_2)_2NHBn$, Na_2CO_3, 80°C, MeCN

Scheme 2.12 Synthesis of the sucrose-based tri- and tetra-aza-crown ethers **2.68** and **2.69**.

Condensation of the diamine **2.64** with di-tosylate of *N*,*N*'-ditosyl-*N*,*N*'-diethanolo-ethylenediamine (**2.70**) under typical conditions, provided the macrocycle **2.71** in 51% yield (Scheme 2.13).[62]



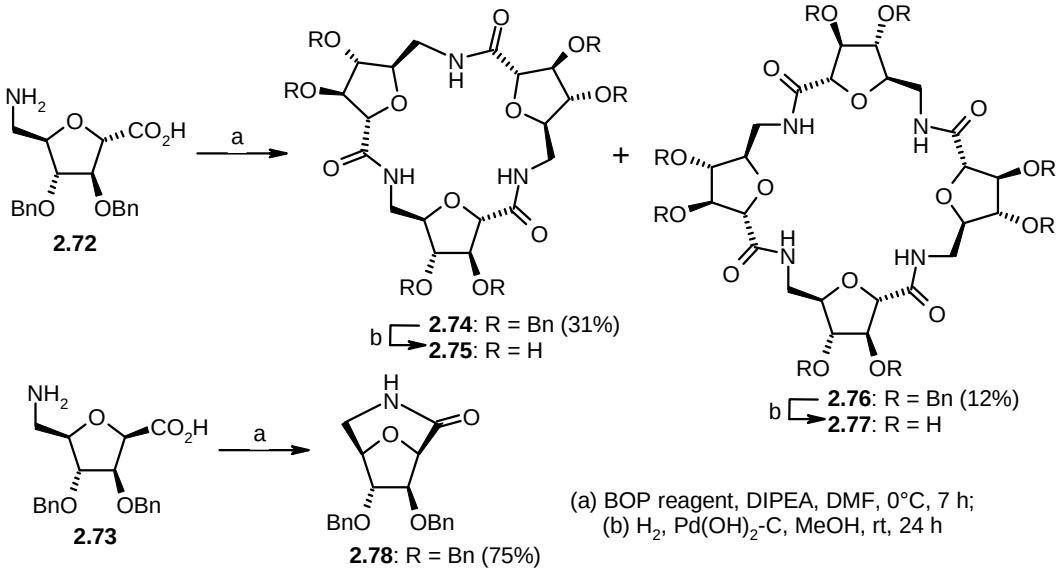
(a) Na_2CO_3, MeCN, reflux, 51%

Scheme 2.11 Synthesis of the sucrose-based tetra-aza-coronand **2.71**.

Sucrose aza-crown ethers: **2.61**, **2.63**, **2.68**, **2.69** and **2.71** showed high binding affinity towards the ammonium cation. The association constants for complexes of these macrocycles with NH_4^+ (used in form of ammonium thiocyanate) determined by the NMR titration method[63] in deuterated acetone were between 110–560 M^{-1}.[60–62] The following studies on sucrose aza-receptors proved also the high enantioselectivity in recognition of chiral ammonium cation. In particular, the NMR titration experiments in deuterated chloroform demonstrated the preferential complexation of the (*S*)-isomer of *α*-phenylethylammonium cation by these receptors.[62]

2.2 Cyclic homooligomers from amino sugars

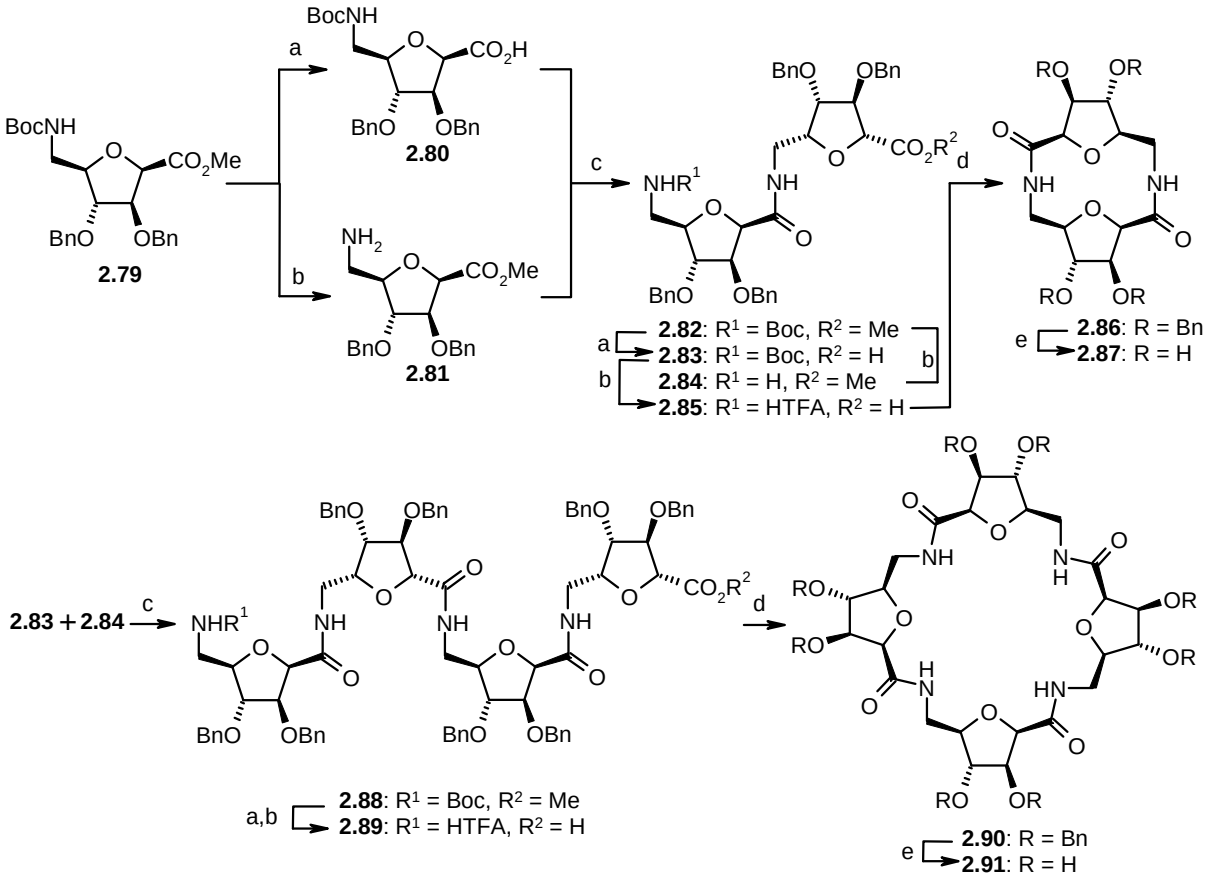
Aminosugars are components of many antibiotics[64–67] and bacterial polysaccharides.[68] Of particular interest are carbohydrate derivatives bearing an amino and carboxylic acid functionality, also known as sugar amino acids (SAAs).[69] Chakraborty *et al.* used 6-amino-2,5-anhydro-6-deoxy-**D**-mannonic (Maa) and its gluconic (Gaa)[70] acids in the synthesis of cyclic homooligomers of furanoid sugar amino acids. Treatment of the H-Maa(Bn_2)-OH (**2.72**) with benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (BOP reagent) and *N*,*N*-diisopropylethylamine (DIPEA) at 0 °C afforded the Bn-protected cyclic products **2.74** and **2.75** in 31% and 12% yields, respectively. Compounds **2.74** and **2.75** were converted, in quantitative yields, into the polyhydroxylated analogs **2.76** and **2.77** by de-benzylation reaction. The glucose-based sugar-amino-acid **2.73** [H-Gaa(Bn_2)-OH], under the same reaction conditions, provided the bicyclic lactam **2.78** as the major product (Scheme 2.14).[71]



Scheme 2.14 Synthesis of homooligomers **2.75** and **2.77** and monomeric lactam **2.78**.

Cyclic homo-oligomers of glucose-amino-acid were prepared by cyclization of the corresponding linear precursors. Thus, Boc-Gaa(Bn_2)-OMe (**2.79**) was transformed into the acid **2.80** and amine **2.81** by selective removal of *tert*-butoxycarbonyl or ester groups, respectively. Coupling of **2.80** with **2.81**, promoted by 1-ethyl-3-[3-(dimethylamino) propyl]-carbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt), furnished the product **2.82**. Subsequent saponification/Boc-deprotection/coupling converted the linear dimer **2.82** into the cyclic compound **2.86**. On the other hand, disaccharide acid **2.83** and

amino ester **2.84** were also obtained. Condensation of these components gave tetramer **2.88**, which – after deprotection of Boc- and ester groups – was converted into the amino acid **2.89**. Intramolecular lactamization of compound **2.89** were implemented as in the previously described formation of the disaccharide analogs. After cleavage of the benzyl groups in **2.86** and **2.90**, cyclic homo-tetrasaccharides **2.87** and **2.91** were obtained (Scheme 2.15).[71]

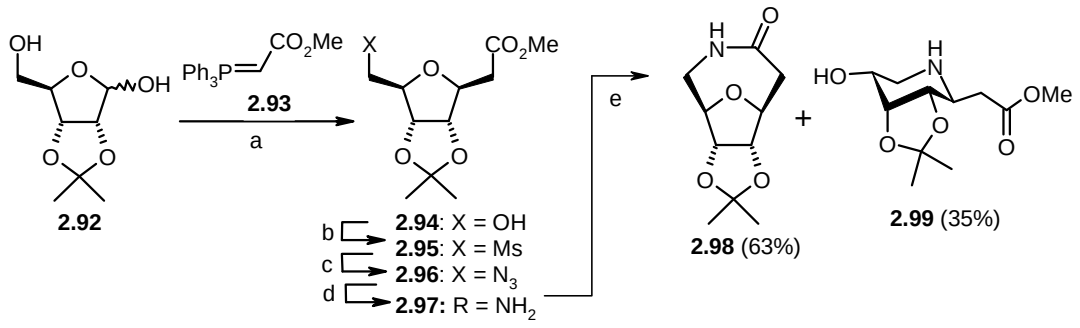


(a) (1) LiOH, THF/MeOH/H_2O; (2) 1N HCl; (b) TFA, CH_2Cl_2; (c) HOBt H_2O, EDCI, DIPEA, CH_2Cl_2; (d) BOP reagent, DIPEA, DMF, 0°C; (e) H_2, $Pd(OH)_2$-C, MeOH

Scheme 2.15 Synthesis of dimeric and tetrameric macrocycles **2.87** and **2.91**.

Wu and co-workers have developed a synthesis of 14-membered cyclic homodimers of furanoid sugar amino acids.[72] Preparation of these furanoid SAA dimers was realized starting from 2,3-*O*-isopropylidene-**D**-ribose (**2.92**). Thus, tandem Wittig-Michael reaction of **2.92** with methyl(triphenylphosphoranylidene) acetate (**2.93**) afforded the β-*C*-furanoside **2.94** as the major product. Mesylation of this alcohol **2.94** followed by substitution of the mesylate with sodium azide provided compound **2.96**,[73] which was then applied as starting material for the preparation of target macrocycles. The aza-*C*-riboside **2.96** was subjected to reduction by hydrogenation which produced the corresponding amino ester **2.97**. Compound **2.97** was treated with sodium methoxide to promote intramolecular amidation between the

amino and the ester functional groups. This process afforded the bicyclic iminosugar **2.98** (63%) as a major product, together with the aza-*C*-glycoside **2.99** (35%) (Scheme 2.16).[74]



(a) CH_3CN, rt, 81%; (b) MsCl, pyridine, rt, 80%; (c) NaN_3, DMF, 75°C, 1h, 89%; (d) H_2, Pd/C, MeOH, rt, 40 min, 92%; (e) NaOMe, MeOH, rt

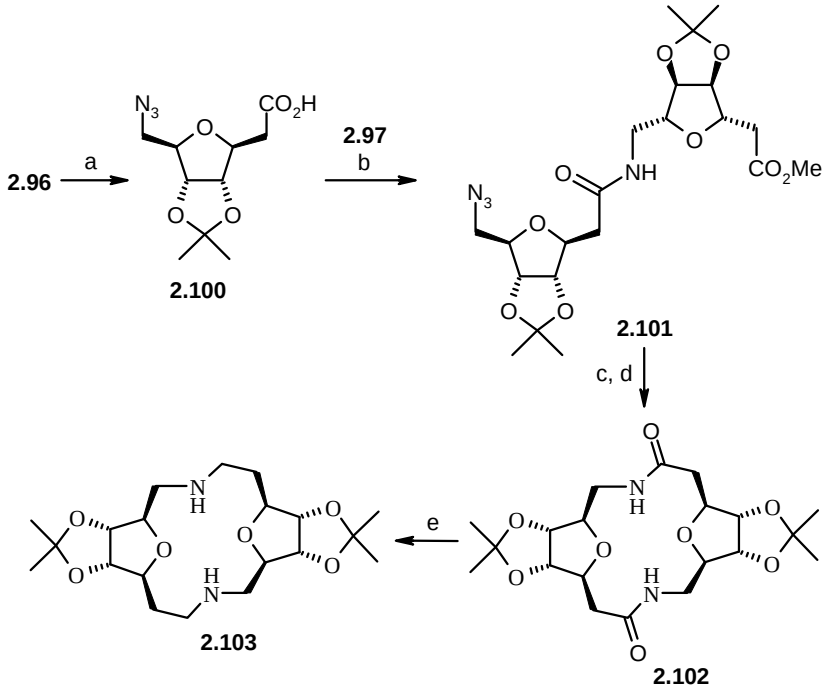
Scheme 2.16 Transformation of 2,3-*O*-isopropylidene-**D**-ribose (**2.92**) into the bicyclic iminosugar **2.98**.

The furanoid cyclic homo-dimers however, can be synthesized from its linear disaccharide derivative. Hydrolysis of the *C*-ribosyl azido-ester **2.96** provided the corresponding azido acid **2.100**. Coupling of the amino ester **2.97** with the azido acid **2.100** [carried out with diethyl phosphoryl cyanide (DEPC) and Et_3N in DMF] afforded the linear dimer **2.101**. The azido group in **2.101** was reduced by catalytic hydrogenation and the resulting amino ester intermediate was treated with K_2CO_3 in MeOH, which induced the intramolecular amidation with the ester leading to the desired *β*-anomer furanoid SAA dimer **2.102** as major product in 87% yield. Reduction of the amide bonds of **2.102** with an excess of $LiAlH_4$ under microwave irradiation completed the assembly of the desired *β*-anomer furanoid SAC ether **2.103** with the C_2-symmetry in 67% yield (Scheme 2.17).[72]

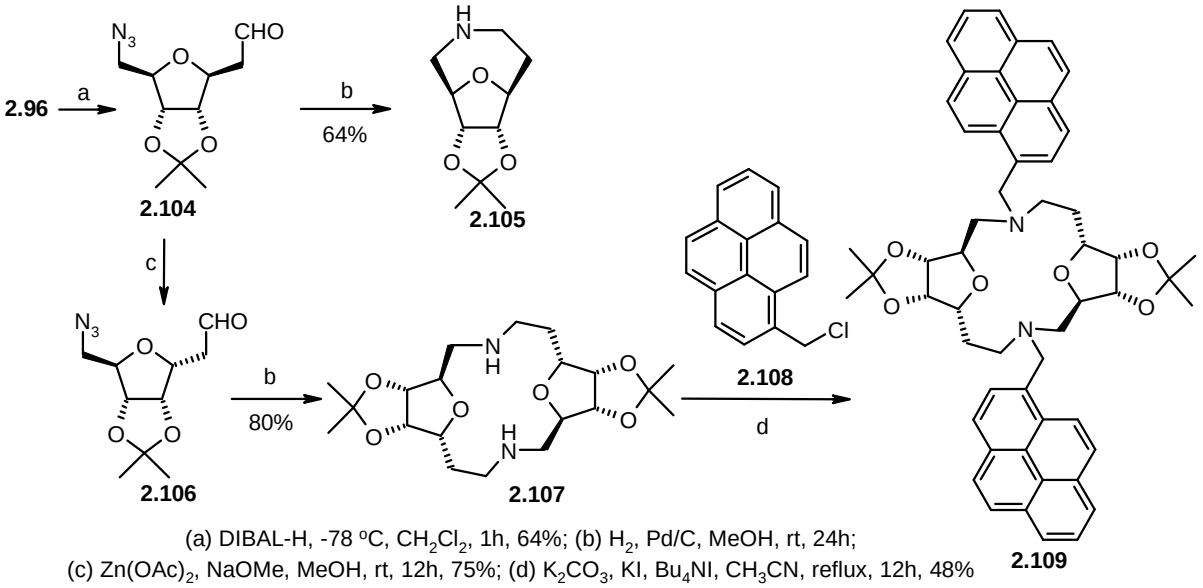
According to another strategy, the cyclic homodimers containing furanoid amino sugar subunits were prepared through one-pot reductive amination of *C*-ribosyl azido-aldehyde monomer. The reaction of **2.96** with DIBAL-H produced the *β*-anomer of *C*-ribosyl azido aldehyde **2.104**. The authors intended to use the reductive amination strategy for cyclodimerization. However, treatment the azido aldehyde **2.104** under palladium-catalyzed hydrogenation conditions led bicyclic compound **2.105** in 64% yield.

To avoid formation of the intramolecular lactam, epimerization of the *β*-anomer of *C*-riboside to the *α*-anomer **2.106** was performed. Treatment of compound **2.104** with NaOMe and $Zn(OAc)_2$ provided the *α*-anomer of *C*-ribosyl azido-aldehyde **2.106** in 75% yield together with *ca* 15% of the remaining starting material. Palladium-catalyzed hydrogenation of the azido-functionality in the *C*-ribosyl-azido aldehyde **2.106** afforded an amine which

underwent spontaneous reaction with the carbonyl grouping of the second molecule and the resulting cyclic di-imine was reduced to target **2.107**. The desired dimer α-anomer furanoid SAC ether **2.107** was isolated in 80% yield (Scheme 2.18).[72]



Scheme 2.17 Synthesis of di-aza-crown ether **2.103**.

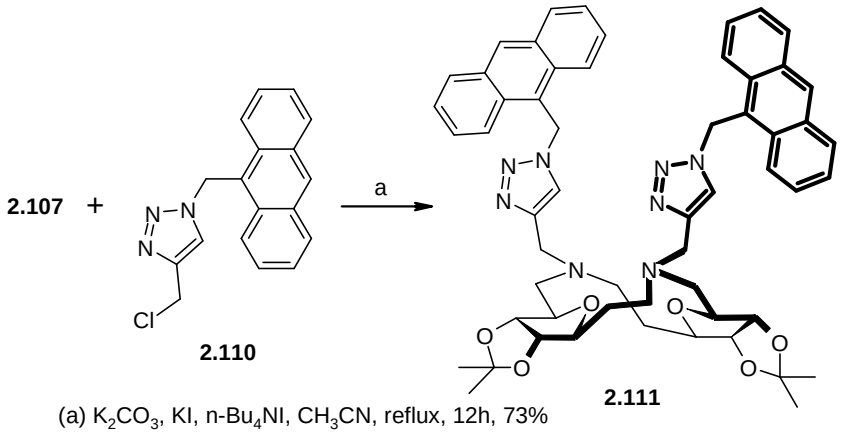


Scheme 2.18 Synthesis of receptor **2.109**.

As mentioned above, the aza-crown ethers have better complexing ability towards transition-metal ions than 'all-oxygen' crown compounds. Combination of such macrocycles (ionophores) with fluorophore moieties is often used in preparation of fluorescent sensors. A lot of such compounds have been developed as sensors for selective detection of transition or heavy metal ions.[75]

Wu and his group have synthesized the SAC-based fluorescent sensor **2.109** which has the furanoid SAC moiety as the binding site and a pyrene moiety as the signaling unit (Scheme 2.18). The authors carried out the study on the complexing properties of **2.109** towards metal ions in MeOH solution. They have examined the chemo-sensing behavior of compound **2.109** by fluorescence measurements in the presence of various metal ions by comparing the fluorescence intensities of the solutions before and after addition of 10 equiv. of the following ten metal ions as their perchlorate salts: Li^+, Na^+, K^+, Ca^{2+}, Mg^{2+}, Hg^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}. The sensor **2.109** exhibits highly selective recognition towards Cu^{2+} (Ka = 7.4×10^1 M^{-1}) and Hg^{2+} (Ka = 4.4×10^3 M^{-1}) ions. Chemosensor **2.109** formed complexes with the Cu^{2+} or Hg^{2+} ion in a 1:1 ligand-to-metal ratio with a detection limit of 1.3×10^{-4} M Cu^{2+} and 1.2×10^{-5} M Hg^{2+}, respectively. The fluorescence enhancement can be attributed to the photoinduced electron transfer (PET) that occurs upon complexation of the nitrogen atoms by metal ion. These results suggest that Cu^{2+} or Hg^{2+} ions can be recognized by the two nitrogen atoms of the linker of cation probe **2.109**.[76]

Another example, represented by the fluorescent sensor **2.111**, based on sugar-aza-crown ether structure with two anthracene-triazolylmethyl groups, was obtained by alkylation of the furanoid SAC ether **2.107** with chloromethyl-1,2,3-triazole **2.110** (Scheme 2.19). Fluoro-ionophoric properties of compound **2.111** were similar to sensor **2.109**. Compound **2.111** also showed high binding affinity to Cu^{2+} and Hg^{2+} cations among a series of metal ions tested as their perchlorate salts in MeOH solution. The association constants for complexes of these macrocycles with Cu^{2+} and Hg^{2+} in methanol were calculated at: 4.0×10^5 M^{-1} and 1.1×10^5 M^{-1}, respectively; the detection limits for the sensing of such ions were 1.39×10^{-6} M and 1.39×10^{-5} M, respectively.[77]



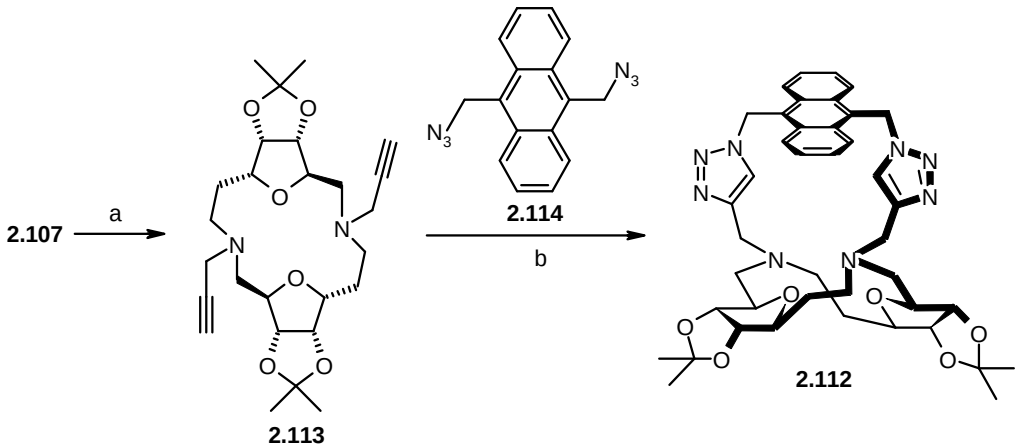
(a) K_2CO_3, KI, n-Bu_4NI, CH_3CN, reflux, 12h, 73%

Scheme 2.19 Synthesis of fluorescent sensor **2.111**.

The furanoid di-aza-crown ether **2.107** was also used for the preparation the triazole-containing cavitand **2.112**. Propargylation of the diamine **2.107** afforded the SAC ether alkyne **2.113** which reacted with 9-(azidomethyl)anthracene (**2.114**) under 'click' conditions [$(EtO)_3P{\cdot}CuI$ as the catalyst in refluxing toluene] gave the cavitand **2.112** in 35% yield (Scheme 2.20). Chemosensor **2.112** exhibits highly selective recognition properties towards Cu^{2+} ion ($K_a = 2.5\times10^4$ M^{-1}) among a series of tested metal ions in MeOH solution.[78]

The authors also investigated the sensing properties of the receptor **2.112** for anions (F^-, Cl^-, Br^-, I^-, NO_3^-, HSO_4^-, $H_2PO_4^-$, AcO^-) using tetrabutylammonium as a counter-ion in methanol.

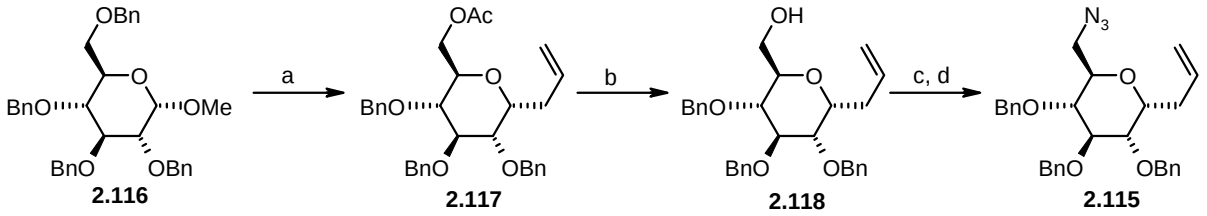
Compound **2.112** showed high selective binding affinity towards HSO_4^- among a series of tested above anions. The association constant for complex of SAC-based cavitand **2.112** with HSO_4^- anion was determined in methanol by fluorescence titration methodology at 8.06×10^5 M^{-1}. NMR studies revealed that the C–H hydrogen bonding between 1,2,3-triazole ring of the receptor **2.112** and hydrogen sulfate ion is crucial for the high selectivity.[79]



(a) propargyl bromide, K_2CO_3, KI, *n*-Bu_4NI, MeCN, reflux, 6h, 78%; (b) $(EtO)_3P{\cdot}CuI$, toluene, 85 °C, 15 min, 300W, 35%

Scheme 2.20 Synthesis of the triazole-containing cavitand **2.112**.

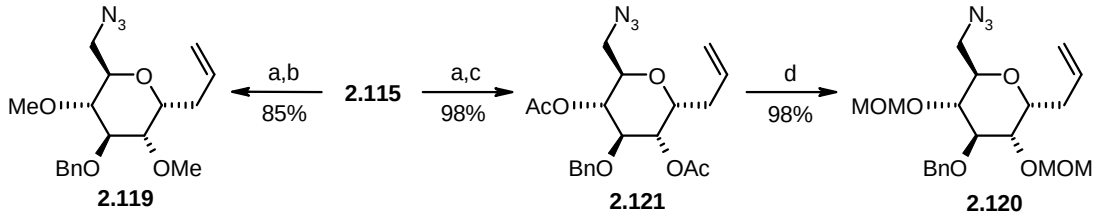
Similar synthetic strategies have been used for the preparation of pyranoid cyclic homo-oligomers. In this the azido *α*-*C*-allyl glucopyranozide **2.115** was chosen as a synthetic precursor. The 6-*O*-acetyl-*α*-*C*-allyl glucoside **2.117** was prepared first from tetra-*O*-benzyl-*α*-**D**-glucopyranoside (**2.116**) by reaction with allyl trimethylsilane in the presence of TMSOTf, followed by addition of Ac_2O. Subsequent deacetylation quantitatively furnished the alcohol **2.118** which was transformed into the azide **2.115** by displacement of the mesylate (Scheme 2.21).[80]



(a) AllylTMS, TMSOTf, CH_2Cl_2, 0 °C, Ar, then Ac_2O, 71%; (b) MeONa, MeOH, rt, 100%; (c) MsCl, TEA, CH_2Cl_2, 0 °C to rt; (d) NaN3, DMF, 90 °C, 75%

Scheme 2.21 Transformation of tetra-*O*-benzyl-*α*-**D**-glucopyranoside (**2.116**) into azide **2.115**.

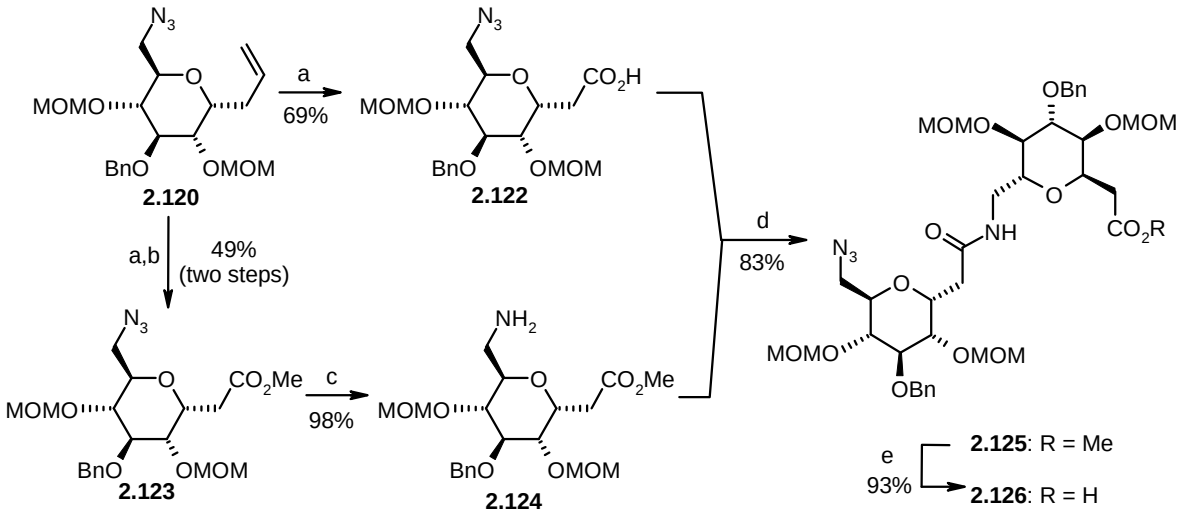
Further, glucopyranoside **2.115** was modified to dimethyl and dimethoxymethyl analogs (**2.119** and **2.120**, respectively). BCl_3-mediated regioselective debenzylation of tribenzyl derivative **2.115** followed by methylation or acetylation provided the corresponding diacetyl and dimethyl glucopyranosides: **2.119** and **2.121**.[81] De-acetylation of **2.121** followed by methoxymethylation furnished **2.120** (Scheme 2.22).[82]



(a) BCl_3 (2.5 eqiuv), CH_2Cl_2, - 78 °C; (b) NaH, MeI; (c) Ac_2O, pyridine; (d) MeONa, MeOH, then NaH, MOMCl, DMF

Scheme 2.22 Synthesis of compound **2.120**.

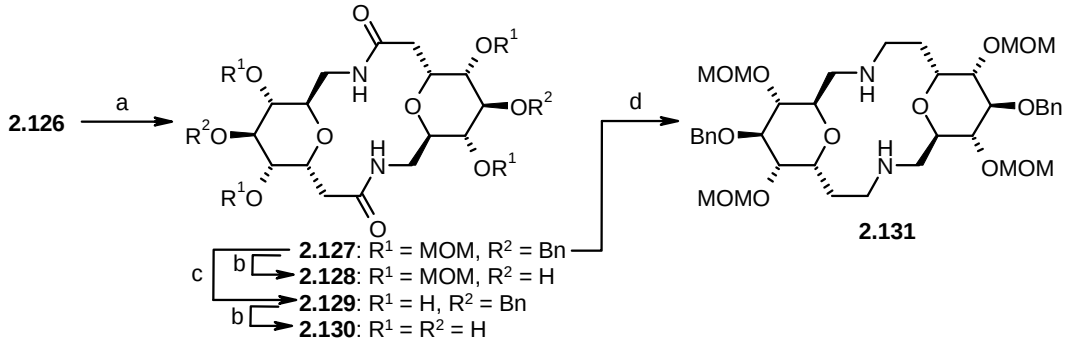
Xie and co-workers used compounds **2.115**, **2.119** and **2.120** as starting materials in the synthesis of cyclic pyranoside homo-oligomer sugar amino acids. Oxidation of the alkene function in glucopyranoside **2.120** with $KMnO_4$ led to carboxylic acid **2.122** which was transformed into the methyl ester **2.123**. Reduction of the azido group in **2.123** afforded the amino-ester **2.124**. Coupling of **2.122** with the amino ester **2.124** promoted by diethyl phosphoryl cyanide (DEPC) and Et_3N gave the linear disaccharide **2.125**. Hydrolysis of the ester group in **2.125** provided the corresponding azido acid **2.126** (Scheme 2.23).[82]



(a) $KMnO_4$, AcOH, aliquat 336, H_2O, CH_2Cl_2, 69%; (b) $NaHCO_3$, MeI, DMF, 49%; (c) PPh_3, H_2O, THF; (d) DEPC, Et_3N, DMF, 83%; (e) LiOH, H_2O/MeOH/THF

Scheme 2.23 Synthesis of linear dimers **2.126**.

After catalytic hydrogenation with Pd/C, the azido function was reduced without debenzylation. Intramolecular macrocyclization of the disaccharide intermediate (DEPC and Et_3N) gave the C_2-symmetric macrocycle **2.127**. Selective or total deprotection of the benzyl and /or methoxymethyl groups in homo-dimer **2.127** gavethe unprotected derivatives: **2.128**, **2.129**, and **2.130**. The 3-*O*-benzyl group seemed to be particularly resistant under the usual debenzylation. However, complete debenzylation could be achieved by the Pd/black catalyzed hydrogenolysis in the presence of AcOH in a mixture of MeOH/EtOAc. Dilactam **2.127** was also transformed into the diamine **2.131** *via* reduction with $BH_3 \cdot THF$ (Scheme 2.24).[82]



(a) (1) H_2, Pd/C, MeOH, (2) DEPC, Et_3N, DMF, 60%; (b) H_2, Pd/C, Pd black, AcOH, MeOH/EtOAc, 99% for **2.128**, 74% for **2.130**; (c) AcCl, MeOH, 98%; (d) BH_3 THF,·THF, reflux, 91%

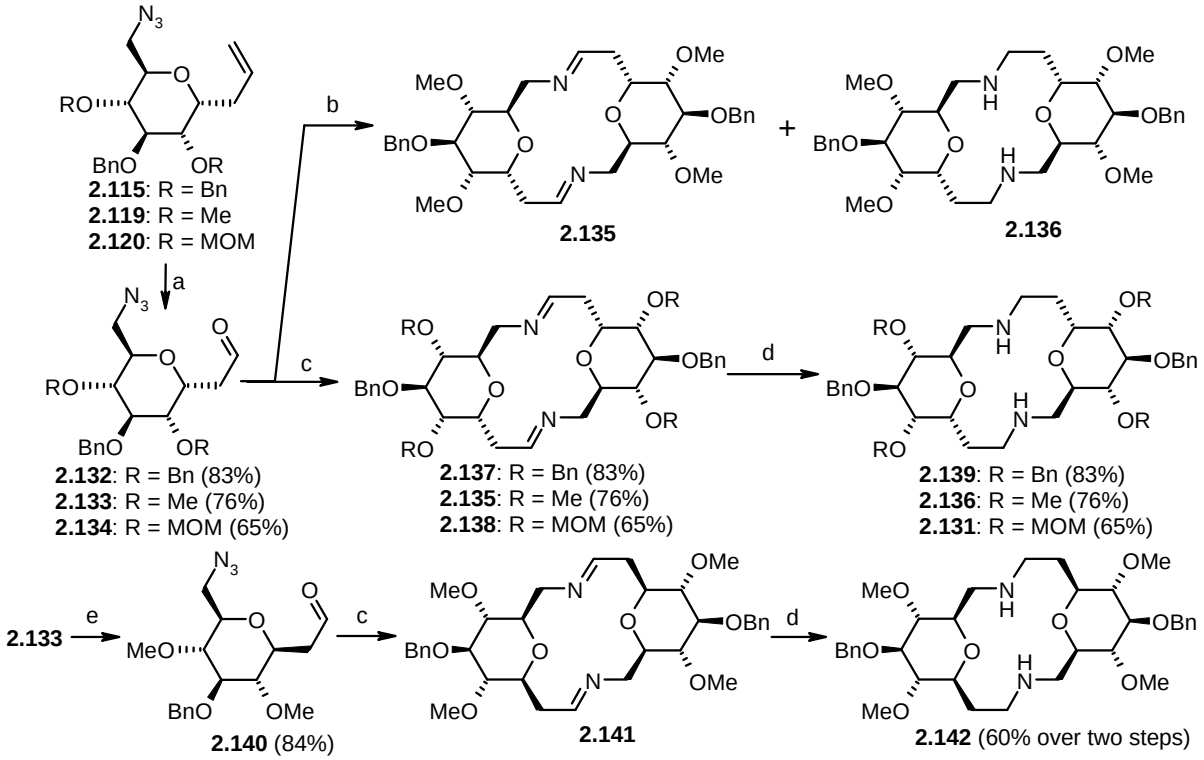
Scheme 2.24 Synthesis of di-aza-crown ether **2.131**.

Xie and co-workers also proposed another approach to pyranoid di-aza-crown ether **2.131** and its analogs. A one-pot OsO_4 dihydroxylation of vinyl group – $NaIO_4$ diol cleavage in *α*-*C*-allyl glucosides: **2.115**, **2.119** and **2.120** led to the corresponding aldehydes **2.132**–**2.134** in good yields (83, 76, and 65%, respectively). Hydrogenation of the azido aldehyde **2.133** provided a mixture of imine intermediate **2.135** and a minute amount of the amine

macrocycle **2.136**. The azide group was totally reduced and converted quantitatively into the imine **2.135**. However, further reduction to amine **2.136** was terminated, probably as a result of catalyst poisoning by the once-formed amine. Application of other catalysts [$Pd(OH)_2$, PtO_2, or Raney Ni] did not improve this transformation. Therefore authors investigated a tandem Staudinger/aza-Wittig (SAW) reaction for cyclodimerization of azido aldehydes **2.132**–**2.134**.

Treatment of the azido aldehyde **2.133** with Ph_3P (1.1 equiv.) in anhydrous THF led efficiently to the cyclic imine dimer **2.135**. An attempt of purification of compound **2.135** over silica gel led to degradation. This difficulty was circumvented by the use of the polymer-bound diphenylphosphine (3 equiv.), thus affording the corresponding cyclic dimers **2.137**, **2.135** and **2.138** in good yields. Reduction of these imines with $NaBH(OAc)_3$ (followed by cleavage of the N-B bonds using Pd/C in methanol) gave the: di-aza-crown ethers **2.139**, **2.136**, and **2.131**, respectively.

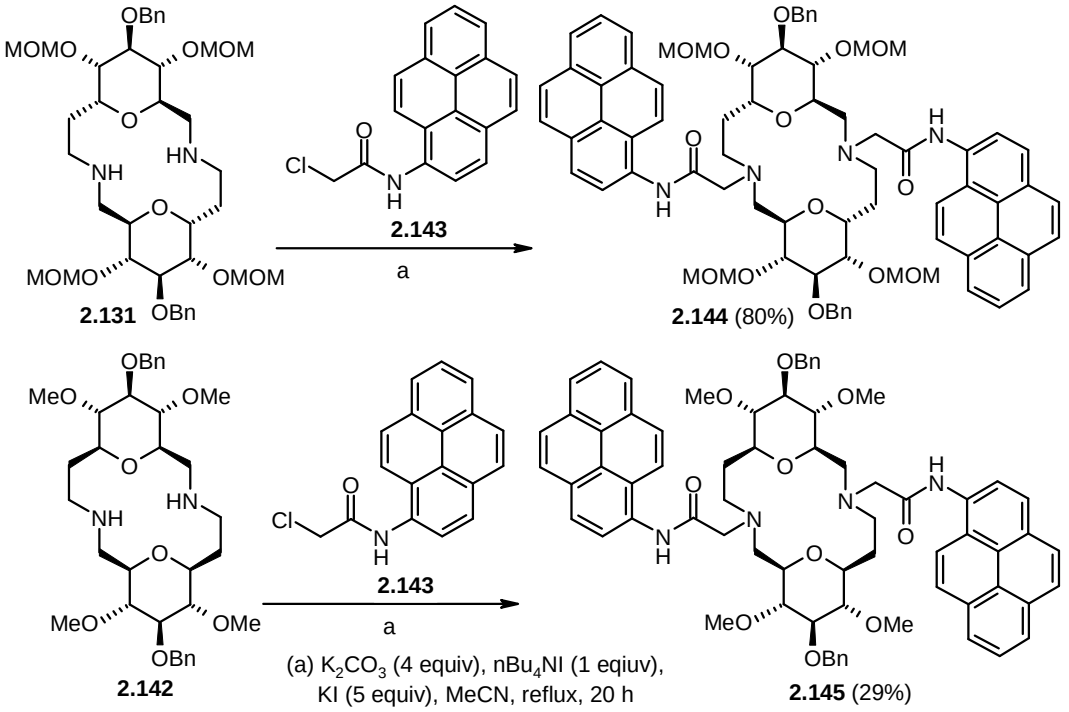
The *α*-*C*-glucosyl aldehyde **2.133** was epimerized to the corresponding *β*-anomer **2.140** using $Zn(OAc)_2$ and MeONa in methanol. Similarly to the *α*-anomer **2.133**, compound **2.140** gave the corresponding cyclic diamine **2.142** in a 60% yield after reduction (Scheme 2.25).[83]



(a) OsO_4 cat., $NaIO_4$, 2,6-lutidine, dioxane/H_2O (3/1), rt, 30 min.; (b) H_2, 10% Pd/C, MeOH, rt, 24 h; (c) polymer-bound diphenylphosphine (3 equiv), THF, Ar, rt, 20 h; (d) (1) $NaBH(OAc)_3$ (5 equiv), THF, rt, 20 h; (2) 10% Pd/C, MeOH, rt, 24 h; (e) $Zn(OAc)_2$ (5 equiv), 0.6 M NaOMe in MeOH, rt, 3 days

Scheme 2.25 Synthesis of macrocyles **2.131**, **2.136**, **2.139**, and **2.142**.

Diaza-crown ethers **2.131** and **2.142** were used in the preparation of SAC-based fluorescent molecular sensors for Cu(II). Treatment of the diamine **2.131** or **2.142** with *N*-(1-pyrenyl)chloroacetamide **2.143**[84] using K_2CO_3 as a base in CH_3CN in the presence of KI and nBu_4NI gave the compounds **2.144** and **2.145** in 80 and 29% yield, respectively (Scheme 2.26).[85]

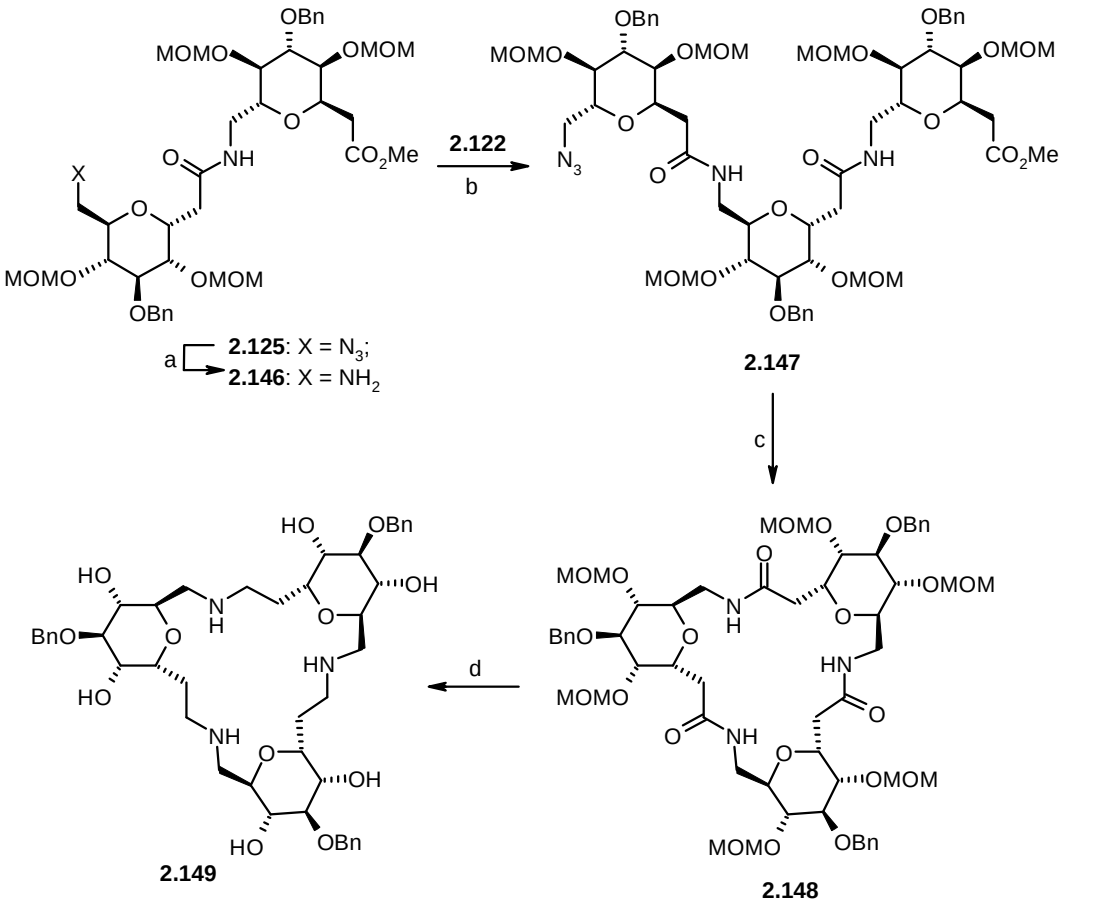


Scheme 2.26 Synthesis of chemosensors **2.144** and **2.145**.

The chemosensor behavior was investigated by the fluorescence measurement in MeOH solution (2 μM) upon excitation at 340 nm. The fluorescence emission of pyrene containing compounds **2.144** and **2.145** was strongly quenched by Cu^{2+} with a 97.5% efficiency. Receptors **2.144** and **2.145** showed a 1:1 stoichiometry with high binding constants (log K_a = 6.7 for **2.144** and 7.8 for **2.145**) and a detection limit in the nanomolar range (~ 40 nM for both ligands).[85]

Schemes 2.27 and 2.28 show the synthesis of orthogonally protected cyclic homo-trimer and homo-tetramer sugar amino acids. Reduction of the azide group in compound **2.125** under Staudinger condition furnished the amine derivative **2.146** in 82% yield. Coupling of this amine with acid **2.122** promoted by DEPC and Et_3N afforded the linear trisaccharide **2.147** in 53% yield. Subsequent saponification/reduction/condensation transformed **2.147** into the macrocyclic triamide **2.148** in 35% yield. Treatment of compound **2.148** with $BH_3 \cdot THF$ led to

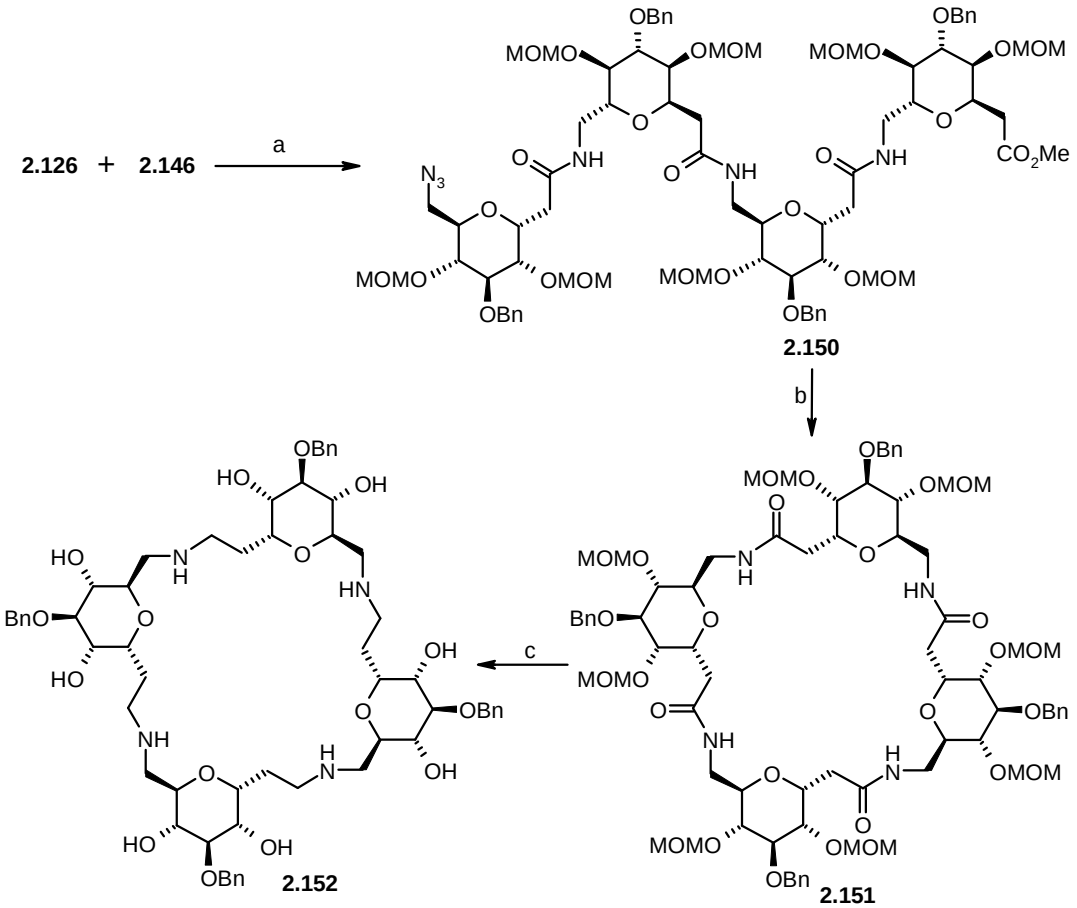
partial deprotection of the methoxymethyl groups. Removal all MOM-substituents with AcCl/MeOH led to the partially deprotected cyclic compound **2.149** (Scheme 2.27).[82]



(a) PPh_3, H_2O, THF, 82%; (b) DEPC, Et_3N, DMF, 53%; (c) (1) LiOH, H_2O/MeOH/THF, (2) H_2, Pd/C, MeOH, (3) DEPC, Et_3N, DMF, 35%; (d) (1) BH_3·THF, THF, reflux, (2) AcCl, MeOH, 42%

Scheme 2.27 Synthesis of trimeric compound **2.149**.

Similarly, condensation of the disaccharide azido acid **2.126** with amino ester **2.146** produced quantitatively the linear tetramer **2.150**, which was converted into the macrocyclic homo-tetramer **2.151** in 62% yield. Amide functional group reduction and MOM-deprotection led to tetra-aza-crown ether **2.152** (Scheme 2.28).[82]

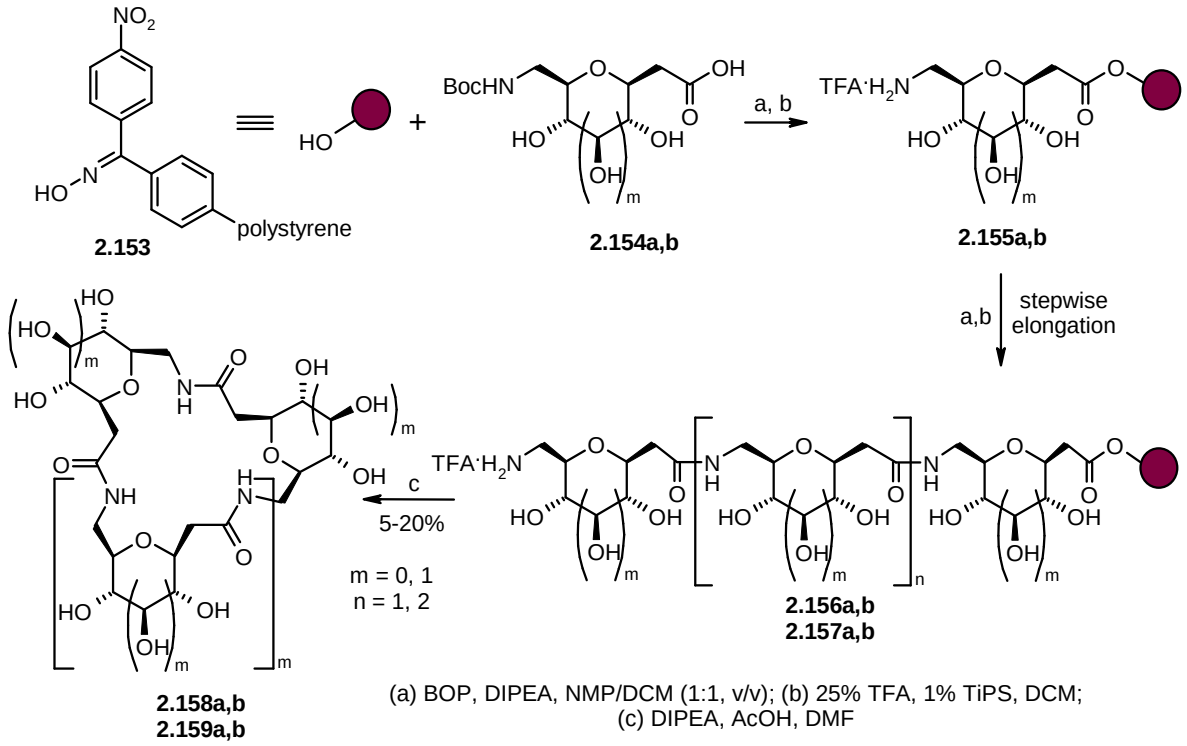


(a) DEPC, Et_3N, DMF, 100%; (b) (1) LiOH, H_2O/MeOH/THF, (2) H_2, Pd/C, MeOH, (3) DEPC, Et_3N, DMF, 62%; (c) (1) BH_3·THF, THF, reflux, (2) AcCl, MeOH, 68%

Scheme 2.28 Synthesis of tetramer **2.152**.

Cyclic homooligomers from sugar amino acids can also be obtained *via* solid-phase synthesis.[86] Organic synthesis on solid phase[87,88] is widely used instrument in the preparation of oligo- and polymer molecules. First, this technique has been applied in peptide chemistry,[87] and then oligonucleotides[89] and oligosaccharides synthesis.[90–93] The advantages of this method are the convenient synthetic procedure, easy purification and excellent yields of the products.

Overhand and co-workers developed an approach to cyclic oligomers consisting of furanoid and pyranoid *ε*-sugar amino acids.[94] Kaiser's *p*-nitrobenzophenone oxime resin (**2.153**)[95,96] was loaded with SAA building block **2.154a,b** in the presence BOP and DIPEA. After Boc-deprotection ammonium trifluoroacetates **2.155a,b** were obtained. By repetition of the coupling/deprotection steps, the linear immobilised precursor trimers **2.156a,b** (n = 0) and tetramers **2.157a,b** (n = 1) were obtained. Treatment of the resin with a 1:1 mixture of DIPEA and acetic acid for 36 h led to macrocyclic homotrimers **2.158a,b** and homotetramers **2.159a,b** in 5 – 20 yields (Scheme 2.29).[94]



Scheme 2.29 Synthesis of homooligomers **2.158a,b** and **2.159a,b**.

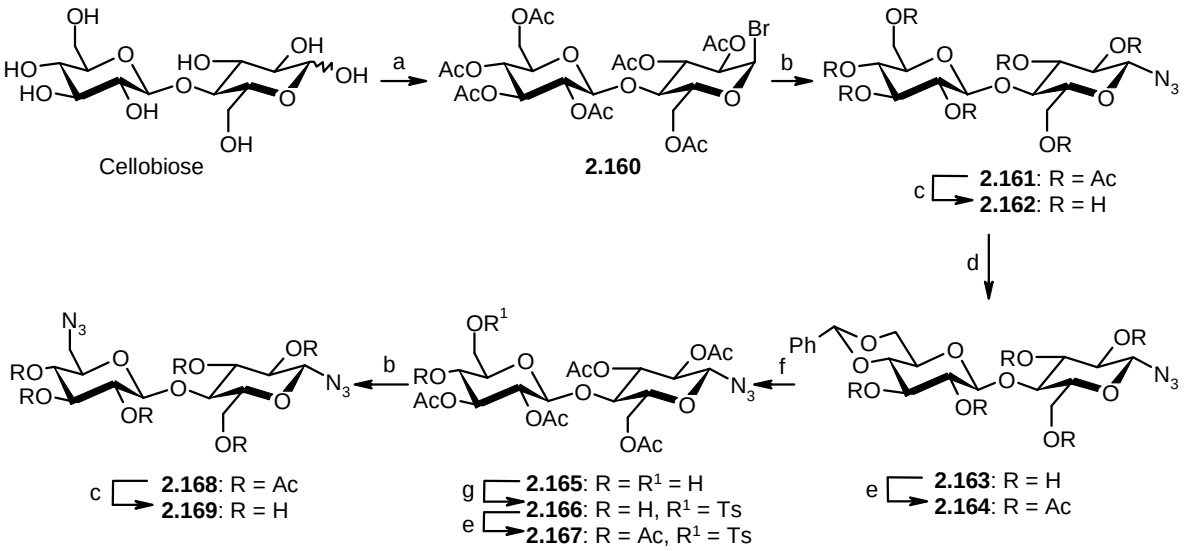
2.3 Sugar–Ureido Cryptands

Cryptands are synthetic bi- and poly-cyclic multidentate hosts. Their complexes with metal cation (cryptaplex) are found to be more stable than complexes of monocyclic corands (coraplex) because of the macrobi(poly)cyclic effect.[1]

Recently, Marsura and co-workers developed an efficient and rapid method for the preparation of a family of macrobicyclic and macrotricyclic cryptands containing the carbohydrate subunit. Central to this achievement was the tandem Staudinger–aza-Wittig (SAW) templated reaction of carbohydrate di-azides with tetraoxadiazacyclooctadecane.[97]

The requisite di-azides were prepared as follows. Bromation of per-*O*-acetyl-α-**D**-cellobiose afforded per-*O*-acetylated glycosyl bromide **2.160**, which was reacted with sodium azides to afford the *β*-glycosyl azide **2.161**.[98,99] After de-*O*-acetylation of cellobiose derivative **2.161**, the resulting azidoglycoside **2.162** was treated with α,α-dimethoxytoluene to give the 4^{II},6^{II}-*O*-benzylidene derivative **2.163**, which was reprotected to **2.164**. Removal of the benzylidene acetal from **2.164** yielded the diol **2.165**. Selective tosylation of the primary hydroxyl group and subsequent acylation of the secondary one furnished the dicacharide derivative **2.167**. Tosylate **2.167** was then converted into the 2,2',3,3',4',6-hexa-*O*-acetyl-

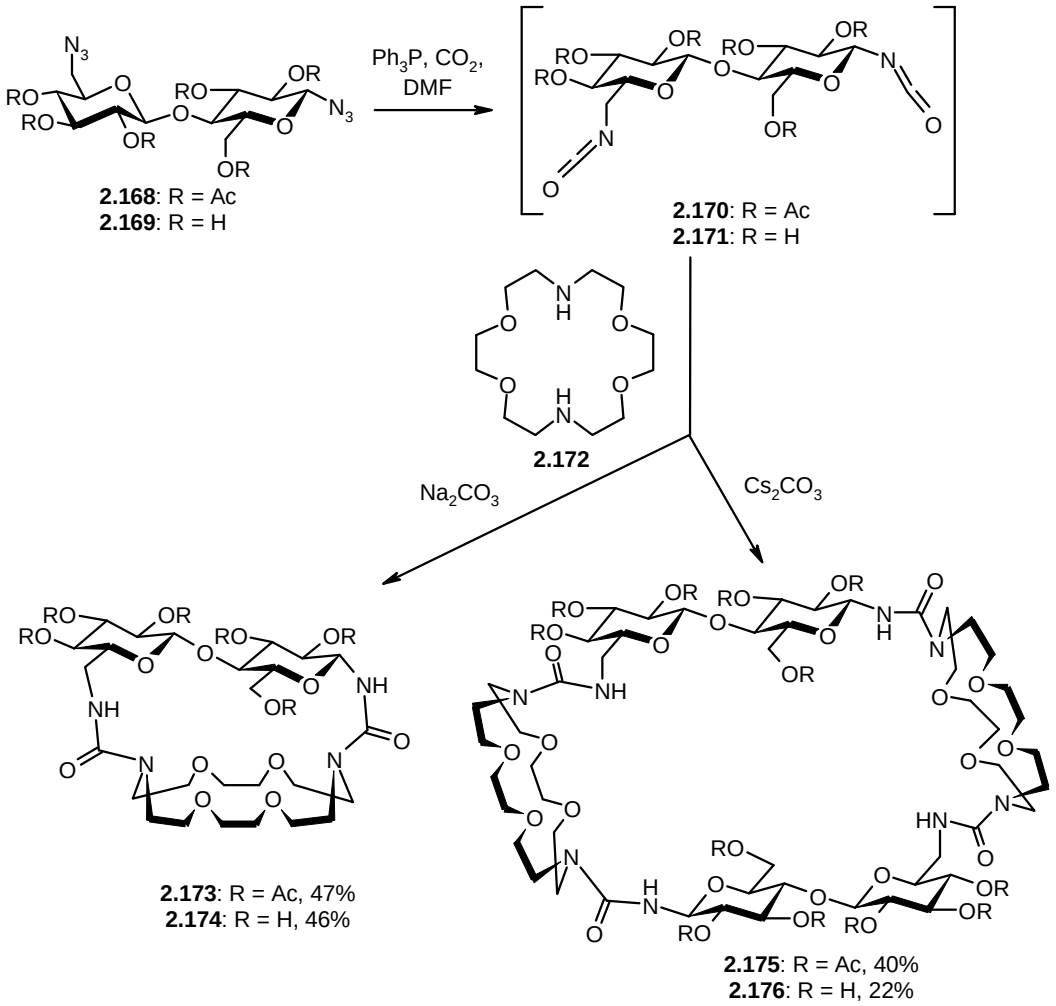
1,6'-diazido-1,6'-dideoxy-*β*-D-cellobiose (**2.168**). Deprotection of **2.168** (MeONa/MeOH) afforded finally the 1,6'-diazido-1,6'-dideoxy-*β*-D-cellobiose (**2.169**) (Scheme 2.30).[97]



(a) (1) Ac_2O, Py; (2) HBr in AcOH (35%), CH_2Cl_2, 0 °C, 30min; (b) NaN_3, DMF, 80 °C, 24h, 88% for **2.161**, 92% for **2.186**; (c) MeONa, MeOH, 3h, rt, 95% for **2.161**, 95% for **2.169**; (d) $PhCH(OMe)_2$, TsOH, DMF, 40 °C, 4h, 72%; (e) Ac_2O, Py, rt, 24h, 87% for **2.164**, 93% for **2.167**; (f) AcOH, 80 °C, 1h, 84%; (g) TsCl, Py, rt, 24h, 70%

Scheme 2.30 Synthesis of cellobiose-based diazides **2.168** and **2.169**.

Disaccharide di-azides **2.168** and **2.169** were used to prepare sugar–ureido cryptands by tandem SAW reaction carried out in anhydrous DMF by using the alkali cation template effect. 1,6-Diazidocellobiose **2.168** and **2.169** reacted with Ph_3P and CO_2 as electrophile to afford 1,6-diisocyanatocellobiose intermediates **2.170** and **2.171**. Thereafter two nucleophilic additions of tetraoxadiazacyclooctadecane **2.172** take place simultaneously with the diisocyanate. Depending on the type of metal cation templates, different macrocycles can be formed. Thus, using sodium cation template (Na_2CO_3), the monocellobiose macrobicycles **2.173** and **2.174** preferentially were obtained (47 and 46%, respectively) as shown in Scheme 2.31. On the other hand, application of cesium template (Cs_2CO_3) in this reaction leads to the formation of biscellobiose macrotricycles. The authors suggest that the formed dimer has a structure depicted by the formulas **2.175** and **2.176** (Scheme 2.31).[97]



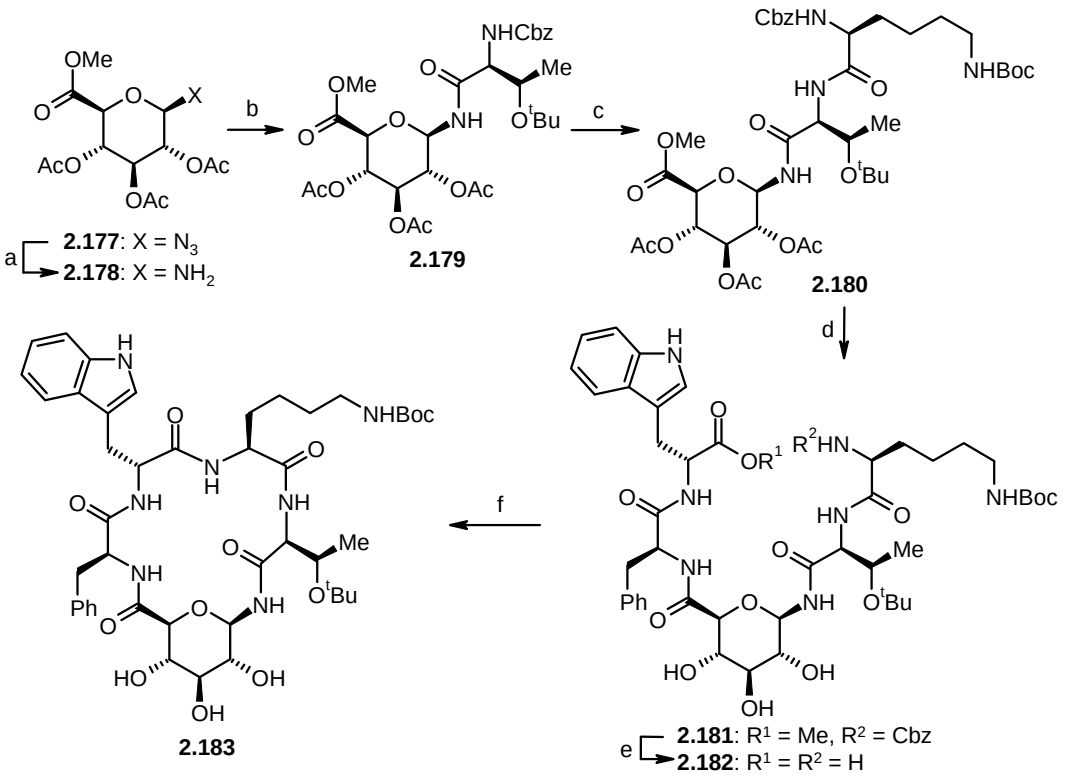
Scheme 2.31 Synthesis of cryptands **2.173**, **2.174**, **2.175** and **2.176**.

2.4 Cyclic peptides containing amino sugar units

Cyclic peptides are widely known because its biological activity.[100] Cyclopeptides with embedded non-peptide moieties are of intense current research interest.[101-103] In this context, sugar amino acids are synthetic analogs of 'normal' amino acids. Implementation of the SAAs in the structure of glyco-conjugates should improve the properties (e.g. solubility) of the peptide units.

Kessler and co-workers have developed synthetic routes to macrocyclic glycopeptides containing different sugar amino acid units. In one of these ways, the authors used pyranoid γ-amino ester **2.178** (prepared from azido ester **2.177** by palladium-catalyzed reduction) as starting material. The free amine **2.178** was unstable due to epimerization. Therefore, hydrogenation of the azide **2.177** on Pd/C was performed in THF since anomerization is known to occur preferably in protic solvents. After isolation of compound **2.178**, the amine

was immediately coupled with IIDQ (1-(isobutoxycarbonyl)-2-isobutoxy-1,2-dihydroquinoline). Subsequent reaction with protected **L**-theonine gave product **2.179**. Removal of the Cbz-group and condensation with **L**-lysine derivative [Cbz-Lys(Boc)-OH] in the presence of EDCl·HCl [1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride] and HOBt as coupling reagents, gave **2.180**. After hydrolysis, this compound was coupled with dipeptide H-Phe-**D**-Trp-OMe under standard conditions. Hydrolysis and Cbz-deprotection in **2.181** provided the amino acid **2.182** which was cyclized to macrocyclic pentapeptide analog **2.183** via TBTU [2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate] (Scheme 2.32).[104]

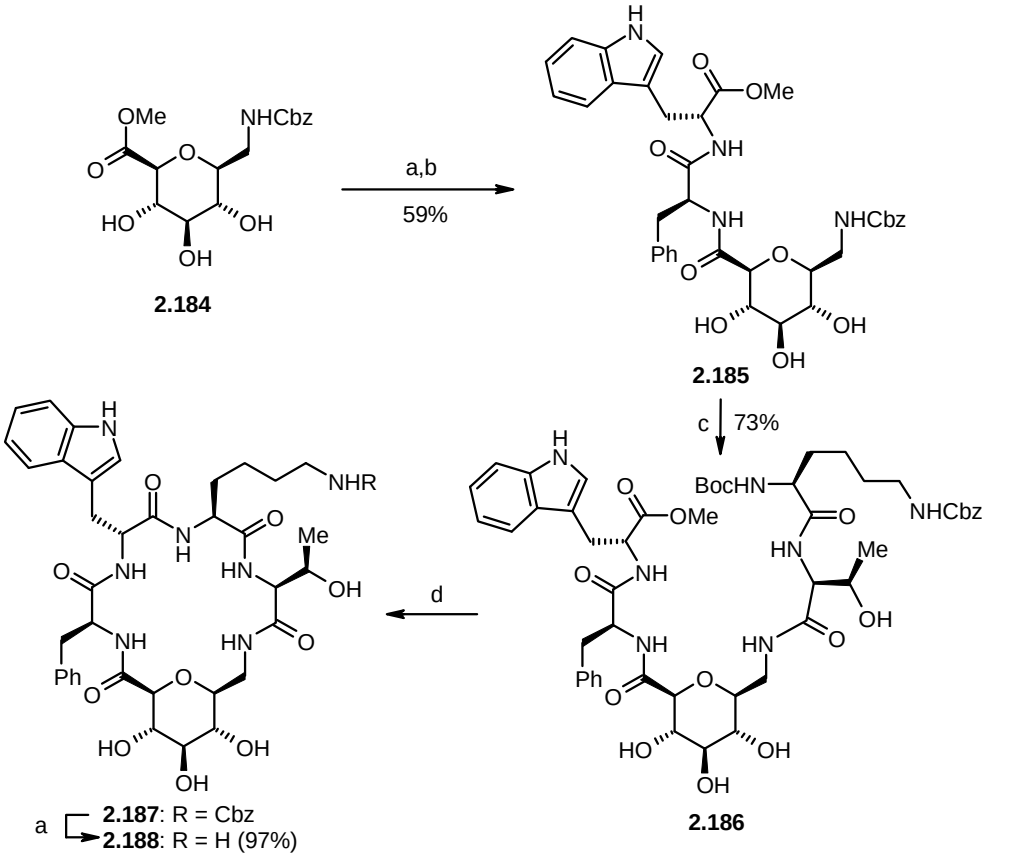


(a) H_2, 10% Pd/C, THF, 0 °C, 2h, quant.; (b) Cbz-Thr(ᵗBu)-OH, IIDQ, 0 °C, 12h, 54%; (c) (1) H_2, 10% Pd/C, AcOEt, rt, 1h, (2) Cbz-Lys(Boc)-OH, EDCl·HCl, HOBt, NMM, THF, 12h, 85%; (d) (1) 1N NaOH, THF, rt, 3h; (2) H-Phe-**D**-Trp-OMe, THF, EDCl·HCl, HOBt, NMM, THF, 12h, 77%; (e) (1) 1N NaOH, MeOH/THF (1:4), 15min, (2) H_2, 10% Pd/C, THF, rt, 1h, 48%; (f) HOBt, TBTU, DIEA, NMP, rt, 1h, 22%

Scheme 2.32 Synthesis of macrocyclic glycopeptide **2.183**.

Another synthetic route to macrocyclic glycopeptides is shown in scheme 2.33. In this case, the pyranoid Cbz-*N*-protected *δ*-amino ester **2.184** was used as starting material. Saponification of ester function and subsequent coupling with H-Phe-**D**-Trp-OMe under standard protocol provided the peptide derivative **2.185**. On the other hand, Cbz-deprotection and condensation with Boc-Lys(Cbz)-**D**-Trp-OH gave the linear compound **2.186** which was

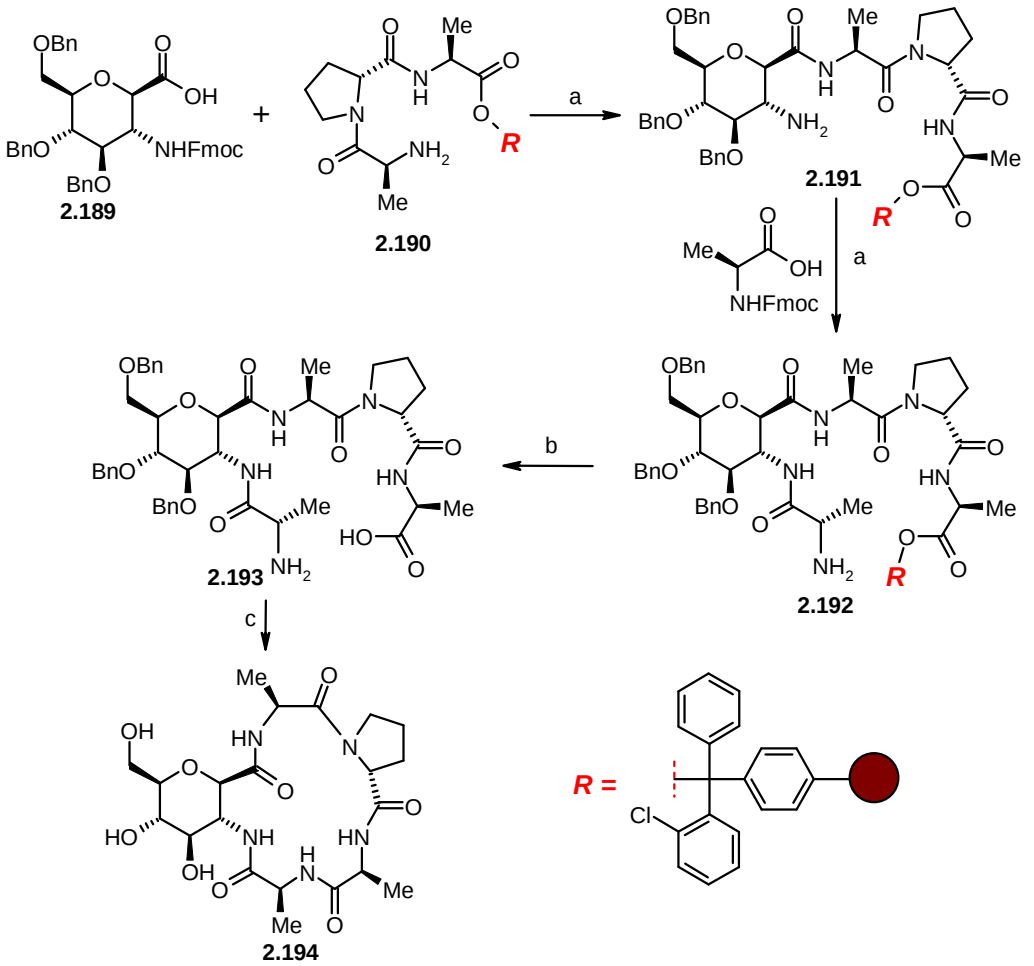
used as the precursor for the preparation of macrocycles **2.187** and **2.188** which backbone is one atom longer than that of the glycopeptide **2.183**.[104,105]



(a) 1N NaOH, MeOH, rt, 2h, (b) H-Phe-D-Trp-OMe, EDCl·HCl, HOBt, NMM, 0 °C, 12h, THF; (c) (1) H_2, 10% Pd/C, MeOH, rt, 1h; (2) Boc-Lys(Cbz)-Thr-OH, EDCl·HCl, HOBt, NMM, THF/DMF (4:1), rt, 10h, 73%; (d) (1) 1N NaOH, MeOH/THF (1:1), rt, 4h, (2) HOBt, DIEA, H_2O, TBTU, DMF, rt, 1h, 56%

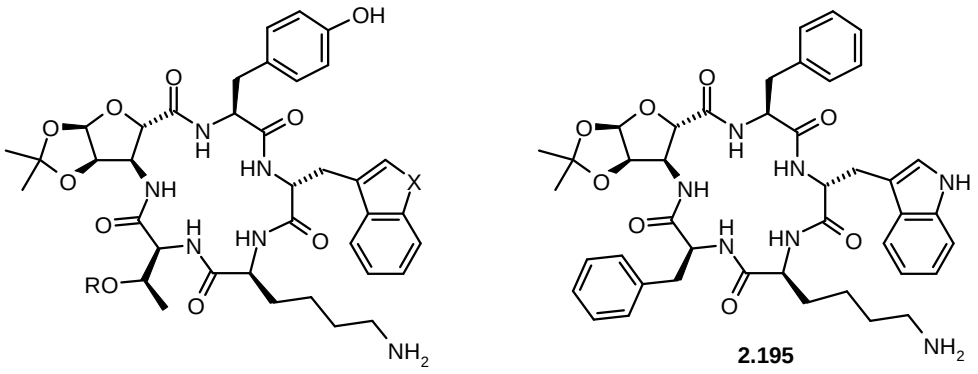
Scheme 2.33 Synthesis of macrocyclic glycopeptide **2.188**.

These authors also described the preparation of glycocyclopeptides containing sugar *β*-amino acids by solid phase synthesis. Dipeptide cross-linked to the 2-chlorotritylchloride resin **2.190** was condensed with SAA-derivative **2.189** to give **2.191**. Chain elongation and Fmoc-deprotection led to linear sugar peptide derivative **2.192**. This peptide immobilized on the polymer support **2.192** was cleaved with CH_2Cl_2/trifluoroethanol/AcOH (8:1:1) to the linear sugar pentapeptide analog **2.193**, which then was cyclized using TBTU as a coupling agent. The subsequent debenzylation led to macrocyclic glycopeptide **2.194** (Scheme 2.34).[104]



Scheme 2.34 Synthesis of macrocycle **2.194**.

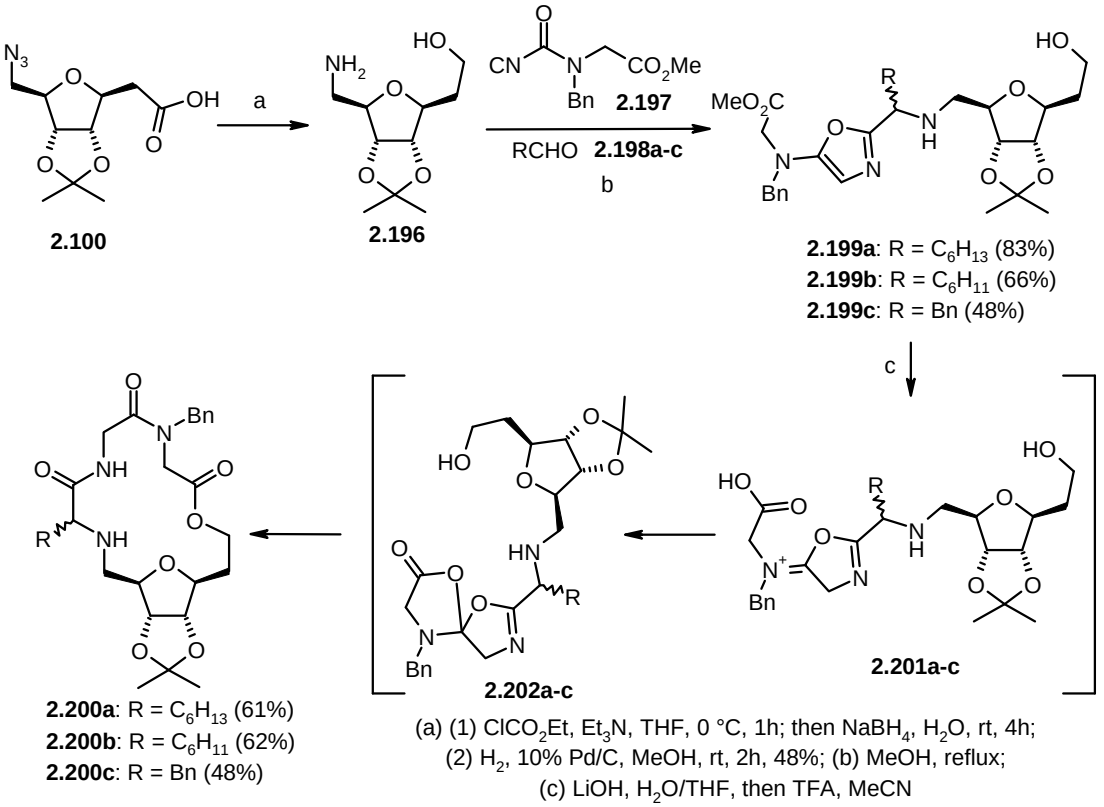
Furthermore, Kessler and co-workers synthesized macrocyclic glycopeptides based on the furanoid sugar *β*-amino acids. Similar methodology to that described in scheme 2.34 was applied in the synthesis of macrocycles **2.194a-c**, **2.195** containing: **L**-threonone, **L**-lysine, **D**-tryptophan, **D**-benzothienylalanine, **L**-tyrosine, **L**-phenylalanine subunits (Figure 2.2). Interestingly, these compound have IC_{50} values in the low μM range, which make them promising candidates for chemotherapeutic drugs against multidrug-resistant carcinoma.[106]



2.194a: R = H, X = NH
2.194b: R = Tr, X = NH
2.194c: R = Tr, X = S

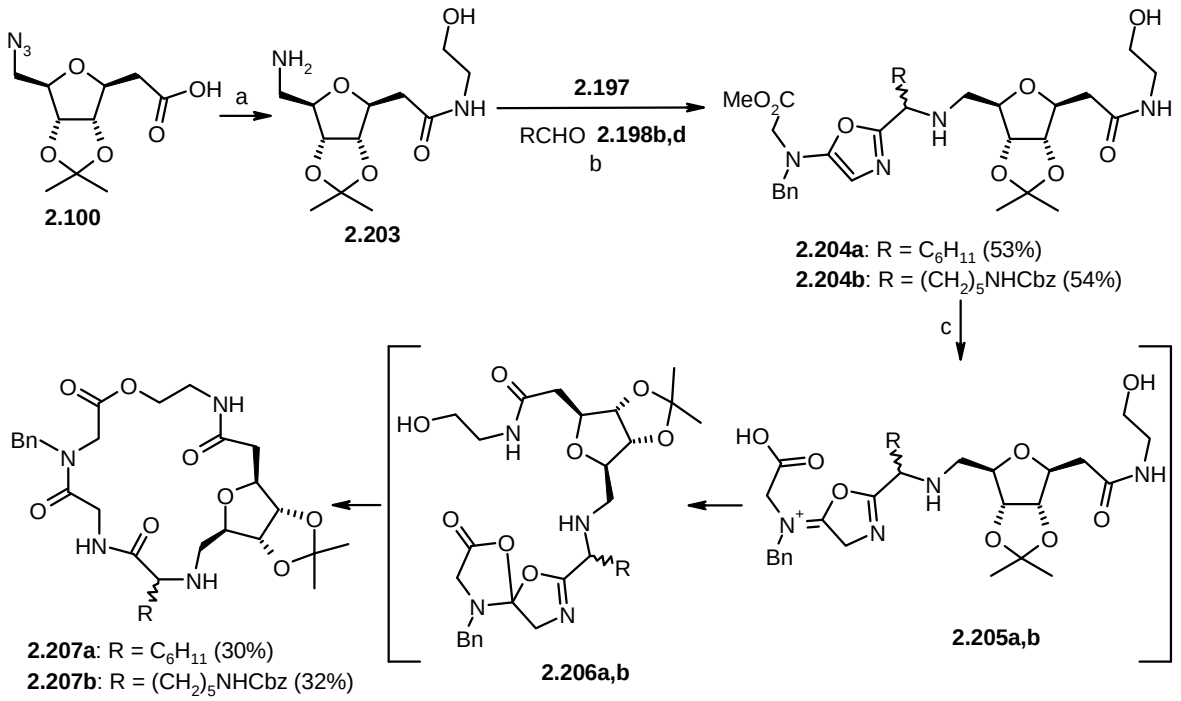
Figure 2.2 Macrocyclic glycopeptides **2.194a–c** and **2.195**.

Zhu and co-workers have developed a synthesis of highly functionalized cyclo-depsipeptides with embedded carbohydrate subunits. The authors used furanoid azido acid **2.100** as starting material. This substrate was transformed into the corresponding sugar amino alcohol **2.196** which was used in a two-step process directed to macrocyclic depsipeptide. Primarily, three-compoment reaction of **2.196** with isocyanoacetamide **2.197** and aldehyde **2.198a–c** (R = *n*-hexyl, cyclohexyl or benzyl) provided the functionalized oxazole **2.199a–c** as an equimolar mixture of two diastereoisomers. Thereafter, saponification of the methyl ester **2.199a–c** (LiOH, THF-H_2O) followed by treatment with trifluoroacetic acid gave macrocycles **2.200a–c**; the proposed mechanism of this process leading to these macrocyclic glyco-depsipeptides is depicted in Scheme 2.35. Thus, protonation (with TFA) of the C-4 position of the oxazole should provide the iminium intermediates **2.201a–c** that are trapped by the vicinal carbonyl oxygen atom to afford the spirolactones **2.202a–c**. Intramolecular nucleophilic addition of the tethered hydroxyl group to the lactone followed by fragmentation, provides the observed macrocycles **2.200a–c**.[107]



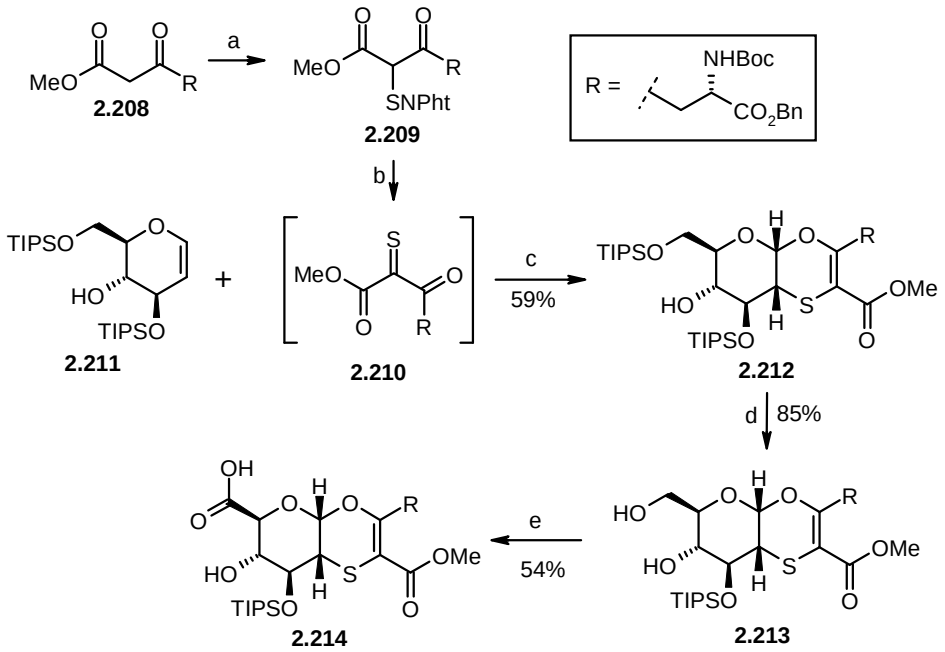
Scheme 2.35 Synthesis of glycopeptides **2.200a–c**.

This concept was also used for the preparation of 19-membered macrocyclic glycopeptides **2.207a,b**. In this case, the azido-acid **2.100** was transformed into the amino alcohol **2.203** by the EDC-mediated coupling with 1,2-aminoalcohol followed by reduction of the azide group. Compound **2.203** provided the corresponding linear oxazolo-SAA derivatives **2.204a,b** by reaction with isocyanate **2.197** and aldehyde **2.198b,d** [R = cyclohexyl or $(CH_2)_5NHCbz$]. Hydrolysis and acid-mediated macrocyclization afforded the cyclo-depsipeptides **2.207a,b** (Scheme 2.36).[107]



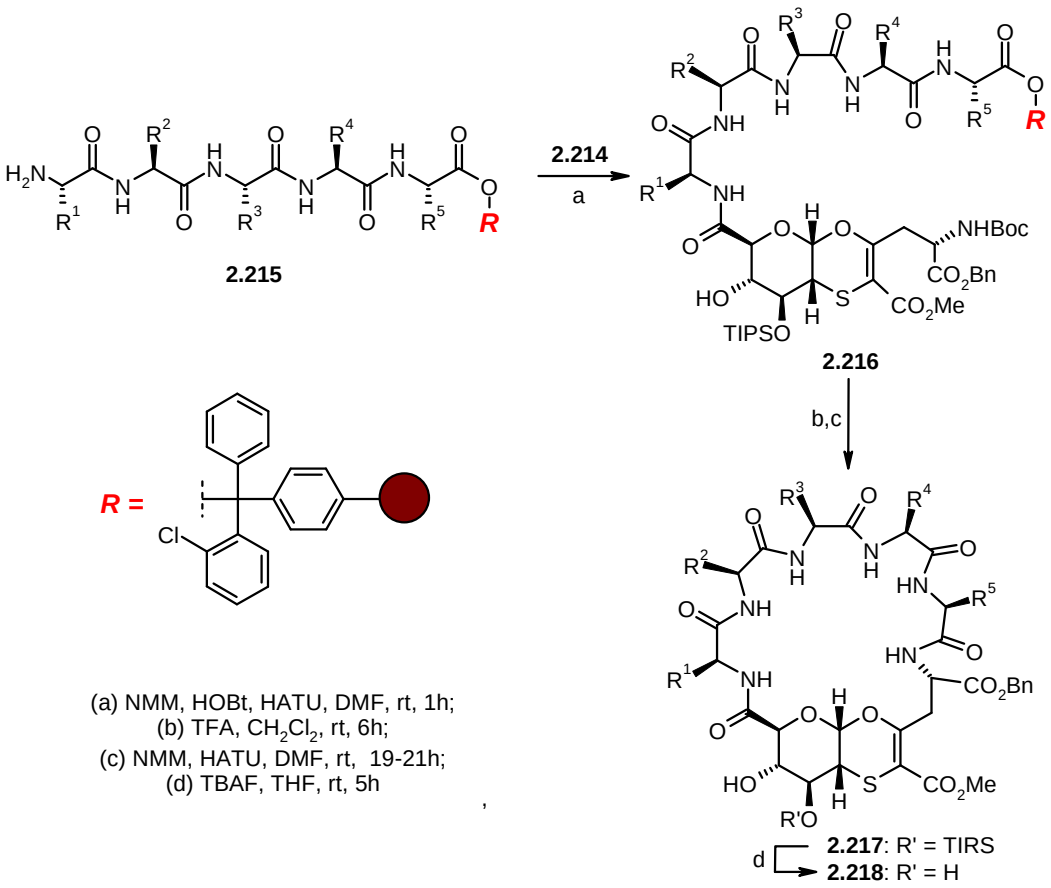
Scheme 2.36 Synthesis of glycopeptides **2.207a,b**.

Nativi and co-authors reported the use of α-*O*-linked glycohomoglutamate **2.212** as versatile, multifunctionalized scaffold in the synthesis of cyclic SAA-peptidomimetics.[108] Compound **2.212** was obtained by chemo-, regio- and stereoselective [4+2]-cycloaddition between glucal **2.211** and aspartic acid derivative **2.210**. *β*-Ketoester **2.208** in reaction with phthalimidosulfenyl chloride (PhtNSCl) provided the α-acyl-*N*-thiophthalimide derivative **2.209** which easily generated the highly reactive thione derivative **2.210** by base treatment.[109] Such transient species can act as heterodienes in reactions with electron-rich alkenes (*e.g.* enol ethers) giving rise to 5,6-dihydro-1,4-oxathiin derivatives.[110] In particular, highly reactive **2.210** was trapped "*in situ*" by glycal derivative **2.211** to give hetero Diels-Alder product **2.212** as diastereomerically pure isomer.[109] Scaffold **2.212**, having two orthogonally protected carboxyl groups (protected α-amino function and a selectively functionalized monosaccharidic unit) was successfully employed to obtain the monosilyl derivative **2.213** which, in turn, was oxidized with TEMPO/BAIB to give the glucuronic derivative **2.214** (Scheme 2.37).[108]



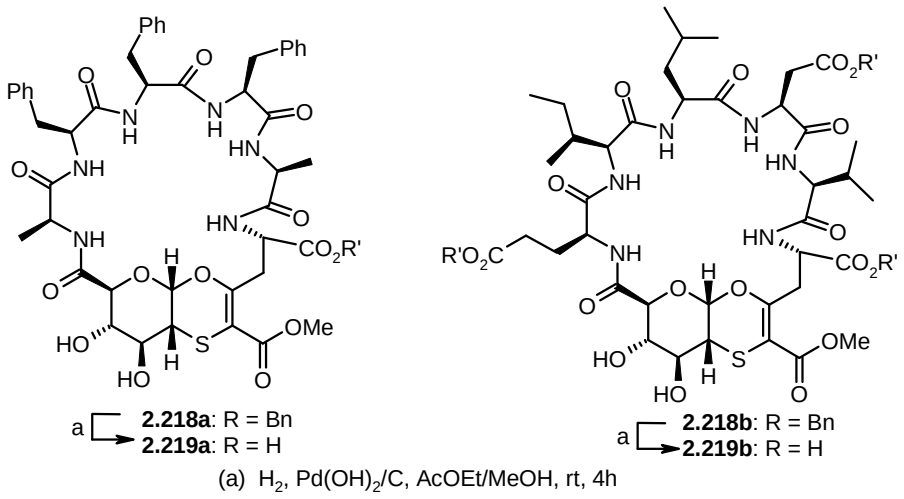
Scheme 2.37 Synthesis of compound **2.214**.

Condensations between **2.214** and pentapeptide derivatives **2.215** were performed under standard conditions to produce compounds **2.216**. Peptidic chains **2.215** as well as SAA derivatives **2.216** were obtained by standard solid-phase strategy, using 2-chlorotrityl resin. Treatment of compounds **2.216** with trifluoroacetic acid led to removal of the resin and Boc protecting group. Intramolecular lactamization of the intermediate products gave the cyclo-glycopeptides **2.217** which were de-silylated providing the product **2.218**.[108]



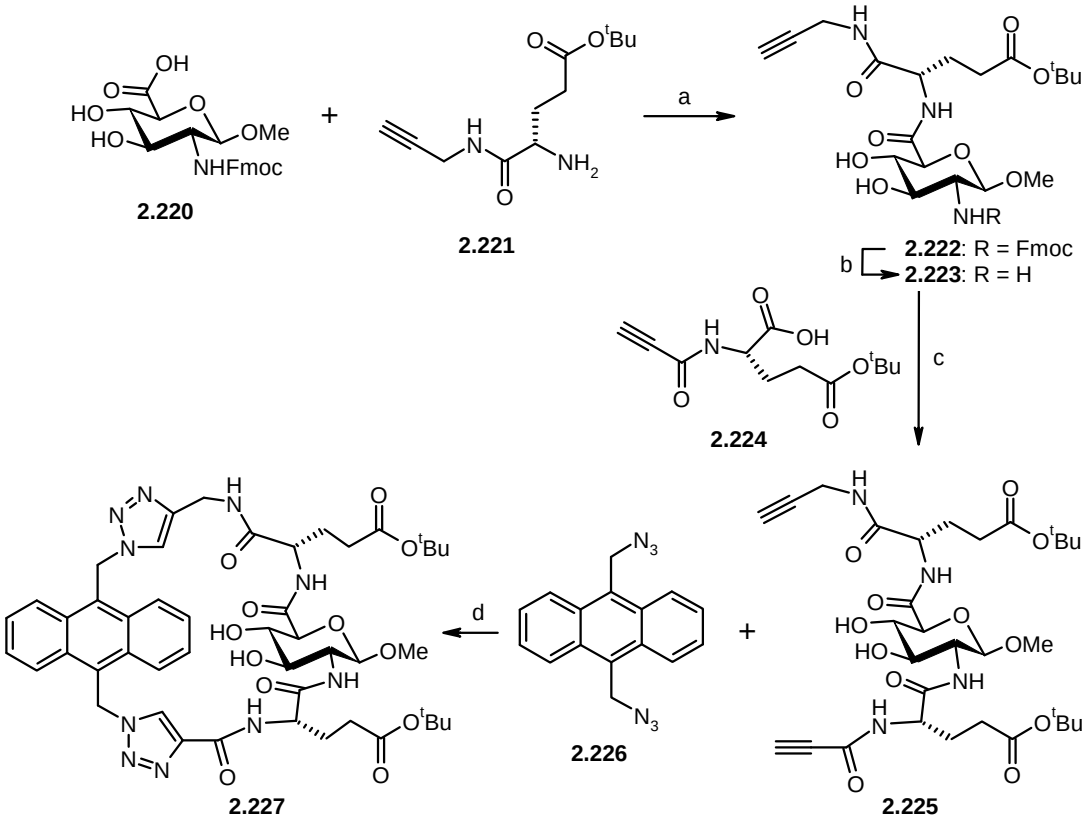
Scheme 2.38 Synthesis of macrocyclic glycopeptide **2.218**.

Debenzylation of **2.218a,b** (see Scheme 2.39) gave the cyclo(SAA**2.214**-Ala-Phe-Phe-Phe-Ala) **2.219a** and cyclo(SAA**2.214**-Glu-Ile-Leu-Asp-Val) **2.219b**. Interestingly, the cyclo SAA peptidomimetic **2.219a** showed activity in the binding assay at the human tachykinin NK_2 receptor.[108]



Scheme 2.39 Synthesis of macrocycles **2.219a,b**.

Nilsson *et al.* reported a short and straightforward route to optically pure, amphiphilic, and fluorescent glucosamine-based macrocycle. Condensation of the Fmoc-*N*-protected sugar amino acid **2.220**[111] with the amide **2.221** (to **2.222)** followed by TBAF-mediated Fmoc-group cleavage in the presence of 1-octanethiol as a dibenzofulvene scavenger gave the desired product propargyl amide **2.223** in 30% over two steps. Coupling of the glutamic acid derivative **2.224** with the amide **2.223** mediated by *N*,*N'*-diisopropylcarbodiimide (DIC) provided **2.225**, which had an unprotected 3-OH and 4-OH function. Huisgen reaction of bis-acetylene **2.225** with 9,10-bis(azidomethyl)anthracene (**2.226**)[112] afforded the sugar-based macrocycle **2.227** in 22% yield.[113]



(a) EDC, HOBt, DIPEA, THF, rt, 12h; (b) TBAF, 1-octanethiol, THF, rt, 15 min, 30% over 2 steps; (c) DIC, HOBt, CH_2Cl_2, rt, 12h, 50%; (d) CuI, DIPEA, MeCN, 45 °C, 3d, 22%

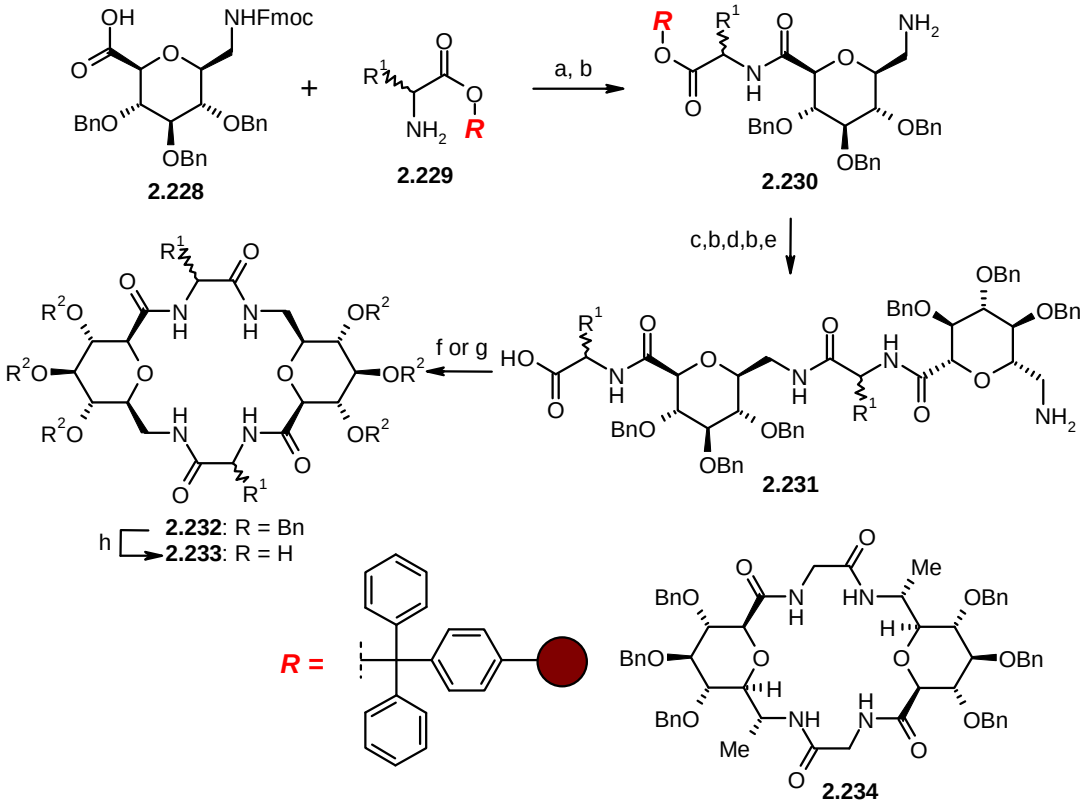
Scheme 2.40 Synthesis of sugar-based macrocycle **2.227**.

2.4.1 C_2-Symmetric macrocyclic glycopeptides

Kessler developed a synthesis of C_2-symmetric cyclopeptides containing glucuronic acid methylamine (Gum) alternating with different α-amino acids (Gly, **L**-Ala, **D**-Ala, **L**-Phe, **D**-Phe, **L**-Lys, or **D**-Lys). Coupling of the Fmoc-Gum$(Bn)_3$-OH (**2.228**) with amino acids fixed on the polymer (**2.229**) followed by Fmoc-deprotection gave products **2.230**. Chain elongation and removal from the resin provided the linear tetrapeptide analogs **2.231** cyclized

further to the macrocyclic glycopeptides **2.232**, debenzylation of which gave unprotected compounds **2.233** (Scheme 2.41).[114]

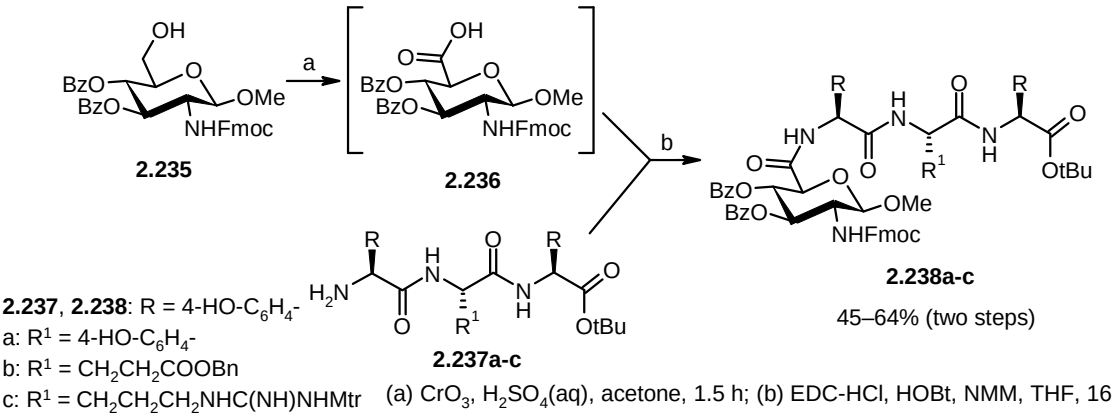
Similar synthetic way was used for preparation of C_2-symmertic macrocyclic glycopeptide **2.234**.[115]



(a) HATU, HOAt, 2,4,6-collidine, DMF, 15 h, rt; (b) 1:4 piperidine/DMF, 30 min, rt; (c) Fmoc-AA-OH, HATU, HOAt, 2,4,6-collidine, DMF, 15 h, rt; (d) **2.228**, HATU, HOAt, 2,4,6-collidine, DMF, 15 h, rt; (e) 1:1:3 TFE/AcOH/DCM or 20 vol % HFIP in DCM; (f) DIC, HOAt, NMM, 9:1 DCM/DMF, 4 days, 0-4 °C; (g) HATU, HOAt, 2,4,6-collidine, DMF, 12h, 0-4 °C; (h) H_2, 5% Pd/C, DMA/MeOH/AcOH (7:2:1), rt, 50 bar

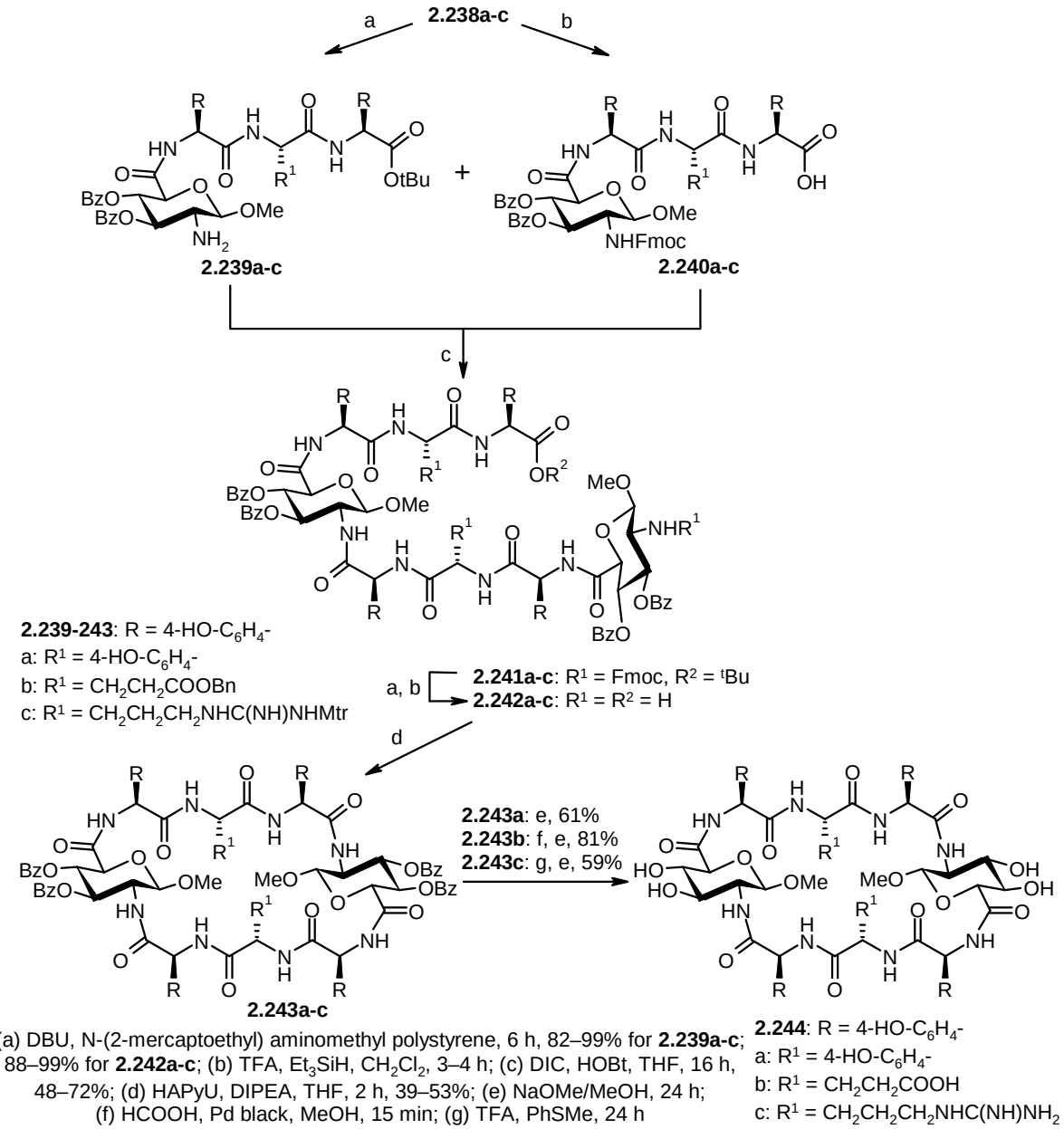
Scheme 2.41 Synthesis of C_2-symmertic macrocyclic glycopeptide **2.234**.

Nilsson and Billing synthesized macrocyclic octapeptide analogs containing pyranoid **D**-sugar amino acid. Methyl 3,4-di-*O*-benzoyl-2-(9-fluorenylmethoxycarbonyl)amino-2-deoxy-*β*-**D**-glucopyranoside **2.235** was oxidized with the Jones's reagent and the crude sugar amino acid **2.236** directly coupled to a *C*-protected tripeptide *tert*-butyl esters (H-Tyr-Tyr-Tyr-O^{t}Bu, H-Tyr-Glu(OBzl)-Tyr-O^{t}Bu or H-Tyr-Arg(Mtr)-Tyr-O^{t}Bu) **2.237a–c** providing sugar amino acid/amino acid hybrids **2.238a–c**.[116]



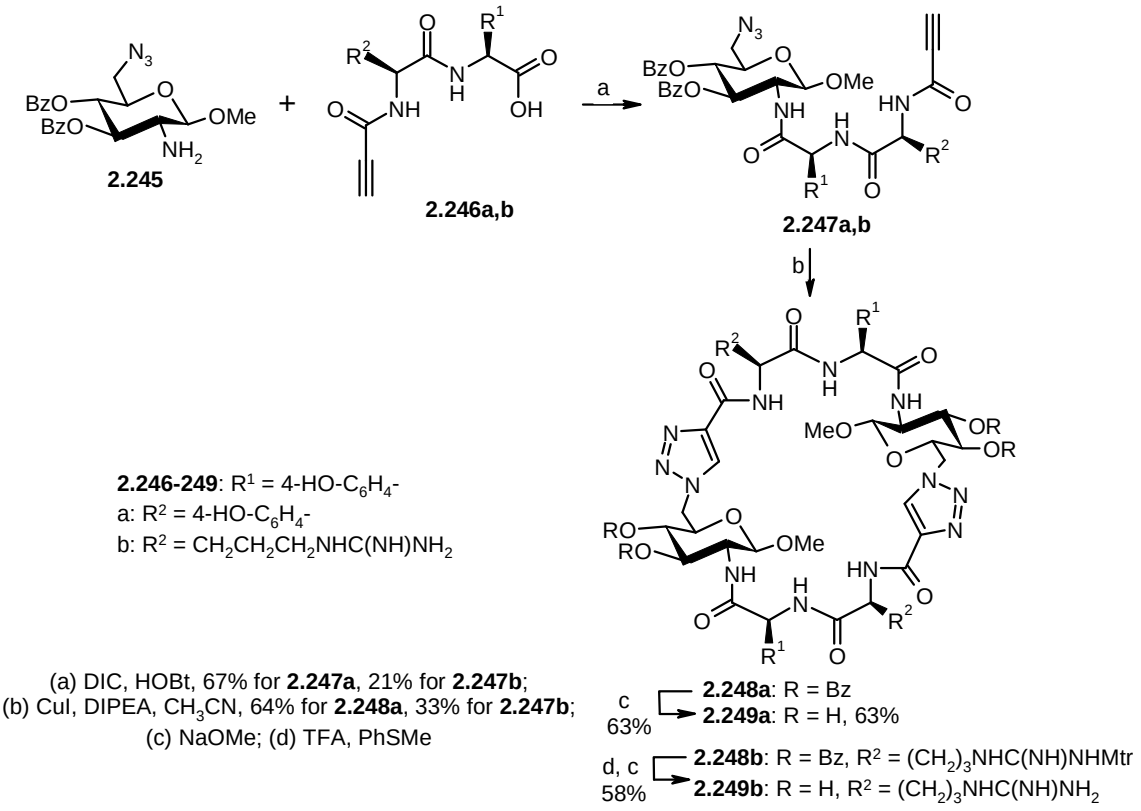
Scheme 2.42 Synthesis of compounds **2.238a–c**.

The *N*-deprotection of compounds **2.238a–c** afforded the amino derivatives **2.239a–c**, whereas *C*-deprotection gave the carboxylic acids **2.240a–c**. Coupling of **2.239a–c** with **2.240a–c** (promoted by DIC and HOBt) gave linear dimers **2.241a–c**. Cleavage of fluorenylmethyloxycarbonyl protective group and hydrolysis of the ester function afforded the amino acid derivatives **2.242a–c**. Intramolecular head-to-head macrocyclization via HAPyU and DIPEA gave C_2-symmetric macrocycles **2.243a–c**. Final deprotection of these derivatives afforded the macrocycles **2.244a–c** (Scheme 2.43), which were found to bind some purine nucleotides, such as 2'-deoxyadenosine-5'-monophosphate (dAMP) and 2'-deoxyguanosine-5'-monophosphate (dGMP), showed weak, but significant, interactions ($K_a \sim 10\ M^{-1}$).[116]



Scheme 2.43 Synthesis of macrocycles **2.244a–c**.

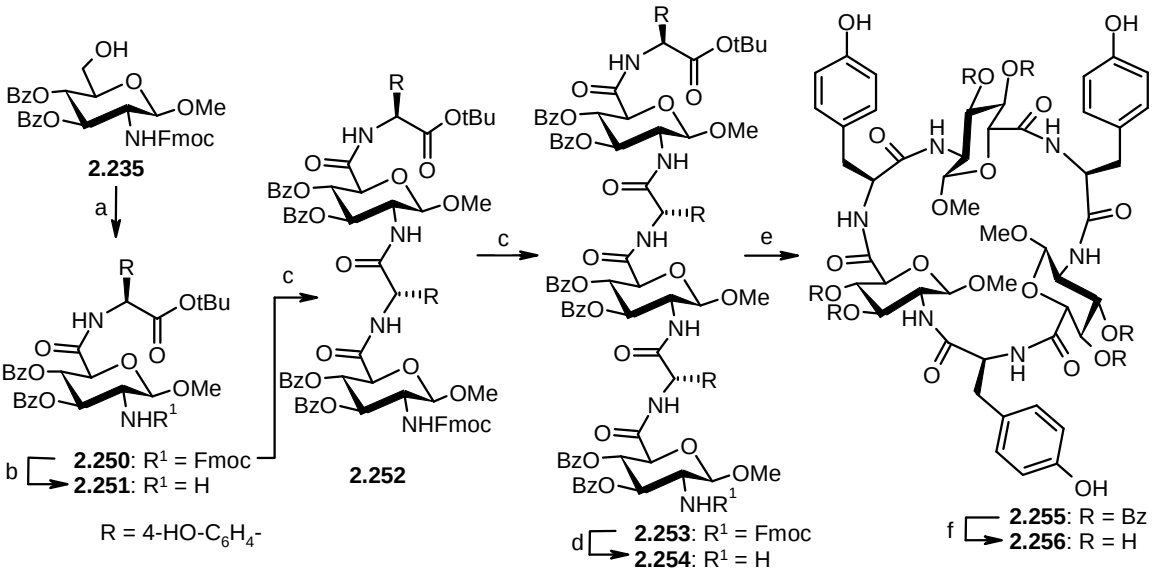
Nilsson and Billing also developed a synthetic method for preparation C_2-symmetric macrocyclic carbohydrate/amino acid hybrids through the copper(I)-catalyzed formation of 1,2,3-triazoles. Acids **2.246a,b** were coupled to the azido amino sugar **2.245** providing the propiolyl-dipeptydo/azidoaminosugar hybrids **2.247a,b**. These compounds, under 'click conditions' underwent the cyclodimerization. C_2-Symmetric macrocyclic compounds **2.248a,b** thus obtained were deprotected to derivatives **2.249a,b** (Scheme 2.44).[117]



Scheme 2.44 Synthesis of C_2-symmetric macrocyclic compounds **2.249a,b**.

2.4.2 C_3-Symmetric macrocyclic glycopeptides

The key intermediate (**2.251**) in the synthesis of C_3-symmetric macrocyclic glycopeptides **2.256** was prepared from the Fmoc-protected D-glucosamine derivative **2.235**. This compound was oxidized with the Jones' reagent to the acid, which then was directly coupled to tyrosine *tert*-butyl ester affording compound **2.250**. Cleavage of the Fmoc protecting group by TBAF and 1-octanethiol led to the amino-ester **2.251**. Hydrolysis of ester group in compound **2.250** followed by its condensation with amino derivative **2.251** afforded the Fmoc-[SAA(di-OBz)-Tyr]$_2$-O^{t}Bu **2.252**. Trimer **2.253** was similarly prepared from dimer **2.252** and amino sugar derivative **2.251**. Cleavage of the Fmoc protective group, hydrolysis of ester functional group and intramolecular amidation reaction gave C_3-symmetric macrocycles **2.255**. Consecutive cleavage of acyl groups furnished the cyclic peptidomimetic **2.256** with alternating sugar amino acid and tyrosine residues (Scheme 2.45).[118]



(a) (1) CrO_3/H_2SO_4(aq)/acetone, (2) H–Tyr–OtBu, EDC · HCl, HOBt, NMM, THF, 16 h, 53%; (b) TBAF, n-$C_8H_{17}SH$, THF, sonication, 5 min, 91%; (c) (1) TFA, Et_3SiH/CH_2Cl_2, 4 h, (2) **2.251**, DIC, HOBt, THF, 16 h, 58% for **2.252**; 68% for **2.253**; (d) DBU, N-(2-mercaptoethyl)aminomethyl polystyrene, 6 h, 98%; (e) (1) TFA, Et_3SiH, CH_2Cl_2, 4 h, (2) HAPyU, DIPEA, THF, 3 h, 27%; (f) NaOMe, MeOH (2 mM), 5 days, 16%

Scheme 2.45 Synthesis of C_3-symmetric macrocyclic compound **2.256**.

2.5 Nitrogen containing glycophanes

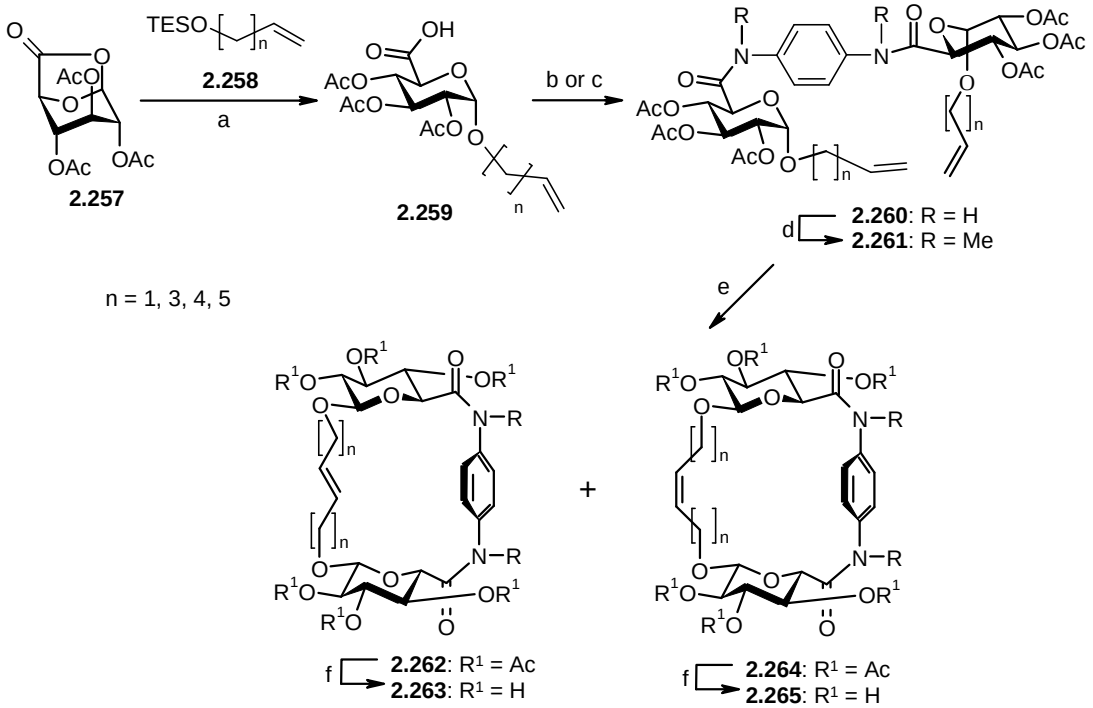
Cyclophanes are macrocycles with two or more aromatic units (benzene or hetero-aromatic rings) incorporated into a larger ring system.[119] The initial goal of the design and synthesis of cyclophanes is the study of molecular strain on benzene rings.[120] It was demonstrated that cyclophanes play an important role in macrocyclic and supramolecular chemistry.[121–123] Cyclophanes have proven to be excellent models for studying the nature of aromatic interactions in both: organic and aqueous solutions.[124] One of the advantages of cyclophanes is their relative inflexibility, so the loss of conformational entropy upon binding of a guest will be minimized.

Penadés *et al.* reported the preparation of cyclophanes with carbohydrate units (named glycophanes).[125–128] These synthetic receptors served as model systems for studies on carbohydrate-carbohydrate interaction in water.[125–128]

Nitrogen containing glycophanes were investigated by Murphy.[129] Strategy for the synthesis of these macrocyclic structures was based on application of metathesis as the ring closing reaction.[130]

The anhydroglucopyranuronic acid **2.257**[131,132] was the initial substrate. The 1,6-lactone **2.257** was converted into the α-**D**-glucopyranosiduronic acids **2.259** by highly selective glycosidation reaction with triethylsilane ethers **2.258** in the presence tin(IV)

chloride. The carboxylic acids **2.259** were then transformed in their acid chlorides and further – by condensation with phenylene-1,4-diamine into the glucuronic acid anilides **2.260**. The alternative approach of transformation of the acids **2.259** into diamide derivatives **2.260** was implemented using HATU and HOBt. Alkylation of the secondary diamides **2.260** by methyl iodide gave the tertiary diamides **2.261**. Macrocyclization of compounds **2.260** and **2.261** in the presence of the Grubbs' catalyst gave a mixture of the paracyclophane-saccharide hybrids **2.262** and **2.264** with the *E*-isomers **2.262** dominated in all cases. Compounds **2.262** and **2.264** were then converted into polyhydroxylated cyclophane analogs **2.263** and **2.265** by deacetylation reaction (Scheme 2.46).[133–135]

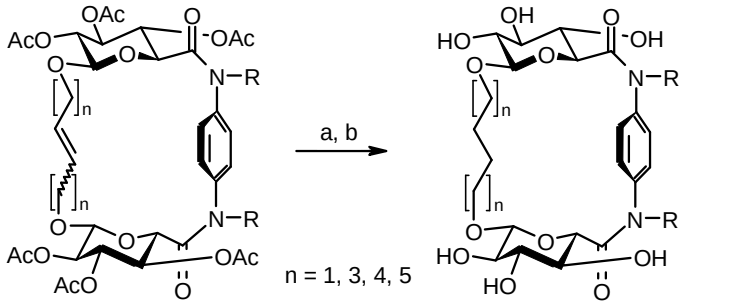


(a) $SnCl_4$, CH_2Cl_2; (b) HATU, HOBt, phenylene-1,4-diamine, DMF; (c) (1) $(COCl)_2$, DMF, CH_2Cl_2; (2) phenylene-1,4-diamine, DIEA, CH_2Cl_2; (d) NaH, MeI, DMF; (e) Grubbs I, CH_2Cl_2; (f) MeONa/MeOH;

Scheme 2.46 Synthesis of glycophanes **2.263** and **2.265**.

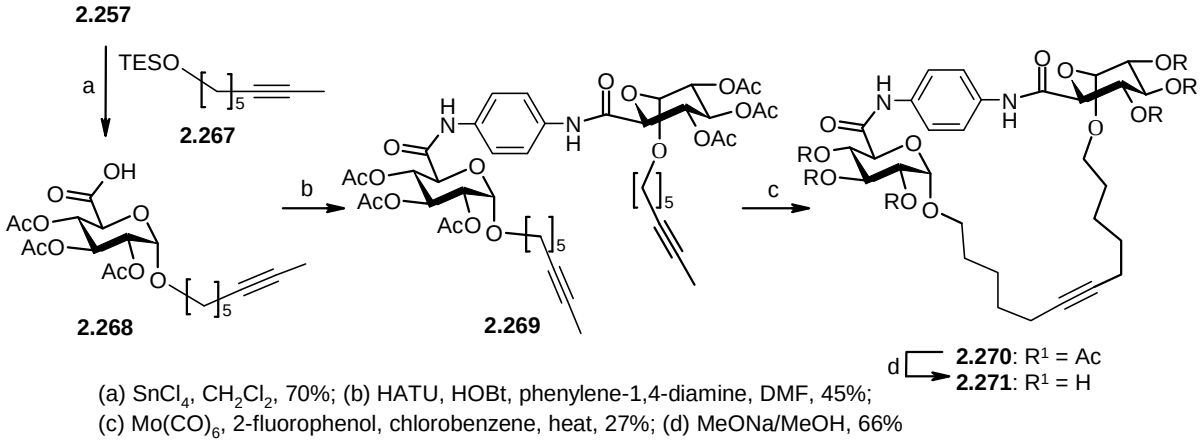
Amphiphilic macrocycles **2.262–2.265** can bind molecules in its hydrophobic cavity. In particular, compound **2.263** (n = 3) forms a complex with 8-anilino-1-naphthalenesulfonate (ANS) which shows switching phenomena similar to *β*-cyclodextrin.[134] Furthermore, crystal structure of this macrocycle shows extensive hydrogen-bonding networks, including participation of water, which may have relevance for modeling carbohydrate–carbohydrate recognition at the cell–cell interphases.[136]

Catalytic hydrogenation of **2.262**/**2.264** followed by deprotection gave **2.266** (Scheme 2.47).[134]



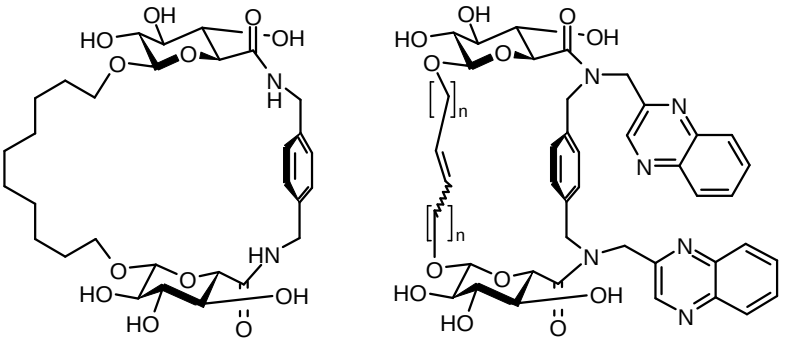
Scheme 2.47 Synthesis of macrocycles **2.266**.

Ring-closing alkyne metathesis (RCAM) was used for the synthesis of glycophanes, having carbon-carbon triple bond. The $SnCl_4$-catalyzed glycosidation of the lactone donor **2.257** with the acetylene derivative **2.267** provided the α-glycoside **2.268**. Coupling of the acid **2.268** with phenylene-1,4-diamine afforded **2.269**. Intramolecular metathesis of terminally methylated alkyne dimer **2.269** and 2-fluorophenol in chlorobenzene in the presence of $Mo(CO)_6$ afforded the expected, containing alkyne unit, macrocycle **2.270**, which after de-*O*-acetylation gave cylophane-sugar hybrid **2.271** (Scheme 2.48).[135]



Scheme 2.48 Synthesis of macrocyclic compound **2.271**.

More conformationally flexible glycophanes **2.272**[135] and **2.273a–b**[137] (Figure 2.3) were prepared from xylene-1,4-diamine. Glycophanes with quinoxaline fragments (**2.273a–b**) can interact with DNA, in the same way as natural depsipeptide backbones. Spectroscopic measurements and melting experiments indicated that glycophane derivatives do bind to DNA. Molecular dynamics simulations showed that the glycophane complexes with DNA octamer binds in a different manner than natural depsipeptide echinomycin. Interestingly, the glycophanes derived from p-xylylenediamine backbone (**2.273a–b**) mono-intercalate,[137] whereas an echinomycin bis-intercalates.[138]

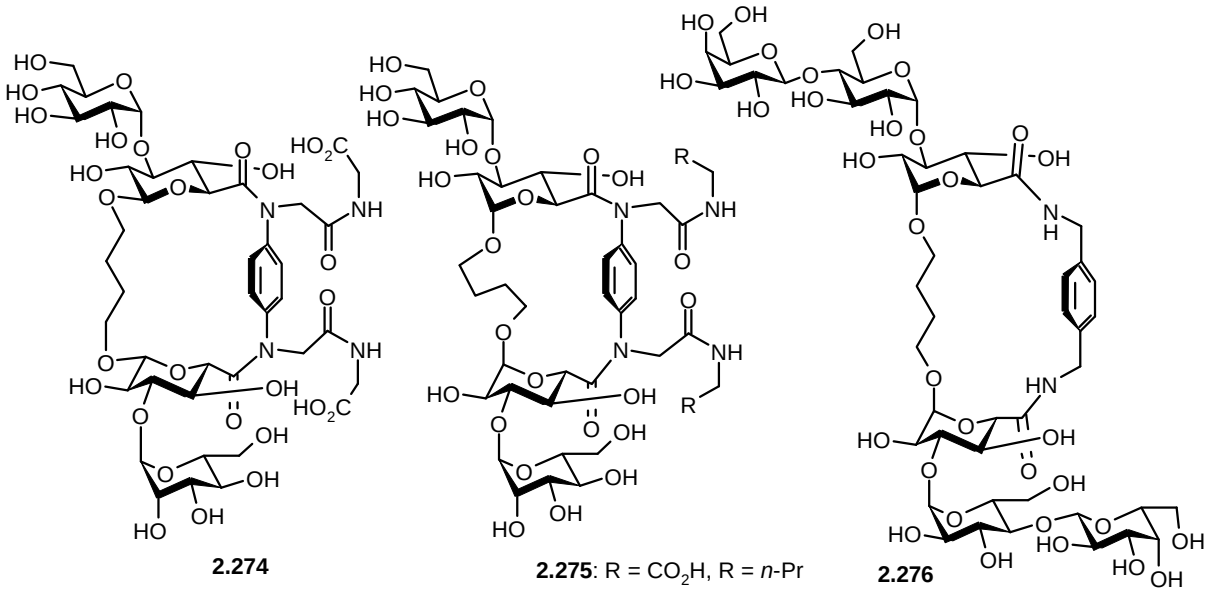


2.272

2.273a: n = 1
2.273b: n = 3

Figure 2.3 Nitrogen containing glycophanes **2.272**, **2.273a,b**.

Murphy also described the preparation of water soluble disaccharide **2.274**, **2.275**,[139] and trisaccharide glycophanes **2.276**[140] (Figure 2.4) which show selective lectin inhibitor activity.



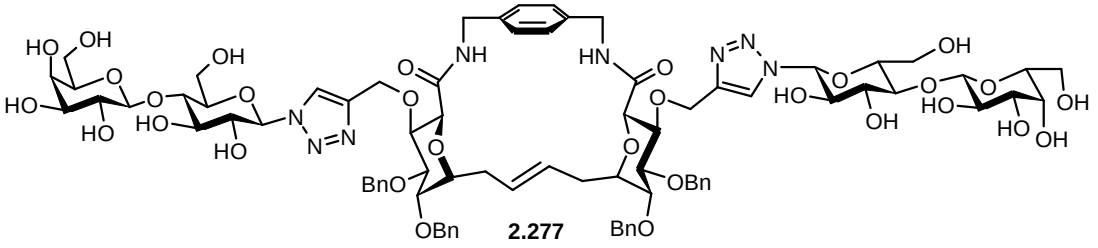
2.274

2.275: R = CO_2H, R = *n*-Pr

2.276

Figure 2.4 Macrocyles **2.274**, **2.275** and **2.276**.

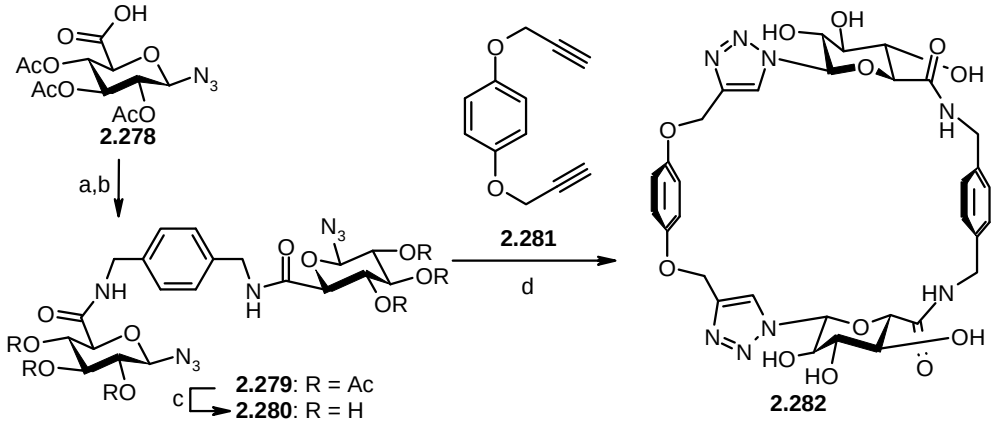
Combination of lactose units with glycophane scaffold by triazole linkers affords a sensor able to distinguish between the galectin subgroups **2.277** (Figure 2.5).[141]



2.277

Figure 2.5 Compound **2.277**.

Another type of glycophanes was prepared also by the click methodology. Sugar azido acid **2.278**[142,143] was converted into the bivalent secondary amide **2.279** *via* reaction of its acid chloride with *p*-xylene-1,4-diamine. Removal of the acetate protecting groups from **2.279** produced **2.280**. Huisgen reaction of bis-azide **2.280** with *p*-bis-propargyloxybenzene **2.281** afforded the glycotriazolophane **2.282** (Scheme 2.49).[144]



(a) $(COCl)_2$, DMF (cat.), CH_2Cl_2; (b) xylene-1,4-diamine, DIEA, CH_2Cl_2;
(c) MeONa, MeOH-CH_2Cl_2 (37% over 3 steps); (d) $CuSO_4$, sodium ascorbate, MeCN-H_2O, 56%

Scheme 2.49 Synthesis of glycotriazolophane **2.282**.

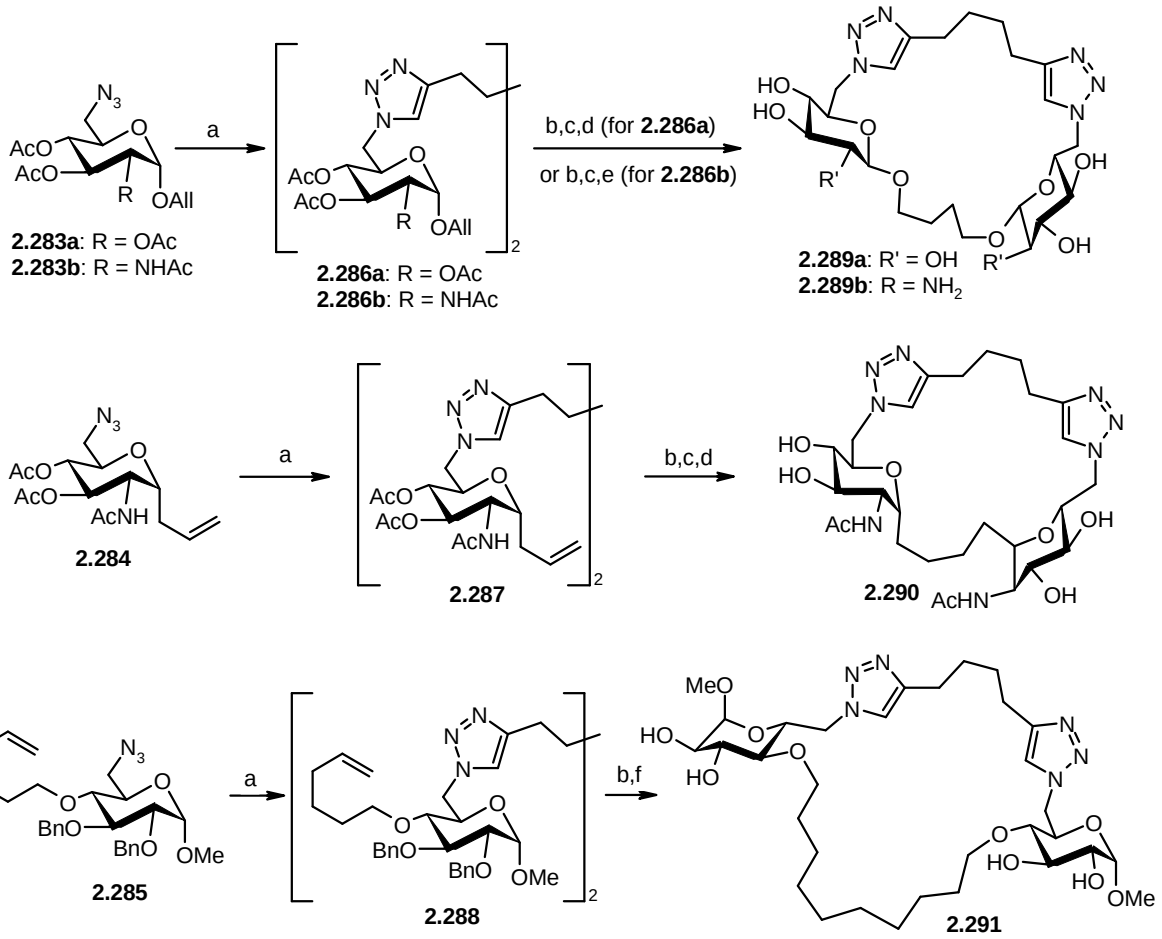
2.6 Macrocycles incorporating carbohydrate subunits connected by 1,2,3-triazole bridges

1,2,3-Triazole derivatives are the most common heterocycle-containing macrocyclic compounds. The 1,3-dipolar cycloaddition of azides and acetylenes, known as Huisgen reaction[145,146] is one of the most convenient processes for the preparation of 1,2,3-triazoles. This process is easy to perform, has high atom economy, and – moreover – the starting materials (azide and acetylene) are usually rather easy to prepare. However, sometimes it gives more than one product (1,4- and 1,5-adduct). The solution to the problem ('click' approach) was provided in 2001 by Sharpless[147] and (independently) by Meldal.[148] The 'click' strategy based on a Huisgen reaction is often used in macrocyclization processes.[149–151]

I have previously described an application of the 1,2,3-triazole chemistry in syntheses of carbohydrate containing macrocycles (Schemes 2.19, 2.20, 2.40, 2.44, 2.49). In this part I will discuss the other examples of such macrocycles.

Dörner and Westermann have developed a synthesis of macrocyclic structures containing two saccharide units *via* a click-dimerization–ring-closing metathesis approach. After

addition of an aqueous copper(II) acetate–sodium ascorbate solution to the mixture of the corresponding carbohydrate azides: **2.283a,b**, **2.284**, **2.285** and 1,7-octadiyne in *tert*-butanol, the carbohydrate dimers **2.286a,b**, **2.287**, **2.288** were obtained. Subsequently, vinyl-groups were coupled by RCM methodology using Grubbs I catalyst. Hydrogenization and/or deacetylation provided the unprotected macrocyclic compounds **2.289a,b**, **2.290**, **2.291** (Scheme 2.50).[152]

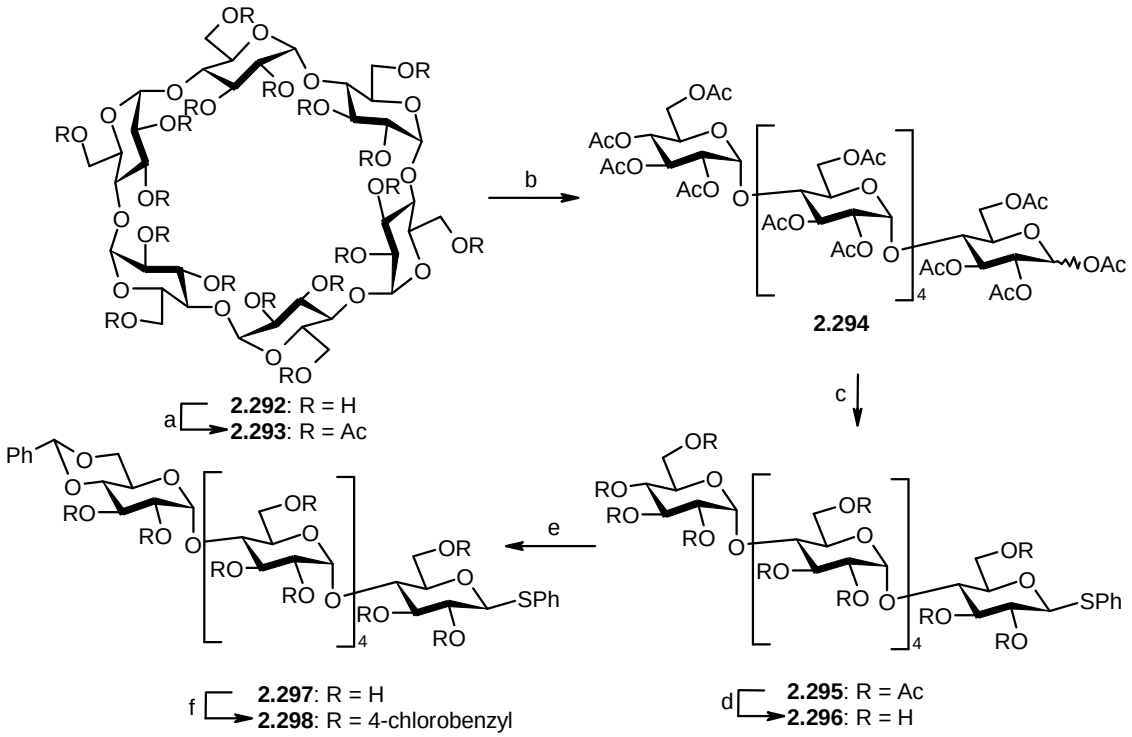


(a) 1,7-octadiyne, sodium ascorbate, $Cu(OAc)_2$, $^tBuOH/H_2O$,12 h, rt; (b) Grubbs I catalyst (5 mol%), CH_2Cl_2, reflux, 12–24 h, 73–95%; (c) H_2, $Pd(OH)_2/C$, MeOH, 87–99%; (d) NaOMe, MeOH, 2 h, 79–99%; (e) NaOH, THF, 12 h, 40%; (f) MeOH, $Pd(OH)_2/C/H2$, 88%

Scheme 2.50 Synthesis of macrocyclic compounds **2.289a,b**, **2.290** and **2.291**.

Vasella and co-workers proposed to utilize the "click" strategy for the preparation of synthetic cyclodextrin analogs.[153] Cleavage of per-*O*-acetylated *α*-CD **2.293** under condition of acetolysis (70% $HClO_4/Ac_2O$) provided the fully acetylated open-chain product **2.294** (*α*:*β* = 9:1). The hexasaccharide **2.294** was converted into phenyl thioglycoside **2.295** according to Hanessian's method.[154] After de-*O*-acetylation of compound **2.295**, the resulting thioglycoside **2.296** was treated with α,α-dibromotoluene according to the method of Garegg

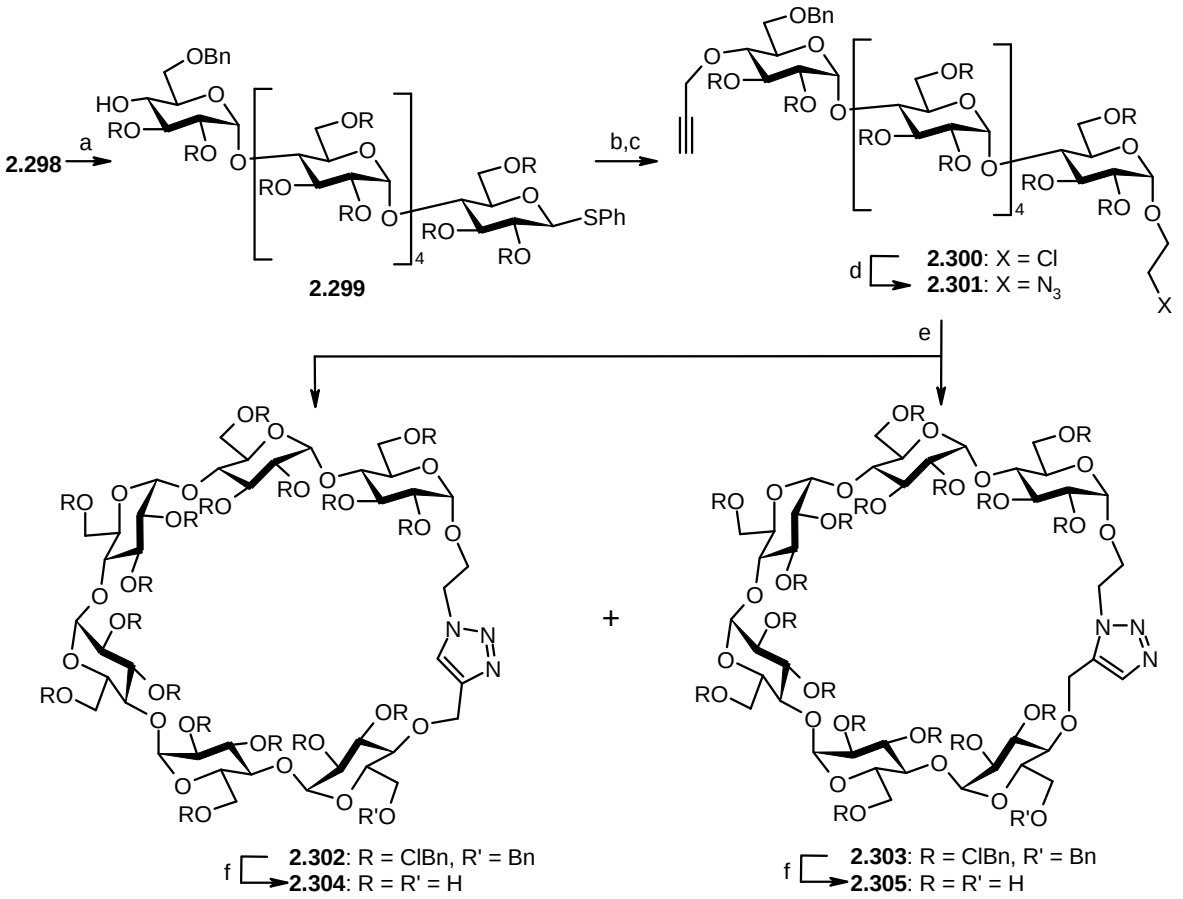
and Swahn[155] to yield the $4^{VI},6^{VI}$-*O*-benzylidene derivative **2.297**, which was then 4-chlorobenzylated to fully protected derivative **2.298** (Scheme 2.51).[156]



a) Ac_2O/Py (quant.); (b) 70% aq. $HClO_4$, Ac_2O, 0 to 23 °C, 95%; (c) ZnI_2, Me_3SiSPh, CH_2Cl_2, 85%; (d) NaOMe/MeOH, 94%; (e) α,α-dibromotoluene, Py; (f) 4-Cl-$C_6H_4CH_2Cl$, Bu_4NI, NaH, DMF, 80%

Scheme 2.51 Synthesis of compound **2.298**.

Reductive ring opening of benzylidene acetal of the hexasaccharide **2.298** yielded the secondary alcohol **2.299**. The free hydroxyl group in **2.299** was alkylated with propargyl bromide and the corresponding propargyl ether was glycosylated with 2-chloroethylalcohol to afford **2.300** as a mixture of anomers (α:β = 9:1) in 85% yield. The anomer (α-**2.300**) was then converted into the azido-alkyne **2.301** by nucleophilic substitution with sodium azide. Intramolecular 1,3-dipolar cycloaddition at 110 °C gave the 1,4- and 1,5-substituted 1,2,3-triazoles **2.302** (24%) and **2.303** (31%), respectively. Their subsequent deprotection with $FeCl_3$ in CH_2Cl_2 gave the α-CD analogs **2.304** and **2.305** respectively (Scheme 2.52).[153]

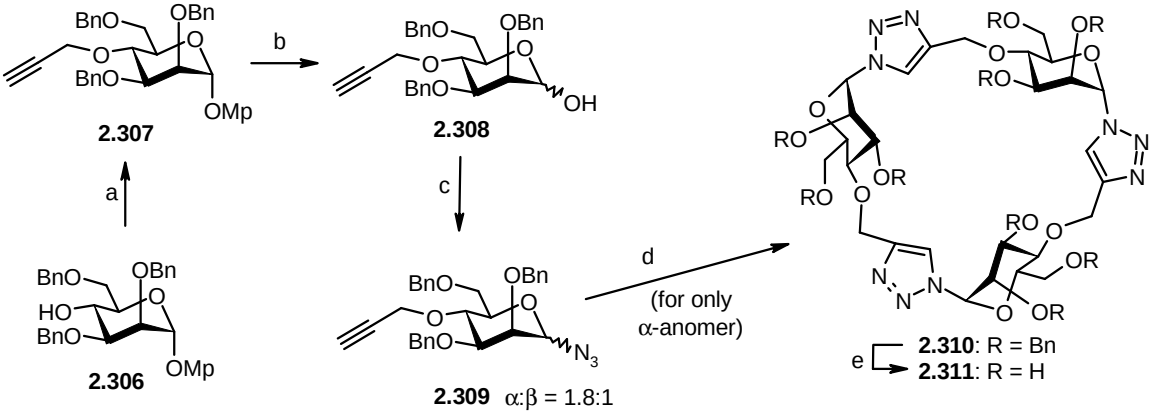


(a) Et_3SiH, BF_3 Et_2O, CH_2Cl_2,74%; (b) $BrCH_2CCH$, NaH, DMF, 87%; (c) $ClCH_2CH_2OH$, NIS, TfOH, molecular sieves, Et_2O, 60, 85%; (d) NaN_3, DMF, 91%; (e) DMF, 110 °C, **2.302** (24%)and **2.303** (31%); (f) $FeCl_3$, CH_2Cl_2, **2.304** (68%); **2.305** (66%)

Scheme 2.52 Preparation of synthetic cyclodextrin analogs **2.304** and **2.305**.

Slightly different methodology of the synthesis of cyclodextrin analogs containing 1,2,3-triazole units was proposed by Gin and co-workers. These authors synthesized highly symmetrical macrocycles by functionalization of mono-, bi- or tri-saccharide azido-acetylenes in macrocyclization reaction.

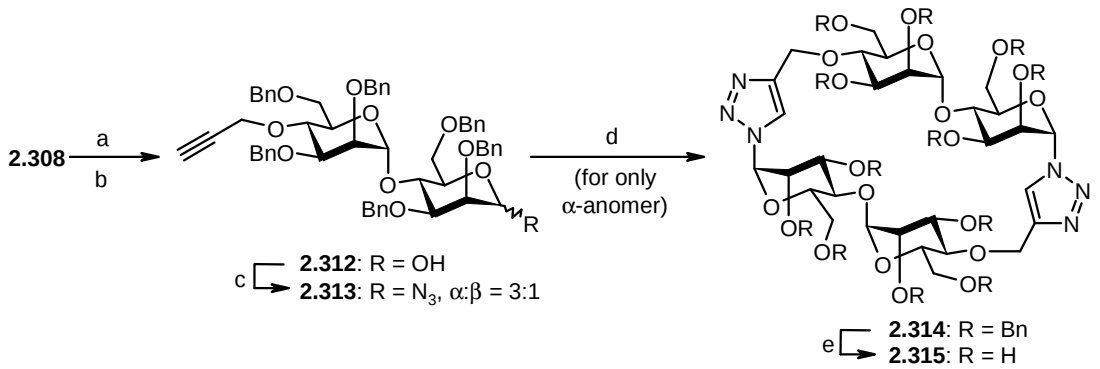
Thus, the terminal alkyne was installed by a C4-*O*-alkylation of *p*-methoxyphenyl 2,3,6-tri-*O*-benzyl-*α*-**D**-mannopyranoside (**2.306**)[157] with propargyl bromide which afforded **2.307**. Anomeric deprotection afforded the hemiacetal **2.308**[158] which then served as an convenient donor for sulfoxide-mediated dehydrative glycosylation.[159] Activation of hemiacetal **2.308** with Ph_2SO and Tf_2O at -45 °C followed by reaction with trimethylsilyl azide afforded the azide **2.309** (α:β = 1.8:1) in 95% yield. Huisgen reaction of *α*-**2.309** gave cyclotrimer **2.310** in 62% yield, together with small amounts of byproducts (tetramer up to hexamer) as evidenced by MALDI-TOF mass spectrometry. Removal of all benzyl groups was effected by transfer hydrogenolysis (with ammonium formate and Pd/C) providing macrocycle **2.311** (Scheme 2.53).[160]



(a) NaH, $HCCCH_2Br$, DMF, 99%; (b) CAN, 4:1 $MeCN/H_2O$, 68%; (c) Ph_2SO, Tf_2O, 3:1 $PhMe/CH_2Cl_2$, $TMSN_3$, Et_3N, 95%; (d) CuI, DBU, 62%; (e) NH_4HCO_2, Pd/C, 99%

Scheme 2.53 Synthesis of macrocycle **2.311**.

Activation of hemiacetal **2.308** (Ph_2SO and Tf_2O at -45 °C in the absence of a triflic acid scavenger) followed by its reaction with the C4-OH in **2.306** provided the disaccharide in good yield and complete α-selectivity. Oxidative removal of the 4-methoxyphenyl acetal afforded the hemiacetal **2.312**,[158] which was glycosylated with trimethylsilyl azide to afford disaccharide **2.313**. The 'click' macrocyclodimerizations gave cyclodimer **2.314** in 89% yield. Considering the possibility of oligomerization of the disaccharide, this high yield may result (presumably) from curved topology of the disaccharide building block that could facilitate cyclization in preference to oligomerization. Cleavage of benzyl protecttive groups in **2.314** afforded the C_2-symmetric olidosaccharide macrocycle **2.315** (Scheme 2.54).[160]

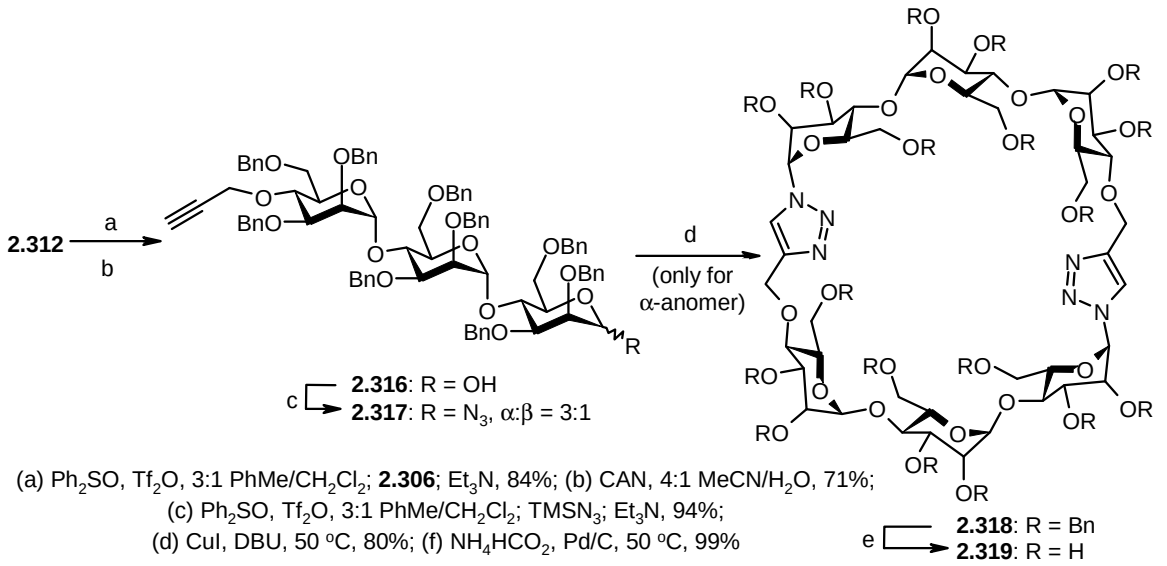


(a) Ph_2SO, Tf_2O, 3:1 $PhMe/CH_2Cl_2$; **2.306**; Et_3N, 90%; (b) CAN, 4:1 $MeCN/H_2O$, 76%; (c) Ph_2SO, Tf_2O, 3:1 $PhMe/CH_2Cl_2$; $TMSN_3$; Et_3N, 94%; (d) CuI, DBU, 89%; (e) NH_4HCO_2, Pd/C, 99%

Scheme 2.54 Synthesis of C_2-symmetrical oligosaccharide macrocycle **2.315**.

An iterative glycosylation of the C-4 nucleophile **2.306** and removal of the anomeric protecting group gave the final hemiacetal **2.316**. Its conversion into the **2.317** glycoside was achieved by the same sequence as for **2.313**. The resulting trisaccharide **2.317** underwent the

[1,3]-dipolar cycloaddition providing the cyclodimer in 80% yield, accompanied with the corresponding cyclotrimer (15% yield). Transfer hydrogenolysis removed quantitatively all 18 benzyl groups and yielded the desired macrocycle **2.319** (Scheme 2.55).[158]



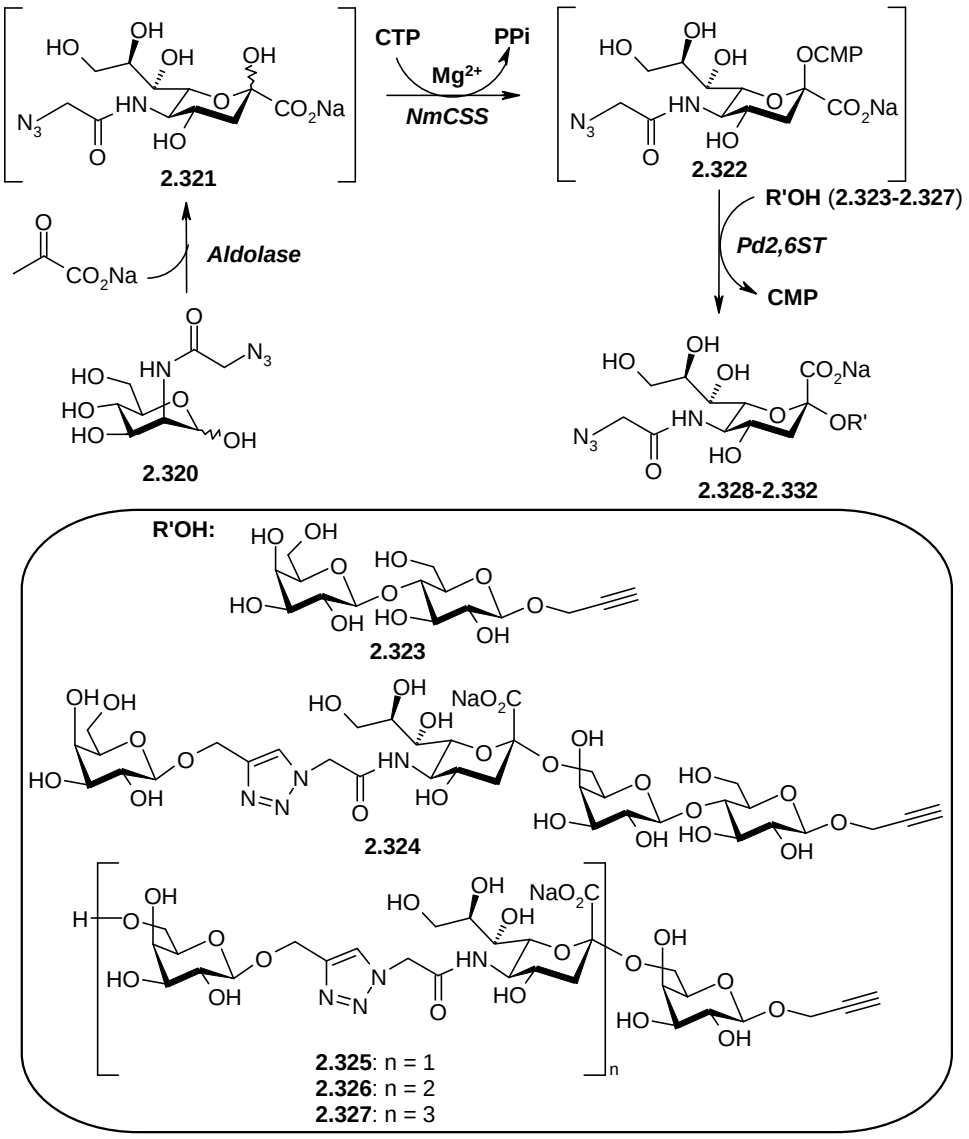
Scheme 2.55 Synthesis of macrocyclic compound **2.319**.

This synthetic strategy allows the synthesis of fully modified cyclodextrin analogs, because different hydroxyl groups can be modified during the synthetic way.

In order to visualize the supramolecular potential of the oligosaccharide macrocycle **2.319**, the standard fluorescence sensor: 8-anilino-1-naphthalene sulfonate (ANS) was tested; the macrocycle **2.319** showed the same binding affinity with ANS as *β*-cyclodextrin.[158]

Chen and co-workers developed the chemoenzymatic method for the preparation of sialic acid, containing structurally defined macrocyclic oligosaccharides of varied sizes.

One-pot reaction of the mannose derivative **2.320** with sodium pyruvate, cytidine-5'-triphosphate (CTP), and three enzymes [*Aldolase*, *Neisseria meningitidis* CMP-sialic acid synthetase (*NmCSS*), *Photobacterium damsela* α-2,6-sialyltransferase (Pd2,6ST)], and alcohols **2.323-2.327** provided the azides **2.328-2.332** (Scheme 2.56).[161]



Scheme 2.56 Synthesis of sialic acid derivatives **2.328–2.332**.

The azide/alkyne-bifunctionalized sialosides **2.328**-**2.332** were transformed into the macrocyclic carbohydrates **2.333**-**2.338** under the standard conditions of copper(I)-catalyzed Huisgen's 1,3-dipolar cycloaddition reaction. Intramolecular cyclization of acyclic sialosides **2.328**, **2.331**, and **2.332** led to the formation of the macrocyclic trisaccharide **2.333** (91%), hexasaccharide **2.336** (70%), and octasaccharide **2.337** (70%), respectively. Treatment of acyclic pentasaccharide **2.329** resulted in the macrocyclic pentasaccharide **2.334** (59% yield) and a macrocyclic decasaccharide **2.338** (30% yield). Similarly, cycloaddition of acyclic tetrasaccharide **2.330** with CuI and DIPEA afforded the desired macrocyclic tetrasaccharide **2.335** in 63% yield and macrocyclic octasaccharide **2.337** in 31% yield (Figure 2.5 and 2.6).[161]

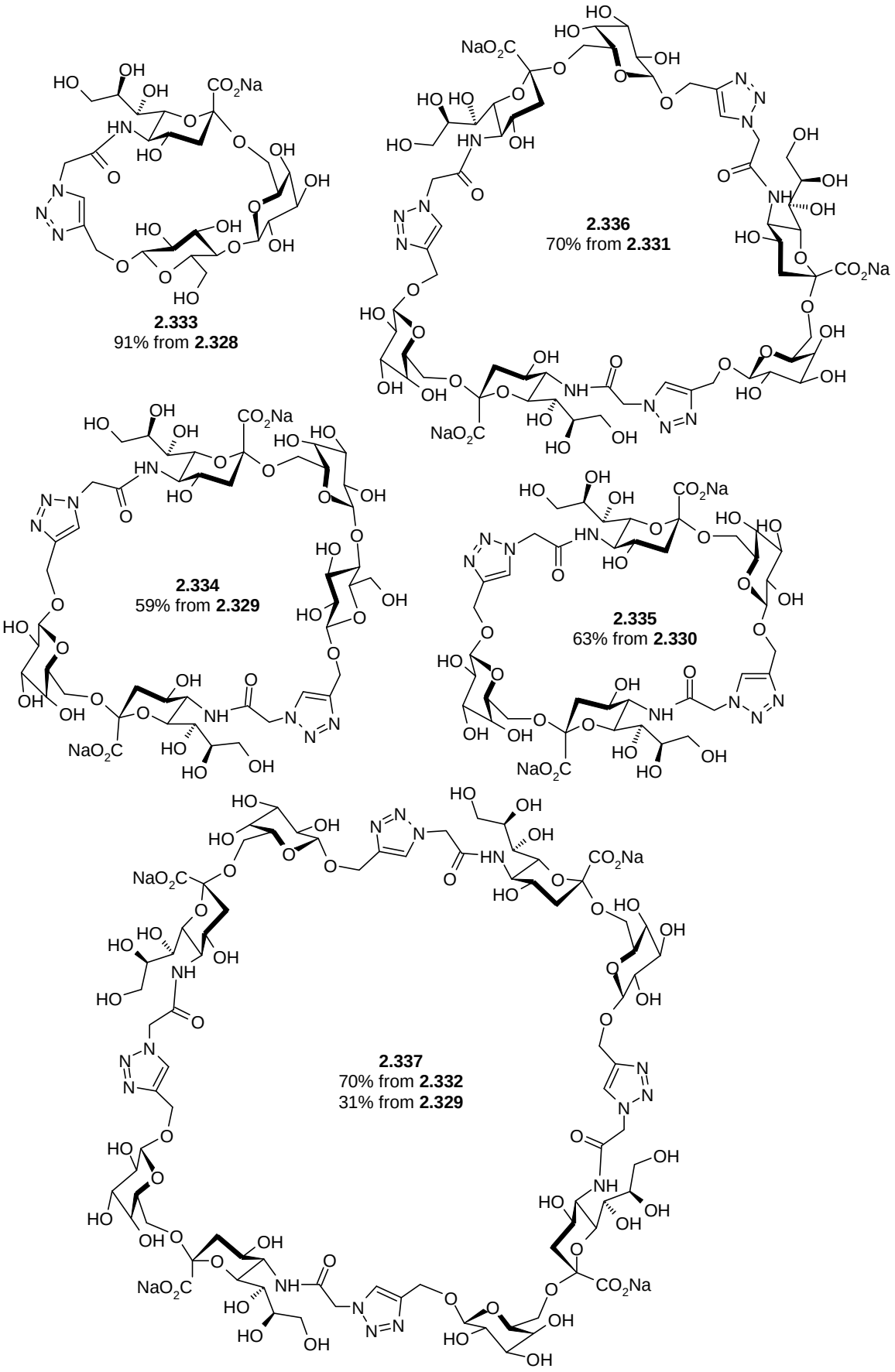


Figure 2.5 Macrocyclic compounds **2.333–2.337**.

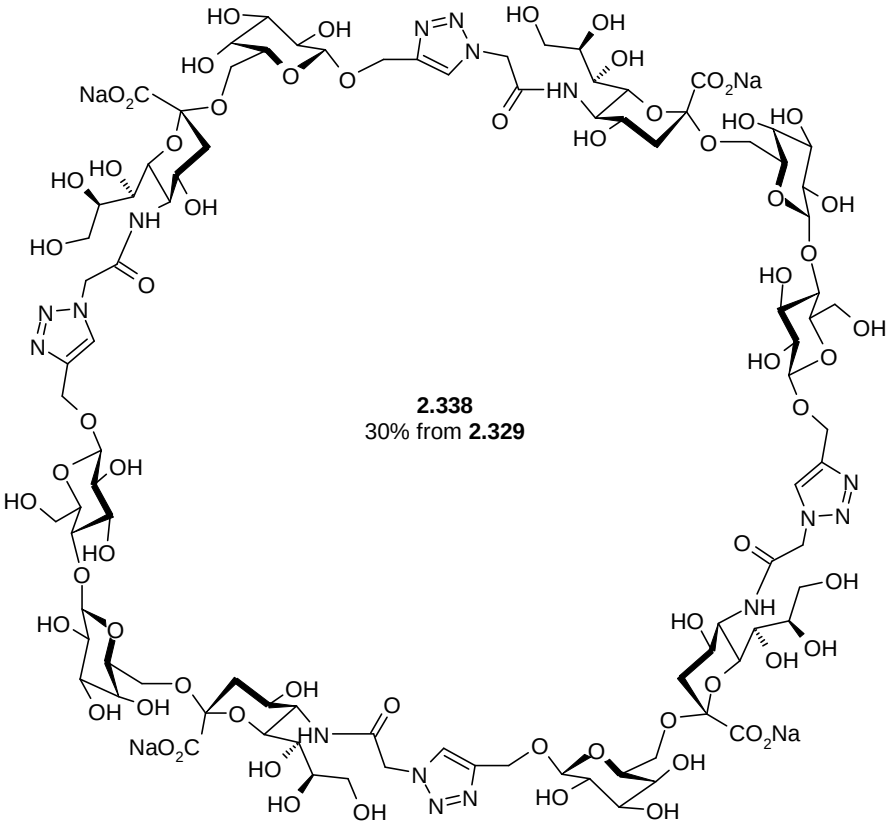
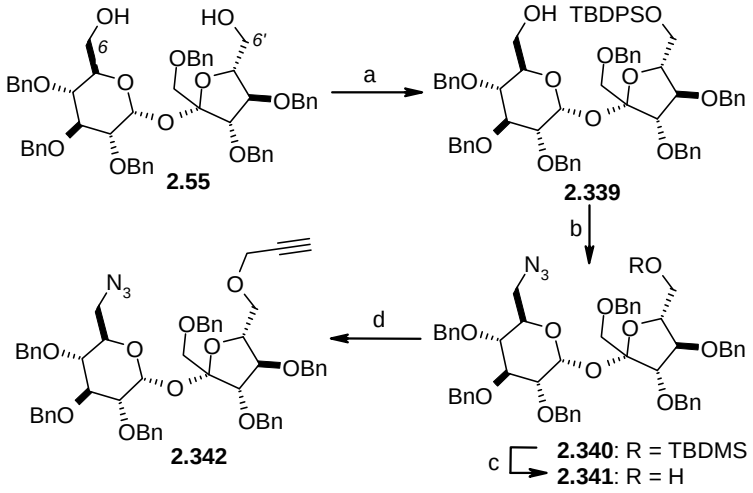


Figure 2.6 Macrocyclic compound **2.338**.

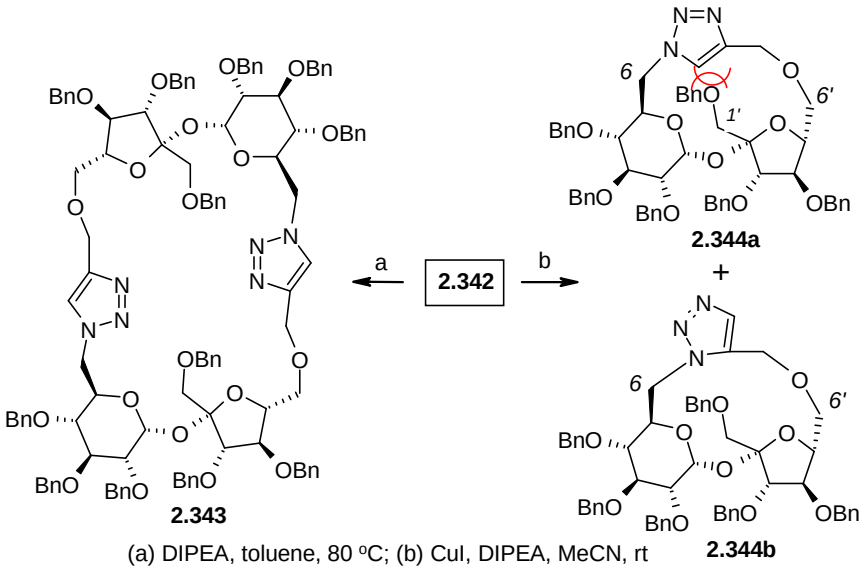
Jarosz and co-workers used recently the click approach for the preparation of the macrocyclic derivatives with sucrose scaffold.

The sucrose azido-acetylene **2.342** – chosen as starting material – was prepared readily taking advantage of the very high affinity of the 'fructose end' (C-6') towards silylation. Selective monosilylation of 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**2.55**) with *tert*-butyl-diphenylsilyl chloride (TBDPSCl) furnished the corresponding monoalcohol **2.339** which thereafter was converted into the azide **2.340**. Deprotection of TBDP-group gave azido-alcohol **2.341** which was propargylated to form **2.342** (Scheme 2.57).[162]

The 1,3-dipolar cycloaddition reaction performed in toluene and without catalyst provided ***only*** the dimer **2.343** (in 45% yield). When this process was catalyzed with Cu(I) species in acetonitrile, monomer **2.344** was formed (*ca.* 50%) with only traces of the dimer. Surprisingly, the monomeric product consisted of two regioisomeric triazoles: **2.344a** and **2.344b** (Scheme 2.58).[162]



Scheme 2.57 Synthesis of sucrose azido-acetylene **2.342**.

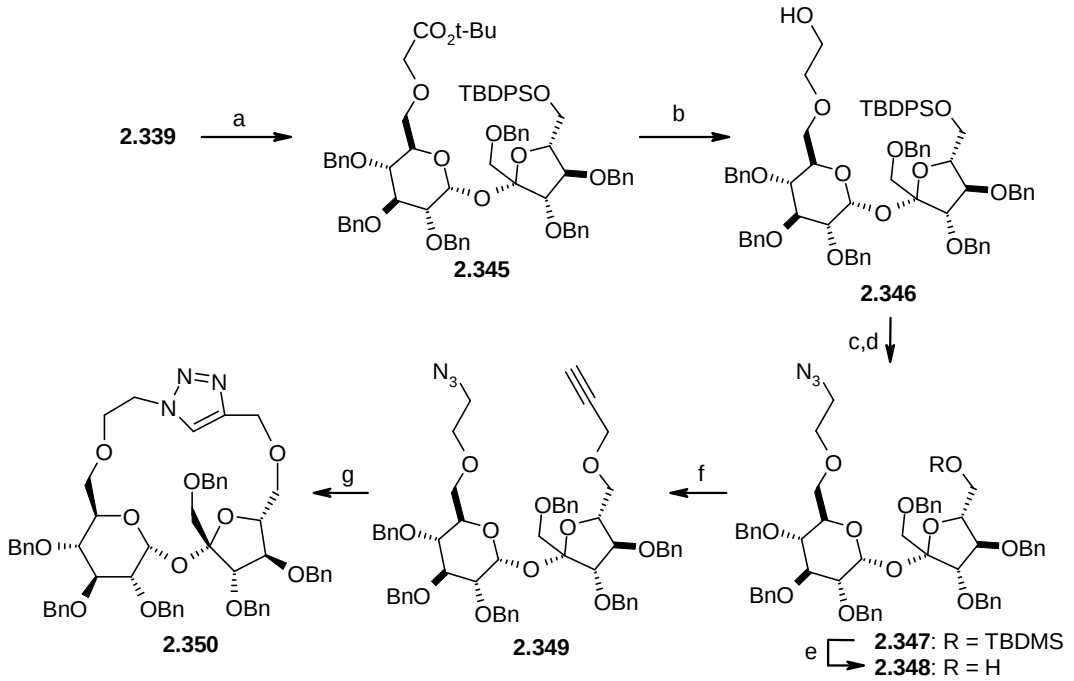


Scheme 2.58 1,3-Dipolar cycloaddition reaction of **2.342**.

The unexpected formation of the 1,5-product **2.344b** might be eventually explained by steric factors. In the expected (from mechanistic point of view) 1,4-isomer **2.344a** the cavity is rather small, so strong repulsion between the triazole proton and the benzyloxy group at the C-1'-position makes this structure not very favored.

If this assumption is correct enlargement of the cavity should result in formation of the mechanistically favored 1,4-isomer exclusively. Indeed, the 'click' cyclization of the elongated azido-acetylene **2.349** catalyzed with Cu(I) species led to the expected monomer **2.350** in good yield. The elongated azido-acetylene **2.349** was prepared by rather classical approach form monoalcohol **2.339**. Reaction of this compound with *tert*-butylchloroacetate afforded the ester **2.345**, which was then converted in a four standard steps into the azido-alcohol **2.348**.

Reaction of this compound with propargyl bromide provided the terminal alkyne **2.349** ready for cyclization (Scheme 2.59).[163]

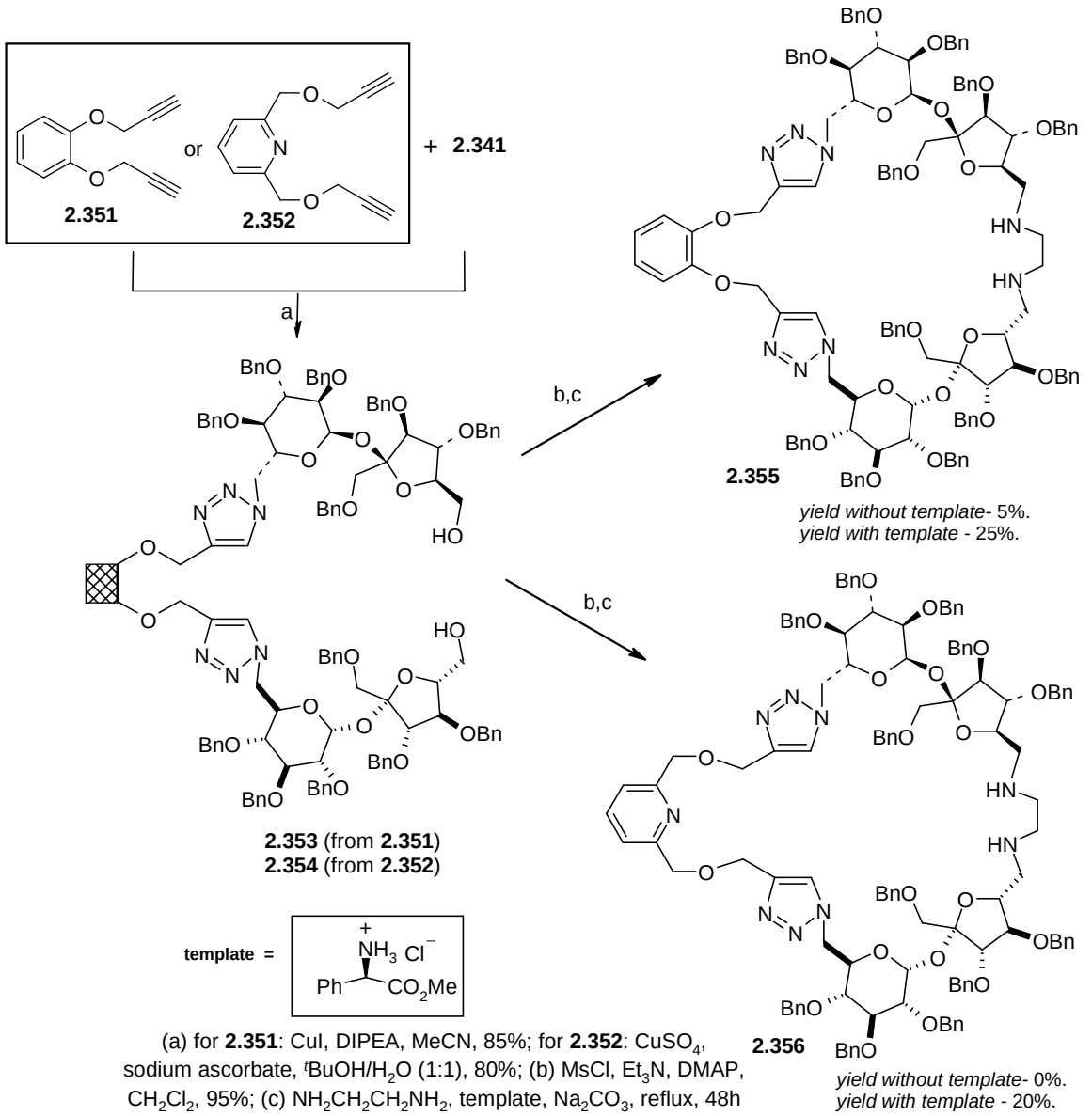


(a) $BrCH_2CO_2{}^tBu$, NaH, DMF, 90%; (b) $LiAlH_4$, THF, 90%; (c) MsCl, CH_2Cl_2, Et_3N, 95%; (d) NaN_3, DMF, 85%; (e) TBAF, THF, 95%; (f) propargyl bromide, NaH, DMF, 85%; (g) CuI, DIPEA, MeCN, 50%

Scheme 2.59 Synthesis of macrocyclic derivative **2.350**.

To prepare more complex symmetrical sucrose macrocycles authors decided to connect two sucrose molecules *via* dialkyne linkers **2.351** and **2.352** (Scheme 2.60) obtained from catechol or 2,6-lutidine by standard metodology.[164]

Each linker might react efficiently with two molecules of sucrose that were functionalized with an azide group at one of the terminal positions. Coupling of sucrose azide **2.341** with both linkers under the Huisgen reaction conditions (CuI-cat/DIPEA/acetonitrile for **2.351**; $CuSO_4$, sodium ascorbate, *t*-BuOH/H_2O for **2.352**) afforded the C_2-symmetrical precursors of macrocycles: **2.353** and **2.354** in good yields. Further steps leading to macrocycles included activation of both terminal hydroxyl groups as mesylates and subsequent reaction with ethylene diamine. Interestingly, the last step was very demanding. The dimesylate derived from **2.353** did not react with ethylene diamine under the standard conditions. The product **2.355** could be obtained only in the presence of template, (*R*)-(-)-2-phenylglycine methyl ester hydrochloride. This template also was effective in cyclization of the dimesylate derived from **2.354**; without template the yield of the corresponding macrocycle was very low (5%) while in the presence of this amino acid derivative 25% of the product **2.356** was obtained (Scheme 2.60).[164]



Scheme 2.60 Synthesis of macrocyclic compounds **2.355** and **2.356**.

2.7 Conclusions

In conclusion, a variety of effective methods for the preparation of nitrogen-containing carbohydrate-based macrocyclic compounds (such as aza-crown ethers, cryptands, cyclic amino sugar homooligomers, cyclopeptides containing amino sugar units, glycophanes, 1,2,3-triazole derivatives) has been reported. The data discussed above clearly pointed at the importance of these macrocyles as hosts in supramolecular chemistry. On the other hand, as can be find out from this rather comprehensive review, the nitrogen-containing sucrose-based receptors were investigated not very detailed.

3 Results and discussion

3.1 Selective functionalization of the terminal positions of sucrose

Sucrose: α-**D**-glucopyranosyl-(1→2)-β-**D**-fructofuranoside (**3.1**, Scheme 3.1), unlike most other disaccharides (maltose, cellobiose, lactose, lactulose, etc.), is a nonreducing sugar. It is composed of glucose and fructose units joined by the α-1→2 glycosidic linkage. Functionalization of sucrose with various groups enables to change its physical properties. In particular, solubility of the protected sucrose derivatives is significantly increased in aprotic organic solvent. The presence of eight hydroxyl groups (three primary and five secondary) in the molecule creates serious problems of their ***selective*** functionalization during the synthesis of structures based on sucrose scaffold. The primary hydroxyl groups of sucrose are able to react selectively with large reagents in such reactions as: alkylation [with trityl chloride (TrCl)[165–169]], silylation [with *tert*-butyldimethylsilyl chloride (TBDMSCl) or *tert*-butyl-diphenylsilyl chloride (TBDPSCl)][170–173], Mitsunobu[174–186] and Appel[173, 187–195] reactions (with triphenylphosphine). Selective oxidation of the primary hydroxyl groups are also possible.[196]

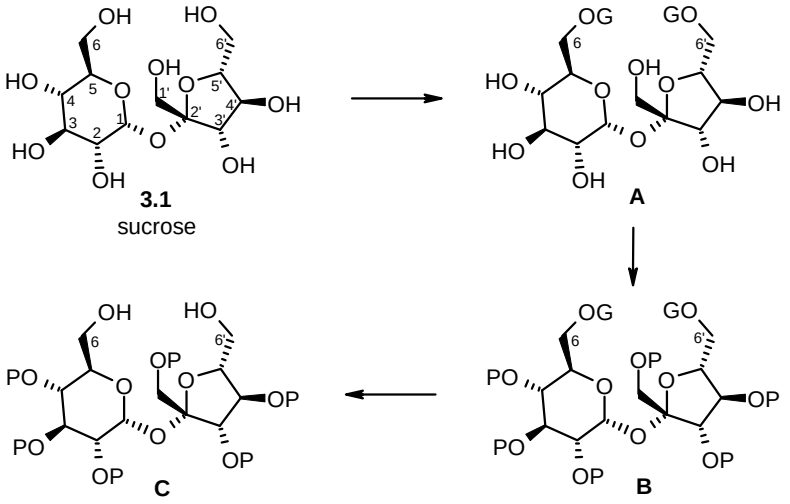
Furthermore, presence of the very labile (in acidic media) anomeric linkage between the C1-(glucose) and C2-(fructose) atoms makes the syntheses of the sucrose analogs trouble-some since in general, even relatively mild, acidic conditions should be rather avoided.

Transformation of sucrose into a useful building block in the synthesis of macrocyclic derivatives, requires a selective protection of the secondary hydroxyl groups. This can be achieved most conveniently with the alkyl groups (methyl, benzyl), because they are stable in a wide range of reactions. The acetyl protecting groups, commonly used in synthetic carbohydrate chemistry, are not very efficient in this case (i.e. synthesis of modified sucrose derivatives), because acetyl function undergoes facile hydrolysis in alkaline media; also it can migrate from the secondary to primary positions (i.e. primary hydroxyl groups).

One of the main goals faced during realization of my PhD Thesis was elaboration of a convenient methodology for the preparation of the building blocks based on sucrose scaffold. Although procedures for the synthesis of sucrose diols having the terminal positions (6- of glucose and 6'- of fructose) free were already described in the literature,[168,197–203] they provide the desired products in rather moderate yield. Since these compounds are planned to

be starting materials for more sophisticated sucrose derivatives, the efficient and effective methods of their preparation are needed.

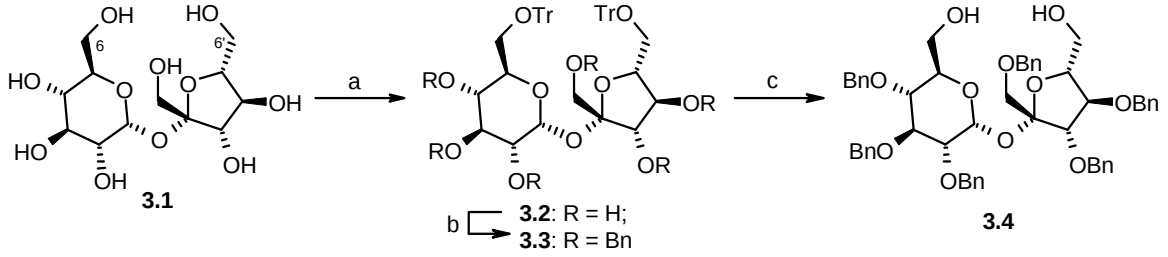
My strategy, shown in Scheme 3.1, to achieve this goal involves: (a) selective protection of the primary hydroxyl groups at the positions: 6 and 6’ (synthesis of compound **A**); (b) protection of the remaining six OH-groups (synthesis of compound **B**); and finally (c) deprotection of hydroxyl groups at the positions 6 and 6’ (synthesis of compound **C**).



Scheme 3.1 General strategy to synthesis of sucrose diols.

Diol of type **C** was selected as a starting material for the synthesis of macrocyclic, sucrose-based receptors. The most convenient, from the point of view of further applications, seemed to be 1’,2,3,3’,4,4’-hexa-*O*-benzylsucrose (**3.4**). This derivative was introduced earlier in our group.[3] Jarosz and Listkowski have developed[3, 200] a useful route to this diol in a three step process: tritylation/benzylation/detritylation. First, selective di-tritylation of the positions 6 and 6’ in sucrose (**3.1**) conducted in pyridine provided 6,6’-di-*O*-tritylsucrose (**3.2**) in 48% yield. Second, benzylation of six hydroxyl groups in compound **3.2** gave 1’,2,3,3’,4,4’-hexa-*O*-benzyl-6,6’-di-*O*-tritylsucrose (**3.3**) in 80% yield. Finally, 1’,2,3,3’,4,4’-hexa-*O*-benzylsucrose (**3.4**) was synthesized *via* detritylation reaction using acetic acid in refluxing toluene (Scheme 3.2).[200]

It was observed, however, that during hydrolysis of the trityl groups in acetic acid, significant decomposition of the molecule (resulting from the cleavage of the anomeric bond) was noted, which lowered the yield of the desired product. Application of other acids (Brønsted or Lewis) to remove the trityl blocks was even less successful; the target diol **3.4.** was obtained in very low yield.

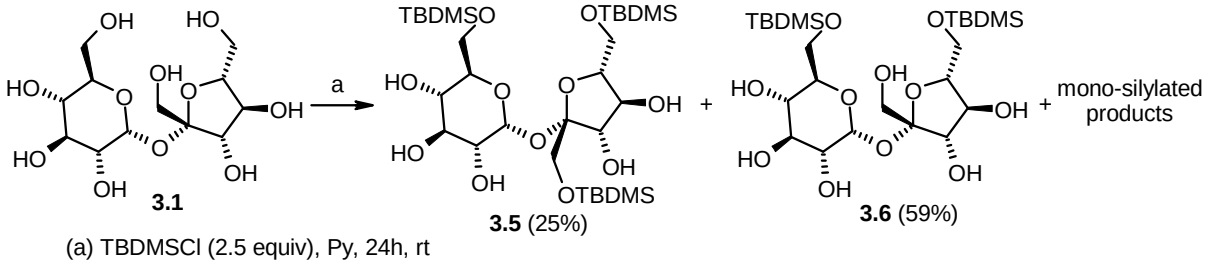


(a) TrCl (2.2 equiv.), Py, 48h, rt, 51%; (b) NaH (7 equiv), BnBr (7 equiv), DMF, 12h, rt, 80%; (c) AcOH, toluene, 2h, reflux, 40%

Scheme 3.2 Synthesis of 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.4**) by tritylation/benzylation/detritylation method.

Because of these limitations, I have decided to elaborate an alternative synthetic way to diol **3.4**. For selective protection of 6 and 6' positions in sucrose, 6,6'-di-*O*-*tert*-butyldimethylsilyl (TBDMS) group was chosen. This function is stable under a variety of reaction conditions (in particular, alkylation in strongly basic media), and at the same can be safely removed (with fluoride anion) in the presence of many other functional groups.

Silylation of sucrose (**3.1**) with 2.5 equiv of *tert*-butyldimethylsilyl chloride in pyridine provided a mixture of tris-, bis-, and mono-silylated products. After flash chromatography 1',6,6'-tri-*O*-*tert*-butyldimethylsilylsucrose (**3.5**, 25%) and 6,6'-di-*O*-*tert*-butyldimethylsilylsucrose (**3.6**, 59%) were isolated (Scheme 3.3).



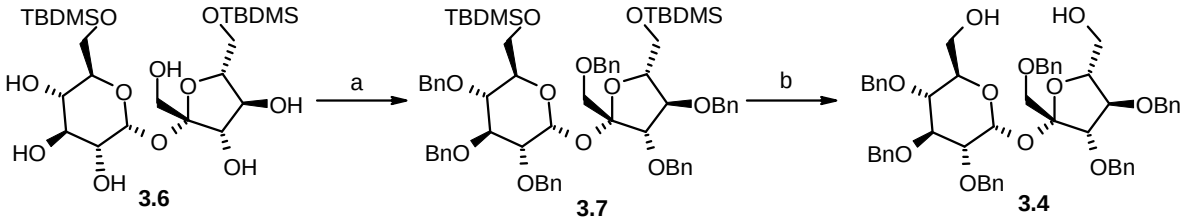
(a) TBDMSCl (2.5 equiv), Py, 24h, rt

Scheme 3.3 Silylation of sucrose.

Protection of the remaining free hydroxyl groups in compound **3.6** (five secondary and one primary at the position 1') as benzyl ethers was achieved with sodium hydride/benzyl bromide; the 6,6'-di-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.7**) was isolated in 83% yield (Scheme 3.4). Interestingly, the use of more equivalents of sodium hydride in this reaction led to significant decrease of the yield the product **3.7**, which resulted most likely from desilylation under strongly basic conditions.

Removal of both silyl protections with an excess of tetrabutylammonium fluoride trihydrate (TBAF·3H_2O) in THF gave 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.4**) in good

(78%) yield (Scheme 3.4). Another advantage of this method is the easy work-up procedure: the product **3.4** was isolated without the tedious extraction.



(a) BnBr (6.5 equiv), NaH (6.3 equiv), DMF, 24h, rt, 83%; (b) TBAF·3H_2O (4 equiv), THF, 12 h, rt, 78%

Scheme 3.4 Synthesis of 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.4**) by silylation/benzylation/desilylation method.

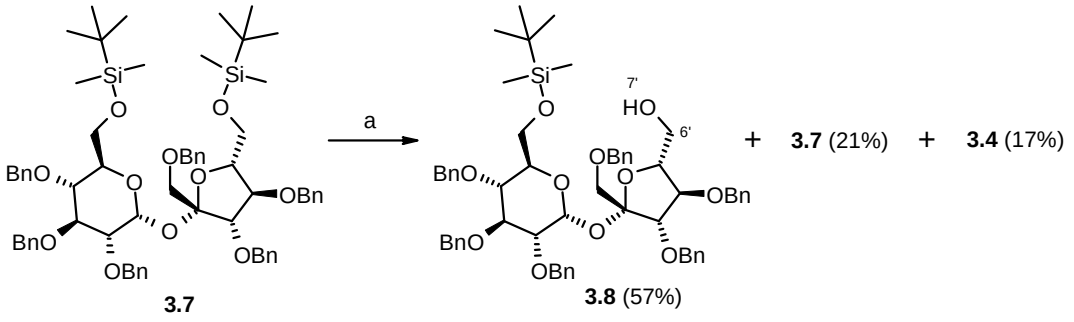
The NMR and mass spectral data (see Chapter 4.2.3.1) of the diol **3.4** obtained in this synthesis were identical with all parameters of the compound **3.4** obtained according to the procedure shown in Scheme 3.2.

The diol was obtained in 38% total yield in this three-step reaction (silylation/ benzylation/desilylation), whereas the yield of **3.4** in the literature procedure (tritylation/ benzylation/detritylation) amounted only to 16%. Accordingly, the significant improvement in yield of the diol 3.4 was achieved.

Previous study from the Jarosz group demonstrated that the silyl protecting group [*tert*-butyldiphenylsilyl (TBDPS)] in 6,6'-bis-silylated sucrose derivatives can be removed with 100% regioselectivity from the 6'-position using one equivalent of desilylating agent (TBAF or HF/Py); the 6-silylated products were, therefore, available in good yields.[2, 168,198,201]

To obtain the monosilylated sucrose alcohol, I have repeated this experiment for the TBDMS-analog **3.7**. Reaction of this compound with 1.1 equiv. of TBAF·3H_2O in THF after 6 h of stirring and flash chromatography gave unreacted bis-silylated substrate **3.7**, mono-silylated product **3.8** and the diol **3.4** in 21, 57 and 17% yield respectively (Scheme 3.5).

The structure of product **3.8** was confirmed by the NMR spectrum, mass spectrum and elemental analysis (see Chapter 4.2.3.2). The position of the TBDMS-group in compound **3.8** was proven by spectral correlations and also by further transformations (to product **3.32**, see Scheme 3.22). In particular, as shown in Figure 3.1, the hydroxyl hydrogen (H-7') atom (resonating at δ = 3.26 ppm) is coupled with two H-6' atoms (at δ = 3.61 and 3.83 ppm) in COSY NMR spectrum of compound **3.8**.



Scheme 3.5 Selective desilylation of 6,6'-di-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.7**).

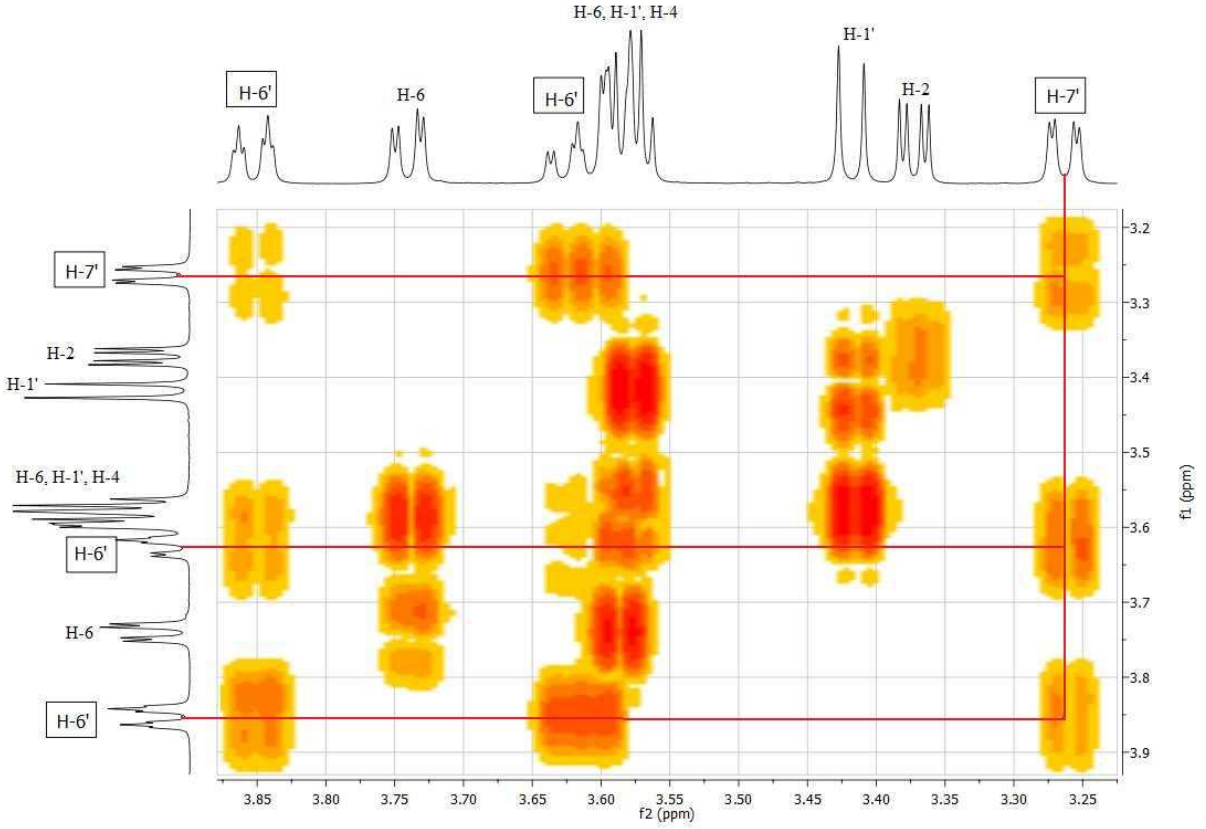
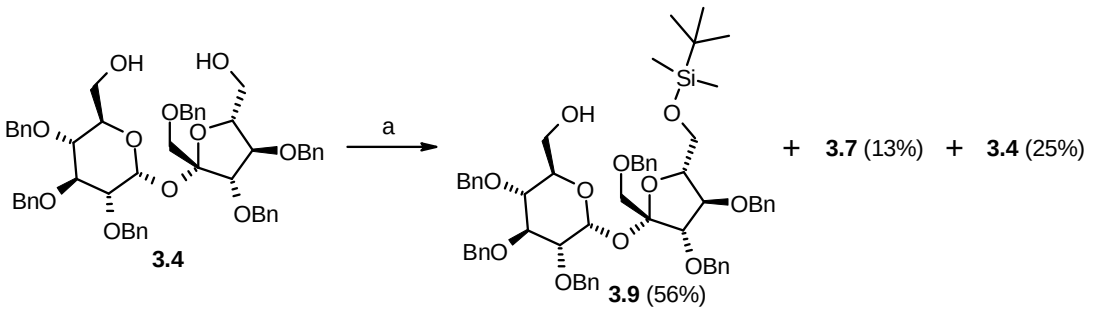


Figure 3.1 COSY NMR spectrum of compound **3.8** (3.2–3.9 ppm range).

Free sucrose, as well as its partially substituted derivatives, is preferentially silylated at the position 6'-OH. Thus, treatment of these compounds with one equiv. of silylating agent (*e.g.* TBDPSCl or TBDMSCl) provided the 6'-O-silyl-substituted sucrose derivatives as major products.[2–4, 162, 168, 171, 173, 198, 201, 204–206]

In order to obtain regioisimer of **3.8** (compound **3.9**), with unprotected (free) hydroxyl group at the 6 position, I conducted a reaction of 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.4**)

with 1.1 equiv. of *tert*-butyldimethylsilyl chloride (TBDMSCl) in CH_2Cl_2 in the presence of DMAP as catalyst and Et_3N as a base; the silyl chloride was added dropwise (3 h) *via* a syringe pump and the stirring was continued for 24 h. This procedure allowed me to obtain (after flash chromatography) 6'-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.9**) in 56% yield, together with the bis-silylated compound **3.7** (13%) and unreacted diol **3.4** (25%) (Scheme 3.6).



(a) TBDMSCl (1.1 equiv), DMAP (cat), Et_3N, CH_2Cl_2, 24 h, rt

Scheme 3.6 Selective silylation of diol **3.4**.

Structure of the product **3.9** was confirmed by the NMR spectrum, mass spectrum and elemental analysis (see Chapter 4.2.4.1). Structure of the regioisomer **3.9** was proven by the spectral correlations and further transformations (to product **3.20**, see Scheme 3.13). In particular, as shown in Figure 3.2, the hydroxyl hydrogen H-7 atom (at δ = 1.96 ppm) is coupled with two H-6 atoms (at δ = 3.50 and 3.64 ppm) in the COSY NMR spectrum of compound **3.9**.

In the molecule of compound **3.4**, **3.8** and **3.9** six benzyl groups are present. These protective groups are stable to a variety of organic reactions and can be selectively removed under hydrogenation conditions. However, presence of six such big groups in the molecule **3.4** and its derivatives significantly increases the molecular mass and complicates the interpretation of NMR spectra of these compounds.

I decided, therefore, to propose an alternative (to diol **3.4**) sucrose-based building block. I have chosen the methyl group as a protecting function, because it is stable under various conditions (*e.g.* catalytic hydrogenation) and because the NMR spectra of the compounds containing this protecting group should be much simpler than those of their per-*O*-benzyl analogs.

To prepare 1',2,3,3',4,4'-hexa-*O*-methylsucrose, both strategies: tritylation and silylation were used.

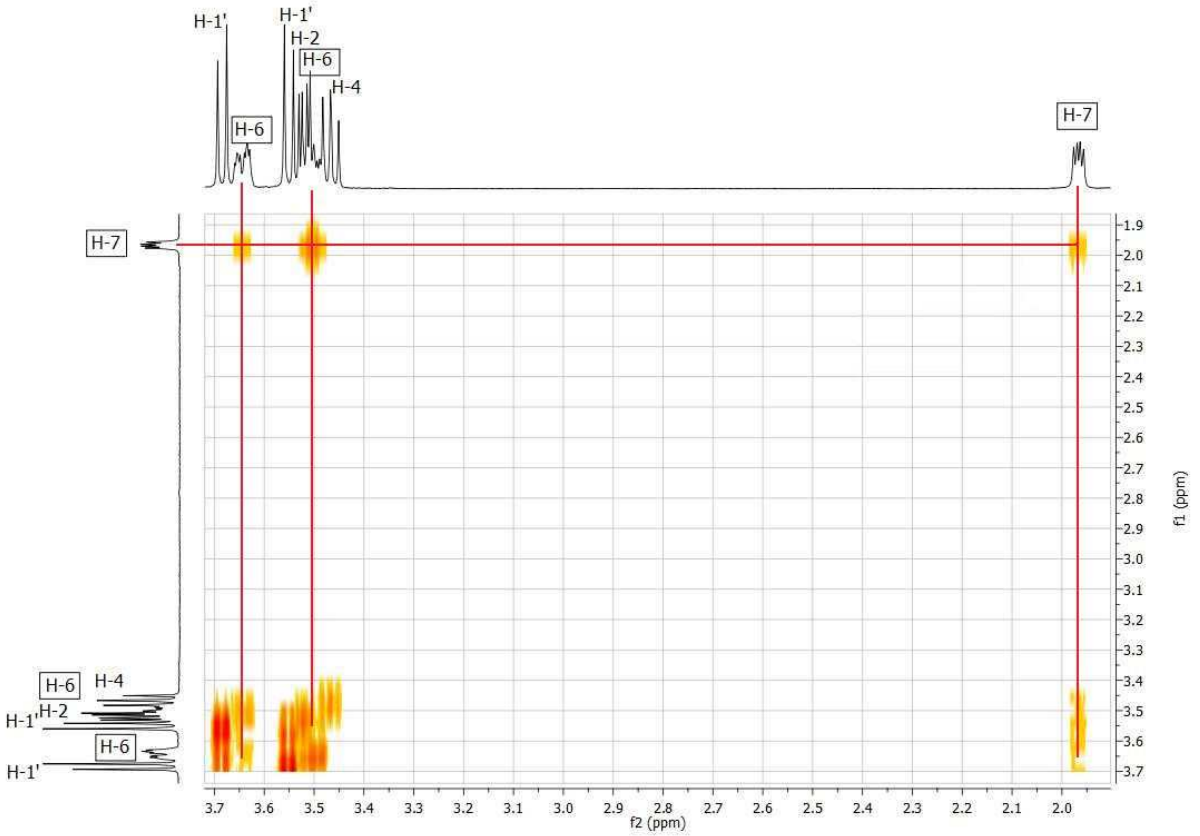
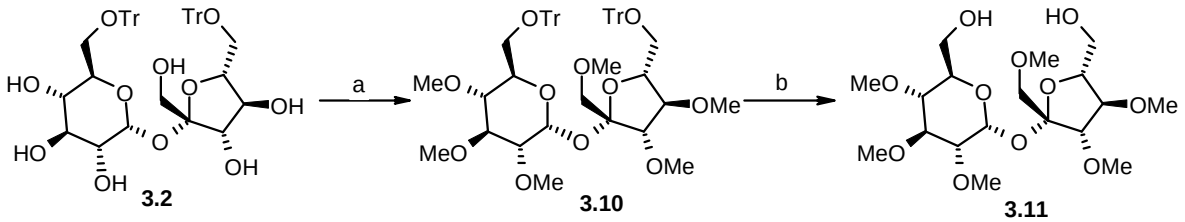


Figure 3.2 COSY NMR spectrum of compound **3.9** (1.9–3.7 ppm range).

Methylation of six hydroxyl groups in 6,6'-di-*O*-tritylsucrose (**3.2**) with methyl iodide in the presence of sodium hydride in DMF gave 1',2,3,3',4,4'-hexa-*O*-methyl-6,6'-di-*O*-trityl-sucrose (**3.10**) in excellent yield (91%). Removal of two trityl groups was achieved under reductive conditions, using sodium in liquid ammonia at –78 °C; 1',2,3,3',4,4'-hexa-*O*-methylsucrose (**3.11**) was isolated in 74% yield (Scheme 3.7). The structures of products **3.10** and **3.11** was confirmed by NMR spectrum, mass spectrum and elemental analysis (see Chapter 4.2.5.1 and 4.2.6).[207]

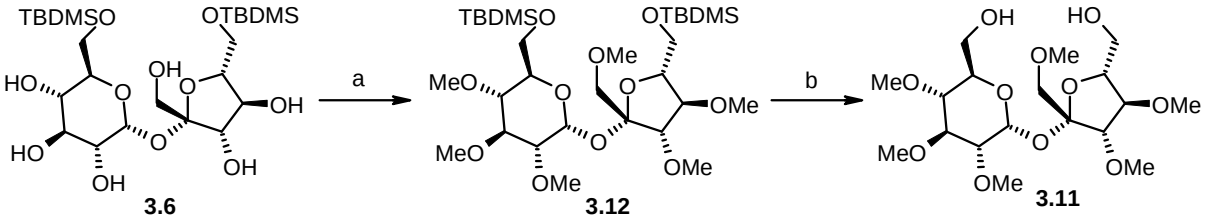


(a) NaH (6.3 equiv.), MeI (6.5 equiv.), DMF, 4h, rt, 91%; (b) Na/NH_3, THF, -78 °C, 2h, 74%

Scheme 3.7 Synthesis of 1',2,3,3',4,4'-hexa-*O*-methylsucrose (**3.11**) by tritylation/methylation/detritylation method.

On the other hand, simple synthesis of 6,6'-di-*O*-*tert*-butyldimethylsilylsucrose (**3.6**) allowed me to propose an alternative method of the preparation of the diol **3.11**. Treatment of compound **3.6** with MeI/NaH afforded 6,6'-di-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-methylsucrose (**3.12**) in excelent yield (95%). Treatment of **3.12** with a TBAF·$3H_2O$ resulted in a cleavage of the TBDMS groups and provided 1',2,3,3',4,4'-hexa-*O*-methyl-sucrose (**3.11**) in 95% yield (Scheme 3.8).[207]

Notably, desilylation of hexa-*O*-methylated sucrose **3.12** is much faster than the hexa-*O*-benzylated analog **3.7**, which may probably result from steric factors. Silicon atoms in molecule **3.12** are sterically more accessible to nucleophilic attack by fluoride anions as compared to molecule of sucrose derivative **3.7**.



(a) MeI (6.5 equiv), NaH (6.3 equiv), DMF, rt, 4h, 95%; (b) TBAF·$3H_2O$ (3 equiv), THF, rt, 3h, 95%

Scheme 3.8 Synthesis of 1',2,3,3',4,4'-hexa-*O*-methylsucrose (**3.11**) by silylation/methylation/desilylation method.

The specific rotation, NMR and mass spectral data of the diol **3.11** obtained in this way are identical to the parameters of this compound obtained according to Scheme 3.7.

1',2,3,3',4,4'-Hexa-*O*-methylsucrose (**3.11**) was already reported in the literature. However, the original procedure proposed by Sachinvala *et al*. was realized in a rather long (7 steps) synthesis from free sucrose in total yield about 36%.[197]

The procedure which I propose in this dissertation offers two alternative and more convenient (three steps) methods for the preparation of **3.11** in total yields of about 34% (in tritylation/methylation/detritylation) or 53% (in silylation/methylation/desilylation).

Compounds **3.4**, **3.8**, **3.9** and **3.11** were then applied as starting materials for the preparation of the target macrocycles.

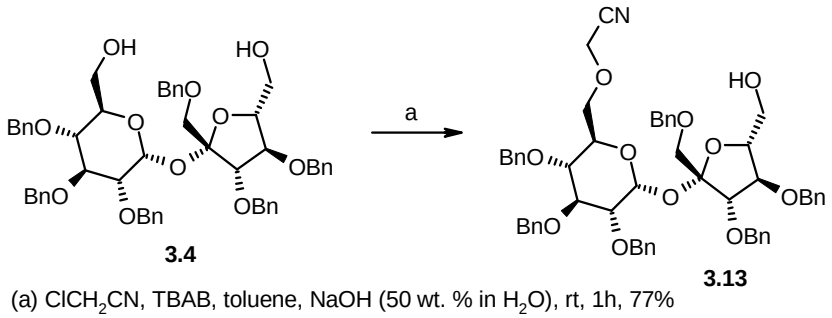
3.2 Synthesis of sucrose aza-crown ethers and their complexing properties

3.2.1 Mono-aza-crown ethers

With protected sucrose containing only two free hydroxyl groups in hands, I decided to apply them in the synthesis of new sucrose aza-crown ethers. Continuing research area started in Jarosz's group (see Chapter 2), I used 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.4**) for the synthesis of this type of receptors. This substrate contains the 11-membered chiral units (from C6 of glucose to C6' of fructose) which is useful platform for chiral crown ethers.

I proposed a new synthetic strategy for the synthesis of aza-crown ethers which includes two different chain elongation at the 6 and 6' positions of sucrose and a ring closure.

The previous studies in Jarosz's group showed that 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.4**) undergoes regioselective alkylation at the *glucose* '*end*' (6-OH); treatment of the diol **3.4** with chloroacetonitrile provides preferentially the 6-*O*-(cyanomethyl)-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.13**) (Scheme 3.9). Position of the alkylation in compound **3.13** was proven by further transformations (oxidation of hydroxyl group at C-6' to aldehyde followed by the Wittig reaction with $Ph_3P{=}CHCO_2Me$) leading to the α,β-unsaturated ester. Spectral correlations of such obtained product proved unambiguously that unsaturation is located at the *fructose* '*end*', hence the alkylation occurred at the 6-OH (glucose part).[208]

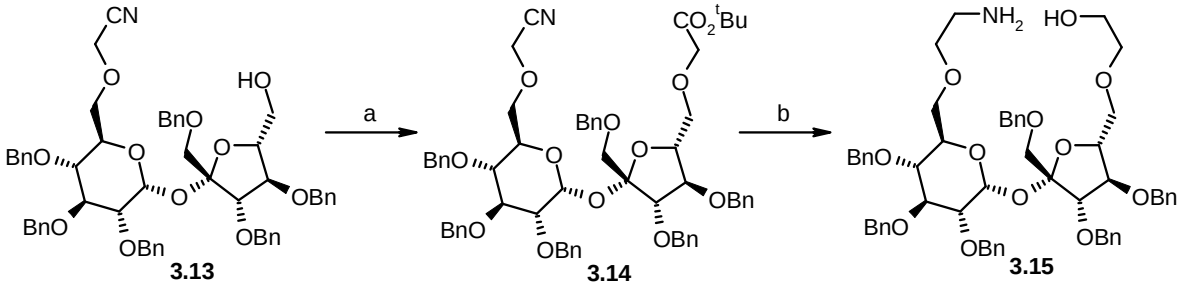


Scheme 3.9 Synthesis of 6-*O*-(cyanomethyl)-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.13**).

This feature (selective alkylation of **3.4** at the *glucose* '*end*') was assigned as the key-reaction in my strategy to prepare the 16-membered sucrose-based aza-crowns.

The free hydroxyl group at the 6'-carbon atom of the monoalcohol **3.13** was alkylated with *tert*-butyl bromoacetate under catalytic phase-transfer conditions (PTC) in the presence of 0.2 equiv. of tetrabutylammonium bromide (TBAB); the cyano-ester **3.14** was obtained in excellent yield (93%). Both, the cyano and ester groups, were reduced with lithium aluminum hydride in THF at –78 °C to provide the corresponding amino alcohol **3.15** in 88% yield

(Scheme 3.10). The structure of product **3.15** was confirmed by NMR spectrum, mass spectrum and elemental analysis (see Chapter 4.2.7).[209]

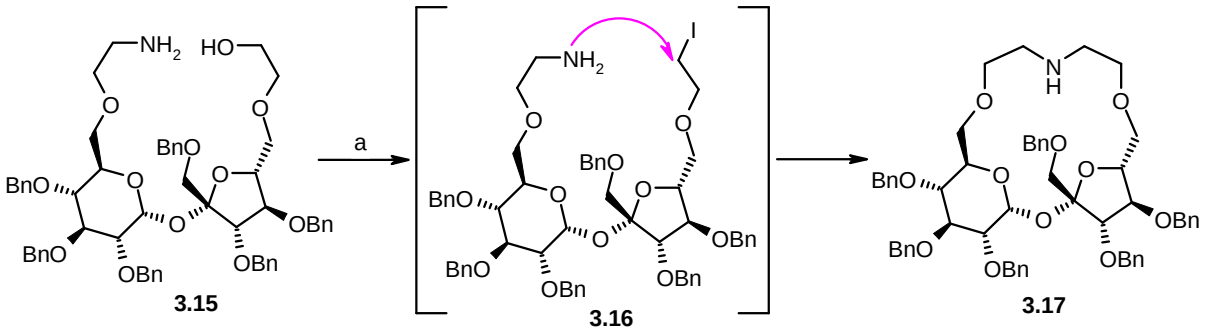


Scheme 3.10 Synthesis of 6-*O*-(2-aminoethyl)-1',2,3,3',4,4'-hexa-*O*-benzyl-6'-*O*-(2-hydroxyethyl)-sucrose (**3.15**).

Amino podand **3.15** was used as a starting material for the preparation of macrocyclic derivatives. This compound was transformed to iodide using the Garegg−Samuelsson procedure[210]: iodine, triphenylphosphine, and imidazole in refluxing toluene. However, I was not able to isolate this compound (**3.16**). After the reaction, I observed formation (in very good yield: 79%) of a product with the molecular ion peak in the mass spectrum at *m/z* = 974.4, whereas the calculated molecular mass for amino iodide **3.16** is 1079 ($[M + Na]^+$ = 1102). These data, as well as elemental analysis, indicated that during the reaction, elimination of hydrogen iodide occurred. Since in the ^1H and ^{13}C NMR spectra no signals of the olefinic protons were seen, the cyclic structure **3.17.** can be postulated. Further support came from the ^{13}C NMR and DEPT spectra which displayed two peaks of secondary carbon atoms in the typical amine range (at δ = 49.18 and 47.59 ppm). The detailed analysis of the NMR spectra (^1H, ^{13}C, COSY, HSQC and HMBC) confirmed the proposed macrocycle structure of **3.17**. Obviously, under the reaction conditions, the amino iodide **3.16** (the primary product of the Garegg−Samuelsson reaction) cyclized spontaneously providing compound **3.17** (Scheme 3.11).

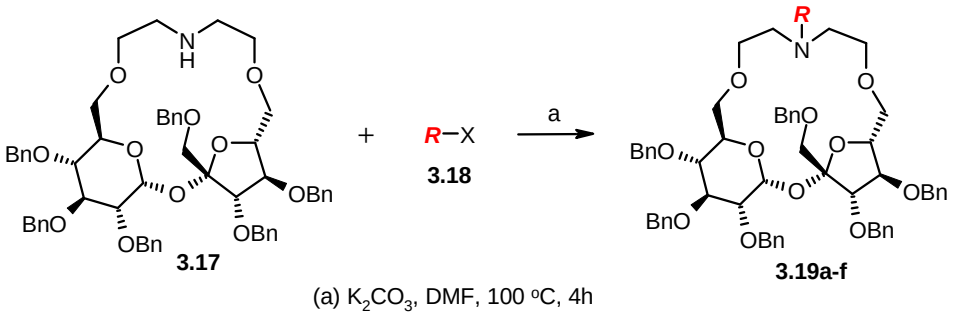
This tandem Garegg−Samuelsson iodination/intramolecular alkylation reactions opened a convenient route to macrocyclic derivatives having a secondary nitrogen atom in the ring.

Presence of this secondary amine functionality in the macrocyclic ring allowed us to modify steric and/or electronic properties of the ring. Aza-crown ethers with a side arm attached to the nitrogen of the macrocyclic ring may enhance and regulate the cation-binding properties. Reaction of the amine **3.17** with the corresponding alkyl halides **3.18** provided the respective derivatives **3.19 a–f** (Scheme 3.12, Table 3.1) in good yields.[209]



Scheme 3.11 Synthesis of 6,6'-(3-azapenta-1,5-di-yl)-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.17**).

Structures of the products **3.19a–f** were characterized and confirmed by NMR spectrum, mass spectrum and elemental analysis (see Chapter 4.2.9).



Scheme 3.12 Alkylation of 6,6'-(3-azapenta-1,5-di-yl)-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.17**).

By this procedure, I have prepared 16-membered macrocycles substituted at the nitrogen atom with: benzyl-, 4-methoxybenzyl-, pyridine-2-ylmethyl-, allyl-, 2-methoxy-2-oxoethyl- and 2-methoxyethyl- units (Table 3.1 and Figure 3.3).

Table 3.1 **Synthesis of macrocyclic receptors** 3.19 a-f.

Entry	R	X	Product	Yield, %
1	Bn	Br	**3.19a**	73
2	4-MeO-C_6H_4-CH_2	Cl	**3.19b**	77
3	Pyridine-2-ylmethyl	Br	**3.19c**	65
4	Allyl	Br	**3.19d**	68
5	$MeOC(O)CH_2$	Br	**3.19e**	72
6	$MeOCH_2CH_2$	Br	**3.19f**	67

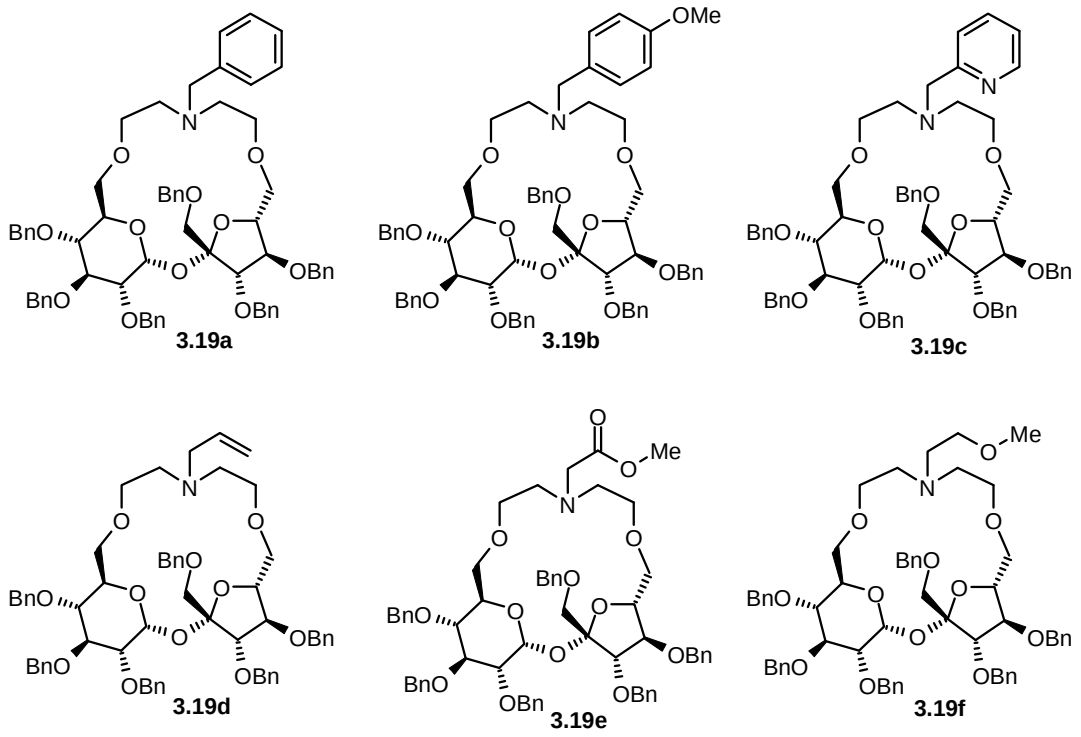


Figure 3.3 Structures of macrocyclic receptors **3.19 a-f.**

Receptors **3.19a-f** were employed in an enantioselective recognition of chiral ammonium cations.

In complexation of primary ammonium cations by aza-crown ethers, polar N^+-H···N and N^+-H···O hydrogen bond interactions are the most important. Additionally, electrostatic interactions between the cation and the electronegative centers of the ligand take place and, if ammonium cation and receptor contain an aromatic moiety, the π–π interactions are possible. In a first set of complexation experiments, I have evaluated the sucrose-based macrocyclic ligand library (**3.19a-f**) in recognition of the *S*- and *R*-*α*-phenylethylammonium chloride (*S*-PEA·HCl and *R*-PEA·HCl). The association constants (K_a) of the complexes of receptors **3.19a–f** with *α*-phenylethylammonium cations were determined by the NMR titration method[63] in $CDCl_3$. This method requires recording of a series NMR spectra of solutions containing both the host (in constant concentration) and the guest (in varying concentration) and an observation of the change in chemical shift of the signal that is sensitive to the formation of the host-guest complex. In case of sucrose-based receptors, such NMR-signal is the peak of anomeric proton atom (H-1). For simplification of the experimental procedure, the series of NMR spectra was recorded for only one NMR tube with the host containing solution and the portions of the solution was added step by step. After that, the difference in chemical shifts between that observed in the host-guest mixture and that observed in the host molecule

(Δδ) were calculated and the experimental titration curve (the change of chemical shift with increasing the concentration of a guest) was drawn. Then, the association constant (K_a) was determined by fitting the data to the empirical equation described by Fielding[211] using program MicroCal Origin®.

In the experiments of complexation of *S*-PEA·HCl by the receptor **3.19a**, I observed the change of chemical shift of the anomeric proton from 5.43 to 5.33 ppm; the titration curve is shown in Figure 3.4. The association constant was calculated as 70 ± 7 M^{-1} (entry 1 in Table 3.2). I did not observed, however, any significant changes of chemical shifts in the NMR spectra during the titration of the receptor **3.19a** with *R*-PEA·HCl which indicates rather low interaction between the host and the guest.

Analogous experiments with macrocycle **3.19b** and *α*-phenylethylammonium chlorides were performed. In this case (Figure 3.5), the replacement of benzyl group at the nitrogen atom for more electro-donating unit: 4-methoxybenzyl group gave the double increase of the $K_{a(S)}$ (140 ± 10 M^{-1}, entry 2 in Table 3.2). Changes of the chemical shifts in the NMR spectra during the titration with *R*-PEA·HCl were not observed either.

Figure 3.6 and Figure 3.7 present the titration curves for receptor **3.19c** with *S*- and *R*-PEA·HCl complexes. The receptor **3.19c** containing the pyridine unit at the nitrogen ring atom shows rather significant affinity to the *S*- ($K_{a(S)}$ = 317 M^{-1}), as well as to the *R*-isomer of PEA·HCl ($K_{a(R)}$ = 67 M^{-1}, entry 3 in Table 3.2). Moreover, in case of *R*-PEA·HCl, the titration experiments showed the change of chemical shifts to the lower NMR field (from 5.416 to 5.466 ppm) which indicates another character of the host-guest interaction.

In other cases the change of chemical shifts occurred to the higher NMR field.

Titration experiments for receptors **3.19d–f** showed gradual increase of the association constants for complexes with *S*-PEA·HCl (Figures 3.8–3.10), and low interaction between these receptors and *R*-PEA·HCl (entry 4–6 in Table 3.2).[209]

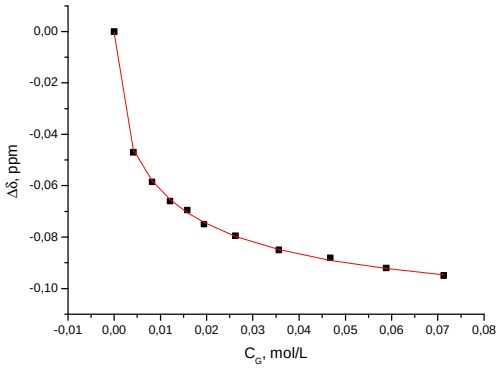


Figure 3.4 Titration curve for receptor **3.19a** and *S*-PEA·HCl complex in $CDCl_3$.

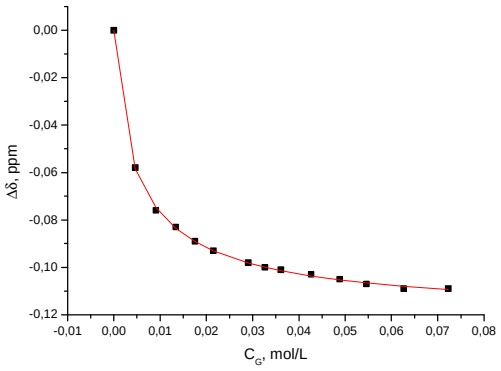


Figure 3.5 Titration curve for receptor **3.19b** and *S*-PEA·HCl complex in $CDCl_3$.

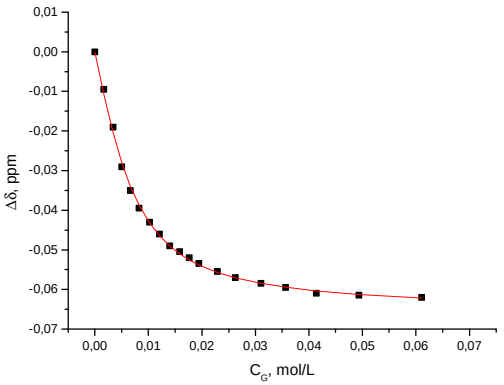


Figure 3.6 Titration curve for receptor **3.19c** and *S*-PEA·HCl complex in $CDCl_3$.

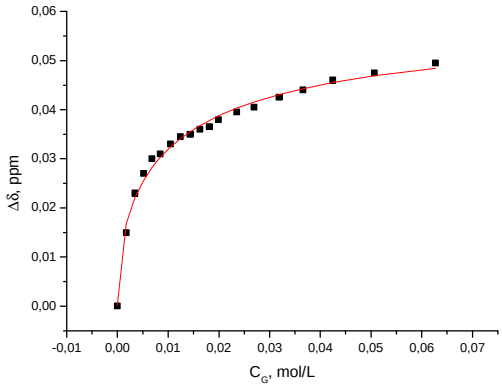


Figure 3.7 Titration curve for receptor **3.19c** and *R*-PEA·HCl complex in $CDCl_3$.

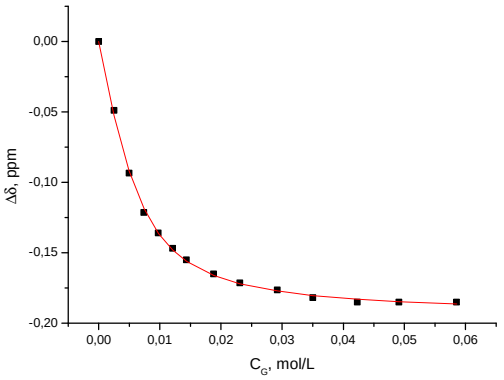


Figure 3.8 Titration curve for receptor **3.19d** and *S*-PEA·HCl complex in $CDCl_3$.

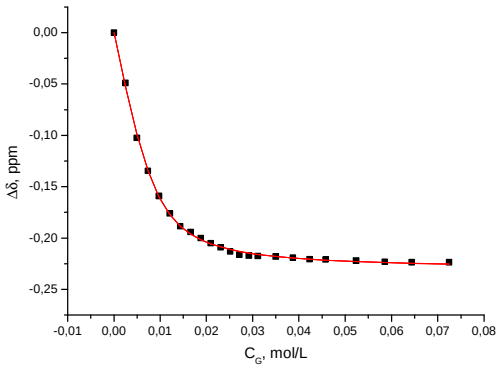


Figure 3.9 Titration curve for receptor **3.19e** and *S*-PEA·HCl complex in $CDCl_3$.

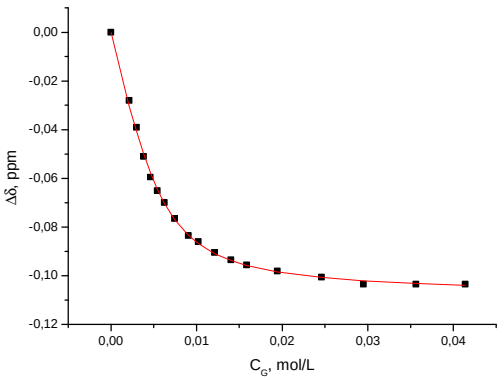


Figure 3.10 Titration curve for receptor **3.19f** and *S*-PEA·HCl complex in $CDCl_3$.

Table 3.2 Stability constants for complexes of ligands **3.19 a-f** with (*S*)- and (*R*)-phenylethylammonium chloride in $CDCl_3$.

Entry	Receptor	$K_{a,(S)}$, M^{-1}	$K_{a,(R)}$, M^{-1}
1	**3.19a**	70 ± 7	*a**
2	**3.19b**	140 ± 10	*a*
3	**3.19c**	317 ± 33	67 ± 6
4	**3.19d**	427 ± 42	*a*
5	**3.19e**	623 ± 48	*a*
6	**3.19f**	733 ± 69	*a*

*a** – No changes of the chemical shift were observed in the NMR during titration.

In summary, all receptors showed much higher affinity towards the *S*-enantiomer (as in case of derivatives **2.63** and **2.69**[61]) but – with exception of macrocycle **3.19c** – the *R*-isomer was not complexed. Moreover, additional ethylenoxy unit placed at the ring nitrogen atom (compound **3.19f**) increased the K_a value (as compared to the '*neutral*' benzylated derivative **3.19a**) by one order of magnitude.

Lariat ether **3.19f**, showing the highest K_a value towards the *S*-*α*-phenylethylammonium chloride was selected as a model to study complexation abilities of such type of receptors towards the amino acid derivatives. Four pairs (alanine, valine, phenylglycine, phenylalanine) of enantiomeric methyl ester ammonium salts were chosen (Figure 3.11).

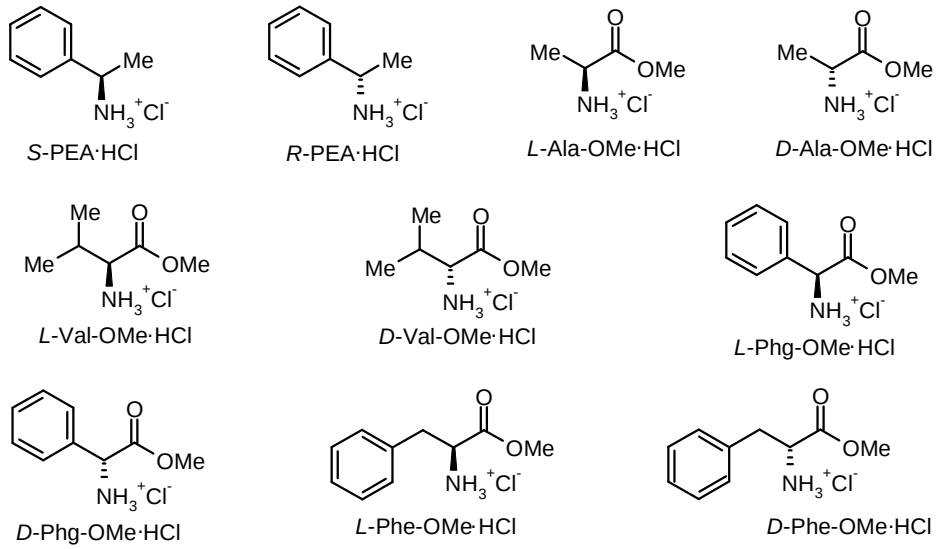


Figure 3.11 Structures of the ammonium guests.

Solubility of these guests in deuterated chloroform is relatively limited, so the experiments were conducted in a mixture $CDCl_3/CD_3OD$ (80:20).

The association constants in $CDCl_3/CD_3OD$ were much higher for these amino acid derived salts than for simple *α*-phenylethylammonium chlorides. The highest K_a value was observed for valine methyl ester hydrochloride (Val-OMe·HCl). Sterically less demanding alanine formed much weaker complexes. However, the enantioselectivity of the complexation was low but showed some regularity; D-aminoacid derivatives formed stronger complexes that L-enantiomers (Table 3.3).[209]

Figures 3.12–3.19 present titration curves for receptor **3.19f** and methyl ester ammonium salt complexes in $CDCl_3$-CD_3OD (80:20).

I also checked complexation abilities of ligand **3.19f** in DMSO-d_6. The results are shown in Table 3.3. Although this time the K_a values were much lower (than in $CDCl_3/CD_3OD$), I observed good enantioselectivity for alanine and a regularity in preferential complexation of all four unnatural D-amino acid derivatives.

Figures 3.20–3.27 present titration curves for receptor 3.19f and methyl ester ammonium salt complexes in DMSO-d_6.

In summary, the receptor **3.19f**, in complexing with methyl ester ammonium hydrochloride, showed not very high enantioselectivity, but unnatural D-amino acid derivatives were complexed better than L-isomers.

Table 3.3 Stability constants for complexes of ligand **3.19f** with amino acid methyl ester hydrochlorides in $CDCl_3$-CD_3OD (80:20) or DMSO-d_6.

Guest	$CDCl_3$-CD_3OD (80:20)		DMSO-d_6	
	K_a, M^{-1}	K_D/K_L	K_a, M^{-1}	K_D/K_L
D-Ala-OMe·HCl	1655 ± 164	2.02	32.4 ± 2.2	2.00
L-Ala-OMe·HCl	820 ± 50		16.2 ± 1.2	
D-Val-OMe·HCl	14740 ± 990	1.03	301 ± 28	1.46
L-Val-OMe·HCl	14380 ± 1500		206 ± 7.0	
D-Phg-OMe· HCl	5510 ± 490	1.37	145 ± 10	1.45
L-Phg-OMe· HCl	4020 ± 350		100 ± 10	
D-Phe-OMe· HCl	3835 ± 150	1.13	162 ± 11	1.28
L-Phe-OMe· HCl	3390 ± 220		127 ± 7.0	

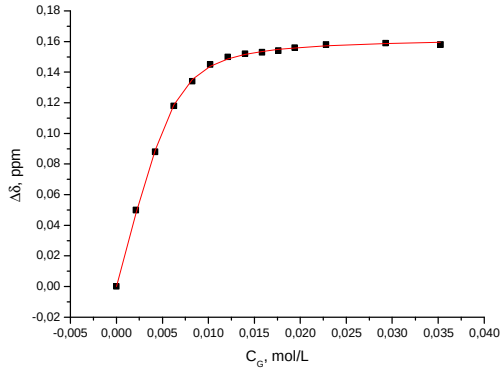


Figure 3.12 Titration curve for receptor **3.19f** and *D*-Ala-OMe·HCl complex in $CDCl_3$-CD_3OD (80:20).

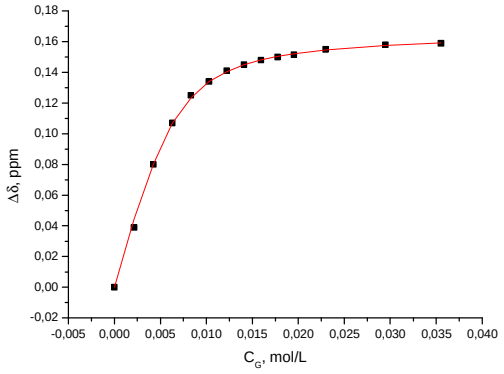


Figure 3.13 Titration curve for receptor **3.19f** and *L*-Ala-OMe·HCl complex in $CDCl_3$-CD_3OD (80:20).

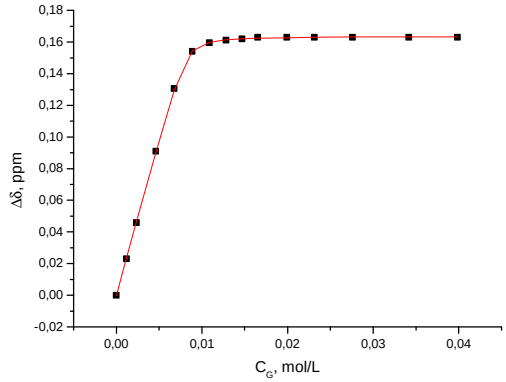


Figure 3.14 Titration curve for receptor **3.19f** and *D*-Val-OMe·HCl complex in $CDCl_3$-CD_3OD (80:20).

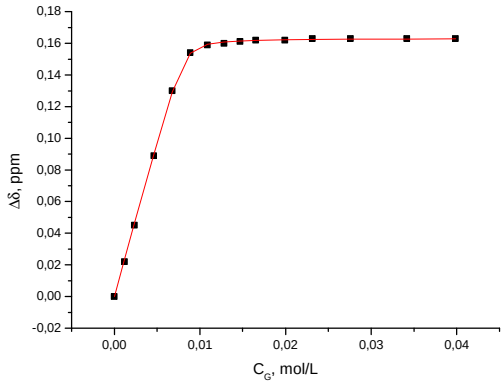


Figure 3.15 Titration curve for receptor **3.19f** and *L*-Val-OMe·HCl complex in $CDCl_3$-CD_3OD (80:20).

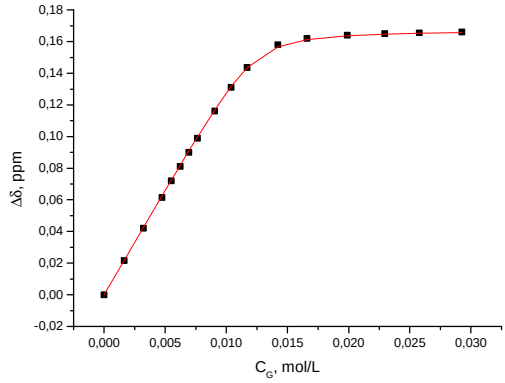


Figure 3.16 Titration curve for receptor **3.19f** and *D*-Phg-OMe·HCl complex in $CDCl_3$-CD_3OD (80:20).

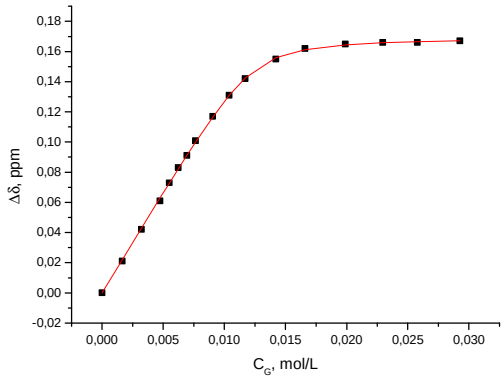


Figure 3.17 Titration curve for receptor **3.19f** and *L*-Phg-OMe·HCl complex in $CDCl_3$-CD_3OD (80:20).

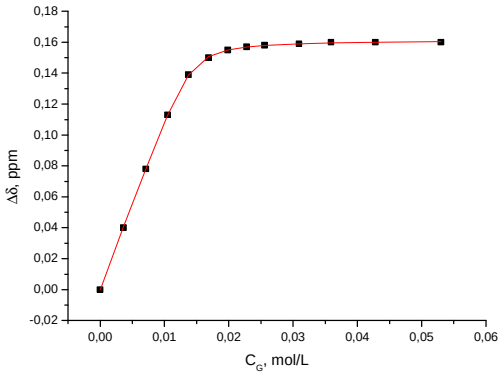


Figure 3.18 Titration curve for receptor **3.19f** and *D*-Phe-OMe·HCl complex in $CDCl_3$-CD_3OD (80:20).

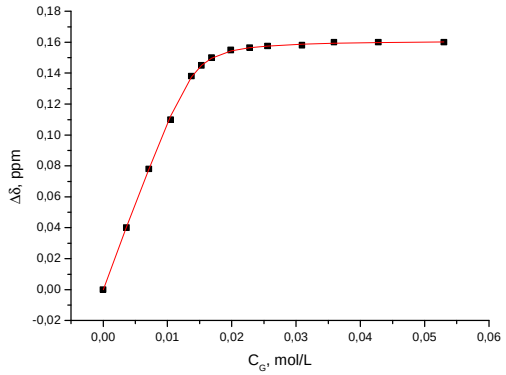


Figure 3.19 Titration curve for receptor **3.19f** and *L*-Phe-OMe·HCl complex in $CDCl_3$-CD_3OD (80:20).

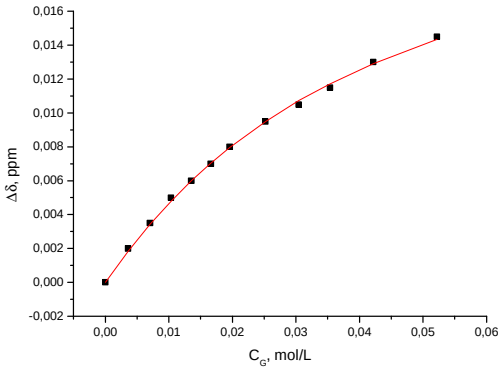


Figure 3.20 Titration curve for receptor **3.19f** and *D*-Ala-OMe·HCl complex in DMSO-d_6.

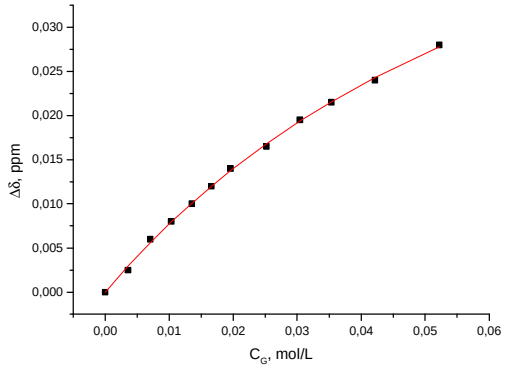


Figure 3.21 Titration curve for receptor **3.19f** and *L*-Ala-OMe·HCl complex in DMSO-d_6.

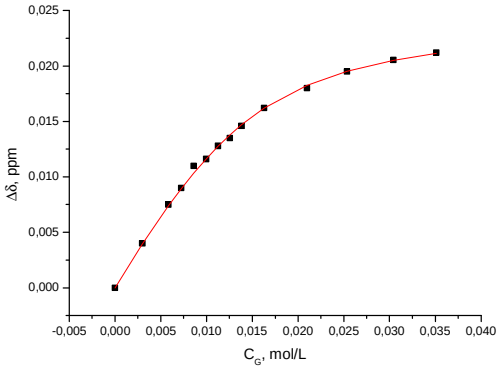


Figure 3.22 Titration curve for receptor **3.19f** and *D*-Val-OMe·HCl complex in DMSO-d_6.

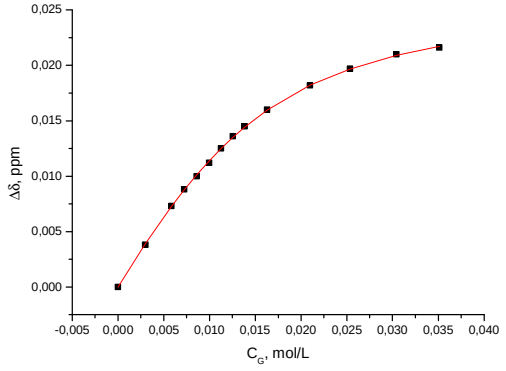


Figure 3.23 Titration curve for receptor **3.19f** and *L*-Val-OMe·HCl complex in DMSO-d_6.

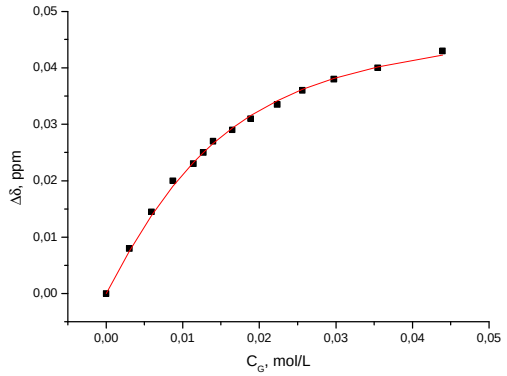


Figure 3.24 Titration curve for receptor **3.19f** and *D*-Phg-OMe·HCl complex in DMSO-d_6.

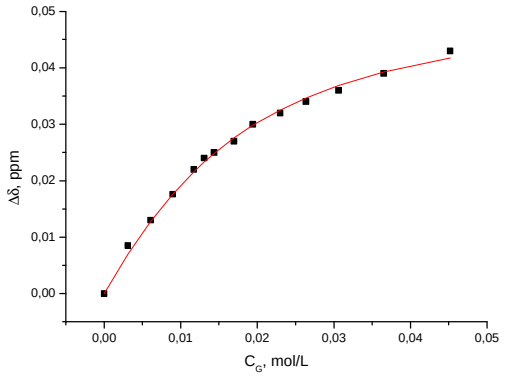


Figure 3.25 Titration curve for receptor **3.19f** and *L*-Phg-OMe·HCl complex in DMSO-d_6.

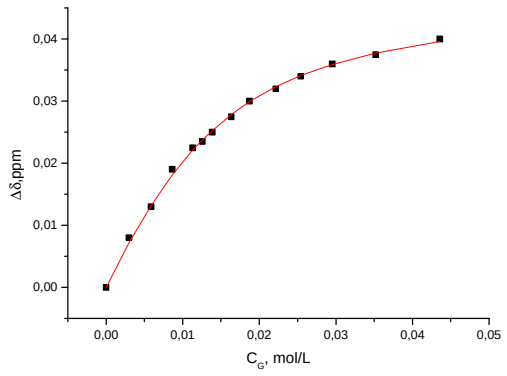


Figure 3.26 Titration curve for receptor **3.19f** and *D*-Phe-OMe·HCl complex in DMSO-d_6.

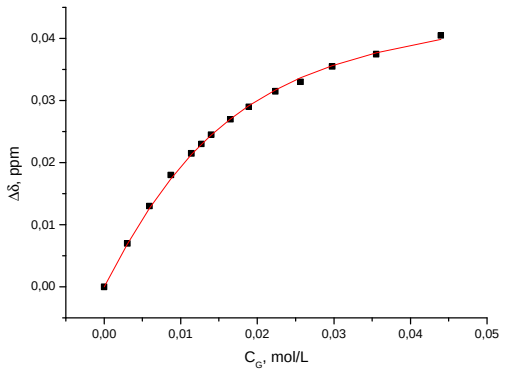


Figure 3.27 Titration curve for receptor **3.19f** and *L*-Phe-OMe·HCl complex in DMSO-d_6.

3.2.1 Di-aza-crown ethers

As mentioned above, mono-aza-crown ether **3.19a** (receptor containing one nitrogen atom) complexed the (*S*)-phenylethylammonium cation with high enentioselectivity but rather moderate association constant.[209] On the other hand, the association constants of complexes of the receptor **2.68** (with three nitrogen atoms in the ring) and *α*-phenylethylammonium cations (*R* and *S*) were substantially higher, but the enantioselectivity of complexation was rather low.[62]

Based on these observations one might suggest that the sucrose-based di-aza-crown ethers might have better complexing properties in terms of association/enantioselectivity.

Therefore, I decided to enlarge the pool of sucrose receptors in order to check out the complexing ability of such macrocycles with two nitrogen atoms in the ring.

Receptors prepared by us up to date (**3.19a–f** or **2.68**) were 'symmetrical', *i.e*. with the same heteroatom at the fructose and *glucose* '*end*' (oxygen or benzylamino group, respectively). During my PhD work I elaborated the convenient route to '*non-symmetrical*' receptors (*i.e.* containing various substituents at *glucose* and *fructose* '*end*').

Two structures with the 'central' nitrogen atom in the ring were designed: one with the second nitrogen atom at the *fructose* '*end*' and the other one with the nitrogen at the *glucose* '*end*' (compounds: **D** and **E**, Figure 3.28).

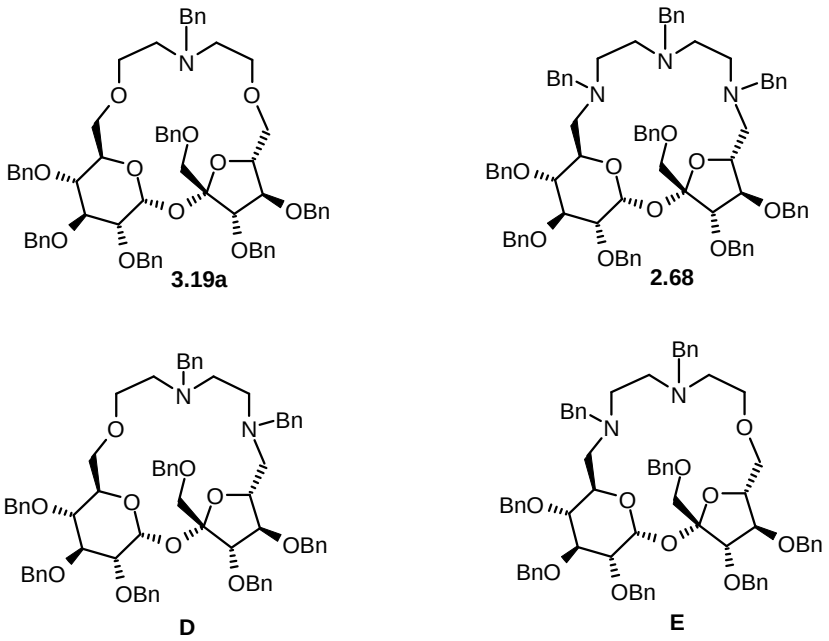
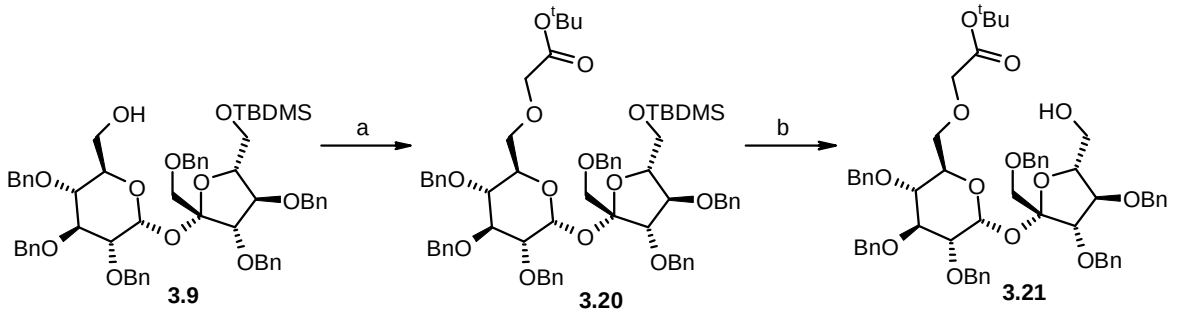


Figure 3.28 Sucrose-based aza-crown ethers **3.19a**, **2.68**, **D** and **E**.

My strategy for the synthesis of these macrocycles was based on: (a) differentiation of the two terminal hydroxyl groups in 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (as shown in Schemes 3.5 and 3.6); (b) elongation of one '*end*' (*glucose* or *fructose*) *via* the C-C-O-synthon; (c) transformation of the remaining '*end*' (*fructose* or *glucose*, respectively) into di-aza half-crown *via* N-C-C-N synthon; (d) a ring closing tandem Appel iodation/intramolecular alkylation reactions.

The synthesis of the first '*non-symmetrical*' macrocycle was initiated from derivative with a non-protected hydroxyl group at the *glucose* '*end*' (**3.9**). The free hydroxyl group at the 6-carbon atom of alcohol **3.9** was alkylated with *tert*-butyl bromoacetate in a two-phase reaction in the presence of 0.2 equiv. of TBAB as a phase-transfer catalyst, providing the ester **3.20** in good yield (84%). Removal of the silyl protection at the *fructose* 6'-OH group with

tetrabutylammonium fluoride trihydrate afforded the 1',2,3,3',4,4'-hexa-*O*-benzyl-6-*O*-(2-*tert*-butoxy-2-oxoethyl)sucrose (**3.21**) in 87% yield (Scheme 3.13).



(a) $BrCH_2CO_2{}^tBu$, Bu_4NBr, THF, NaOH (50% aq.), rt., 3h, 84%; (b) $TBAF{\cdot}3H_2O$, THF, rt., 1h, 87%

Scheme 3.13 Synthesis of 1',2,3,3',4,4'-hexa-*O*-benzyl-6-*O*-(2-*tert*-butoxy-2-oxoethyl)sucrose (**3.21**).

The structure of compounds **3.20** and **3.21** was confirmed by the NMR spectrum, mass spectrum and elemental analysis (see Chapters 4.2.10 and 4.2.11).

In the HMBC NMR spectrum of ester **3.20**, the C-6 atom (resonating at δ = 69.72 ppm) is coupled with two H-7 atoms (at δ = 3.84 and 3.95 ppm), whereas the C-7 atom (at δ = 69.30 ppm) is coupled with two H-6 atoms (at δ = 3.44 and 3.67 ppm) (Figure 3.29). This correlation data additionally confirmed the position of the selective silylation in diol **3.4** (Scheme 3.6).

Next steps in the proposed method should be conversion of the 6'-OH group into the benzylamino group. A methodology proposed by Lewandowski seemed to be the most convenient way to achieve this goal.[62] It consists of mesylation of the free OH followed by a S_N2 displacement of the mesyl group with benzylamine (which was used to synthesize **2.68**, see Chapter 2). Treatment of the alcohol **3.21** with methanesulfonyl chloride in the presence of triethylamine as a base in CH_2Cl_2 gave the expected compound **3.22** in 96% yield. However, the reaction with benzylamine proceeded very slowly; the desired amine was obtained in rather low yield and was contaminated by side-products. After 4 h of heating, the mixture in DMF at 100 °C, the amine **3.23** was isolated only in 26% yield (Scheme 3.14).

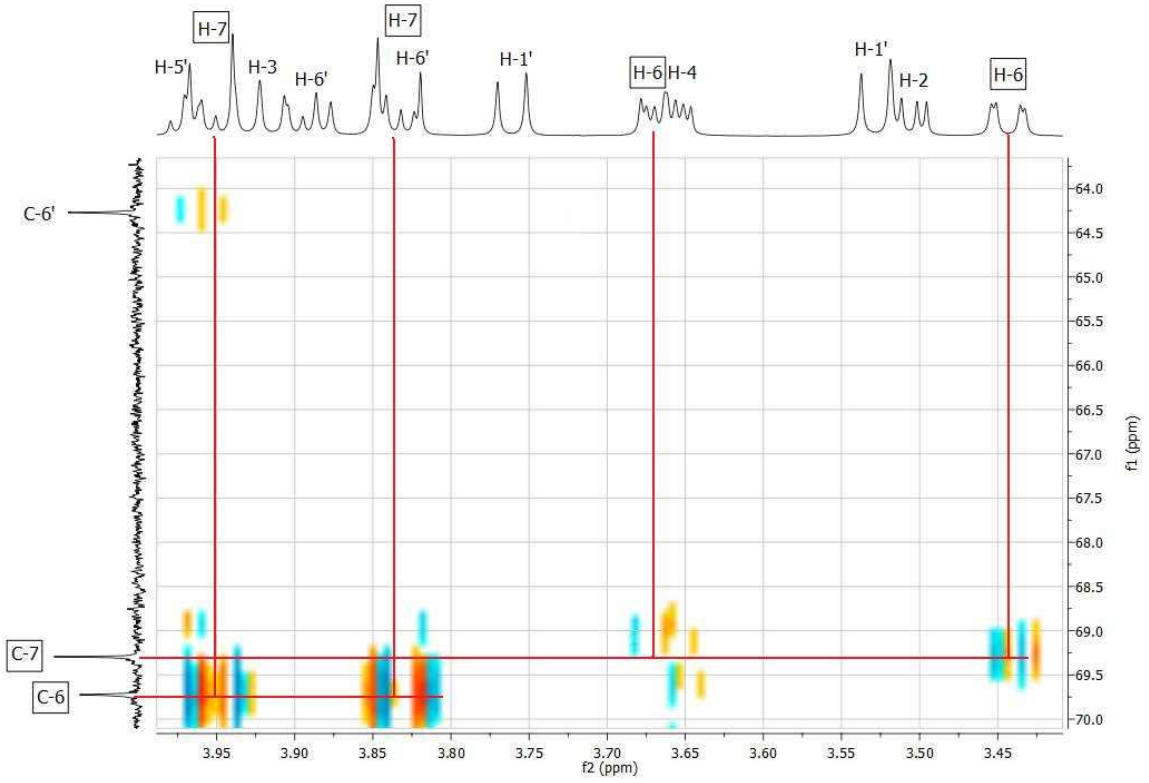
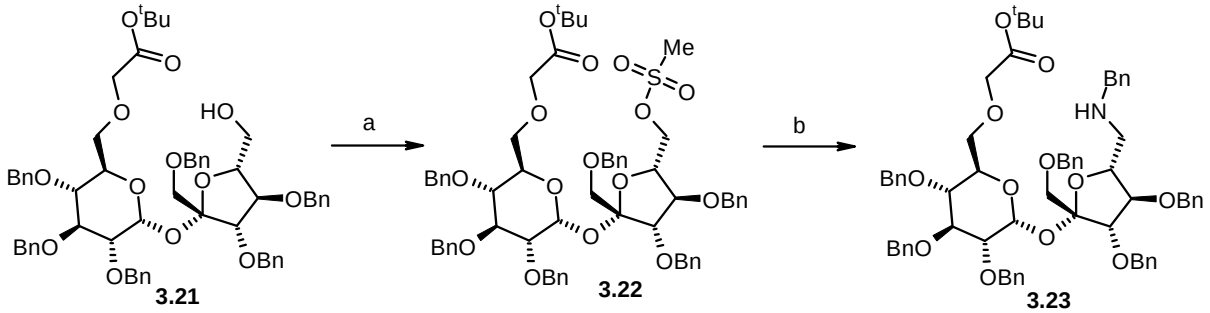


Figure 3.29 HMBC spectrum of compound **3.20** (3.42–3.98 ppm for ^{1}H NMR; 64–70 ppm for ^{13}C NMR range).



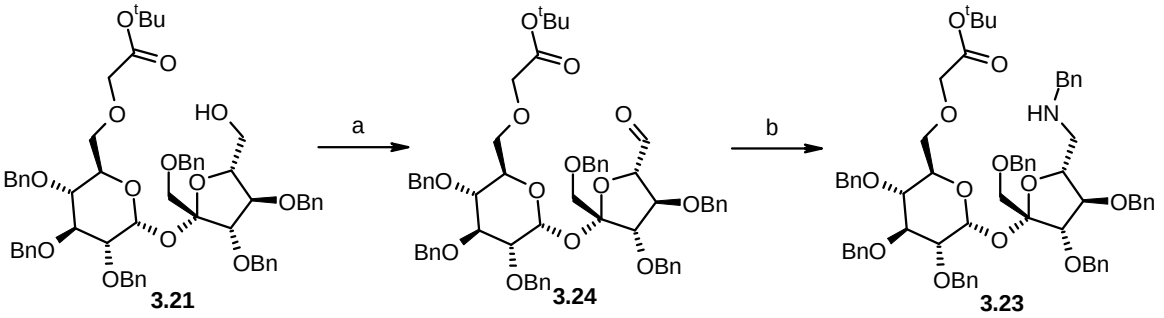
(a) MsCl, Et_3N, CH_2Cl_2, 1h, rt, 96%; (b) $BnNH_2$, DMF, K_2CO_3, 4h, 100°C, 26%

Scheme 3.14 Synthesis of 6'-benzyloamino-6'-deoxy-1',2,3,3',4,4'-hexa-*O*-benzyl-6-*O*-(2-*tert*-butoxy-2-oxoethyl)sucrose (**3.23**) by mesylation/alkylation method.

This 'failure' motivated me to modify the process. Therefore, I turned my attention to an alternative method of introduction of an amino functionality: the reductive amination.

Oxidation of the fructose hydroxyl group (C6'-OH) to an aldehyde under the Swern conditions afforded almost quantitatively the aldehyde **3.24**. Further reaction of the crude aldehyde with benzylamine and $NaCNBH_3$ provided the desired amine **3.23** in 74% yield (Scheme 3.15). The spectral characteristics (NMR and mass) clearly confirmed the identity of

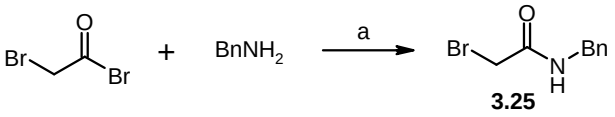
this product and the one that was obtained by alkylation of benzylamine (Scheme 3.14). Accordingly, possible epimerization at the C-5' atom during the transformation of the alcohol **3.21** into amine **3.23** (by Swern oxidation/reductive amination method) should be excluded.



(a) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, 10 min, then Et_3N, 30 min;
(b) $BnNH_2$, AcOH, $MgSO_4$, 1h, then $NaBH_3CN$, rt., 12h, 74% (for two steps)

Scheme 3.15 Synthesis of 6'-benzyloamino-6'-deoxy-1',2,3,3',4,4'-hexa-*O*-benzyl-6-*O*-(2-*tert*-butoxy-2-oxoethyl)sucrose (**3.23**) by oxidation/reductive amination method.

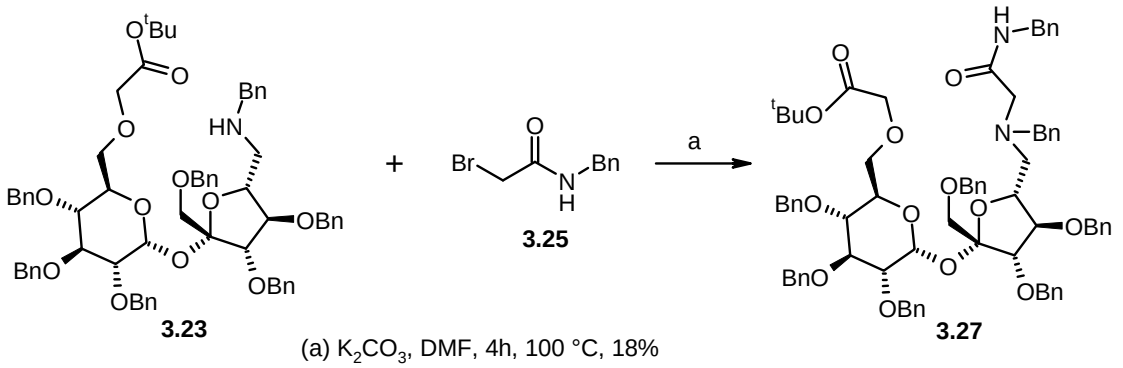
Next step of the synthesis of the first '*non-symmetrical*' macrocycle required elongation of the terminal position at the *fructose* '*end*'. This was achieved by alkylation of the '*fructose*' nitrogen atom in **3.23** with *N*-benzyl-2-bromoacetamide (**3.25**) (Scheme 3.17); the desired product was obtained in excellent yield (96%) according to the method shown in Scheme 3.16.



(a) CH_2Cl_2, -20 °C, 30 min, 96%

Scheme 3.16 Synthesis of *N*-benzyl-2-bromoacetamide (**3.25**).

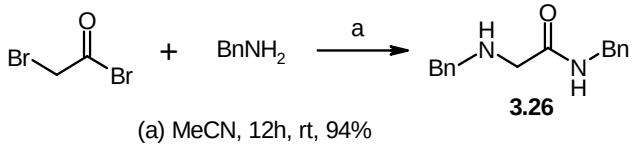
Alkylation of secondary amine **3.23** with the alkylating agent **3.25** in the presence K_2CO_3 as a base proceeded slowly. After 4 h of heating, the product **3.27** was isolated in only 18% yield (Scheme 3.17).



Scheme 3.17 Synthesis of compound **3.27** by alkylation method.

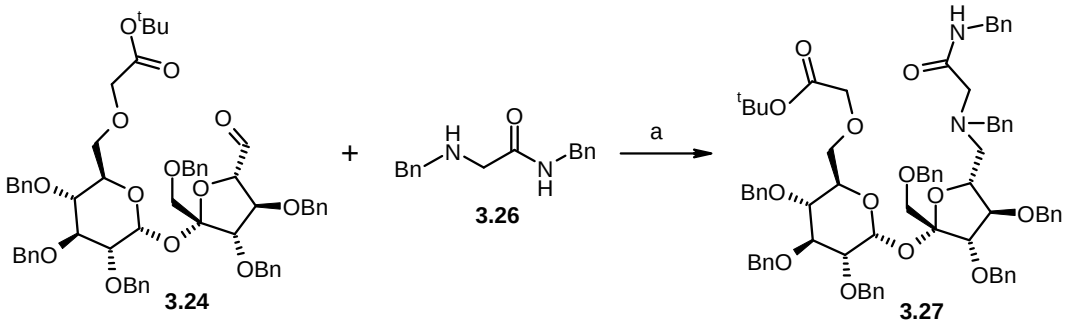
To improve yield of the product **3.27**, I decided to replace the alkylation reaction by reductive amination. This time the synthetic tactics was changed towards a more convergent route.

The key compound in this process was *N*-benzyl-2-(benzylamino)acetamide (**3.26**), which was obtained by reaction of bromoacetyl bromide with two equivalents of benzylamine. The product **3.26** was isolated after purification by flash chromatography in 94% yield. (Scheme 3.18).



Scheme 3.18 Synthesis of *N*-benzyl-2-(benzylamino)acetamide (**3.26**).

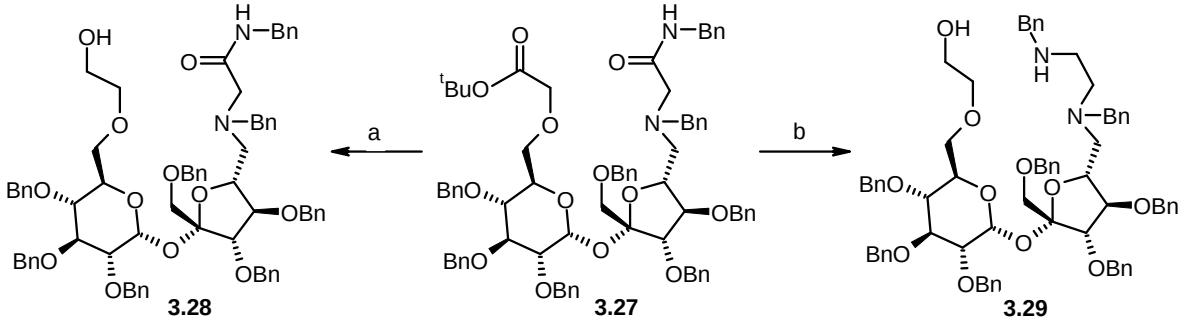
The secondary amine **3.26** was applied in reductive amination of the aldehyde **3.24**, which provided the amido-ester **3.27** in 71% yield (Scheme 3.19). The spectral characteristics (NMR and mass) clearly confirmed the identity of this product and the one obtained by alkylation method (Scheme 3.17). However, in this case, the reductive amination should be carefully monitored in order to obtain the best results; in basic media formation of the adventitious isomeric product was observed, which significantly lowered yield of the desired amine. Probably, under harsh basic conditions partial epimerization at the C5'-carbon occured.



Scheme 3.19 Synthesis of compound **3.27** by reductive amination method.

All in all, changing approach from mesylation/alkylation to Swern oxidation/reductive amination allows to reduce the number of synthetic steps, significantly increasing yield of the product **3.27**.

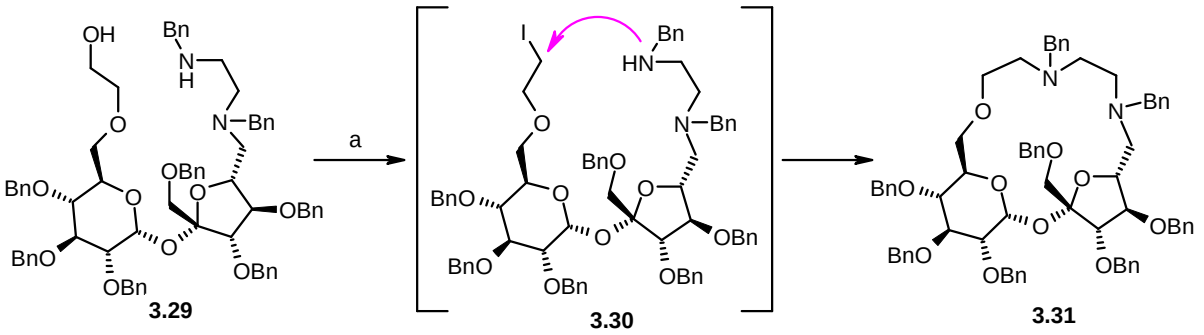
Reduction of both: ester and amide functions in compound **3.27** should provide the aminoalcohol 3.29. Indeed, treatment of substrate **3.27** with $LiAlH_4$ in THF at reflux provided the expected compound **3.29** in good yield (73%). Noteworthy, at room temperature only the ester group was reduced (to amidoalcohol **3.28**) (Scheme 3.20).



Scheme 3.20 Reduction of *N*-(2-benzyloamino-2-oxoethyl)-*N*-benzylo-6'-amino-6'-deoxy-1',2,3,3',4,4'-hexa-*O*-benzyl-6-*O*-(2-*tert*-butoxy-2-oxoethyl)-sucrose (**3.27**).

Reaction of the aminoalcohol **3.29** with the Garegg−Samuelsson reagent (TPP/imidazole/I_2[210]) afforded the unstable iodide **3.30**, which spontaneously underwent intramolecular cyclization to the desired macrocycle **3.31** (possessing the benzylamino group at the *fructose* '*end*') in 72% yield (Scheme 3.21).

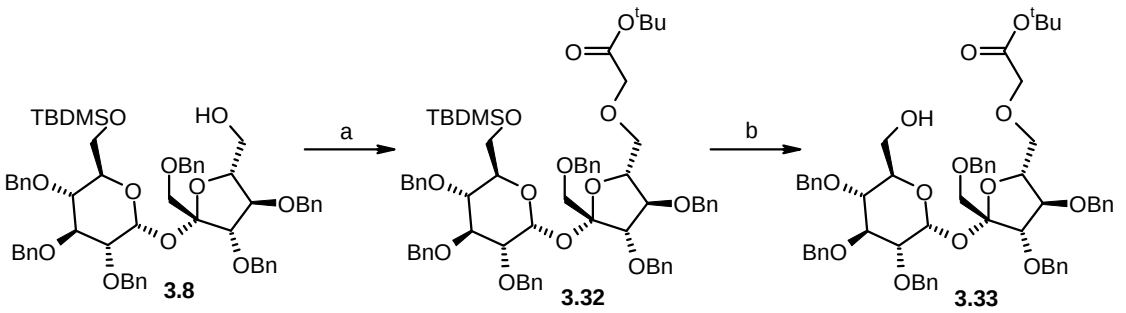
The detailed analysis of the NMR spectra (^1H, ^{13}C, COSY, HSQC and HMBC), as well as mass spectrum and elemental analysis, showed that the product of this reaction is the macrocycle **3.31**.



(a) I_2, Ph_3P, imidazole, toluene, reflux, 4h, 72%

Scheme 3.21 Synthesis of macrocycle **3.31**.

A similar strategy was used for preparation of the second '*unsymmetrical*' diaza-crown having the benzylamino group at the *glucose* '*end*'. Thus, alkylation of the alcohol **3.8** with *tert*-butylbromoacetate under the PTC conditions provided the corresponding sucrose-based ester **3.32** (in 77% yield) which – after desilylation with TBAF·$3H_2O$ – was converted into the compound **3.33** (Scheme 3.22).



(a) $BrCH_2CO_2{}^tBu$, Bu_4NBr, THF, NaOH (50% aq.), rt., 3h, 77%; (b) TBAF·$3H_2O$, THF, rt., 4h, 71%

Scheme 3.22 Synthesis of 1',2,3,3',4,4'-hexa-*O*-benzyl-6'-*O*-(2-*tert*-butoxy-2-oxoethyl)-sucrose (**3.33**).

The structure of compounds **3.32** and **3.33** was confirmed by the NMR spectrum, mass spectrum and elemental analysis (see Chapters 4.2.21 and 4.2.22).

In the HMBC NMR spectrum of ester **3.32**, the C-6' atom (resonating at δ = 72.88 ppm) is coupled with two H-7' atoms (at δ = 3.94 and 4.02 ppm), whereas the C-7' atom (at δ = 69.06 ppm) is coupled to two H-6' atoms (at δ = 3.73 and 3.79 ppm) (Figure 3.30). This correlation data additionally confirmed the position of the selective desilylation in compound **3.7** (Scheme 3.5).

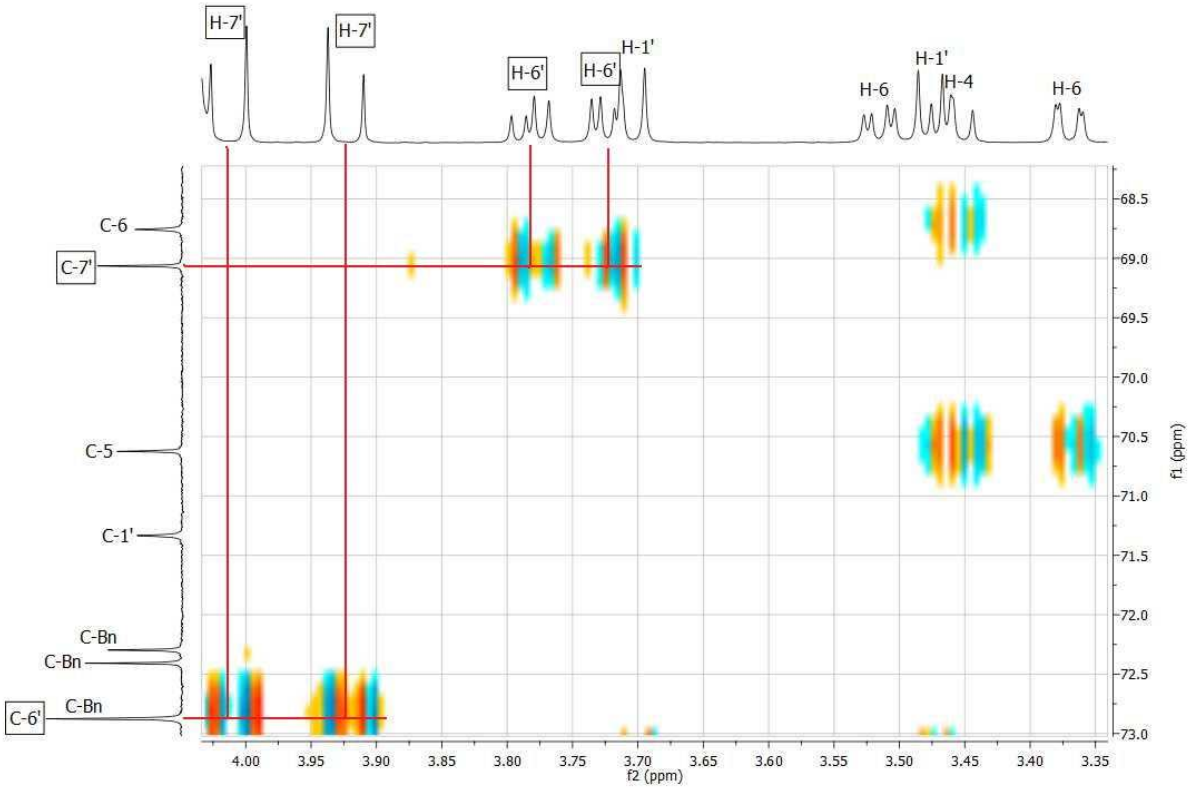
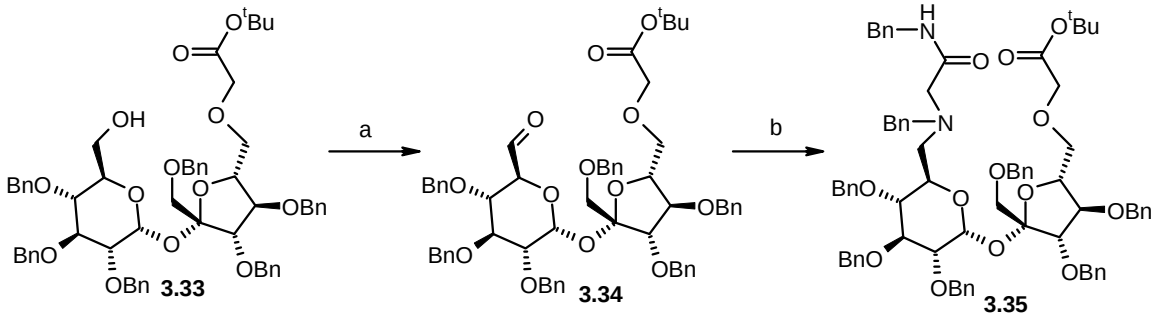


Figure 3.30 HMBC spectrum of compound **3.32** (3.35–4.07 ppm for ^{1}H NMR; 68.5–73.0 ppm for ^{13}C NMR range).

Oxidation of alcohol **3.33** under the Swern conditions (to the aldehyde **3.34**) followed by reductive amination with the amine **3.26** gave the amide-ester **3.35** in 74% yield (over two steps; Scheme 3.23).



(a) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N; (b) $BnNHCH_2C(O)NHBn$ (**3.26**), AcOH, $MgSO_4$, 1h, then $NaBH_3CN$, rt, 12 h, 74% (for two steps)

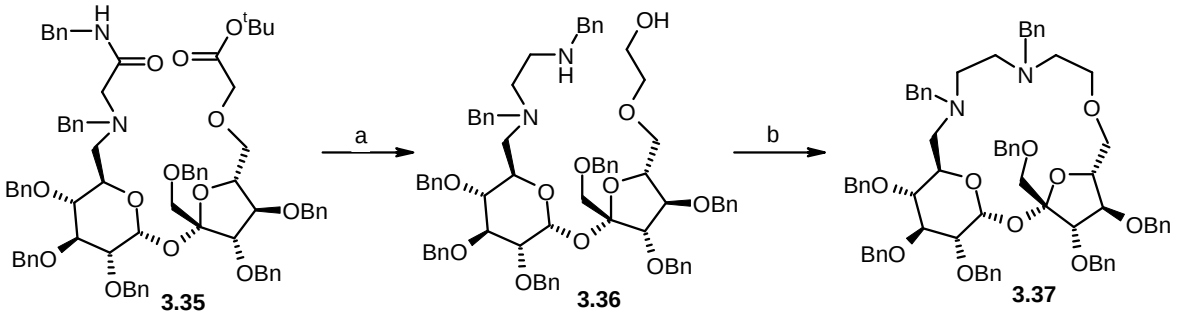
Scheme 3.23 Synthesis of *N*-(2-benzyloamino-2-oxoethyl)-*N*-benzylo-6-amino-6-deoxy-1',2,3,3',4,4'-hexa-*O*-benzyl-6'-*O*-(2-*tert*-butoxy-2-oxoethyl)-sucrose (**3.35**).

Structure of the product **3.35** was assigned on the basis of the NMR spectra, mass spectrum and elemental analysis (see Chapter 4.2.23). In ^{1}H NMR spectrum, the spin-spin

coupling constant between H-4 and H-5 ($J_{4,5}$) is 9.6 Hz, which is typical for glucose derivatives. Accordingly, the epimerization at the C-5 atom during the transformation of alcohol **3.33** to amine **3.35** did not occurred.

Reduction of compound **3.35** with $LiAlH_4$ in THF at reflux (as described for **3.27**) provided the corresponding amino alcohol **3.36**. The ring closing reaction of this "*half-crown*" (**3.36**) with I_2/Ph_3P/imidazole resulted in formation of the macrocycle **3.37** in 72% yield (Scheme 3.24).

Structure of the product **3.37** was confirmed by the NMR spectra, mass spectrum and elemental analysis (see Chapter 4.2.24). A detailed analysis of the NMR spectra (^1H, ^{13}C, COSY, HSQC and HMBC), as well as mass spectrum and elemental analysis, of the product obtained in the Garegg−Samuelsson reaction proved the cyclic structure of **3.37** (see Chapter 4.2.25).



(a) $LiAlH_4$, THF, reflux, 2h, 84%; (b) I_2, Ph_3P, imidazole, toluene, reflux, 4h, 74%

Scheme 3.24 Synthesis of macrocycle **3.37**.

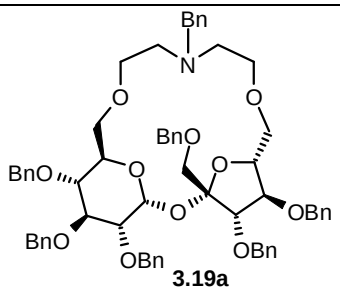
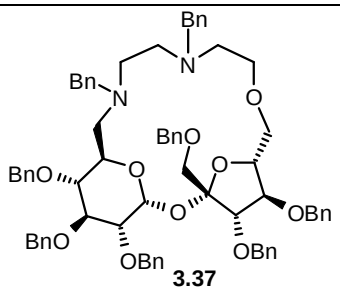
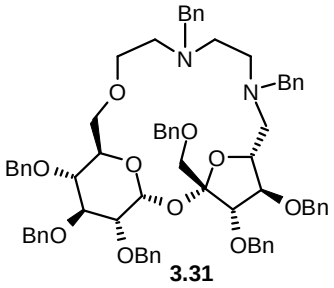
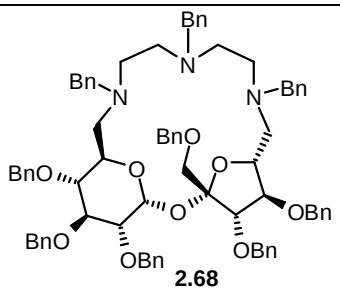
Receptors **3.31** and **3.37** were employed in the enantioselective recognition of *α*-phenyl-ethylammonium chloride: (*S*)-PEA·HCl and (*R*)-PEA·HCl. Association constants were determined by the NMR titration method in $CDCl_3$ (as described for the receptors **3.19a–f**). A shift of the signal of the anomeric proton (H-1) of sucrose was monitored during the experiment. The K_a values for the receptors: **3.31**, **3.37**, and (previously obtained) **3.19a** and **2.68** with (*S*)-PEA·HCl and (*R*)-PEA·HCl are shown in Table 3.4.

As we observed earlier, the mono-aza-crown ether **3.19a** selectively complexed the (*S*)-*α*-phenylammonium cation, but the value of K_a was low (70 M^{-1}). On the other hand, complexation of the (*S*)-PEA cation by tri-aza-crown ether **2.68** was much stronger (K_a~1200) but the enantioselectivity was relatively low ($K_{a(S)}/K_{a(R)}$ ~ 1.5).[62]

Di-aza-crown ether **3.37** formed complexes with the (*S*)-PEA·HCl and (*R*)-PEA·HCl, having the association constants K_a = 309 and 131 M^{-1} respectively; the enantioselectivity was rather moderate ($K_{a(S)}/K_{a(R)}$ ~ 2.4).

On the other hand, receptor **3.31** selectively complexed only the (*S*)-*α*-phenylethylammonium cation (K_a = 522 M^{-1}; Table 3.4).

Table 3.4 Stability constants for complexes of receptors **3.19a**, **3.31**, **3.37** and **2.68** with (*S*)- and (*R*)-phenylethylammonium chloride in $CDCl_3$.

Receptor	$K_{a,(S)}$, M^{-1}	$K_{a,(R)}$, M^{-1}
 **3.19a**	70 ± 7	*a**
 **3.37**	309 ± 23	131 ± 6
 **3.31**	522 ± 33	*a*
 **2.68**	1244 ± 192	837 ± 104

*a** – No changes of the chemical shift were observed in the NMR during titration.

Replacing the oxygen atom by the amino group at the C6 position increases the association constant for the *S*-cation of phenylethylammonium hydrochloride from 70 to 309 M^{-1}. However, it also increases the complexing ability of the *R*-cation. Similar replacement at the position C6' (compound **3.31**) also increases K_a for the *S*-isomer of PEA·HCl, but the receptor remains inactive for *R*-isomer of PEA·HCl.

These results suggest that the step-wise replacement of the oxygen atoms by the amino group increases complexing activity of the receptor. However, presence of the nitrogen atom at the position C6 decreases enantioselectivity. The disposition of the nitrogen substituents in the sucrose aza-crown ethers is crucial for high enantioselective recognition.

Figures 3.31–3.33 present the titration curves for receptors **3.31** and **3.37** and *α*-phenylethylammonium chlorides complexes in $CDCl_3$.

In general, complexing ability of the sucrose-based receptors towards the (*S*)-*α*-phenylammonium cation is increased with the number of nitrogen atoms in the macrocylic ring. Selectivity of the complexation of this cation, however, depends on the position of the nitrogen functions in the ring; it is decreased in case of the compound where the *glucose* oxygen atom (at the C6-position) is replaced by nitrogen.

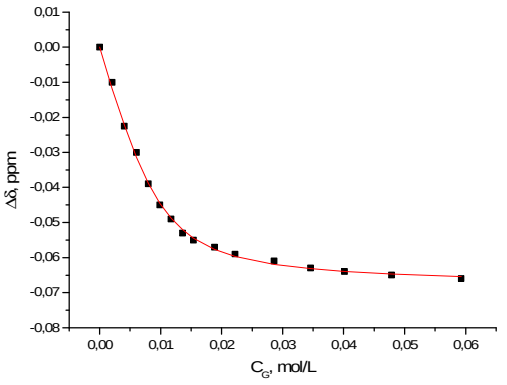


Figure 3.31 Titration curve for receptor **3.31** and *S*-PEA·HCl complex in $CDCl_3$.

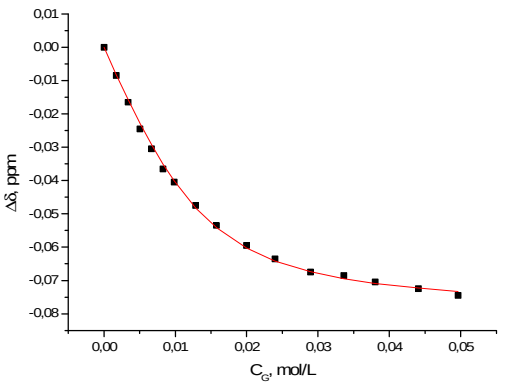


Figure 3.32 Titration curve for receptor **3.37** and *S*-PEA·HCl complex in $CDCl_3$.

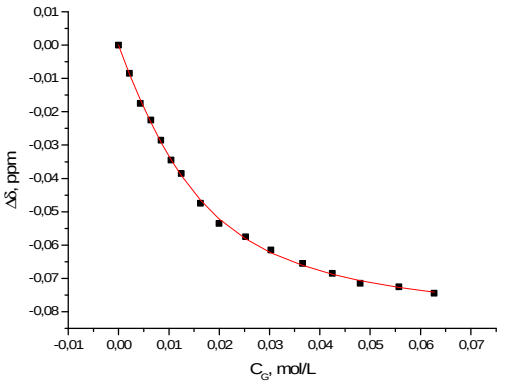


Figure 3.33 Titration curve for receptor **3.37** and *R*-PEA·HCl complex in $CDCl_3$.

3.3 Synthesis of diamide-linked sucrose macrocycles

The large ring lactams represent another important type of macrocycles containing nitrogen atom(s). Amide groups, because of their proton donor-acceptor properties, are applied as building blocks in the synthesis of macrocyclic receptors. Some of the most common platforms in supramolecular chemistry are isophthalic and pyridine-2,6-diamides.[8] Macrocyclic compounds with such aromatic platforms play an important role as receptors for anions,[212–214] ion pairs,[215–218] zwitterions (*e.g.*, dopamine[217]), and amino acid derivatives.[219] The anion-complexing properties of these amides were exploited in the template syntheses of catenane,[220–225] rotaxane,[225–235] and pseudorotaxane[236,237] systems. Macrocycles incorporating the pyridine-2,6-diamide functionality are known as molecular turnstiles.[238,239]

Such macrocyclic diamides are usually synthesized from isophthalic and 2,6-pyridine-dicarboxylic acids (or isophthaloyl and 2,6-pyridinedicarbonyl dichlorides) in combination with other building blocks, such as polyethylene glycol (PEG) reagents, [220,221,226–231] chiral 1,2-diamines,[219] calix[4]arenes, [214,216,225,233,] and calix[4]diquinones. [218,222,235]

Combination of the sucrose scaffold with isophthalic or pyridine-2,6-diamide units may open a useful way to a new type of chiral receptors with interesting properties.

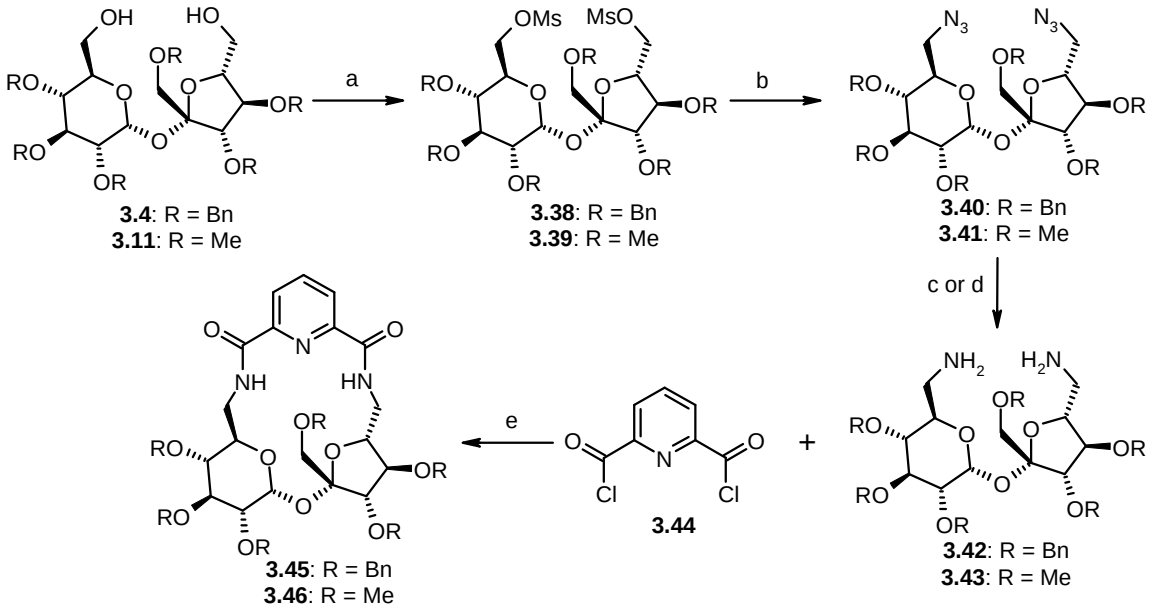
These considerations prompted me to elaborate a methodology for the preparation of chiral compounds of this type with sucrose scaffold. As I already found, this disaccharide is a convenient platform for receptors displaying very good enantioselectivity in the complexation of *α*-phenylethylamine and good towards other chiral amines. Therefore, I planned to synthesize the sucrose-based diamines and apply them in the condensation with isophthaloyl and 2,6-pyridinedicarbonyl dichlorides.

The first model synthesis is showed in Scheme 3.25.

The diols **3.4** and **3.11** were converted into the corresponding mesylates **3.38** and **3.39** under the standard conditions (in 97 and 92% yields respectively). Treatment of these compounds with sodium azide in DMF at 100 °C provided the products: **3.40** and **3.41** in very good yields (87 and 74% respectively).

Structures of the diazido derivatives **3.40** and **3.41** were confirmed by the IR, NMR and mass spectra, as well as elemental analysis (see Chapters 4.2.27.1 and 4.2.27.2). In particular, in their IR spectra, the characteristical signals from the N_3-groups were observed at 2101 (for compound **3.40**) and 2100 cm^{-1} (for compound **3.40**).

The diazide **3.40** was further transformed into the di-amine **3.42** *via* reduction with $LiAlH_4$. Hydrogenation of the 6,6'-dazido-1',2,3,3',4,4'-hexa-*O*-methyl-6,6'-dideoxysucrose (**3.41**) provided the di-amine **3.43**. Crude compounds **3.42** and **3.43** were reacted with 2,6-pyridinedicarbonyl dichloride (**3.44**) in the presence of triethylamine as a base. 16-Membered macrocylic diamides **3.45** and **3.46** were obtained in very good yields (70 and 67% respectively). The structures of dilactames **3.45** and **3.46** were confirmed by the IR, NMR and mass spectra, as well as elemental analysis (see Chapters 4.2.30.1 and 4.2.30.2). In the IR spectra of these compounds, the characteristical signals from the amido-groups (C=O) were observed at 1683 and 1686 cm^{-1} for **3.45** and **3.46**, respectively.



(a) MsCl (2.5 equiv), Et_3N (3 equiv), CH_2Cl_2, rt, 1h, 97% for **3.38** and 92% for **3.39**;
(b) NaN_3 (5 equiv), DMF, 100 °C, 12h, 86% for **3.40** and 74% for **3.41**;
(c) $LiAlH_4$, THF, -78 °C to rt, 1h; (d) H_2, Pd/C, AcOEt/MeOH (1:1), rt, 12h;
(e) Et_3N, (3 equiv), CH_2Cl_2, rt, 1h, 70% for **3.45** (over two steps) and 67% for **3.46** (over two steps)

Scheme 3.25 Synthesis of dilactams **3.45** and **3.46**.

This initial success motivated me to perform the synthesis of macrocycles with larger macrocyclic cavity. Such macrocycles would contain the chiral sucrose subunit (which is suitable for complexing the ammonium cation) and the diamide grouping (commonly used unit for recognition of anions). Therefore, they might be, probably, used as receptors for recognition of *e.g.* amino acids.

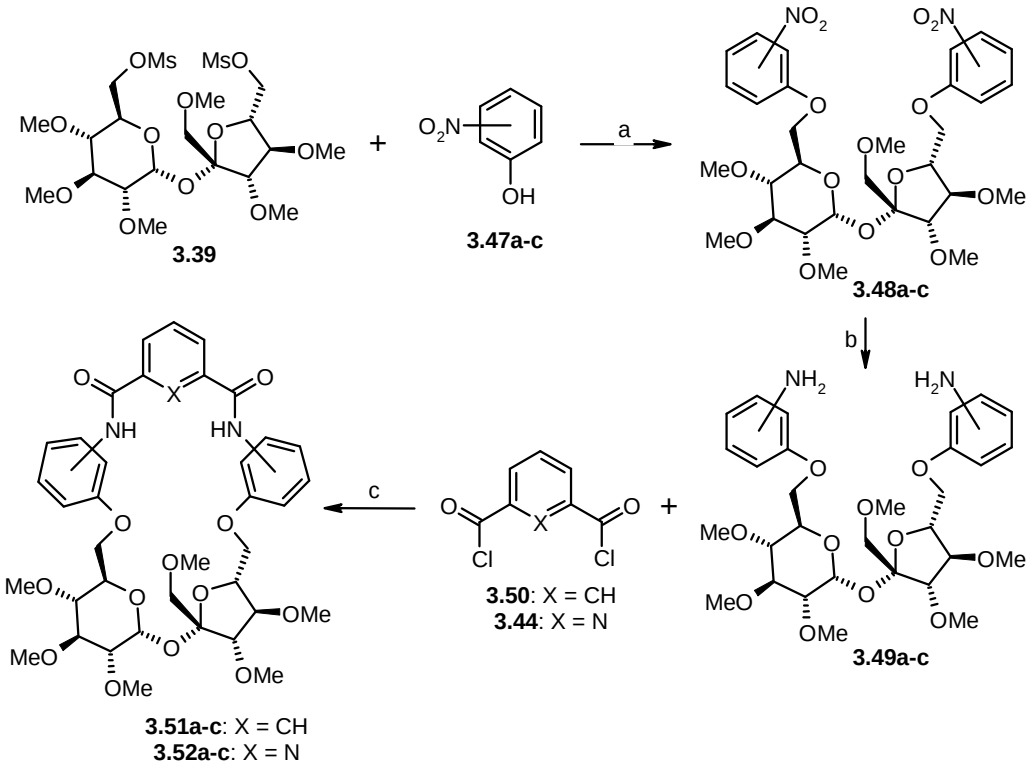
The synthesis of new sucrose-based macrocyclic diamides with aryl linkers was initiated from 1',2,3,3',4,4'-hexa-*O*-methyl-6,6'-di-*O*-(methylsulfonyl)sucrose (**3.39**). Its condensation with 2 equiv. of the proper nitro-phenol **3.47a–c** (*o*-, *m*-, *p*- respectively) provided the expected 6,6'-di-*O*-nitrophenyl-1',2,3,3',4,4'-hexa-*O*-methylsucroses: **3.48a**

(85%), **3.48b** (90%) and **3.48c** (88%). Hydrogenation of these nitro-compounds afforded the respective di-amines: 6,6'-di-*O*-aminophenyl-1',2,3,3',4,4'-hexa-*O*-methylsucroses **3.49a–c** in excellent (94, 96 and 91%) yield (Scheme 3.26).

The structures of the dinitro and diamino derivatives (**3.48a–c** and **3.49a–c**, respectively) were confirmed by the IR, NMR and mass spectra, and elemental analysis (see Chapters 4.2.31.1–3 and 4.2.32).

These diamines were used for the preparation of macrocyclic bis-amides under high dilution conditions. Condensation of *o*-diamine **3.49a** with isophthaloyl or 2,6-pyridine-dicarbonyl dichlorides (**3.50** and **3.44** respectively) afforded the expected macrocyclic derivatives **3.51a** or **3.52a** in 77 and 78% yield (Scheme 3.26, Figure 3.34). The excellent yields of the cyclization can be explained by a good-preorganization of the molecule of the substrate.

Reaction of the *m*-diamine **3.49b** with reagents **3.50** or **3.44** proceeded analogously, although the corresponding diamides **3.51b** and **3.52b** were formed in lower yields (57% and 62% respectively) (Scheme 3.26, Figure 3.34).



Scheme 3.26 Synthesis of dilactams **3.51a–c** and **3.52a–c**.

Condensation of the *p*-diamine **3.49c** with acid dichlorides **3.50** and **3.44** under the same conditions was, however, more complex.

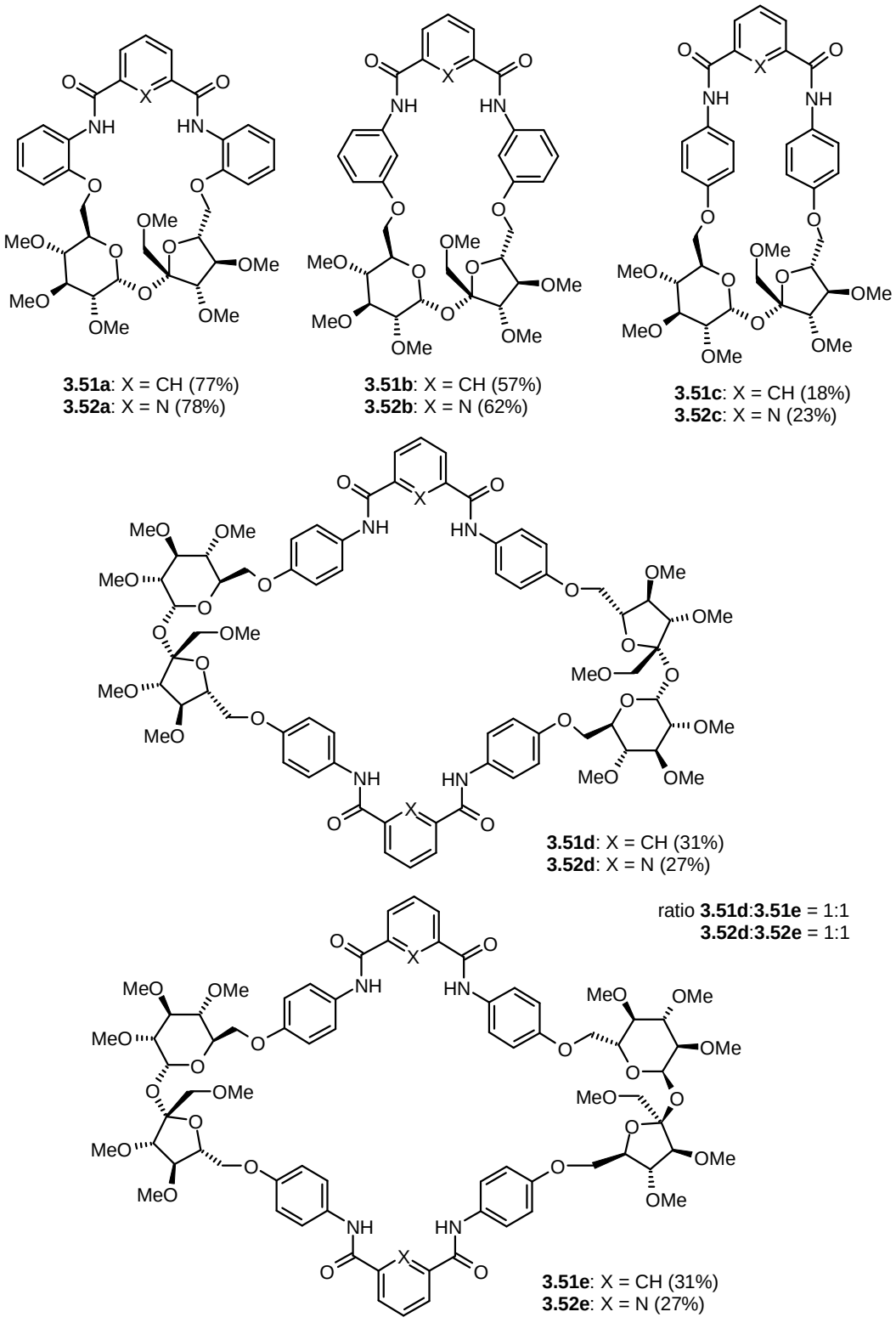


Figure 3.34 Macrocyclic diamides **3.51a–e** and **3.52a–e**.

The expected product **3.51c** was formed in very low yield (18%) in reaction with **3.50**. Furthermore, I also isolated an inseparable mixture of a large number of 'minor' products. Similar reaction of **3.49c** with dichloride **3.44** proceeded analogously affording the product **3.52c** in 23% yield (Figure 3.34) and an inseparable mixture of 'minor' products.

The structures of dilactames **3.51a–c** and **3.52a–c** were confirmed by the IR, NMR and mass spectra, as well as elemental analysis (see Chapters 4.2.34.1–6). In their IR spectra the characteristical signals from the amido-groups (C=O) were observed at 1676, 1651 and 1644 cm^{-1} for compounds **3.51a**, **3.51b** and **3.51c**, respectively; 1690, 1669 and 1662 cm^{-1} for compounds **3.52a**, **3.52b** and **3.52c**, respectively.

The solubility of dilactams **3.51b,c** and **3.52c** in most organic solvents (ethyl acetate, chloroform, methylene chloride, ect.) is very limited. The peaks in NMR spectra of these compounds in $CDCl_3$ of DMSO-d_6 at room temperature were very broad. Therefore, such spectra were recorded in DMSO-d_6 at 80 or 110 °C. This phenomenon indicates possible π-π-interaction between two phenyl ring in macrocyclic molecules.

The low yields of dilactams **3.51c** and **3.52c** motivated me to look more carefully at these inseparable mixture of products. The mass spectrum of the mixture obtained together with **3.51c**, showed only one peak at *m/z* = 1499.5 which is equal to $[2M + Na]^+$. The molecular ion detected for the second mixture (in reaction leading to **3.52a**) contained also only one peak at *m/z* = 1501.6 which is equivalent to $[2M + Na]^+$.

These data, as well as a detailed analysis of the NMR spectra (^1H, ^{13}C, COSY, HSQC and HMBC) clearly showed that these inseparable mixtures are composed of the two dimers **3.51d**/**3.51e** and **3.52d**/**3.52e** (Figure 3.34).

Thus, the reaction of diamine **3.49c** with dichloride **3.50** gave, except monomeric product **3.51c**, two dimeric products **3.51d** and **3.51e** in 62% overall yield. The yield of the mixture of dimers **3.52d/3.52e** was 54%. Other byproducts of the cyclocondensation reactions were not isolated. Although these dimers could not be isolated in pure form, the proportions of **3.51d**:**3.51e** and **3.52d**:**3.52e** were estimated as 1:1 basing on integration of aromatic signals in the ^1H NMR spectrum.

As shown in Figure 3.35, in the ^1H NMR spectrum of compounds **3.52d** and **3.52e** the integration of all aromatic signals, except two signals of H^A atoms, are doubled. It is due to the fact that compound **3.51d**, **3.51e**, **3.52d** and **3.52e** are C_2-symmetrical. In case of macrocyclic tetraamides **3.51d** and **3.52d** the rotational axis is perpendicular to the "molecular" plane (Figure 3.36) and all atoms of the molecules have their "twin". All groups (incuding protons H^A) are homotopic, *i.e.* they are exchangable by this C_2-axis. In case of

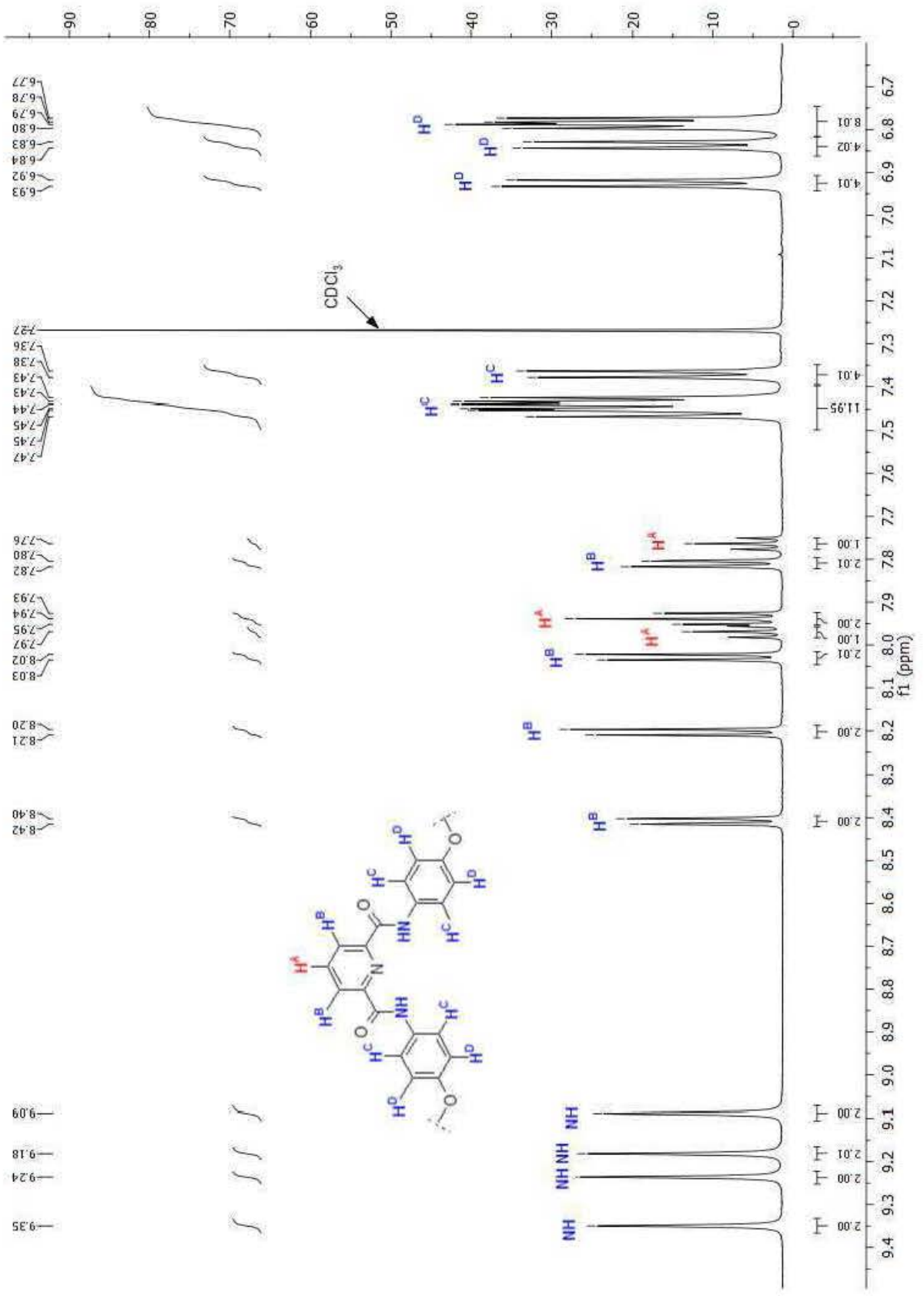


Figure 3.35 ^{1}H NMR spectrum of compounds **3.52d** and **3.52e** (aromatic part).

macrocycles **3.51e** and **3.52e**, however, the rotational axis passes through both H^A atoms (Figure 3.37). All groups in the molecule are exchangable by this axis (they are homotopic) except the atoms (including H^A atoms) located on this axis which are diastereotopic, i.e. they must have different chemical shifts.

The relative orientations of the amino groups in the energetically accessible conformations of substrates **3.49a-c** define the direction of macrolactamization. For compound **3.49c**, conformations in which two amino gproups are mutually close, have low populations, reducing the probability of formation of dilactams **3.51c** and **3.52c**; thus, 2:2-cyclisation becomes dominant.

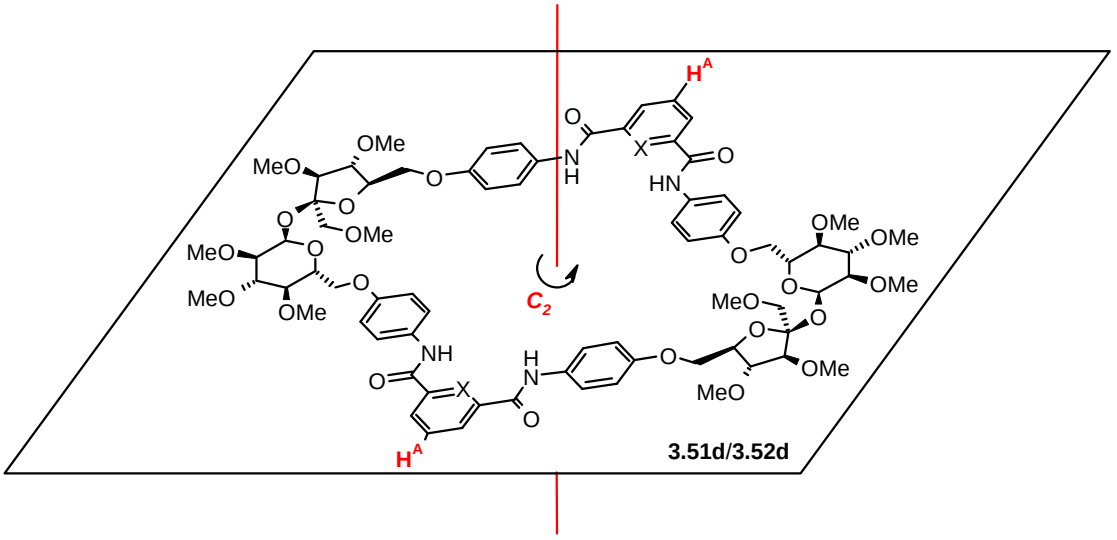


Figure 3.36 C_2-symmetrical macrocyclic diamides **3.51d** and **3.52d**.

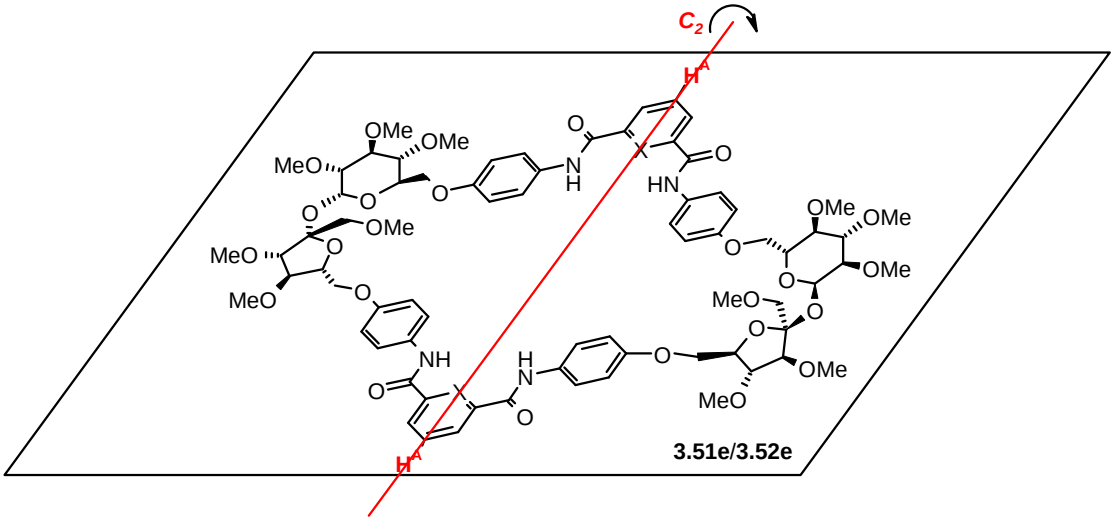
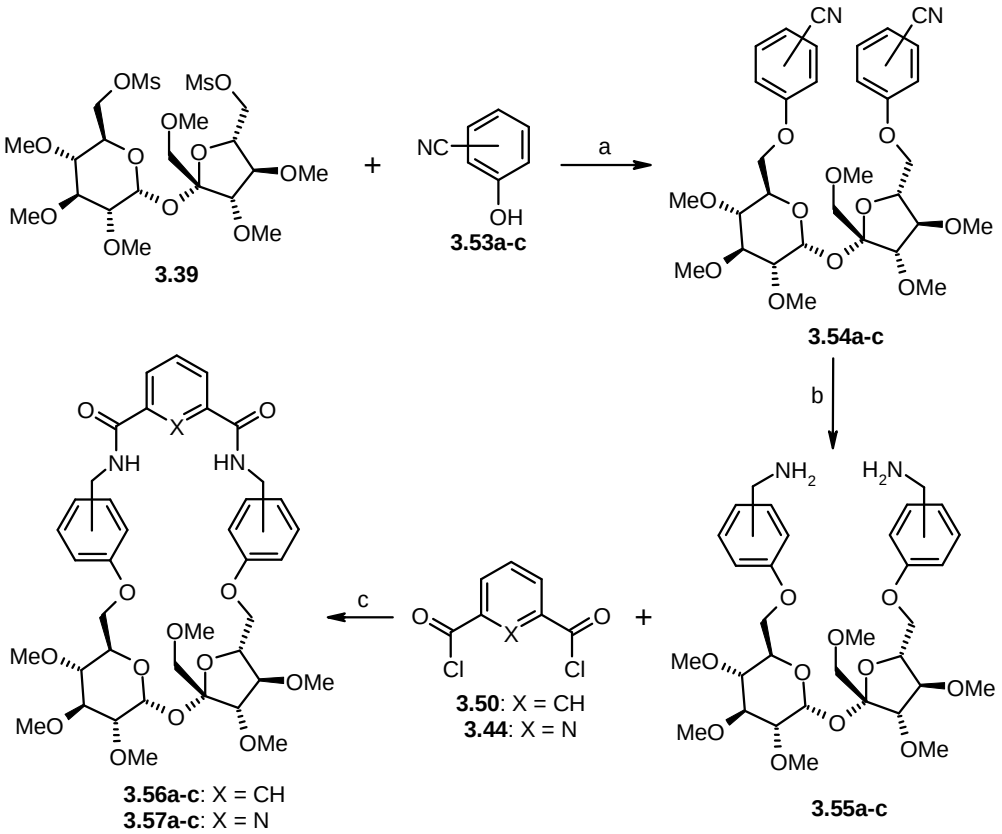


Figure 3.37 C_2-symmetrical macrocyclic diamides **3.51e** and **3.52e**.

Next step of my research was realized by the synthesis of the homologated analogs of macrocycles **3.51a–c** and **3.52a–c**. For achieving this goal, nitrophenols were replaced by cyanophenols.

1',2,3,3',4,4'-Hexa-*O*-methyl-6,6'-di-*O*-(methylsulfonyl)sucrose (**3.39**) was treated with 2 equiv. of the appropriate, commercially available cyanophenol (**3.53a–c**; *o*, *m*, *p*, respectively) in DMF in the presence of potassium carbonate, which provided the 6,6'-di-*O*-(cyanophenyl)-1',2,3,3',4,4'-hexa-*O*-methylsucroses (**3.54a–c**) in 81–84% yield (Scheme 3.27).[240]

The structures of dinitriles **3.54a–c** were confirmed by the IR, NMR and mass spectra as well as elemental analysis (see Chapters 4.2.31.4–6). In their IR spectra the characteristical signals of the cyano-groups (C≡N) were observed at 2228, 2231 and 2225 cm^{-1} for compounds **3.54a**, **3.54b** and **3.54c**, respectively.



(a) K_2CO_3 (5 equiv), DMF, 100 °C, 24h; (b) $LiAlH_4$, THF, 60°C, 1h;
(c) Et_3N, (3 equiv), CH_2Cl_2, rt, 1h

Scheme 3.27 Synthesis of dilactams **3.56a–c** and **3.57a–c**.

These compounds were quantitatively reduced (with $LiAlH_4$) to the 6,6'-di-*O*-[(amino-methyl)phenyl]-1',2,3,3',4,4'-hexa-*O*-methylsucroses (**3.55a–c**) which were used in the subsequent reactions without further purification. The crude bis-amines **3.53a–c** were

subjected to cyclocondensation reaction with isophthaloyl or 2,6-pyridinedicarbonyl dichlorides (**3.50** and **3.44**, respectively); the closure of the ring occurred easily and sucrose-based dilactams **3.56a–c** and **3.57a–c** (which are twice homologated by methylene groups as compared to compounds: **3.51a–c** and **3.52 a–c**) were formed (Scheme 3.27).

To avoid formation of the dimeric byproducts, these reactions were performed in dilute solution. In all cases a 1:1-product (**3.56a–c** and **3.57a–c**) was formed in good yield (63–74 %; Figure 3.38).

The structures of dilactames **3.56a–c** and **3.57a–c** were confirmed by the IR, NMR and mass spectra as well as elemental analysis (see Chapters 4.2.34.9–14). In their IR spectra the characteristical signals from the amido-groups (C=O) were observed at 1658, 1654 and 1649 cm^{-1} for compounds **3.56a**, **3.56b** and **3.56c**, respectively, and 1674, 1679 and 1671 cm^{-1} for compounds **3.57a**, **3.57b** and **3.57c**, respectively.

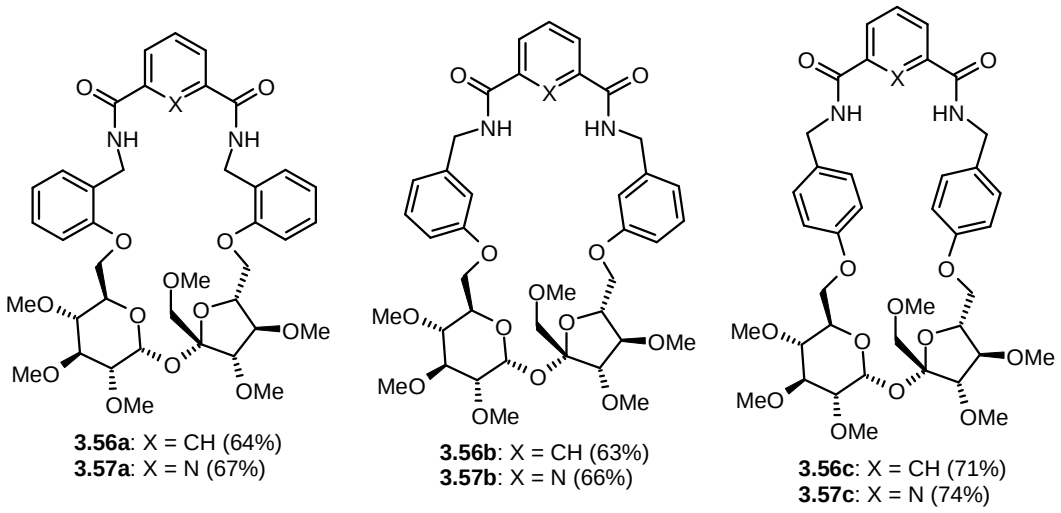


Figure 3.38 Macrocyclic diamides **3.56a–c** and **3.57a–c**.

The conformational mobility (less rigid structure) of the diamine **3.55c**, differing from **3.49c** (which upon reaction with dichlorides **3.50** or **3.44** gave both: the monomers and the dimers; Scheme 3.26) only in the length of the chain, allowed to suppress a formation of the dimer and obtain monomeric macrocycles in good yields.

This strategy was applicable to the synthesis of sucrose-derived macrocycles containing isophthalic and pyridine-2,6-diamide groups.

3.4 Conclusions

My dissertation covers the synthesis and characterization of macrocyclic nitrogen-containing receptors with sucrose scaffold, as well as their application in the enantioselective complexation of chiral amines.

I consider the following achievements as the most significant:

- Elaboration of a convenient methodology for the preparation of building blocks based on sucrose scaffold. Using two methodologies: tritylation/alkylation/detritylation and silylation/alkylation/desilylation, the free sucrose was converted into 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.4**) and 1',2,3,3',4,4'-hexa-*O*-methylsucrose (**3.11**) (Figure 3.39).

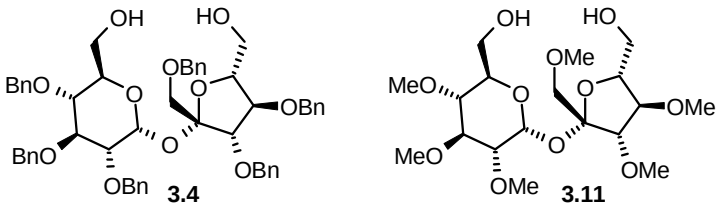
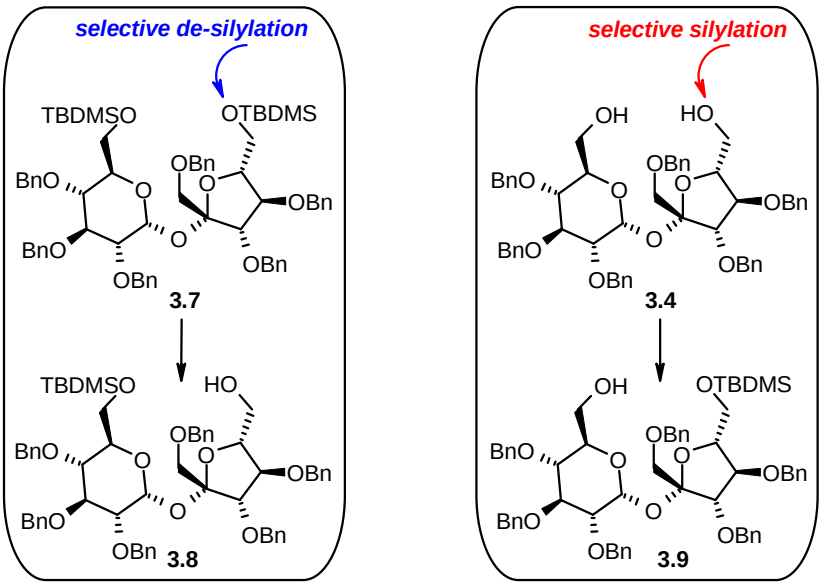


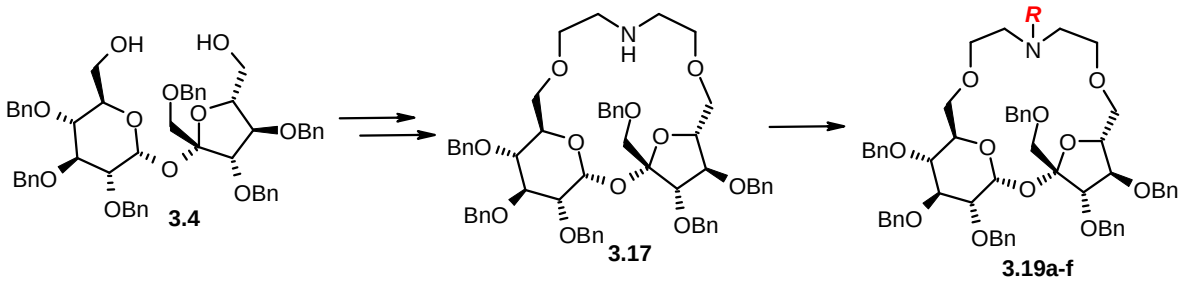
Figure 3.39 Synthesized sucrose diols **3.4** and **3.11**.

- Preparation of the mono-silylated derivatives *via* selective desilylation of compound **3.7** at the C6'-(*fructose* '*end*') position or its selective silylation in compound **3.4** (products **3.8** and **3.9**, respectively; Scheme 3.28).



Scheme 3.28 Preparation of the mono-silylater sucrose derivatives **3.8** and **3.9**.

- Synthesis of the macrocycle **3.17** with a secondary amine functionality which served as a precursor in the synthesis of various *N*-substituted analogues **3.19a–f** (Scheme 3.29).



Scheme 3.29 Synthesized sucrose diols **3.4** and **3.11**.

- Investigation of the complexing properties of the receptors **3.19a–f**. These compounds showed very good enantioselectivity towards the *α*-phenylethylammonium chloride in $CDCl_3$ [much stronger complexes with the *S*-cation were formed]. Macrocycle **3.19f**, which has 2-methoxyethyl-moiety at the ring-nitrogen atom, also exhibited satisfactory enantioselectivity toward amino acid methyl ester hydrochlorides in $CDCl_3$–CD_3OD as well as in DMSO-d_6.
- The design, synthesis, and investigation of the complexing properties of 'unsymmetrical' di-aza-crown ethers with sucrose scaffold (**3.31** and **3.37**; Figure 3.40). The enantioselectivity of the complexation of the (*S*)- and (*R*)-*α*-phenylethylammonium cation strongly depends on the position of the nitrogen atom(s) in the macrocyclic ring. Receptors possessing the oxygen atom at the 'glucose part' (at the C6-position) selectively complex the (*S*)-cation. When the 'glucose' oxygen is replaced by a nitrogen enantioselectivity is low.

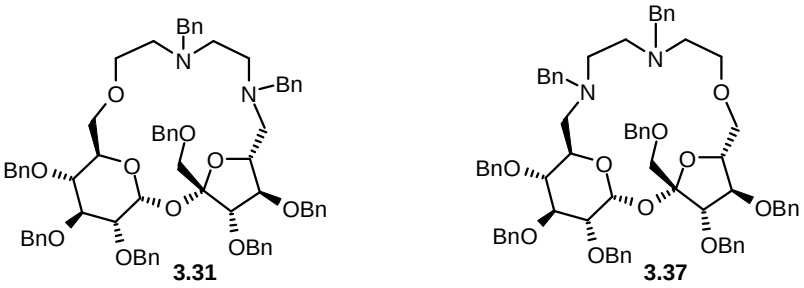


Figure 3.40 Synthesized sucrose-based di-aza-crown ethers **3.31** and **3.37**.

- Simple and efficient synthesis of macrocyclic diamides containing the sucrose subunit (**3.45**, **3.46**, **3.51a–c**, **3.52a–c**, **3.56a–c**, and **3.57a–c**; Figure 3.41). Presence of sucrose and isophthalic or 2,6-pyridinedicarbonate units in these scaffolds makes them promising receptors. It is worth pointing out that the sucrose *p*-diamine **3.49c** upon reaction with an acid dichloride **3.44** and **3.50** afforded only small amounts of the desired monomer; the main products were dimers (with the C_2-symmetry) which could be distinguished by NMR.

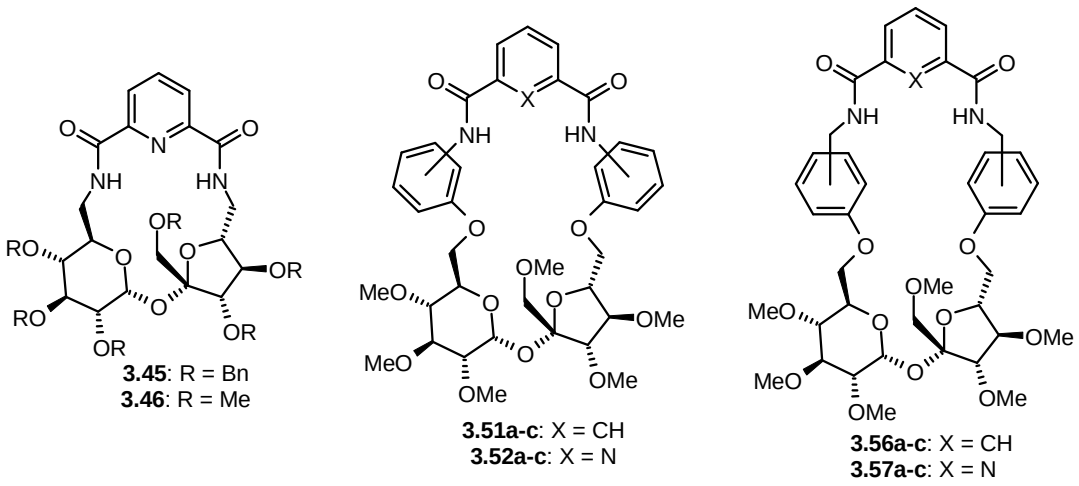


Figure 3.41 Synthesized dilactams **3.45**, **3.46**, **3.51a–c**, **3.52a–c**, **3.56a–c** and **3.57a–c**.

4 Experimental part

4.1 General notes

All reported NMR spectra were recorded with a Varian-Vnmrs-600 MHz spectrometer (at 600 and 150 MHz for ^{1}H and ^{13}C NMR spectra, respectively) or a Varian Mercury 400 MHz spectrometer (at 400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively) for solutions in $CDCl_3$ at room temperature unless otherwise stated. Reported chemical shifts (δ, ppm) were determined relative to TMS as the internal standard. Most of the resonances were assigned by COSY (^{1}H–^{1}H) and gradient selected HSQC and HMBC correlations. IR spectra ($CHCl_3$, film) were recorded with a Perkin Elmer FT-IR Spectrum 2000. Mass spectra were recorded with an ESI/MS Mariner (PerSeptive Biosystem) mass spectrometer. Elemental analyses were obtained using a Perkin-Elmer 2400 CHN analyzer. Optical rotation was measured with a Jasco DIP-360 digital polarimeter; solutions were prepared in $CHCl_3$, CH_2Cl_2, MeOH or DMSO (c = 1). Melting points were measured on Automatic Melting Point Apparatus (EZ-Melt, Stanford Research Systems) and are not corrected. Flash and column chromatographic separations were performed on silica gel (Merck, 230–400 mesh). Reactions progress was controlled by thin layer chromatography (TLC), carried out on commercially available aluminiun plates covered with silica gel (60 F_{254}, Merck). Organic solutions were dried over anhydrous magnesium sulfate.

For identification of sucrose-containing products and interpretation of their NMR spectra a standard numbering convention[241] of carbon and hydrogen atoms in the sucrose molecule is used: the glucose atoms are numbered 1 through 6; whereas the fructose atoms are numbered 1’ through 6’. The atoms of groups attached to the *glucose* or *fructose* ‘*end*’ are numbered with the continuation of series of natural numbers.

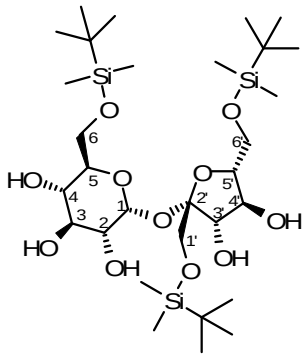
4.2 Synthesis and characterization of obtained compounds

4.2.1 Silylation of sucrose with *tert*-butyldimethylsilyl chloride[207]

Sucrose (17.1 g, 50 mmol) was dissolved in boiling pyridine (500 mL). Upon cooling to rt, a solution of *tert*-butyldimethylsilyl chloride (18.8 g, 125 mmol) in pyridine (100 mL) was added dropwise (during 20 min), and the mixture was stirred for 24 h at rt. Pyridine was evaporated and the products were isolated by flash chromatography (hexanes–ethyl acetate,

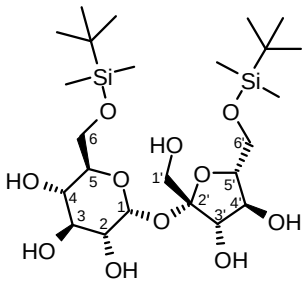
35:65 to 100% ethyl acetate) to afford 1',6,6'-tri-*O*-*tert*-butyldimethylsilylsucrose (3.5, 8.6 g, 25%) and 6,6'-di-*O*-*tert*-butyldimethylsilylsucrose (3.6, 16.9 g, 59%).

4.2.1.1 1',6,6'-Tri-*O*-*tert*-butyldimethylsilylsucrose (3.5)



TLC [(hexanes/AcOEt (1:4)]: R_f = 0.63. White solid, m.p. 108 °C. $[\alpha]_D^{25}$ = +50.4 (MeOH). ^{1}H NMR (600 MHz, CD_3OD): δ = 5.39 (1H, d, $J_{1,2}$ 3.9 Hz, H-1), 4.17 (1H, d, $J_{3',4'}$ 8.7 Hz, H-3'), 3.87–3.92 (2H, m, H-4', H-6'), 3.81–3.86 (3H, m, H-6', 2 × H-6), 3.78 (1H, m, H-5), 3.70 (1H, d, $J_{1',1'}$ 11.2 Hz, H-1'), 3.68 (1H, m, H-5'), 3.66 (1H, d, H-1'), 3.61 (1H, dd, $J_{3,2}$ 9.8 Hz, $J_{3,4}$ 9.0 Hz, H-3), 3.54 (1H, dd, $J_{4,5}$ 9.8 Hz, H-4), 3.32 (1H, dd, H-2), 0.912 (9H, s, ^{t}Bu), 0.909 (9H, s, ^{t}Bu), 0.900 (9H, s, ^{t}Bu), 0.81–0.95 (18H, m, 6 × Me) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ = 105.55(C-2'), 93.25(C-1), 83.86 (C-5'), 77.47 (C-3'), 75.80 (C-4'), 74.98(C-3), 74.26 (C-5), 73.21(C-2), 71.34 (C-4), 65.86 (C-6'), 64.27 (C-1'), 64.00 (C-6), 26.61 (triple intensity, 3C-^{t}Bu), 26.50 (triple intensity, 3C-^{t}Bu), 26.44 (triple intensity, 3C-^{t}Bu), 19.44 (C_{quat}, ^{t}Bu), 19.21 (C_{quat}, ^{t}Bu), 19.18 (C_{quat}, ^{t}Bu), -4.84, -4.93, -4.97, -5.05, -5.22 (6 × *C*H_3-Si) ppm. HRMS (ESI) calcd for $C_{30}H_{64}O_{11}NaSi_3$ $[M+Na]^+$: 707.3649, found: 707.3647. Analysis for $C_{30}H_{64}O_{11}Si_3$ (685.10): Calcd: C, 52.60; H, 9.42. Found: C, 52.51; H, 9.34.

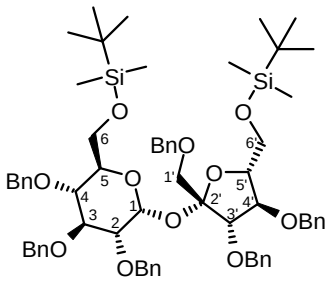
4.2.1.2 6,6'-Di-*O*-*tert*-butyldimethylsilylsucrose (3.6)



TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.45. White solid, m.p. 184 °C. $[\alpha]_D^{20}$ = +53.0 (MeOH). ^{1}H NMR (600 MHz, CD_3OD): δ = 5.47 (1H, d, $J_{1,2}$ 3.8 Hz, H-1), 4.04 (1H, d, $J_{3',4'}$ 8.0 Hz, H-3'), 3.89–3.95 (2H, m, H-4', H-6'), 3.81–3.86 (3H, m, H-6', 2 × H-6), 3.78 (1H, ddd, *J* 9.9 Hz, *J* 3.4 Hz, *J* 3.1 Hz, H-5), 3.72–3.76 (1H, m, H-5'), 3.67 (1H, dd, *J* 9.4 Hz, *J* 9.3 Hz, H-3), 3.59 (1H, d, $J_{1',1'}$ 12.2 Hz, H-1'), 3.58 (1H, d, H-1'), 3.35–3.39 (2H, m, H-2, H-4), 0.91 (9H, s, ^{t}Bu), 0.90 (9H, s, ^{t}Bu), 0.08–0.09 (12H, m, 4 × Me) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ = 105.36 (C-2'), 93.04 (C-1), 83.98 (C-5'), 79.20 (C-3'), 76.42 (C-4'), 74.93 (C-3), 74.35 (C-5), 73.27 (C-2), 71.22 (C-4), 66.04 (C-6'), 64.35 (C-1'), 63.93 (C-6), 26.59 (triple intensity, 3C-^{t}Bu), 26.50 (triple intensity, 3C-^{t}Bu), 19.41 (C_{quat}, ^{t}Bu), 19.23 (C_{quat}, ^{t}Bu), -4.85, -4.89, -4.99, -5.08 (4 × *C*H_3-Si) ppm. HRMS (ESI) calcd for $C_{24}H_{50}O_{11}NaSi_2$ $[M + Na]^+$: 593.2784, found: 593.2800. Analysis for $C_{24}H_{50}O_{11}Si_2$ (570.83): Calcd: C, 50.50; H, 8.83. Found: C, 50.51; H, 8.84.

4.2.2 Preparation of 6,6'-di-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-benzyl-sucrose (3.7)

Sodium hydride (60% dispersion in mineral oil, 6.3 g, 157.5 mmol) was added in portions at 5 °C – 10 °C to a stirred solution of 6,6'-di-*O*-*tert*-butyldimethylsilylsucrose (3.6, 14.27 g, 25 mmol) in DMF (300 mL) and the mixture was stirred at rt for 30 min. Benzyl bromide (19.3 mL, 162.5 mmol) was added dropwise during 15 min. and the mixture was stirred for 24 h at rt. Excess of hydride was decomposed by careful addition of water (20 mL) and the mixture was partitioned between water (300 mL) and ether (200 mL). The layers were separated and the aqueous one extracted with ethyl acetate (3 × 200 mL). Combined organic solutions were washed with water (100 mL) and brine (100 mL), dried, concentrated, and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 98:2) to afford pure product **3.7** (23.1 g, 83%). TLC [hexanes/AcOEt (8:1)]: R_f = 0.45. Colorless oil. $[\alpha]_D^{21}$ = +34.8 ($CHCl_3$). ^{1}H NMR (600 MHz): δ = 7.26–7.38 (30H, m, H-Ar), 5.92 (1H, d, $J_{1,2}$ 3.8 Hz, H-1), 4.93 (1H, d, *J* 10.8 Hz, benzylic H), 4.86 (1H, d, *J* 11.1 Hz, benzylic H), 4.77 (1H, d, *J* 10.8 Hz, benzylic H), 4.74 (1H, d, *J* 11.2 Hz, benzylic H), 4.69 (1H, d, *J* 11.5 Hz, benzylic H), 4.68 (1H, d, *J* 10.8 Hz, benzylic H), 4.64 (3H, d, *J* 11.9 Hz, benzylic H), 4.54 (1H, d, *J* 11.5 Hz, benzylic H), 4.52 (1H, d, *J* 11.2 Hz, benzylic H), 4.48 (1H, d, $J_{3',4'}$ 8.0 Hz, H-3'), 4.46 (1H, d, *J* 12.5 Hz, benzylic H), 4.35 (1H, dd, $J_{4,',5'}$ 7.0 Hz, H-4'), 3.92–3.97 (3H, m, H-3, H-5', H-6'), 3.85–3.91 (2H, m, H-5, H-6'), 3.73 (1H, d, $J_{1',1'}$ 10.8 Hz, H-1'), 3.69 (1H, dd, *J* 9.4 Hz, *J* 9.8 Hz, H-4), 3.59 (1H, dd, $J_{6,6}$ 11.6 Hz, $J_{6,5}$ 2.7 Hz, H-6), 3.56 (1H, d, H-1'), 3.47–3.51 (2H, m, H-2, H-6), 0.92 (9H, s, ^{t}Bu), 0.88 (9H, s, ^{t}Bu), 0.10 (3H, s, SiCH_3), 0.08 (3H, s, SiCH_3), 0.02 (3H, s, SiCH_3), 0.01 (3H, s, SiCH_3) ppm. ^{13}C NMR (150 MHz): δ = 139.01, 139.00, 138.6, 138.5, 138.1, 138.0 (C_{quat}, 6 × Ph), 127.35–128.40 (30C, m, C-Ph), 104.1 (C-2'), 89.2 (C-1), 84.1 (C-3'), 82.1 (C-3), 81.8 (C-4'), 80.7 (C-5'), 80.5 (C-2), 77.3 (C-4), 75.7, 74.7, 73.4, 73.2, 72.8, 72.0 (6 × OCH_2Ph), 71.7 (C-1'), 71.5 (C-5), 63.6 (C-6'), 61.6 (C-6), 26.02 (triple intensity, 3C-^{t}Bu), 25.98 (triple intensity, 3C-^{t}Bu), 18.4 (C_{quat}, ^{t}Bu), 18.3 (C_{quat}, ^{t}Bu), -5.1, -5.2, -5.37, -5.39 (4 × SiCH_3) ppm. HRMS (ESI) calcd for $C_{66}H_{86}O_{11}NaSi_2$ $[M + Na]^+$: 1133.5601, found: 1133.5654. Analysis for $C_{66}H_{86}O_{11}Si_2$ (1111.59): Calcd: C, 71.32; H, 7.80. Found: C, 71.31; H, 7.82.

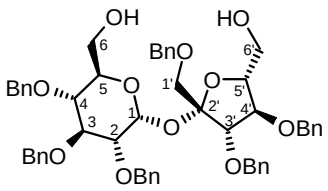


4.2.3 Desilylation of 6,6'-di-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (3.7)

Procedure 1: To a solution of 6,6'-di-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-benzyl-sucrose (**3.7**, 22.2 g, 20.0 mmol) in THF (300 mL) tetrabutylammonium fluoride trihydrate (22.3 g, 80.0 mmol) was added and the mixture was stirred for 12 h at rt. The solvent was then evaporated *in vacuo* and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 85:15 to 60:40) to give 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.4**, 13.8 g, 78%).

Procedure 2: To a solution of compound **3.7** (1.11 g, 1.00 mmol) in THF (20 mL) tetrabutylammonium fluoride trihydrate (0.31 g, 1.10 mmol) was added and the mixture was stirred for 6 h at rt. The solvent was then evaporated *in vacuo* and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 90:10 to 60:40) to give (unreacted) 6,6'-di-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.7**, 0.24 g, 21%), 6-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.8**, 0.57 g, 57%), and 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.4**, 0.15 g, 17%).

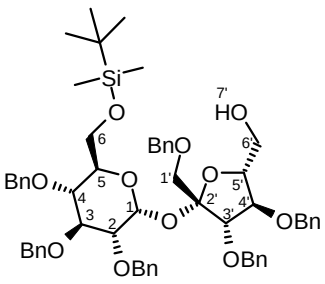
4.2.3.1 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (3.4)



TLC [hexanes/AcOEt (1:1)]: R_f = 0.25. Colorless oil. $[\alpha]_D^{20}$ = +50.2 ($CHCl_3$). ^{1}H NMR (600 MHz): δ = 7.20–7.38 (30H, m, H-Ar), 5.49 (1H, d, $J_{1,2}$ 3.5 Hz, H-1), 4.87 (1H, d, *J* 10.9 Hz, benzylic H), 4.86 (1H, d, *J* 11.1 Hz, benzylic H), 4.76 (1H, d, *J* 11.1 Hz, benzylic H), 4.71 (1H, d, *J* 11.6 Hz, benzylic H), 4.69 (1H, d, *J* 11.6 Hz, benzylic H), 4.67 (1H, d, *J* 12.0 Hz, benzylic H), 4.62 (1H, d, *J* 11.6 Hz, benzylic H), 4.61 (1H, d, *J* 11.1 Hz, benzylic H), 4.57 (1H, d, *J* 11.6 Hz, benzylic H), 4.49 (1H, d, *J* 11.6 Hz, benzylic H), 4.47 (1H, d, *J* 12.1 Hz, benzylic H), 4.42 (1H, d, $J_{3',4'}$ 7.6 Hz, H-3'), 4.32 (1H, d, *J* 12.0 Hz, benzylic H), 4.33 (1H, dd, $J_{4',5'}$ 7.9 Hz, H-4'), 4.15 (1H, ddd, *J* 1.9 Hz, $J_{5,6}$ 5.3 Hz, $J_{5,4}$ 10.2 Hz, H-5), 3.99 (1H, dd, $J_{3,4}$ 9.3 Hz, $J_{3,2}$ 9.5 Hz, H-3), 3.96 (1H, dt, $J_{5',6'}$ 2.5 Hz, H-5'), 3.83 (1H, dd, $J_{6',6'}$ 11.1 Hz, H-6'), 3.81 (1H, dd, $J_{6,6}$ 12.3 Hz, H-6), 3.63 (1H, dd, H-6), 3.59 (1H, dd, H-6'), 3.57 (1H, d, $J_{1',1'}$ 11.1 Hz, H-1'), 3.50 (1H, dd, H-2), 3.45 (1H, d, H-1'), 3.43 (1H, dd, H-4) ppm. ^{13}C NMR (150 MHz): δ = 138.6, 138.3, 138.13, 138.11, 138.0, 137.7 (C_{quat}, 6 × Ph), 127.50–128.45 (30C, m, C-Ph), 103.9 (C-2'), 90.7 (C-1), 83.5 (C-3'), 81.7 (C-3), 81.0 (C-5'), 79.9 (C-4'), 79.5 (C-2), 77.6 (C-4), 75.6, 75.0, 73.4, 73.3, 73.1, 72.5 (6 × O*C*H_2Ph), 73.0 (C-5), 71.3 (C-1'), 61.9 (C-6), 61.0 (C-6') ppm. HRMS (ESI) calcd for $C_{54}H_{58}O_{11}Na$ [M

+ Na]$^+$: 905.3871, found: 905.3853. Analysis for $C_{54}H_{58}O_{11}$ (883.06): Calcd: C, 73.45; H, 6.62. Found: C, 73.42; H, 6.51.

4.2.3.2 6-*O*-*Tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (3.8)

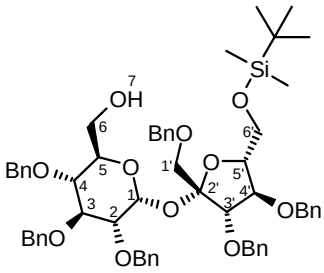


TLC [hexanes/AcOEt (4:1)]: R_f = 0.30. Colorless oil. $[\alpha]_D^{17}$ = +50.0 ($CHCl_3$). ^{1}H NMR (600 MHz): δ = 7.18–7.38 (30H, m, ArH), 5.47 (1H, d, $J_{1,2}$ 3.2 Hz, H-1), 4.83 (1H, d, *J* 11.4 Hz, benzylic H), 4.68 (1H, d, *J* 11.5 Hz, benzylic H), 4.67 (1H, d, *J* 12.0 Hz, benzylic H), 4.66 (1H, d, *J* 11.7 Hz, benzylic H), 4.59 (1H, d, *J* 12.0 Hz, benzylic H), 4.57 (1H, d, *J* 11.5 Hz, benzylic H), 4.56 (1H, d, *J* 12.0 Hz, benzylic H), 4.50 (1H, d, *J* 11.4 Hz, benzylic H), 4.46 (1H, d, *J* 11.5 Hz, benzylic H), 4.45 (1H, d, $J_{3',4'}$ 8.0 Hz, H-3'), 4.38 (1H, d, *J* 12.0 Hz, benzylic H), 4.37 (1H, d, *J* 12.2 Hz, benzylic H), 4.34 (1H, dd, $J_{4',5'}$ 8.0 Hz, H-4'), 4.21 (1H, d, *J* 12.0 Hz, benzylic H), 4.07–4.10 (2H, m, H-3, H-5), 3.98 (1H, m, H-5'), 3.83 (1H, m, H-6'), 3.72 (1H, dd, $J_{6,6}$ 11.0 Hz, $J_{6,5}$ 2.8 Hz, H-6), 3.61 (1H, m, H-6'), 3.54–3.60 (3H, m, H-6, H-1',H-4), 3.40 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.36 (1H, dd, $J_{2,3}$ 9.5 Hz, H-2), 3.26 (1H, dd, $J_{7',6'}$ 10,7 Hz, $J_{7',6'}$ 2.4 Hz, H-7'), 0.92 (9H, s, ^{t}Bu), 0.04 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3) ppm. ^{13}C NMR (150 MHz): δ = 138.47, 138.17, 138.09, 138.05, 137.87, 137.80 (C_{quat}, 6 × Ph), 127.22–128.30 (30C, m, C-Ph), 103.63 (C-2'), 91.00 (C-1), 83.52 (C-3'), 81.17 (C-5'), 79.93 (C-2), 79.38 (C-4'), 78.58 (C-4), 74.72, 73.57, 73.56, 73.11, 72.81, 72.41 (6 × OCH_2Ph), 73.47 (C-3), 71.64 (C-1'), 71.51 (C-5), 68.13 (C-6), 61.06 (C-6'), 26.03 (triple intensity, 3C-^{t}Bu), 18.01 (C_{quat}, ^{t}Bu), -4.13, -4.30 (2 × CH_3-Si) ppm. HRMS (ESI) calcd for $C_{60}H_{72}O_{11}NaSi$ [M + Na]$^+$: 1019.4736, found: 1019.4741. Analysis for $C_{60}H_{72}O_{11}Si$ (997.32): Calcd: C, 72.26; H, 7.28. Found: C, 72.22; H, 7.17.

4.2.4 Selective silylation of 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (3.4)

To a solution of 1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.4**, 4.42 g, 5.0 mmol), DMAP (0.05 g, 0.4 mmol), and triethylamine (2.8 mL, 20 mmol) in CH_2Cl_2 (100 mL), a solution of *tert*-butyldimethylsilyl chloride (0.83 g, 5.5 mmol) in CH_2Cl_2 (15 mL) was added over 180 min, and the mixture was stirred for 24 h at rt. The solvent was then evaporated and the resulting mixture was separated by flash chromatography (hexanes–ethyl acetate, 90:10 to 70:30) to afford 6,6'-di-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.7**, 0.72 g, 13%), 6'-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.9**, 2.81 g, 56%) and unreacted diol **3.4** (1.1 g, 25%).

4.2.4.1 6'-*O*-*Tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (3.9)



TLC [hexanes/AcOEt (4:1)]: R_f = 0.35. Colorless oil. $[\alpha]_D^{22}$ = +40.3 (CH_2Cl_2). ^{1}H NMR (600 MHz): δ = 7.24–7.36 (30H, m ArH), 5.97 (1H, d, $J_{1,2}$ 3.8 Hz, H-1), 4.94 (1H, d, *J* 10.8 Hz, benzylic H), 4.87 (1H, d, *J* 11.1 Hz, benzylic H), 4.76 (1H, d, *J* 10.8 Hz, benzylic H), 4.72 (1H, d, *J* 11.1 Hz, benzylic H), 4.70 (1H, d, *J* 11.4 Hz, benzylic H), 4.62 (1H, d, *J* 11.5 Hz, benzylic H), 4.61 (2H, d, *J* 11.7 Hz, benzylic H), 4.58 (1H, d, *J* 11.5 Hz, benzylic H), 4.52 (1H, d, *J* 11.4 Hz, benzylic H), 4.51 (1H, d, *J* 11.0 Hz, benzylic H), 4.48 (1H, d, *J* 11.0 Hz, benzylic H), 4.46 (1H, d, $J_{3',4'}$ 7.6 Hz, H-3'), 4.37 (1H, dd, $J_{4',5'}$ 7.3 Hz, H-4'), 4.03 (1H, m, H-5), 3.89–3.97 (3H, m, H-3, H-5', H-6'), 3.82 (1H, dd, $J_{6',6'}$ 10.7 Hz, $J_{6',5'}$ 3.6 Hz, H-6'), 3.68 (1H, d, $J_{1',1'}$ 10.8 Hz, H-1'), 3.64 (1H, m, H-6), 3.54 (1H, d, H-1'), 3.51 (1H, dd, $J_{2,3}$ 9.6 Hz, H-2), 3.44–3.50 (2H, m, H-6, H-4), 1.96 (1H, m, H-7), 0.90 (9H, s, ^{t}Bu), 0.07 (3H, s, SiCH_3), 0.06 (3H, s, SiCH_3) ppm. ^{13}C NMR (150 MHz): δ = 138.91, 138.41, 138.37, 138.22, 137.89, 137.78 (C_{quat}, 6 × Ph), 127.48–128.38 (30C, m, C-Ph), 104.29 (C-2'), 88.66 (C-1), 83.61 (C-3'), 81.93 (C-3), 80.81 (C-4'), 80.67 (C-5'), 80.12 (C-2), 77.80 (C-4), 75.61, 74.94, 73.47, 73.09, 72.64, 71.85 (6 × O*C*H_2Ph), 72.00 (C-1'), 71.23 (C-5), 62.96 (C-6'), 62.06 (C-6), 25.91 (triple intensity, 3C-^{t}Bu), 18.38 (C_{quat}, ^{t}Bu), -5.37, -5.40 (2 × *C*H_3-Si) ppm. HRMS (ESI) calcd for $C_{60}H_{72}O_{11}NaSi$ $[M + Na]^+$: 1019.4736, found: 1019.4747. Analysis for $C_{60}H_{72}O_{11}Si$ (997.32): Calcd: C, 72.26; H, 7.28. Found: C, 72.06; H, 7.20.

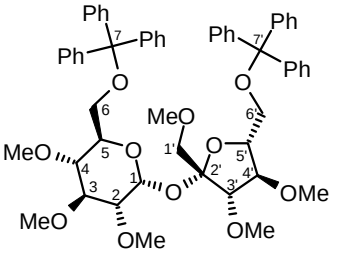
6,6'-Di-*O*-tritylsucrose (3.2) was prepared according to the literature procedure.[163]

4.2.5 Methylation procedure[207]

Sodium hydride (60% dispersion in mineral oil, 0.70 g, 17.5 mmol) was added in portions at 5 °C – 10 °C to a stirred solution of 6,6'-di-*O*-tritylsucrose (3.2, 2.07 g, 2.5 mmol) or 6,6'-di-*O*-*tert*-butyldimethylsilylsucrose (3.6, 1.43 g, 2.5 mmol) in DMF (30 mL) and the mixture was stirred at rt for 30 min. Methyl iodide (1.1 mL, 17.5 mmol) was added dropwise, and the mixture was stirred for 24 h at rt. Excess of hydride was decomposed by careful addition of water (5 mL) and the mixture was partitioned between water (40 mL) and ether (50 mL). The layers were separated and the aqueous one extracted with ethyl acetate (3 × 50 mL). Combined organic solutions were washed with water (40 mL) and brine (30 mL), dried, concentrated, and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 90:10) to afford pure 1',2,3,3',4,4'-hexa-*O*-methyl-6,6'-di-*O*-*trityl*sucrose (**3.10**,

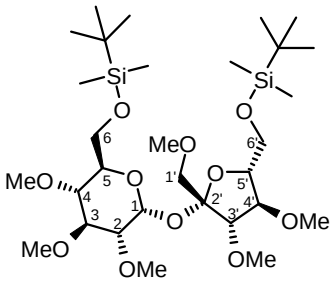
2.08 g, 2.3 mmol, 91%) or 6,6'-di-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-methyl-sucrose (**3.12**, 1.56 g, 2.4 mmol, 95%).

4.2.5.1 1',2,3,3',4,4'-Hexa-*O*-methyl-6,6'-di-*O*-*trityl*sucrose (3.10)



TLC [hexanes/AcOEt (3:1)]: R_f = 0.31. White solid, m.p. 80 °C. $[\alpha]_D^{22}$ = +33.1 (CH_2Cl_2). ^{1}H NMR (600 MHz): δ = 7.51–7.55 (6H, m, 6H-Ph), 7.45–7.49 (6H, m, 6H-Ph), 7.25–7.30 (6H, m, 6H-Ph), 7.21–7.25 (6H, m, 6H-Ph), 7.15–7.20 (6H, m, 6H-Ph), 5.97 (1H, d, $J_{1,2}$ 3.8 Hz, H-1), 4.29 (1H, dd, $J_{4',3'}$ 8.7 Hz, $J_{4',5'}$ 8.7 Hz, H-4'), 3.99 (1H, d, H-3'), 3.94 (1H, m, H-5), 3.78 (1H, m, H-5'), 3.62 (1H, dd, $J_{4,3}$ 9.2 Hz, $J_{4,5}$ 10.0 Hz, H-4), 3.59 (3H, s, 3H-CH_3), 3.40–3.51 (5H, m, 2H-1', H-6, 2H-6'), 3.39 (3H, s, 3H-CH_3), 3.38 (3H, s, 3H-CH_3), 3.37 (1H, dd, $J_{3,2}$ 9.7 Hz, H-3), 3.33 (3H, s, 3H-CH_3), 3.25 (3H, s, 3H-CH_3), 3.20 (3H, s, 3H-CH_3), 3.16 (1H, m, H-6), 3.08 (1H, dd, H-2) ppm. ^{13}C NMR (150 MHz): δ = 144.13 (3C_{quat}-Ph), 143.64 (3C_{quat}-Ph), 128.87 (6C-Ph), 128.78 (6C-Ph), 127.84 (6C-Ph), 127.65 (6C-Ph), 127.03 (3C-Ph), 126.81 (3C-Ph), 103.74 (C-2'), 87.99 (C-1), 86.92 (C-7'), 86.00 (C-7), 85.20 (C-3'), 83.59 (C-3), 81.32 (C-2), 80.74 (C-4'), 79.73 (C-4), 78.53 (C-5'), 75.78 (C-1'), 70.62 (C-5), 62.68 (C-6'), 62.00 (C-6), 60.82, 60.38, 59.48, 58.59, 58.21, 57.65 (6 × O*C*H_3) ppm. HRMS (ESI) calcd for $C_{56}H_{62}O_{11}Na$ $[M + Na]^+$: 933.4184, found: 933.4198. Analysis for $C_{56}H_{62}O_{11}$ (911.11): Calcd: C, 73.82; H, 6.86. Found: C, 73.61; H, 6.97.

4.2.5.2 6,6'-Di-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.12)



TLC [hexanes/AcOEt (2:1)]: R_f = 0.52. Colorless oil. $[\alpha]_D^{22}$ = +47.9 (CH_2Cl_2). ^{1}H NMR (600 MHz): δ = 5.73 (1H, d, $J_{1,2}$ 3.8 Hz, H-1), 4.02 (1H, d, $J_{3',4'}$ 8.0 Hz, H-3'), 3.99 (1H, dd, $J_{4',5'}$ 7.4Hz, H-4'), 3.85–3.89 (2H, m, H-6, H-6'), 3.78 (1H, dd, $J_{6',5'}$ 4.2 Hz, $J_{6',6'}$ 11.0 Hz, H-6'), 3.72–3.77 (3H, m, H-5, H-5', H-6), 3.63 (3H, s, 3H-CH_3), 3.57 (3H, s, 3H-CH_3), 3.54 (1H, d, $J_{1',1'}$ 10.8 Hz, H-1'), 3.46 (3H, s, 3H-CH_3), 3.44 (3H, s, 3H-CH_3), 3.43 (3H, s, 3H-CH_3), 3.42 (1H, m, H-3), 3.42 (1H, d, H-1'), 3.41 (3H, s, 3H-CH_3), 3.30 (1H, dd, $J_{4,3}$ 9.5 Hz, $J_{4,5}$ 9.4 Hz, H-4), 3.07 (1H, dd, $J_{2,3}$ 9.6 Hz, H-2), 0.902 (9H, s, ^{t}Bu), 0.896 (9H, s, ^{t}Bu), 0.075 (3H, s, CH_3Si), 0.067 (3H, s, CH_3Si), 0.065 (3H, s, CH_3Si), 0.060 (3H, s, CH_3Si) ppm. ^{13}C NMR (150 MHz): δ = 103.65 (C-2'), 88.44 (C-1), 85.40 (C-3'), 83.32 (C-3), 82.66 (C-4'), 81.54 (C-2), 80.44 (C-5'), 78.82 (C-4), 74.77 (C-1'), 71.35 (C-5), 63.41 (C-6'), 61.66 (C-6), 60.69, 60.24, 59.45, 58.60,

58.43, 57.66 (6 × O*C*H$_3$), 25.94 (triple intensity, 3C-^{t}Bu), 25.94 (triple intensity, 3C-^{t}Bu), 18.37 (C$_{quat}$, ^{t}Bu), 18.32 (C$_{quat}$, ^{t}Bu), –5.16, –5.35, –5.45, –5.48 (4 × Si*C*H$_3$) ppm. HRMS (ESI) calcd for $C_{30}H_{62}O_{11}NaSi_2$ $[M + Na]^+$: 677.3723, found: 677.3726. Analysis for $C_{30}H_{62}O_{11}Si_2$ (654.99): Calcd: C, 55.01; H, 9.54. Found: C, 55.11; H, 9.62.

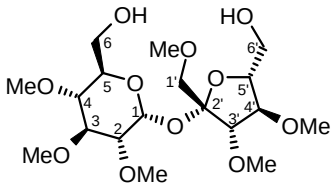
4.2.6 Preparation of 1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.11)[207]

Route a

To a solution of 1',2,3,3',4,4'-hexa-*O*-methyl-6,6'-di-*O*-tritylsucrose (**3.10**, 1.82 g, 2.0 mmol) in dry THF (25 mL) and liquid NH_3 (30 mL) at –78 °C small pieces of Na (0.14 g, 6.0 mmol) were added over 20 min and the dark blue solution was stirred for 2h at –78 °C. Excess of Na was decomposed by addition of NH_4Cl (0.2 g, 3.7 mmol) and the mixture was allowed to reach room temperature. Ethyl acetate (40 mL) and water (50 mL) were added, the layers were separated, and the aqueous one extracted with ethyl acetate (5 × 70 mL). Combined organic solutions were dried and concentrated, and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 40:60 to 0:100) to afford pure compound **3.11** (0.63 g, 1.4 mmol, 74%).

Route b

6,6'-Di-*O*-*tert*-butyldimethylsilyl-1',2,3,3',4,4'-hexa-*O*-methylsucrose (**3.12**, 655 mg, 1.0 mmol) was dissolved in THF (20 mL). Tetrabutylammonium fluoride trihydrate (837 mg, 3.0 mmol) was added and the mixture was stirred for 3 h. The solvent was then evaporated *in vacuo* and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 40:60 to 0:100) to give the title compound (406 mg, 0.9 mmol, 95%).



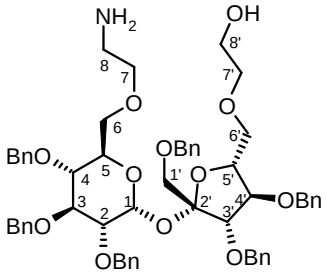
TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.55. Colorless oil. $[\alpha]_D^{22}$ = +62.8 (CH_2Cl_2) {lit.$[\alpha]_D^{22}$ = +61.7 (acetone)}[198]. ^{1}H NMR (600 MHz): δ = 5.46 (1H, d, *J* 3.7 Hz, H-1), 4.05 (1H, d, $J_{3',4'}$ 7.7 Hz, H-3'), 4.02 (1H, dd, $J_{4',5'}$ 7.6 Hz, H-4'), 3.98 (1H, ddd, $J_{5,4}$ 10.2 Hz, $J_{5,6}$ 2.0 Hz, $J_{5,6}$ 1.9 Hz, H-5), 3.83–3.89 (3H, m, H-5', H-6, H-6'), 3.58–3.71 (2H, m, H-6, H-6'), 3.62 (3H, s, 3H-CH_3), 3.55 (3H, s, 3H-CH_3), 3.54 (1H, d, $J_{1',1'}$ 10.8 Hz, H-1'), 3.503 (3H, s, 3H-CH_3), 3.497 (3H, s, 3H-CH_3), 3.493 (3H, s, 3H-CH_3), 3.47 (1H, dd, H-3), 3.42 (3H, s, 3H-CH_3), 3.38 (1H, d, H-1'), 3.11 (1H, dd, $J_{2,3}$ 9.7 Hz, H-2), 3.04 (1H, dd, $J_{4,3}$ 9.1 Hz, H-4) ppm. ^{13}C NMR (150 MHz): δ = 103.41 (C-2'), 89.94 (C-1), 85.10 (C-3'), 83.00 (C-3), 81.44 (C-2), 80.88 (C-4'), 80.83 (C-5'), 79.65 (C-4), 74.33 (C-1'), 72.84 (C-5), 61.85 (C-6), 61.00 (C-6'), 60.66, 60.46, 59.44, 59.11, 58.71, 58.39 (6 × O*C*H$_3$) ppm. HRMS

(ESI) calcd for $C_{18}H_{34}O_{11}Na$ $[M + Na]^+$: 449.1993, found: 449.2012. Analysis for $C_{18}H_{34}O_{11} + H_2O$ (444.49): Calcd: C, 48.64; H, 8.16. Found: C, 48.79; H, 8.09.

1',2,3,3',4,4'-Hexa-*O*-benzyl-6-*O*-cyanomethylsucrose (3.13)[207] and **1',2,3,3',4,4'-hexa-*O*-benzyl-6'-*O*-(2-*tert*-butoxy-2-oxoethyl)-6-*O*-cyanomethylsucrose (3.14)**[209] were prepared according to the literature procedure.

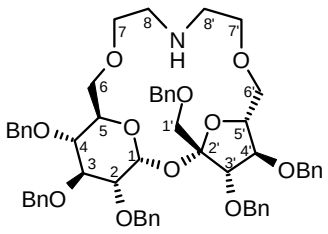
4.2.7 Synthesis of 6-*O*-(2-aminoethyl)-1',2,3,3',4,4'-hexa-*O*-benzyl-6'-*O*-(2-hydroxyethyl)-sucrose (3.15)[209]

This reaction was conducted under an argon atmosphere. To a solution of compound **3.14** (2.053 g, 1.98 mmol) in dry THF (200 mL) $LiAlH_4$ (0.602 g, 15.85 mmol) was added slowly at –78 °C. After 15 min, the mixture was allowed to reach room temperature and then stirred for 10 h. Excess of hydride was carefully decomposed with water (50 mL) and aqueous sat. potassium bisulfate ($KHSO_4$, 100 mL). Ethyl acetate (300 mL) was added, the layers were separated, and the aqueous one extracted with ethyl acetate (3 × 150 mL). Combined organic solutions were dried, concentrated, and the resulting residue was purified by flash chromatography (dichloromethane–methanol, 91:9) to afford pure compound **3.15** (1.692 g, 1.74 mmol, 88%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.12. Yellowish oil. $[\alpha]_D$ = +54.0 ($CHCl_3$). ^{1}H NMR (600 MHz): δ = 7.40–7.37 (30H, m H-Ar), 5.92 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.92 (1H, d, *J* 11.0 Hz, benzylic H), 4.82 (1H, d, *J* 11.2 Hz, benzylic H), 4.75 (1H, d, *J* 11.0 Hz, benzylic H), 4.71 (1H, d, *J* 11.9 Hz, benzylic H), 4.65 (1H, d, *J* 11.7 Hz, benzylic H), 4.64 (1H, d, *J* 11.3 Hz, benzylic H), 4.63 (1H, d, *J* 12.1 Hz, benzylic H), 4.61 (1H, d, *J* 12.1 Hz, benzylic H), 4.59 (1H, d, *J* 11.7 Hz, benzylic H), 4.52 (1H, d, *J* 11.2 Hz, benzylic H), 4.47 (1H, d, *J* 11.3 Hz, benzylic H), 4.46 (1H, d, *J* 11.9 Hz, benzylic H), 4.45 (1H, d, $J_{3',4'}$ 8.1 Hz, H-3'), 4.39 (1H, dd, $J_{4',5'}$ 8.1 Hz, H-4'), 4.07 (1H, m H-5), 3.99 (1H, m, H-5'), 3.92 (1H, dd, $J_{3,2}$ 9.3 Hz, $J_{3,4}$ 9.2 Hz, H-3), 3.78 (1H, dd, $J_{6',6'}$ 11.0 Hz, $J_{6',5'}$ 2.7 Hz, H-6'), 3.69 (1H, d, $J_{1',1'}$ 10.8 Hz, H-1'), 3.60 (1H, dd, $J_{6',5'}$ 4.2 Hz, H-6'), 3.56 (1H, d, H-1'), 3.50–3.55 (2H, m, H-4, H-8'), 3.42–3.49 (4H, m, 2H-7', H-8', H-2), 3.38 (1H, m, H-7), 3.28–3.33 (2H, m, 2H-6), 3.27 (1H, m, H-7), 2.78–2.88 (2H, m, 2H-8) ppm. ^{13}C NMR (150 MHz): δ = 138.97, 138.57, 138.20, 138.14, 138.06, 137.86 (C_{quat}, 6 × Ph), 127.40–128.45 (30C, m, C-Ph), 104.09 (C-2'), 88.76 (C-1), 83.66 (C-3'), 81.81 (C-3), 80.26 (C-4'), 79.40 (C-2), 78.96 (C-5'), 77.37 (C-4), 75.28, 74.69, 73.39, 72.77, 72.60, 72.20 (6 × O*C*H_2Ph), 72.50 (C-7'), 72.16 (C-1'), 71.06 (C-7), 70.56 (C-5), 70.04 (C-6'), 69.11 (C-6), 61.35 (C-8'), 40.94 (C-8) ppm. HRMS (ESI) calcd for



$C_{58}H_{68}O_{12}$ $[M + H]^+$: 970.4736, found: 970.4715. Anal. for $C_{58}H_{67}NO_{12} \cdot H_2O$ (988.17): Calcd: C, 70.50; H, 7.04; N, 1.42. Found: C, 70.37; H, 7.10; N, 1.37.

4.2.8 Synthesis of 6,6'-(3-azapenta-1,5-di-yl)-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (3.17). General procedure for intramolecular tandem iodation/macrocyclization of amino alcohols.[209]

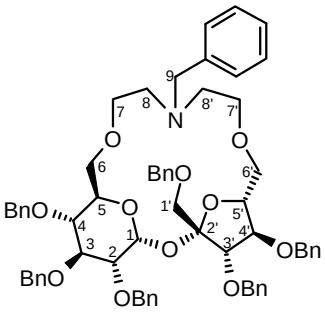


Compound **3.15** (1.550 g, 1.60 mmol) in toluene (300 mL) was refluxed with PPh_3 (0.503 g, 1.92 mmol) for 10 min and cooled to 80 °C. Imidazole (0.544 g, 7.99 mmol) was added, followed by slow addition (during 10 min) of a solution of iodine (0.527 g, 2.08 mmol) in toluene (50 mL), and the mixture was boiled under reflux for 4 h. Then it was concentrated and the residue was taken up in ethyl acetate (300 mL). The organic phase was washed with saturated aqueous $Na_2S_2O_3$ and water, dried, concentrated, and the resulting residue was purified by column chromatography (ethyl acetate, then ethyl acetate–methanol, 10:1) to afford the macrocycle **3.17** (1.205 g, 1.27 mmol, 79%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.29. Yellowish oil. $[\alpha]_D^{23}$ = +38.9 ($CHCl_3$). ^{1}H NMR (600 MHz): δ = 7.16–7.40 (30H, m, H-Ar), 5.83 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.92 (1H, d, *J* 10.9 Hz, benzylic H), 4.87 (1H, d, *J* 11.9 Hz, benzylic H), 4.81 (1H, d, *J* 11.9 Hz, benzylic H), 4.81 (1H, d, *J* 11.3 Hz, benzylic H), 4.77 (1H, d, *J* 10.9 Hz, benzylic H), 4.69 (1H, d, *J* 11.7 Hz, benzylic H), 4.64 (1H, d, *J* 12.1 Hz, benzylic H), 4.63 (1H, d, *J* 11.7 Hz, benzylic H), 4.62 (1H, d, *J* 11.0 Hz, benzylic H), 4.53 (1H, d, *J* 11.3 Hz, benzylic H), 4.50 (1H, d, $J_{3',4'}$ 8.1 Hz, H-3'), 4.48 (1H, d, *J* 12.1 Hz, benzylic H), 4.43 (1H, d, *J* 11.0 Hz, benzylic H), 4.34 (1H, dd, $J_{4',5'}$ 8.6 Hz, H-4'), 4.23 (1H, ddd, $J_{5,4}$ 10.1 Hz, $J_{5,6}$ 2.8 Hz, $J_{5,6}$ 1.6 Hz, H-5), 3.92–3.99 (3H, m, H-5', H-7, H-6'), 3.90 (1H, dd, $J_{3,2}$ 9.7 Hz, $J_{3,4}$ 8.9 Hz, H-3), 3.86 (1H, m, H-7'), 3.70 (1H, dd, $J_{6,6}$ 11.7 Hz, $J_{6,5}$ 2.8 Hz, H-6), 3.61–3.69 (2H, m, H-7', H-7), 3.60 (1H, d, $J_{1',1'}$ 10.7 Hz, H-1'), 3.51–3.59 (3H, m, H-6', H-1', H-4), 3.42 (1H, dd, H-2), 3.16 (1H, dd, H-6), 2.92–2.97 (2H, m, H-8, H-8'), 2.86 (1H, m, H-8'), 2.79 (1H, m, H-8) ppm. ^{13}C NMR (150 MHz): δ = 138.81, 138.55, 138.52, 138.04, 137.85, 137.66 (C_{quat}, 6 × OCH_2Ph), 127.35–128.40 (30C, m, C-Ph), 103.63 (C-2'), 88.28 (C-1), 84.02 (C-3'), 81.30 (C-3), 79.12 (C-2), 78.79 (C-5'), 78.69 (C-4'), 77.27 (C-4), 75.31, 74.61, 73.41, 72.74, 72.55, 72.46 (6 × O*C*H_2Ph), 73.44 (C-1'), 71.50 (C-5), 71.06 (C-6), 68.62 (C-6'), 67.20 (C-7), 65.30 (C-7'), 49.18 (C-8), 47.59 (C-8') ppm. HRMS (ESI) calcd for $C_{58}H_{65}NO_{11}Na$ $[M + Na]^+$: 974.4450, found: 974.4463. Anal. for $C_{58}H_{65}NO_{11}$ (952.16): Calcd: C, 73.16; H, 6.88; N, 1.47. Found: C, 73.38; H, 6.73; N, 1.32.

4.2.9 General procedure for the synthesis of compounds 3.19 a–f[209]

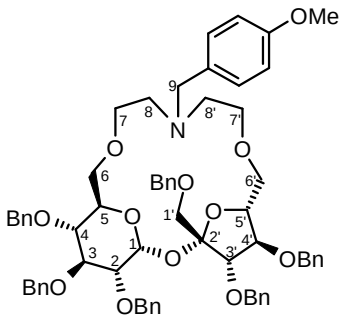
To a solution of compound **3.17** (190 mg, 0.20 mmol) in dry DMF (15 mL), K_2CO_3 was added (56 mg, 0.40 mmol) followed by the corresponding alkyl halide **3.18** (0.40 mmol). The mixture was stirred for 4 h at 100°C and cooled to rt. Water (50 mL) and AcOEt (50 mL) were added, phases were separated and the aqueous one extracted with AcOEt (4 × 50 mL). Combined organic solutions were washed with water (2 × 30 mL), brine (30 mL), dried, concentrated, and the resulting residue was purified by column chromatography (hexanes–ethyl acetate, 1:1 to 0:1) to afford pure macrocycle **3.19 a–f**.

4.2.9.1 6,6'-(3-Azabenzylpenta-1,5-di-yl)-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (3.19a)



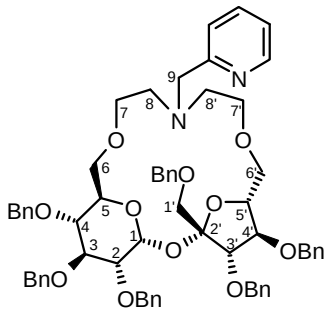
Yield: 152 mg (0.15 mmol, 73%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.71. Yellowish oil. $[\alpha]_D^{22}$ = +28.1 ($CHCl_3$). ^{1}H NMR (600 MHz): δ = 7.15–7.35 (35H, m H-Ar), 5.43 (1H, d, $J_{1,2}$ 3.2 Hz, H-1), 4.87 (1H, d, *J* 11.1 Hz, benzylic H), 4.86 (1H, d, *J* 10.9 Hz, benzylic H), 4.71 (1H, d, *J* 10.9 Hz, benzylic H), 4.70 (1H, d, *J* 11.6 Hz, benzylic H), 4.69 (1H, d, *J* 12.0 Hz, benzylic H), 4.67 (1H, d, *J* 11.1 Hz, benzylic H), 4.65 (1H, d, *J* 11.6 Hz, benzylic H), 4.62 (1H, d, *J* 11.5 Hz, benzylic H), 4.52 (2H, d, *J* 11.5 Hz, benzylic H), 4.44 (1H, d, *J* 12.0 Hz, benzylic H), 4.43 (1H, d, $J_{3',4'}$ 7.2 Hz, H-3'), 4.25 (1H, d, *J* 11.8 Hz, benzylic H), 4.23 (1H, m, H-5), 4.19 (1H, dd, $J_{4',5'}$ 7.2 Hz, H-4'), 4.04–4.09 (2H, m, H-3, H-5'), 3.91 (1H, dd, $J_{5',6'}$ 6.5 Hz, $J_{6',6'}$ 10.0 Hz, H-6'), 3.81 (1H, dd, $J_{5',6'}$ 5.9 Hz, H-6'), 3.65–3.72 (2H, m, H-6, H-7'), 3.60–3.64 (2H, m, H-1', H-7'), 3.59 (2H, s, 2H-9), 3.44–3.52 (4H, m, H-2, H-1', 2H-7), 3.42 (1H, ddd, $J_{5,6}$ 7.9 Hz, $J_{5,6}$ 8.0 Hz, $J_{6,6}$ 10.3 Hz, H-6), 3.20 (1H, dd, *J* 9.1 Hz, *J* 9.4 Hz, H-4), 2.88 (1H, m, H-8'), 2.65–2.78 (3H, m, 2H-8, H-8') ppm. ^{13}C NMR (150 MHz): δ = 139.47, 138.76, 138.65, 138.55, 138.24, 138.03, 137.96 (C_{quat}, 7 × Ph), 126.80–128.85 (35C, m, C-Ph), 104.13 (C-2'), 90.09 (C-1), 84.91 (C-4'), 83.65 (C-3'), 81.63 (C-3), 79.99 (C-5'), 79.95 (C-2), 79.45 (C-4), 75.46, 74.79, 73.45, 73.15, 72.74, 72.14 (6 × O*C*H_2Ph), 72.19 (C-6'), 71.70 (C-6), 71.03 (C-1'), 70.93 (C-5), 70.72 (C-7), 69.06 (C-7'), 60.37 (C-9), 53.51 (C-8'), 53.15 (C-8) ppm. HRMS (ESI) calcd for $C_{65}H_{72}NO_{11}$ $[M + H]^+$: 1042.5099, found: 1042.5077. Analysis for $C_{65}H_{71}NO_{11}$ (1042.29): Calcd: C, 74.90; H, 6.87; N, 1.34. Found: C, 74.87; H, 6.79; N, 1.38.

4.2.9.2 6,6'-[3-Aza(4-methoxybenzyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (3.19b)



Yield: 165 mg (0.15 mmol, 77%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.48. Yellowish oil. $[\alpha]_D^{19}$ = +17.3 ($CHCl_3$). ^{1}H NMR (600 MHz): δ = 7.18–7.35 (32H, m ArH), 6.78 (2H, d, *J* 8.7 Hz, H-Ar), 5.44 (1H, d, $J_{1,2}$ 3.1 Hz, H-1), 4.87 (1H, d, *J* 11.2 Hz, benzylic H), 4.86 (1H, d, *J* 10.8 Hz, benzylic H), 4.72 (1H, d, *J* 11.2 Hz, benzylic H), 4.71 (1H, d, *J* 11.9 Hz, benzylic H), 4.69 (1H, d, *J* 11.9 Hz, benzylic H), 4.68 (1H, d, *J* 12.5 Hz, benzylic H), 4.65 (1H, d, *J* 11.9 Hz, benzylic H), 4.62 (1H, d, *J* 11.5 Hz, benzylic H), 4.54 (1H, d, *J* 11.2 Hz, benzylic H), 4.53 (1H, d, *J* 11.5 Hz, benzylic H), 4.44 (1H, d, *J* 12.5 Hz, benzylic H), 4.43 (1H, d, $J_{3',4'}$ 7.0 Hz, H-3'), 4.25 (1H, d, *J* 11.8 Hz, benzylic H), 4.24 (1H, m, H-5), 4.20 (1H, dd, $J_{4',5'}$ 7.0 Hz, H-4'), 4.05–4.09 (2H, m, H-3, H-5'), 3.92 (1H, m, H-6'), 3.81 (1H, m, H-6'), 3.71 (3H, s, OCH_3), 3.66–3.71 (2H, m, H-6, H-7'), 3.62 (1H, d, $J_{1',1'}$ 11.2 Hz, H-1'), 3.61 (1H, m, H-7'), 3.53 (2H, s, 2H-9), 3.45–3.51 (4H, m, H-2, H-1', 2H-7), 3.42 (1H, m, H-6), 3.21 (1H, dd, *J* 9.4 Hz, *J* 9.8 Hz, H-4), 2.85 (1H, m, H-8'), 2.64–2.77 (3H, m, 2H-8, H-8') ppm. ^{13}C NMR (150 MHz): δ = 158.57 (C_{Ar}-OMe), 138.79, 138.68, 138.59, 138.27, 138.05, 137.98 (C_{quat}, 6 × Ph), 127.20–128.45 (33C, m, C-Ar), 113.45 (2C-Ar), 104.15 (C-2'), 90.13 (C-1), 84.97 (C-4'), 83.68 (C-3'), 81.66 (C-3), 80.02 (C-5'), 79.98 (C-2), 79.47 (C-4), 75.48, 74.82, 73.47, 73.17, 72.78, 72.17 (6 × OCH_2Ph), 72.21 (C-6'), 71.76 (C-6), 71.07 (C-1'), 70.99 (C-5), 70.81 (C-7), 69.09 (C-7'), 59.71 (C-9), 55.17 (OCH_3), 53.38 (C-8'), 53.06 (C-8) ppm. HRMS (ESI) calcd for $C_{66}H_{74}NO_{12}$ $[M + H]^+$: 1072.5206, found: 1072.5221. Analysis for $C_{66}H_{73}NO_{12}$ (1072.32): Calcd: C, 73.93; H, 6.86; N, 1.31. Found: C, 73.90; H, 6.65; N, 1.32.

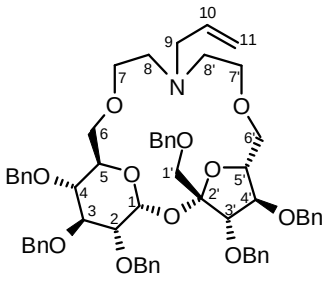
4.2.9.3 6,6'-[3-Aza(pyridine-2-ylmethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (3.19c)



Yield: 136 mg (0.13 mmol, 65%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.36. Yellow oil. $[\alpha]_D^{24}$ = +21.9 (CH_2Cl_2). ^{1}H NMR (600 MHz): δ = 8.47 (1H, m, H-Py), 7.53 (1H, td, *J* 7.8 Hz, *J* 1.7 Hz, H-Py), 7.50 (1H, t, *J* 7.8 Hz, H-Py), 7.19–7.34 (30H, m, H-Ar), 7.80 (1H, m, H-Py), 5.44 (1H, d, $J_{1,2}$ 3.2 Hz, H-1), 4.86 (1H, d, *J* 11.1 Hz, benzylic H), 4.85 (1H, d, *J* 10.9 Hz, benzylic H), 4.71 (1H, d, *J* 11.0 Hz, benzylic H), 4.70 (1H, d, *J* 11.2 Hz, benzylic H), 4.69 (1H, d, *J* 11.6

Hz, benzylic H), 4.65 (2H, s, benzylic H), 4.62 (1H, d, *J* 11.5 Hz, benzylic H), 4.52 (2H, d, *J* 11.3 Hz, benzylic H), 4.44 (1H, d, *J* 12.0 Hz, benzylic H), 4.43 (1H, d, $J_{3',4'}$ 7.1 Hz, H-3'), 4.26 (1H, d, *J* 12.1 Hz, benzylic H), 4.23 (1H, m, H-5), 4.18 (1H, dd, $J_{4',5'}$ 7.1 Hz, H-4'), 4.04–4.09 (2H, m, H-3, H-5'), 3.91 (1H, dd, $J_{5',6'}$ 6.4 Hz, $J_{6',6'}$ 9.1 Hz, H-6'), 3.83 (1H, dd, $J_{5',6'}$ 6.0 Hz, H-6'), 3.79 (1H, d, *J* 14.7 Hz, H-9), 3.75 (1H, d, *J* 14.7 Hz, H-9), 3.69–3.73 (1H, m, H-7'), 3.62–3.67 (2H, m, H-6, H-7'), 3.61 (1H, d, *J* 11.0 Hz, H-1'), 3.46–3.51 (4H, m, H-2, H-1', 2H-7), 3.39 (1H, dd, $J_{5,6}$ 8.3 Hz, $J_{6,6}$ 10.2 Hz, H-6), 3.19 (1H, dd, *J* 9.1 Hz, *J* 9.9 Hz, H-4), 2.92–2.96 (1H, m, H-8'), 2.75–2.80 (3H, m, 2H-8, H-8') ppm. ^{13}C NMR (150 MHz): δ = 159.97 (C-Py), 148.77 (C-Py), 138.71, 138.63, 138.47, 138.19, 138.01, 137.91 (C_{quat}, 6 × Ph), 136.45 (C-Py), 127.30–128.40 (30C, m, C-Ph), 123.08 (C-Py), 121.87 (C-Py), 104.18 (C-2'), 90.22 (C-1), 84.88 (C-4'), 83.70 (C-3'), 81.63 (C-3), 79.99 (C-5'), 79.96 (C-2), 79.48 (C-4), 75.48, 74.86, 73.50, 73.19, 72.69 (5 × O*C*H$_2$Ph), 72.39 (C-6'), 72.17 (O*C*H$_2$Ph), 71.78 (C-6), 71.00 (C-1'), 70.99 (C-5), 70.36 (C-7), 68.96 (C-7'), 61.97 (C-9), 54.02 (C-8'), 53.51 (C-8) ppm. HRMS (ESI) calcd for $C_{64}H_{71}N_2O_{11}$ $[M + H]^+$: 1043.5052, found: 1043.5067. Analysis for $C_{64}H_{70}N_2O_{11}$ (1043.28): Calcd: C, 73.68; H, 6.76; N, 2.69. Found: C, 73.91; H, 6.62; N, 2.75.

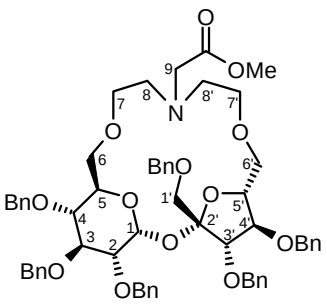
4.2.9.4 6,6'-[3-Aza(prop-2-en-1-yl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (3.19d)



Yield: 135 mg (0.14 mmol, 68%). TLC [AcOEt/MeOH/H$_2$O (45:5:3)]: R_f = 0.39. Yellowish oil. $[\alpha]_D^{23}$ = +29.1 ($CHCl_3$). ^{1}H NMR (600 MHz): δ = 7.19–7.35 (30H, m, H-Ar), 5.80 (1H, ddt, $J_{10,11'}$ 17.1 Hz, $J_{10,11}$ 10.2 Hz, $J_{10,9}$ 6.5 Hz, H-10), 5.42 (1H, d, $J_{1,2}$ 3.2 Hz, H-1), 5.12 (1H, dd, $J_{11,11'}$ 1.3 Hz, H-11'), 5.12 (1H, dd, H-11), 4.87 (1H, d, *J* 10.9 Hz, benzylic H), 4.85 (1H, d, *J* 10.8 Hz, benzylic H), 4.71 (1H, d, *J* 10.8 Hz, benzylic H), 4.70 (1H, d, *J* 11.5 Hz, benzylic H), 4.69 (1H, d, *J* 11.8 Hz, benzylic H), 4.67 (1H, d, *J* 11.3 Hz, benzylic H), 4.66 (1H, d, *J* 11.8 Hz, benzylic H), 4.61 (1H, d, *J* 11.5 Hz, benzylic H), 4.54 (1H, d, *J* 10.9 Hz, benzylic H), 4.52 (1H, d, *J* 11.3 Hz, benzylic H), 4.42 (1H, d, *J* 12.1 Hz, benzylic H), 4.41 (1H, d, $J_{3',4'}$ 7.1 Hz, H-3'), 4.26 (1H, d, *J* 12.1 Hz, benzylic H), 4.21 (1H, m, H-5), 4.15 (1H, dd, $J_{4',5'}$ 7.1 Hz, H-4'), 4.04–4.08 (2H, m, H-3, H-5'), 3.88 (1H, dd, $J_{6',6'}$ 10.1 Hz, $J_{5',6'}$ 6.4 Hz, H-6'), 3.79 (1H, dd, $J_{5',6'}$ 6.0 Hz, H-6'), 3.67–3.73 (2H, m, H-6, H-7'), 3.62 (1H, d, $J_{1',1'}$ 10.9 Hz, H-1'), 3.61 (1H, m, H-7'), 3.46–3.53 (4H, m, H-2, H-1', 2H-7), 3.42 (1H, dd, $J_{6,6}$ 10.4 Hz, $J_{5,6}$ 8.0 Hz, H-6), 3.21 (1H, dd, *J* 9.7 Hz, *J* 9.3 Hz, H-4), 3.09 (2H, d, $J_{9,10}$ 6.5 Hz, 2H-9), 2.81–2.86 (1H, m,

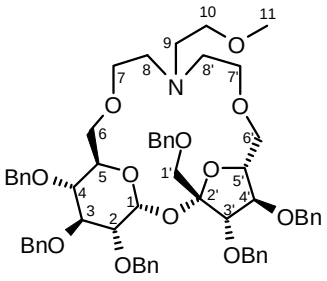
H-8'), 2.68–2.74 (3H, m, 2H-8, H-8') ppm. ^{13}C NMR (150 MHz): δ = 138.78, 138.67, 138.56, 138.27, 138.04, 137.95 (C_{quat}, 6 × Ph), 135.87 (C-10), 127.25–128.55 (30C, m, C-Ph), 117.37 (C-11), 104.13 (C-2'), 90.14 (C-1), 84.87 (C-4'), 83.67 (C-3'), 81.62 (C-3), 79.95 (C-2), 79.90 (C-5'), 79.45 (C-4), 75.47, 74.82, 73.45, 73.17, 72.74 (5 × O*C*H$_2$Ph), 72.21 (C-6'), 72.15 (O*C*H$_2$Ph), 71.79 (C-6), 70.94 (C-5), 70.92 (C-1'), 70.59 (C-7), 68.92 (C-7'), 59.06 (C-9), 54.14 (C-8'), 53.12 (C-8) ppm. HRMS (ESI) calcd for $C_{61}H_{70}NO_{11}$ $[M + H]^+$: 992.4943, found: 992.4977. Analysis for $C_{61}H_{69}NO_{11}$ (992.23): Calcd: C, 73.84; H, 7.01; N, 1.41. Found: C, 73.69; H, 7.12; N, 1.45.

4.2.9.5 6,6'-[3-Aza(2-methoxy-2-oxoethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (3.19e)



Yield: 147 mg (0.14 mmol, 72%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.37. Yellowish oil. $[\alpha]_D^{23}$ = +24.6 (CH_2Cl_2). ^{1}H NMR (600 MHz): δ = 7.19–7.35 (30H, m, H-Ar), 5.41 (1H, d, $J_{1,2}$ 3.2 Hz, H-1), 4.86 (1H, d, *J* 11.4 Hz, benzylic H), 4.85 (1H, d, *J* 11.0 Hz, benzylic H), 4.64–4.72 (5H, m, benzylic H), 4.61 (1H, d, *J* 11.6 Hz, benzylic H), 4.53 (1H, d, *J* 11.1 Hz, benzylic H), 4.51 (1H, d, *J* 11.7 Hz, benzylic H), 4.44 (1H, d, *J* 12.1 Hz, benzylic H), 4.41 (1H, d, $J_{3',4'}$ 7.2 Hz, H-3'), 4.27 (1H, d, *J* 12.0 Hz, benzylic H), 4.21 (1H, m, H-5), 4.15 (1H, dd, $J_{4',5'}$ 7.2 Hz, H-4'), 4.03–4.07 (2H, m, H-3, H-5'), 3.91 (1H, dd, $J_{6',6'}$ 10.1 Hz, $J_{5',6'}$ 6.4 Hz, H-6'), 3.78 (1H, dd, $J_{5',6'}$ 5.9 Hz, H-6'), 3.67–3.71 (2H, m, H-6, H-7'), 3.65 (3H, s, C*H*$_3$), 3.57–3.63 (2H, m, H-7, H-7'), 3.44–3.51 (4H, m, H-2, H-7, 2H-1'), 3.39–3.43 (1H, m, H-6), 3.39 (2H, s, 2H-9), 3.20 (1H, dd, *J* 10.1 Hz, *J* 9.0 Hz, H-4), 3.00–3.06 (1H, m, H-8'), 2.79–2.93 (3H, m, 2H-8, H-8') ppm. ^{13}C NMR (150 MHz): δ = 171.97 (*C*O$_2$Me), 138.79, 138.69, 138.58, 138.28, 138.07, 137.96 (C_{quat}, 6 × Ph), 127.25–128.40 (30C, m, C-Ph), 104.09 (C-2'), 90.10 (C-1), 84.76 (C-4'), 83.65 (C-3'), 81.66 (C-3), 79.95 (C-2), 79.92 (C-5'), 79.42 (C-4), 75.49, 74.82, 73.44, 73.20, 72.71 (5 × O*C*H$_2$Ph), 72.25 (C-6'), 72.16 (O*C*H$_2$Ph), 71.75 (C-6), 70.97 (C-7), 70.86 (C-5), 70.08 (C-1'), 69.07 (C-7'), 55.76 (C-9), 59.06 (C-9), 53.93 (C-8'), 53.42 (C-8), 51.28 (O*C*H$_3$) ppm. HRMS (ESI) calcd for $C_{61}H_{69}NO_{13}$ $[M + Na]^+$: 1046.4661, found: 1046.4656. Analysis for $C_{61}H_{69}NO_{11}$ (1024.23): Calcd: C, 71.53; H, 6.79; N, 1.37. Found: C, 71.75; H, 6.92; N, 1.46.

4.2.9.6 6,6'-[3-Aza(2-methoxyethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (3.19f)

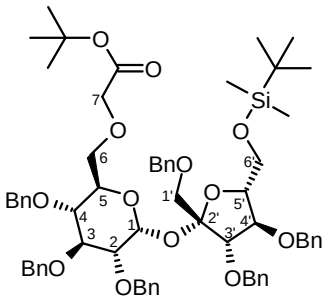


Yield: 135 mg (0.13 mmol, 67%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.33. Yellowish oil. $[\alpha]_D^{22}$ = +31.7 ($CHCl_3$). ^{1}H NMR (600 MHz): δ = 7.17–7.35 (30H, m H-Ar), 5.41 (1H, d, $J_{1,2}$ 3.3 Hz, H-1), 4.87 (1H, d, *J* 11.0 Hz, benzylic H), 4.86 (1H, d, *J* 10.8 Hz, benzylic H), 4.70 (1H, d, *J* 11.1 Hz, benzylic H), 4.69 (1H, d, *J* 11.5 Hz, benzylic H), 4.68 (1H, d, *J* 10.8 Hz, benzylic H), 4.66 (2H, d, *J* 11.8 Hz, benzylic H), 4.61 (1H, d, *J* 11.5 Hz, benzylic H), 4.54 (1H, d, *J* 11.1 Hz, benzylic H), 4.51 (1H, d, *J* 11.8 Hz, benzylic H), 4.44 (1H, d, *J* 12.0 Hz, benzylic H), 4.41 (1H, d, $J_{3',4'}$ 7.2 Hz, H-3'), 4.25 (1H, d, *J* 12.0 Hz, benzylic H), 4.20 (1H, m, H-5), 4.14 (1H, dd, $J_{4',5'}$ 7.0 Hz, H-4'), 4.03–4.10 (2H, m, H-3, H-5'), 3.86 (1H, dd, $J_{5',6'}$ 6.5 Hz, $J_{6',6'}$ 10.0 Hz, H-6'), 3.79 (1H, dd, $J_{5',6'}$ 6.0 Hz, H-6'), 3.67–3.72 (2H, m, H-6, H-7'), 3.60–3.66 (2H, m, H-1', H-7'), 3.49–3.53 (2H, m, 2H-7), 3.45–3.49 (2H, m, H-1', H-2), 3.39–3.43 (3H, m, H-6, 2H-10), 3.28 (3H, s, 3H-11), 3.20 (1H, dd, *J* 9.4 Hz, *J* 9.6 Hz, H-4), 2.86–2.92 (1H, m, H-8'), 2.74–2.79 (3H, m, H-8', 2H-8), 2.67 (2H, t, *J* 5.9 Hz, 2H-9) ppm. ^{13}C NMR (150 MHz): δ = 138.78, 138.71, 138.58, 138.30, 138.07, 137.99 (C_{quat}, 6 × Ph), 127.25–128.40 (30C, m, C-Ph), 104.19 (C-2'), 90.14 (C-1), 84.80 (C-4'), 83.74 (C-3'), 81.63 (C-3), 79.99 (C-2), 79.94 (C-5'), 79.46 (C-4), 75.44, 74.79, 73.45, 73.20, 72.61, 72.19 (6 × O*C*H_2Ph), 72.17 (C-6'), 71.77 (C-6), 71.13 (C-10), 71.06 (C-1'), 70.97 (C-5), 70.69 (C-7), 69.08 (C-7'), 58.76 (C-11), 55.19 (C-9), 54.07 (C-8), 53.91 (C-8') ppm. HRMS (ESI) calcd for $C_{61}H_{72}NO_{12}$ $[M + H]^+$: 1010.5049, found: 1010.5003. Analysis for $C_{61}H_{71}NO_{12}$ (1010.25): Calcd: C, 72.52; H, 7.08; N, 1.39. Found: C, 72.67; H, 7.19; N, 1.32.

4.2.10 Synthesis of 1',2,3,3',4,4'-hexa-*O*-benzyl-6-*O*-(2-*tert*-butoxy-2-oxoethyl)-6'-*O*-*tert*-butyldimethylsilylsucrose (3.20). General procedure for alkylation of alcohols with *tert*-butyl bromoacetate

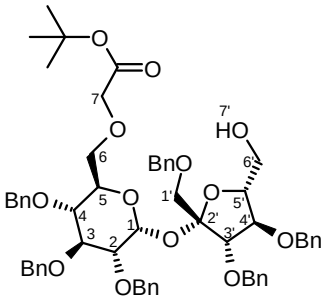
To a solution of alcohol **3.9** (1.77 g, 1.77 mmol) in toluene (50 mL) tetrabutylammonium bromide (57 mg, 0.18 mmol) was added followed by 50% aqueous NaOH (50 mL). A solution of *tert*-butyl bromoacetate (0.78 mL, 5.31 mmol) in toluene (10 mL) was added and the mixture was vigorously stirred at room temperature for 12 h. The layers were separated and the aqueous one extracted with ether (2 × 100 mL). Combined organic solutions were washed with water (100 mL) and brine (50 mL), dried, concentrated, and the resulting residue

was purified by flash chromatography (hexanes–ethyl acetate, 85:15) to afford pure product **3.20** (1.66 g, 1.50 mmol, 84%). TLC [hexanes/AcOEt (3:1)]: R_f = 0.55. Yellowish oil. $[\alpha]_D^{20}$ = +27.8 ($CHCl_3$). ^{1}H NMR (600 MHz): δ = 7.20–7.33 (30H, m H-Ar), 5.81 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 4.92 (1H, d, *J* 11.0 Hz, benzylic H), 4.85 (1H, d, *J* 10.9 Hz, benzylic H), 4.75 (1H, d, *J* 11.0 Hz, benzylic H), 4.73 (1H, d, *J* 10.9 Hz, benzylic H), 4.66 (1H, d, *J* 11.4 Hz, benzylic H), 4.65 (1H, d, *J* 11.3 Hz, benzylic H), 4.62 (1H, d, *J* 11.2 Hz, benzylic H), 4.60 (1H, d, *J* 11.7 Hz, benzylic H), 4.55 (1H, d, *J* 11.7 Hz, benzylic H), 4.53 (1H, d, *J* 11.3 Hz, benzylic H), 4.49 (1H, d, *J* 11.4 Hz, benzylic H), 4.46 (1H, d, *J* 11.2 Hz, benzylic H), 4.44 (1H, d, $J_{3',4'}$ 7.3 Hz, H-3'), 4.25 (1H, dd, $J_{4',5'}$ 6.9 Hz, H-4'), 4.01 (1H, dt, $J_{4,5}$ 9.9 Hz, $J_{5,6}$ 2.3 Hz, H-5), 3.87–3.98 (4H, m, H-6', H-3, H-7, H-5'), 3.81–3.86 (2H, m, H-7, H-6'), 3.76 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.64–3.69 (2H, m, H-4, H-6), 3.53 (1H, d, H-1'), 3.51 (1H, dd, $J_{2,3}$ 9.7 Hz, H-2), 3.44 (1H, dd, $J_{6,6}$ 11.0 Hz, H-6), 1.43 (9H, s, O^t*Bu*), 0.89 (9H, s, Si^t*Bu*), 0.07 (3H, s, SiCH_3), 0.06 (3H, s, SiCH_3) ppm. ^{13}C NMR (150 MHz): δ = 169.29 ($CO_2{}^t$Bu), 139.03, 138.83, 138.44, 138.42, 138.11, 137.95 (C_{quat}, 6 × Ph), 127.35–128.35 (30C, m, C-Ph), 104.47 (C-2'), 89.78 (C-1), 84.24 (C-3'), 82.75 (C-4'), 81.98 (C-3), 81.43 (C-5'), 81.18 (C_{quat}, O^{t}Bu), 79.87 (C-2), 77.25 (C-4), 75.51, 74.76, 73.45, 73.13, 72.49, 71.99 (6 × OCH_2Ph), 71.06 (C-1'), 70.68 (C-5), 69.72 (C-6), 69.30 (C-7), 64.27 (C-6'), 28.09 (triple intensity, 3C-O^t*Bu*), 25.97 (triple intensity, 3C-Si^t*Bu*), 18.37 (C_{quat}, Si^t*Bu*), -5.28, -5.32 (2 × SiCH_3) ppm. HRMS (ESI) calcd for $C_{66}H_{82}O_{13}NaSi$ $[M + Na]^+$: 1133.5417, found: 1133.5456. Analysis for $C_{66}H_{82}O_{13}Si$ (1111.47): Calcd: C, 71.32; H, 7.44. Found: C, 71.51; H, 7.56.



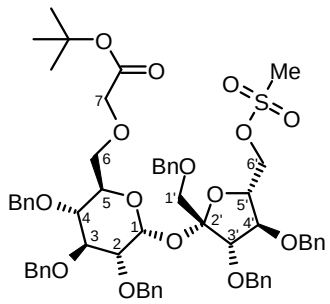
4.2.11 Preparation of 1',2,3,3',4,4'-hexa-*O*-benzyl-6-*O*-(2-*tert*-butoxy-2-oxoethyl)sucrose (3.21)

Desilylation of **3.20** was performed as desribed previously (see 4.2.3) starting from 1.56 g (1.40 mmol) of compound **3.20** and 0.59 g (2.10 mmol) of tetrabutylammonium fluoride trihydrate in 40 mL THF. Reaction mixture was stirred for 5 h. After evaporation of the solvent *in vacuo* and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 75:25) to afford pure product **3.21** (1.22 g, 1.22 mmol, 87%). TLC [hexanes/AcOEt (3:1)]: R_f = 0.21. Colorless oil. $[\alpha]_D^{21}$ = +14.9 ($CHCl_3$). IR: *v* = 3473, 3063, 3031, 2925, 2869, 1747, 1497, 1454, 1393, 1367, 1308, 1229, 1209, 1148, 1088, 1074, 1028, 1002, 952, 912, 845, 736, 698 cm^{-1}. ^{1}H NMR (600 MHz): δ = 7.19–7.34 (30H, m, H-Ar), 5.51



(1H, d, $J_{1,2}$ 3.5 Hz, H-1), 4.87 (1H, d, *J* 11.1 Hz, benzylic H), 4.86 (1H, d, *J* 10.8 Hz, benzylic H), 4.79 (1H, d, *J* 11.1 Hz, benzylic H), 4.79 (1H, d, *J* 10.8 Hz, benzylic H), 4.68 (2H, d, *J* 11.5 Hz, benzylic H), 4.62 (1H, d, *J* 11.8 Hz, benzylic H), 4.60 (1H, d, *J* 11.5 Hz, benzylic H), 4.56 (1H, d, *J* 11.8 Hz, benzylic H), 4.48 (1H, d, *J* 11.5 Hz, benzylic H), 4.47 (1H, d, *J* 12.2 Hz, benzylic H), 4.45 (1H, d, $J_{3',4'}$ 8.0 Hz, H-3'), 4.34 (1H, dd, $J_{4',5'}$ 8.0 Hz, H-4'), 4.28 (1H, d, *J* 11.8 Hz, benzylic H), 4.06 (1H, dt, $J_{4,5}$ 9.8 Hz, $J_{5,6}$ 1.8 Hz, H-5), 3.99 (1H, d, *J* 16.0 Hz, H-7), 3.96–4.01 (2H, m, H-5', H-3), 3.88 (1H, d, H-7), 3.82–3.86 (2H, m, H-6, H-6'), 3.76 (1H, dd, $J_{3,4}$ 9.4 Hz, H-4), 3.57–3.63 (3H, m, H-6, H-1', H-6'), 3.55 (1H, dd, $J_{2,3}$ 9.8 Hz, H-2), 3.47 (1H, d, $J_{1',1'}$ 11.4 Hz, H-1'), 3.18 (1H, dd, $J_{7',6'}$ 10.4 Hz, $J_{7',6'}$ 2.6 Hz, H-7'), 1.45 (9H, s, H-^{t}Bu) ppm. ^{13}C NMR (150 MHz): δ = 169.20 (*C*O$_2^t$Bu), 138.81, 138.62, 138.29, 138.18, 138.15, 137.80 (C_{quat}, 6 × Ph), 127.45–128.38 (30C, m, C-Ph), 103.86 (C-2'), 91.13 (C-1), 83.60 (C-3'), 81.77 (C-3), 81.45 (C_{quat}, O^{t}Bu), 81.22 (C-5'), 79.68 (C-4'), 79.28 (C-2), 77.08 (C-4), 75.46, 74.92, 73.42, 73.27, 72.91, 72.50 (6 × O*C*H$_2$Ph), 71.35 (C-5), 71.16 (C-1'), 69.30 (C-6), 69.27 (C-7), 61.24 (C-6'), 28.11(triple intensity, 3C-^{t}Bu) ppm. HRMS (ESI) calcd for $C_{60}H_{68}O_{13}Na$ $[M + Na]^+$: 1019.4552, found: 1019.4567. Analysis for $C_{60}H_{68}O_{13}$ (997.20): Calcd: C, 72.27; H, 6.87. Found: C, 72.10; H, 6.80.

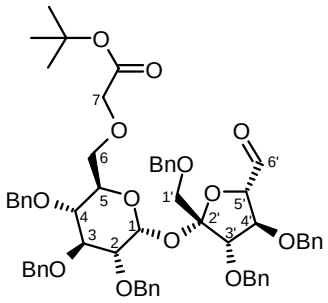
4.2.12 Synthesis of 1',2,3,3',4,4'-hexa-*O*-benzyl-6-*O*-(2-*tert*-butoxy-2-oxoethyl)-6'-*O*-(methylsulfonyl)sucrose (3.22). General procedure for mesylation of alcohols with methanesulfonyl chloride



Alcohol **3.21** (200 mg, 0.20 mmol) was dissolved in CH_2Cl_2 (10 mL) to which Et_3N (56 μL, 0.40 mmol) was added, and the mixture was stirred at rt. Subsequently MsCl (23 μL, 0.30 mmol) was added dropwise and, after 1 h, H_2O (10 mL). Phase were separated and the aqueous one extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes–AcOEt, 80:20) to give compound **3.22** (208 mg, 0.30 mmol, 96%). TLC [hexanes/AcOEt (3:1)]: R_f = 0.38. Colorless oil. $[\alpha]_D^{21}$ = +32.1 ($CHCl_3$). IR: *ν* = 3089, 3063, 3030, 2977, 2927, 2870, 1746, 1497, 1454, 1359, 1230, 1209, 1176, 1147, 1090, 1074, 1028, 1000, 960, 843, 736, 697, 528 cm^{-1}. ^{1}H NMR (600 MHz): δ = 7.20–7.34 (30H, m, H-Ar), 5.55 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 4.91 (1H, d, *J* 11.1 Hz, benzylic H), 4.86 (1H, d, *J* 11.1 Hz, benzylic H), 4.79 (1H, d, *J* 11.1 Hz,

benzylic H), 4.68 (1H, d, *J* 11.1 Hz, benzylic H), 4.65 (1H, d, *J* 11.5 Hz, benzylic H), 4.63 (1H, d, *J* 10.1 Hz, benzylic H), 4.60 (1H, d, *J* 11.5 Hz, benzylic H), 4.58 (1H, d, *J* 11.5 Hz, benzylic H), 4.49–4.54 (4H, m, H-6', 3 × benzylic H), 4.44 (1H, d, $J_{3',4'}$ 7.5 Hz, H-3'), 4.36 (1H, d, *J* 12.2 Hz, benzylic H), 4.26 (1H, dd, $J_{5',6'}$ 3.2 Hz, $J_{6',6'}$ 10.9 Hz, H-6'), 4.19 (1H, td, $J_{4',5'}$ 7.5 Hz, H-5'), 4.10 (1H, dd, H-4'), 4.04 (1H, ddd, $J_{4,5}$ 10.4 Hz, $J_{5,6}$ 4.3 Hz, $J_{5,6}$ 1.8 Hz, H-5), 3.97 (1H, dd, $J_{3,4}$ 9.3 Hz, $J_{3,2}$ 10.0 Hz, H-3), 3.90 (1H, d, $J_{7,7}$ 16.5 Hz, H-7), 3.87 (1H, d, H-7), 3.69 (1H, d, $J_{1',1'}$ 11.1 Hz, H-1'), 3.67 (1H, dd, $J_{6,6}$ 10.4 Hz, H-6), 3.58 (1H, dd, H-6), 4.56 (1H, dd, H-4), 3.51 (1H, dd, H-2), 3.49 (1H, d, H-1'), 2.94 (3H, s, C*H*$_3$-S), 1.44 (9H, s, O^t*Bu*) ppm. ^{13}C NMR (150 MHz): δ = 169.19 (*C*O$_2{}^t$Bu), 138.79, 138.44, 138.12, 138.00, 137.73, 137.67 (C_{quat}, 6 × Ph), 127.45–128.43 (30C, m, C-Ph), 104.82 (C-2'), 90.55 (C-1), 83.48 (C-3'), 81.83 (C-3), 81.80 (C-4'), 81.35 (C_{quat}, O^{t}Bu), 79.58 (C-2), 78.18 (C-5'), 77.49 (C-4), 75.46, 74.83, 73.35, 72.93, 72.80, 72.72 (6 × O*C*H$_2$Ph), 70.81 (C-5), 70.60 (C-6'), 70.46 (C-1'), 69.96 (C-6), 68.86 (C-7), 37.08 (*C*H$_3$-S), 28.08 (triple intensity, 3C-O^t*Bu*) ppm. HRMS (ESI) calcd for $C_{61}H_{70}O_{15}SNa$ [M + Na]$^+$: 1097.4328, found: 1097.4321. Analysis for $C_{61}H_{70}O_{15}S$ (1075.29): Calcd: C, 68.14; H, 6.56; S, 2.98. Found: C, 68.28; H, 6.55; S, 3.21.

4.2.13 Synthesis of 1',2,3,3',4,4'-hexa-*O*-benzyl-6-*O*-(2-*tert*-butoxy-2-oxoethyl)-6'-aldehydosucrose (3.24). General procedure for Swern oxidation



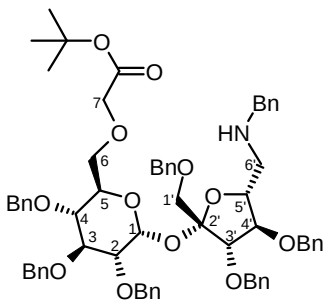
To a cooled to –78 °C solution of oxalyl chloride (157 μL, 1.79 mmol) in CH_2Cl_2 (20 mL) a solution of DMSO (360 μL, 5.10 mmol) in CH_2Cl_2 (3 mL) was added at within 5 min. After 10 min alcohol **3.21** (510 mg, 0.51 mmol) in CH_2Cl_2 (10 mL) was added dropwise and mixture was stirred for 30 min at –78 °C. Then Et_3N (520 μL, 3.86 mmol) was added and the mixture was allowed to attain rt. Water (20 mL) was added, the organic layer was separated, dried, and concentrated in vacuo. The crude product **3.24** (505 mg, 0.507 mmol, 99%) was used in the next step without further purification.

4.2.14 Synthesis of 6'-benzyloamino-6'-deoxy-1',2,3,3',4,4'-hexa-*O*-benzyl-6-*O*-(2-*tert*-butoxy-2-oxoethyl)sucrose (3.23)

Method 1 (Alkylation): Compound **3.22** (180 mg, 0.17 mmol) was dissolved in DMF (5 mL). Benzylamine (55 μL, 0.50 mmol) and K_2CO_3 (69 mg, 0.50 mmol) were added and the mixture was stirred for 4 h at 100°C and cooled to rt. Water (10 mL) and AcOEt (25 mL) were added, phases were separated and the aqueous one extracted with AcOEt (3 × 20 mL). Combined

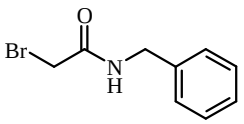
organic solutions were washed with water (2 × 10 mL), brine (10 mL), dried, concentrated in vacuo, and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 75:25 to 50:50) to afford pure compound **3.23** (48 mg, 0.04 mmol, 26%).

Method 2 (Reductive amination): To a solution of crude aldehyde **3.24** (505 mg, 0.51 mmol) in CH_2Cl_2 (20 mL) acetic acid (105 μL, 1.83 mmol), benzylamine (166 μL, 1.52 mmol) and $MgSO_4$ (~200 mg) were added, and the mixture was stirred at rt. After 1 h sodium cyanoborohydride (38 mg, 0.60 mmol) was added and mixture was stirred overnight. Water (70 mL), 0.1 M solution NH_3 (20 mL) and CH_2Cl_2 (20 mL) were added, phase were separated, and the aqueous one extracted with CH_2Cl_2 (3 × 50 mL). Combined organic solutions were washed with water (30 mL) and brine (30 mL), dried, concentrated, and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 90:10 to 50:50) to afford pure compound **3.23** (409 mg, 0.38 mmol, 74%).



TLC [hexanes/AcOEt (1:1)]: R_f = 0.23. Yellowish oil. $[\alpha]_D^{21}$ = +41.6 ($CHCl_3$). IR: ν = 3330, 3088, 3063, 3031, 3006, 2924, 2869, 2329, 2168, 1747, 1605, 1496, 1454, 1393, 1367, 1255, 1229, 1209, 1146, 1088, 1073, 1028, 1003, 914, 845, 736, 697 cm^{-1}. ^1H NMR (600 MHz): δ = 7.20–7.36 (35H, m, H-Ar), 5.68 (1H, br s, H-1), 4.89 (1H, d, *J* 11.1 Hz, benzylic H), 4.86 (1H, d, *J* 11.0 Hz, benzylic H), 4.73 (1H, d, *J* 11.0 Hz, benzylic H), 4.67 (1H, d, *J* 11.4 Hz, benzylic H), 4.61–4.66 (4H, m, 4 × benzylic H), 4.55 (1H, d, *J* 12.0 Hz, benzylic H), 4.49 (1H, d, *J* 11.6 Hz, benzylic H), 4.45 (1H, d, *J* 11.3 Hz, benzylic H), 4.42 (1H, d, $J_{3',4'}$ 7.4 Hz, H-3'), 4.40 (1H, d, *J* 12.4 Hz, benzylic H), 4.08–4.17 (3H, m, H-4', H-5, H-5'), 3.95 (1H, dd, $J_{3,2}$ 9.3 Hz, $J_{3,4}$ 9.3 Hz, H-3), 3.79–3.86 (3H, m, H-7', 2H-7), 3.66 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.53–3.58 (3H, m, H-2, H-4, H-7'), 3.52 (1H, d, H-1'), 3.43–3.47 (2H, m, H-6, H-6'), 3.06–3.13 (2H, m, H-6, H-6'), 1.41 (9H, s, 9 × H-^{t}Bu) ppm. ^{13}C NMR (150 MHz): δ = 169.62 (C-8), 139.85, 138.79, 138.51, 138.23, 138.11, 138.10, 137.88 (C_{quat}, 7 × Ph), 128.29–128.53 (35C, m, C-Ph), 104.35 (C-2'), 90.20 (C-1), 83.85 (C-3'), 83.59 (C-4'), 81.97 (C_{quat}, O^{t}Bu), 81.75 (C-3), 79.60 (C-2), 79.60 (C-4), 77.56 (C-5'), 75.40, 74.79, 73.46, 72.80, 72.70, 72.49 (6 × O*C*H_2Ph), 71.64 (C-1'), 70.68 (C-5), 70.07 (C-6), 68.91 (C-7), 53.07 (C-6'), 52.99 (C-7'), 28.08 (triple intensity, 3C-^{t}Bu) ppm. HRMS (ESI) calcd for $C_{67}H_{76}NO_{12}$ $[M + H]^+$: 1086.5362, found: 1086.5339. Analysis for $C_{67}H_{75}NO_{12}$ (1086.34): Calcd: C, 74.08; H, 6.96; N, 1.29. Found: C, 73.79; H, 7.15; N, 1.48.

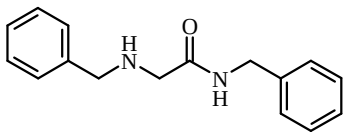
4.2.15 *N*-benzyl-2-bromoacetamide (3.25)



Benzylamine (2.51 mL, 23.0 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and the solution was cooled to –20 °C. Bromoacetyl bromide (1.00 mL, 11.5 mmol) was slowly added to a vigorously stirred mixture. After stirring for 30 min, the mixture was allowed to reach room temperature and water (20 mL) was added. Phase were separated and the aqueous one extracted with CH_2Cl_2 (3 × 20 mL). Combined organic solutions were washed with water (20 mL) and brine (10 mL), dried, concentrated in vacuo, and the resulting precipitate was recrystallized from CH_2Cl_2 to afford pure product **3.25** (2.52 g, 11.0 mmol, 96%). White solid, m.p. 111 °C. ^{1}H NMR (400 MHz): δ = 7.25–7.39 (5H, m), 6.81 (1H, br s), 4.48 (2H, d, *J* 6.0 Hz), 3.92 (2H, s) ppm. ^{13}C NMR (100 MHz): δ = 165.28, 137.22, 128.80 (2C), 127.77, 127.71 (2C), 44.17, 29.11 ppm. Analysis for $C_9H_{10}BrNO$ (228.09): Calcd: C, 47.39; H, 4.42; Br, 35.03; N, 6.14. Found: C, 47.54; H, 4.50; Br, 35.13; N, 6.13.

4.2.16 *N*-benzyl-2-(benzylamino)acetamide (3.26)

Bromoacetyl bromide (0.50 mL, 5.74 mmol) was added dropwise to a vigorously stirred solution of the benzylamine (3.70 mL, 33.87 mmol) in dry acetonitrile (30 mL) at 0 °C. The temperature was kept below 10 °C during the addition. Then the reaction mixture was allowed to reach rt and stirred for 12 h. Aqueous saturated potassium carbonate (30 mL) and AcOEt (20 mL) were added, phases were separated, and the aqueous one extracted with AcOEt (3 × 40 mL). Combined organic solutions were washed with water (40 mL), and brine (30 mL), dried, concentrated, and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 50:50 to 0:100) to afford pure compound **3.26** (1.38 g, 5.42 mmol, 94%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.47. Yellowish oil. IR: ν = 3316, 3086, 3063, 3029,

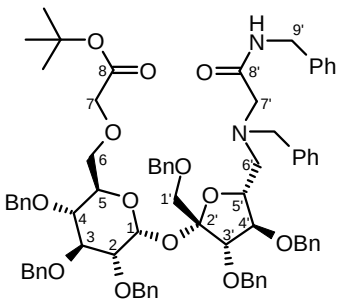


2923, 2836, 1953, 1878, 1810, 1659, 1604, 1585, 1526, 1496, 1454, 1426, 1360, 1331, 1253, 1203, 1124, 1080, 1028, 1002, 910, 829, 737, 698, 613 cm^{-1}. ^{1}H NMR (400 MHz): δ = 7.55 (1H, br s), 7.17–7.36 (10H, m), 4.44 (2H, d, *J* 6.0 Hz), 3.74 (2H, s), 3.33 (2H, s), 1.82 (1H, br s) ppm. ^{13}C NMR (100 MHz): δ = 171.31, 139.19, 138.28, 128.59 (2C), 128.50 (2C), 128.01 (2C), 127.57 (2C), 127.33, 127.28, 53.89, 51.85, 42.88 ppm. HRMS (ESI) calcd for $C_{16}H_{19}N_2O$ $[M + H]^+$: 255.1492, found: 255.1501. Analysis for $C_{16}H_{18}N_2O$ (254.33): Calcd: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.68; H, 7.37; N, 11.19.

4.2.17 Preparation of *N*-(2-benzyloamino-2-oxoethyl)-*N*-benzylo-6'-amino-6'-deoxy-1',2,3,3',4,4'-hexa-*O*-benzyl-6-*O*-(2-*tert*-butoxy-2-oxoethyl)-sucrose (3.27)

Method 1 (Alkylation): Secondary amine **3.23** (380 mg, 0.35 mmol) was alkylated with *N*-benzyl-2-bromoacetamide (**3.25**, 120 mg, 0.52 mmol) and K_2CO_3 (338 mg, 1.05 mmol) in DMF (10 mL) as above (see 4.2.14, *method 1*). The crude product was purificated by flash chromatography (hexanes–ethyl acetate, 85:15 to 75:25) to yield compound **3.27** (78 mg, 0.06 mmol, 18%).

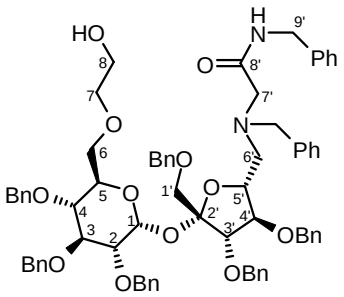
Method 2 (Reductive amination): Reaction of the crude aldehyde **3.24** (480 mg, 0.48 mmol) with the amine **3.26** (368 mg, 1.45 mmol), acetic acid (82 μL, 1.45 mmol), and $NaCNBH_3$ (36 mg, 0.58 mmol) in 20 mL CH_2Cl_2 was carried out as above (see 4.2.14, *method 2*). The crude product was purificated by flash chromatography (hexanes–ethyl acetate, 85:15 to 75:25) to yield compound **3.27** (424 mg, 0.34 mmol, 71%).



TLC [hexanes/AcOEt (2:1)]: R_f = 0.34. Colorless oil. $[\alpha]_D^{21}$ = +38.7 ($CHCl_3$). IR: ν = 3357, 3087, 3063, 3030, 3005, 2924, 2869, 1952, 1877, 1810, 1747, 1676, 1605, 1585, 1517, 1496, 1453, 1393, 1366, 1307, 1257, 1227, 1208, 1145, 1088, 1074, 1028, 1002, 913, 845, 736, 697, 599, 560 cm^{-1}. ^1H NMR (600 MHz): δ = 7.66 (1H, t, *J* 6.6 Hz, NH), 7.09–7.39 (40H, m, H-Ar), 5.44 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 4.87 (1H, d, *J* 10.8 Hz, benzylic H), 4.85 (1H, d, *J* 10.8 Hz, benzylic H), 4.75 (1H, d, *J* 10.8 Hz, benzylic H), 4.70 (1H, d, *J* 10.8 Hz, benzylic H), 4.64 (1H, d, *J* 11.4 Hz, benzylic H), 4.59 (1H, d, *J* 11.4 Hz, benzylic H), 4.58 (1H, d, *J* 11.4 Hz, benzylic H), 4.56 (1H, d, *J* 11.4 Hz, benzylic H), 4.48 (1H, d, *J* 11.4 Hz, benzylic H), 4.46 (1H, d, *J* 11.4 Hz, benzylic H), 4.39 (1H, d, $J_{3',4'}$ 7.8 Hz, H-3'), 4.38 (1H, d, *J* 12.0 Hz, benzylic H), 4.35 (1H, d, *J* 12.0 Hz, benzylic H), 4.32 (2H, t, *J* 6.6 Hz, 2 × H-9'), 4.04 (1H, dt, $J_{4',5'}$ 7.8 Hz, $J_{5',6'}$ 2.4 Hz, H-5'), 3.99–4.03 (1H, m H-5), 3.90–3.95 (2H, m, H-3, H-4'), 3.85 (1H, d, *J* 16.8 Hz, H-7), 3.82 (1H, d, H-7), 3.78 (1H, d, *J* 13.8 Hz, N-CH_2-Ph), 3.63 (1H, d, $J_{1',1'}$ 10.8 Hz, H-1'), 3.59–3.63 (3H, m, H-4, H-6, N-CH_2-Ph), 3.48 (1H, dd, $J_{2,3}$ 9.6 Hz, H-2), 3.44 (1H, dd, $J_{6,6}$ 10.8 Hz, $J_{5,6}$ 1.8 Hz, H-6), 3.41 (1H, d, H-1'), 3.36 (1H, d, *J* 16.8 Hz, H-7'), 3.21 (1H, d, H-7'), 2.96 (1H, dd, $J_{5',6'}$ 8.4 Hz, $J_{6',6'}$ 13.8 Hz, H-6'), 2.79 (1H, dd, $J_{5',6'}$ 2.4 Hz, H-6'), 1.43 (9H, s, 9 × H-^{t}Bu) ppm. ^{13}C NMR (150 MHz): δ = 171.28 (C-8'), 169.12 (C-8), 138.82, 138.68, 138.44, 138.18, 138.09, 138.01, 137.96, 137.86 (C_{quat}, 8 × Ph), 127.11–129.04 (40C, m, C-Ph), 104.33 (C-2'), 90.11 (C-1), 83.27 (C-3'), 83.20 (C-4'), 81.92 (C-3), 81.27 (C_{quat}, O^{t}Bu), 79.59 (C-2), 78.81 (C-5'), 77.35 (C-4), 75.41, 74.75, 73.29, 72.79, 72.63,

72.42 (6 × O*C*H$_2$Ph), 71.33 (C-1'), 70.68 (C-5), 69.85 (C-6), 68.95 (C-7), 60.09 (N-*C*H$_2$-Ph), 58.66 (C-6'), 58.49 (C-7'), 42.78 (C-9'), 28.09 (triple intensity, 3C-^{t}Bu) ppm. HRMS (ESI) calcd for $C_{76}H_{84}N_2O_{13}Na$ $[M + Na]^+$: 1255.5865, found: 1255.5802. Analysis for $C_{78}H_{84}N_2O_{13}$ (1233.52): Calcd: C, 74.00; H, 6.86; N, 2.27. Found: C, 74.23; H, 6.94; N, 2.42.

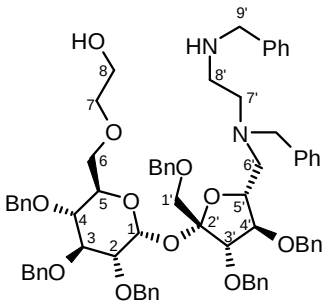
4.2.18 Preparation of *N*-(2-benzyloamino-2-oxoethyl)-*N*-benzylo-6'-amino-6'-deoxy-1',2,3,3',4,4'-hexa-*O*-benzyl-6-*O*-(2-hydroxyethyl)-sucrose (3.28)



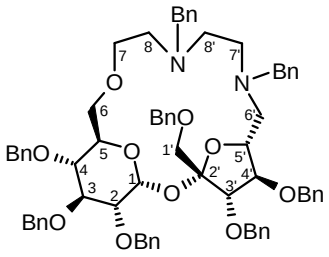
Amido ester **3.27** (125 mg, 0.10 mmol) was reduced with $LiAlH_4$ (38 mg, 1.00 mmol) in THF (5 mL) as above (see 4.2.7). The product was isolated by flash chromatography (hexanes–ethyl acetate, 35:65) to afford pure compound **3.28** (91 mg, 0.08 mmol, 77%). TLC [hexanes/AcOEt (1:2)]: R_f = 0.55. Colorless oil. $[\alpha]_D^{22}$ = +41.1 ($CHCl_3$). ^{1}H NMR (600 MHz): δ = 7.70 (1H, t, *J* 5.9 Hz, NH), 7.12–7.34 (40H, m, H-Ar), 5.36 (1H, d, $J_{1,2}$ 3.5 Hz, H-1), 4.86 (1H, d, *J* 11.0 Hz, benzylic H), 4.85 (1H, d, *J* 11.0 Hz, benzylic H), 4.75 (1H, d, *J* 11.0 Hz, benzylic H), 4.65 (1H, d, *J* 11.4 Hz, benzylic H), 4.62 (1H, d, *J* 11.5 Hz, benzylic H), 4.60 (1H, d, *J* 13.0 Hz, benzylic H), 4.59 (1H, d, *J* 11.0 Hz, benzylic H), 4.55 (1H, d, *J* 11.5 Hz, benzylic H), 4.46 (1H, d, *J* 11.4 Hz, benzylic H), 4.45 (1H, d, *J* 12.0 Hz, benzylic H), 4.37–4.42 (3H, m, H-3', H-9', benzylic H), 4.32 (1H, d, *J* 12.0 Hz, benzylic H), 4.28 (1H, dd, *J* 15.1 Hz, *J* 5.3 Hz, H-9'), 4.08 (1H, ddd, $J_{4',5'}$ 7.8 Hz, $J_{5',6'}$ 8.6 Hz, $J_{5',6'}$ 2.6 Hz, H-5'), 3.99 (1H, m H-5), 3.95 (1H, dd, $J_{3,2}$ 9.3 Hz, $J_{3,4}$ 9.4 Hz, H-3), 3.88 (1H, dd, $J_{4',3'}$ 7.8 Hz, H-4'), 3.68 (1H, d, *J* 13.5 Hz, N-C*H*$_2$-Ph), 3.65 (1H, d, N-C*H*$_2$-Ph), 3.62 (2H, m, 2H-8), 3.61 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.54–3.58 (2H, m, H-4, H-6), 3.41–3.48 (3H, m, H-2, 2H-7), 3.38 (1H, m, H-6), 3.37 (1H, d, H-1'), 3.30 (1H, d, $J_{7',7'}$ 17.0 Hz, H-7'), 3.26 (1H, d, H-7'), 2.92 (1H, dd, $J_{6',6'}$ 13.8 Hz, $J_{6',5'}$ 8.6 Hz, H-6'), 2.77 (1H, dd, $J_{6',5'}$ 2.6 Hz, H-6'), 2.68 (1H, br s, OH) ppm. ^{13}C NMR (150 MHz): δ = 171.43 (C-8'), 138.70, 138.44, 138.34, 138.17, 138.15, 137.96, 137.84, 137.79 (C_{quat}, 8 × Ph), 127.17–129.06 (40C, m, C-Ph), 104.43 (C-2'), 90.28 (C-1), 83.26 (C-4'), 83.17 (C-3'), 81.84 (C-3), 79.81 (C-2), 78.28 (C-5'), 77.65 (C-4), 75.48, 74.89, 73.29, 73.05, 72.52, 72.33 (6 × O*C*H$_2$Ph), 72.90 (C-7), 71.11 (C-1'), 70.93 (C-5), 69.68 (C-6), 61.58 (C-8), 59.53 (N-*C*H$_2$-Ph), 58.67 (C-6'), 58.53 (C-7'), 42.92 (C-9) ppm. HRMS (ESI) calcd for $C_{72}H_{78}N_2O_{12}Na$ $[M + Na]^+$: 1185.5447, found: 1185.5416. Analysis for $C_{72}H_{78}N_2O_{12}$ (1233.52): Calcd: C, 74.33; H, 6.76; N, 2.41. Found: C, 74.48; H, 6.85; N, 2.51.

4.2.19 Preparation of *N*-(2-benzyloaminoethyl)-*N*-benzylo-6'-amino-6'-deoxy-1',2,3,3',4,4'-hexa-*O*-benzyl-6-*O*-(2-hydroxyethyl)-sucrose (3.29)

This reaction was conducted under an argon atmosphere. To a vigorously stirred and cooled to 0 °C solution of the amido ester **3.27** (211 mg, 0.17 mmol) in dry THF (10 mL), a 1M solution of $LiAlH_4$ in THF (1.7 mL) was slowly added. After stirring 15 min, the mixture was warmed up and stirred for 1.5 h at reflux. After cooling to 0 °C the excess of hydride was carefully decomposed with water (15 mL) and aqueous potassium bisulfate ($KHSO_4$, 10 mL). Ethyl acetate (30 mL) was added, the layers were separated, and the aqueous one extracted with ethyl acetate (3 × 30 mL). Combined organic solutions were dried, concentrated, and the resulting residue was purified by flash chromatography (dichloromethane–methanol, 88:12) to afford pure product **3.29** (144 mg, 0.125 mmol, 73%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.43. Colorless oil. $[\alpha]_D^{21}$ = +40.4 (CH_2Cl_2). ^{1}H NMR (600 MHz): δ = 7.13–7.35 (40H, m, H-Ar), 5.47 (1H, d, $J_{1,2}$ 3.5 Hz, H-1), 4.87 (1H, d, *J* 11.0 Hz, benzylic H), 4.86 (1H, d, *J* 11.1 Hz, benzylic H), 4.73 (1H, d, *J* 11.0 Hz, benzylic H), 4.68 (1H, d, *J* 11.4 Hz, benzylic H), 4.55–4.62 (4H, m, benzylic H), 4.51 (1H, d, *J* 12.1 Hz, benzylic H), 4.49 (1H, d, *J* 11.4 Hz, benzylic H), 4.45 (1H, d, *J* 11.7 Hz, benzylic H), 4.40 (1H, d, $J_{3',4'}$ 7.3 Hz, H-3'), 4.39 (1H, d, *J* 12.1 Hz, benzylic H), 4.16 (1H, ddd, $J_{5',4'}$ 7.7 Hz, $J_{5',6'}$ 7.7 Hz, $J_{5',6'}$ 3.6 Hz, H-5'), 4.06 (1H, m, H-5), 3.97 (1H, dd, $J_{3,2}$ 9.2 Hz, $J_{3,4}$ 9.4 Hz, H-3), 3.92 (1H, dd, H-4'), 3.70 (1H, d, *J* 13.8 Hz, Ph-CH_2-N), 3.66 (1H, d, $J_{1',1'}$ 11.1 Hz, H-1'), 3.51–3.63 (7H, m, H-6, 2H-8, Ph-CH_2-N, 2H-9', H-4), 3.41–3.49 (5H, m, H-2, 2H-7, H-1', H-6), 2.94 (1H, dd, $J_{6',6'}$ 14.0 Hz, H-6'), 2.82 (1H, dd, H-6'), 2.62–2.73 (4H, m, 2H-7', 2H-8') ppm. ^{13}C NMR (150 MHz): δ = 140.26 (C_{quat}-Ph-CH_2-NH), 139.42 (C_{quat}-Ph-CH_2-N), 138.80, 138.54, 138.33, 138.22, 138.18, 138.00 (C_{quat}, 6 × Ph), 126.72–128.96 (40C, m, C-Ph), 104.57 (C-2'), 90.01 (C-1), 83.89(C-4'), 83.46 (C-3'), 81.88 (C-3), 79.93 (C-2), 78.34 (C-5'), 77.75 (C-4), 75.47, 74.81, 72.98, 72.82, 72.57, 72.26 (6 × O*C*H_2Ph), 73.30 (C-7), 71.31 (C-1'), 70.74 (C-5), 69.71 (C-6), 61.48 (C-8), 58.65 (N-*C*H_2-Ph), 57.56 (C-6'), 53.79 (C-7'), 53.36 (C-9'), 46.57(C-8') ppm. HRMS (ESI) calcd for $C_{72}H_{81}N_2O_{11}$ $[M + H]^+$: 1149.5835, found: 1149.5842. Analysis for $C_{72}H_{80}N_2O_{11}$ (1149.45): Calcd: C, 75.24; H, 7.02; N, 2.44. Found: C, 75.47; H, 7.05; N, 2.53.



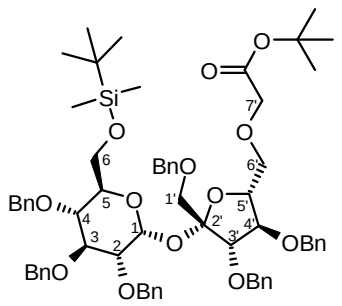
4.2.20 6,6'-[3,5-Di(azabenzyl)hexa-1,6-di-yl]-6'-deoxy-1',2,3,3',4,4'-hexa-O-benzylsucrose (3.31)



Preparation of **3.31** was performed as desribed previously (see 4.2.8) starting from 115 mg (0.10 mmol) of amino alcohol **3.29** in 40 mL toluene. The crude product was purificated by flash chromatography (dichloromethane–methanol, 100:0 to 90:10) to afford pure compound **3.31** (82 mg, 0.72 mmol, 72%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.60. Yellowish oil. $[\alpha]_D^{23}$ = +11.1 (CH_2Cl_2). ^{1}H NMR (600 MHz): δ = 7.12–7.35 (40H, m, H-Ar), 5.49 (1H, d, $J_{1,2}$ 3.3 Hz, H-1), 4.87 (1H, d, *J* 10.6 Hz, benzylic H), 4.86 (1H, d, *J* 10.6 Hz, benzylic H), 4.79 (1H, d, *J* 11.8 Hz, benzylic H), 4.71 (1H, m, H-5'), 4.70 (1H, d, *J* 11.0 Hz, benzylic H), 4.68 (1H, d, *J* 11.8 Hz, benzylic H), 4.66 (1H, d, *J* 11.8 Hz, benzylic H), 4.53 (1H, d, *J* 11.0 Hz, benzylic H), 4.47 (1H, d, *J* 11.9 Hz, benzylic H), 4.46 (1H, d, *J* 12.0 Hz, benzylic H), 4.44 (1H, d, *J* 11.9 Hz, benzylic H), 4.39 (1H, d, *J* 12.0 Hz, benzylic H), 4.37 (1H, d, *J* 11.8 Hz, benzylic H), 4.27 (1H, m, H-5), 4.26 (1H, d, $J_{3',4'}$ 2.8 Hz, H-3'), 4.13 (1H, dd, $J_{4',5'}$ 5.2 Hz, H-4'), 4.10 (1H, dd, $J_{3,2}$ 9.3 Hz, $J_{3,4}$ 9.2 Hz, H-3), 3.71 (1H, dd, $J_{6,6}$ 9.9 Hz, $J_{6,5}$ 1.7 Hz, H-6), 3.67 (1H, d, $J_{1',1'}$ 11.2 Hz, H-1'), 3.65 (1H, d, *J* 13.8 Hz, Ph-CH_2-N), 3.59 (1H, d, *J* 13.8 Hz, Ph-CH_2-N), 3.50–3.54 (4H, m, H-2, H-1', 2 × Ph-CH_2-N), 3.43–3.47 (2H, m, 2H-7), 3.36 (1H, dd, $J_{6,5}$ 8.7 Hz, H-6), 3.19 (1H, dd, $J_{4,5}$ 9.8 Hz, H-4), 2.97 (1H, dd, $J_{6',6'}$ 13.6 Hz, $J_{6',5'}$ 5.7 Hz, H-6'), 2.65–2.82 (7H, m, H-6', 2H-7', 2H-8, 2H-8') ppm. ^{13}C NMR (150 MHz): δ = 139.77 (C_{quat}-Ph-CH_2-NH), 139.66 (C_{quat}-Ph-CH_2-NH), 138.71, 138.66, 138.34, 138.29, 138.26, 138.22 (C_{quat}, 6 × Ph), 128.99–126.56 (40C, m, C-Ph), 105.28 (C-2'), 90.57 (C-1), 84.66 (C-3'), 84.48 (C-4'), 81.76 (C-3), 79.97 (C-2), 79.57 (C-4), 77.64 (C-5'), 75.43, 74.79, 73.37, 73.26, 72.24, 71.56 (6 × O*C*H_2Ph), 72.20 (C-6), 71.27 (C-1'), 70.87 (C-5), 70.87 (C-7), 60.74 (N-*C*H_2-Ph), 59.99 (N-*C*H_2-Ph), 53.61 (C-6'), 52.89 (C-8), 52.47 (C-8'), 50.78 (C-7') ppm. HRMS (ESI) calcd for $C_{72}H_{79}N_2O_{10}$ $[M + H]^+$: 1131.5735, found 1131.5724. Analysis for $C_{72}H_{78}N_2O_{10}$ (1131.43): Calcd: C, 76.43; H, 6.95; N, 2.48. Found: C, 76.58; H, 6.89; N, 2.41.

4.2.21 Synthesis of 1',2,3,3',4,4'-hexa-*O*-benzyl-6'-*O*-(2-*tert*-butoxy-2-oxoethyl)-6-*O*-*tert*-butyldimethylsilylsucrose (3.32)

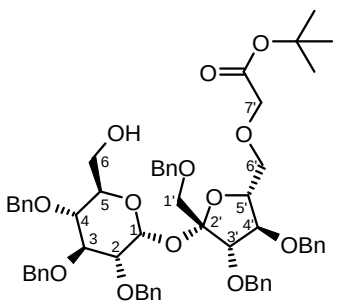
1',2,3,3',4,4'-Hexa-*O*-benzyl-6-*O*-*tert*-butyldimethylsilylsucrose (**3.8**) (479 mg, 0.48 mmol) was alkylated with *tert*-butyl bromoacetate as above (see 4.2.10). The crude product was purificated by flash chromatography (hexanes–ethyl acetate, 89:11) to afford pure compound **3.32** (411 mg, 0.37 mmol, 77%). TLC [hexanes/AcOEt (3:1)]: R_f = 0.55. Colorless oil. $[\alpha]_D^{22}$



= +40.7 (CH_2Cl_2). ^{1}H NMR (600 MHz): δ = 7.14–7.34 (30H, m, H-Ar), 5.65 (1H, d, $J_{1,2}$ 3.5 Hz, H-1), 4.83 (1H, d, *J* 11.4 Hz, benzylic H), 4.66 (1H, d, *J* 11.4 Hz, benzylic H), 4.61 (1H, d, *J* 11.7 Hz, benzylic H), 4.46–4.57 (7H, m, benzylic H), 4.42 (1H, d, $J_{3',4'}$ 7.3 Hz, H-3'), 4.39 (1H, d, *J* 12.2 Hz, benzylic H), 4.36 (1H, d, *J* 12.0 Hz, benzylic H), 4.03–4.15 (4H, m, H-5', H-4', H-3, H-5), 4.02 (1H, d, $J_{7',7'}$ 16.3 Hz, H-7'), 3.94 (1H, d, H-7'), 3.79 (1H, dd, $J_{6',6'}$ 10.4 Hz, $J_{6',5'}$ 6.8 Hz, H-6'), 3.73 (1H, dd, $J_{6',5'}$ 4.1 Hz, H-6'), 3.71 (1H, d, $J_{1',1'}$ 11.1 Hz, H-1'), 3.52 (1H, dd, $J_{6,6}$ 10.7 Hz, $J_{6,5}$ 3.5 Hz, H-6), 3.48 (1H, d, H-1'), 3.47 (1H, dd, $J_{4,5}$ 10.1 Hz, $J_{4,3}$ 8.9 Hz, H-4), 3.38 (1H, dd, $J_{6,5}$ 2.0 Hz, H-6), 3.32 (1H, dd, $J_{2,3}$ 9.5 Hz, H-2), 1.45 (9H, s, H-O^t*Bu*), 0.89 (9H, s, H-Si^t*Bu*), 0.012 (3H, s, H-SiCH_3), 0.010 (3H, s, H-SiCH_3) ppm. ^{13}C NMR (150 MHz): δ = 169.36 ($CO_2{}^t$Bu), 138.68, 138.26, 138.22, 138.21, 137.99, 137.96 (C_{quat}, 6 × Ph), 127.17–128.28 (30C, m, C-Ph), 104.57 (C-2'), 90.08 (C-1), 83.84 (C-3'), 82.41 (C-4'), 81.36 (C_{quat}, O^t*Bu*), 79.85 (C-2), 79.73 (C-5'), 79.00 (C-4), 74.56, 73.38, 73.35, 72.88, 72.41, 72.30 (6 × OCH_2Ph), 73.78 (C-3), 72.88 (C-6'), 71.33 (C-1'), 70.62 (C-5), 69.06 (C-7'), 68.76 (C-6), 28.11 (triple intensity, 3C-O^t*Bu*), 26.05 (triple intensity, 3C-Si^t*Bu*), 18.11 (C_{quat}, Si^t*Bu*), -3.96, -4.24 (2 × SiCH_3) ppm. HRMS (ESI) calcd for $C_{66}H_{82}O_{13}NaSi$ $[M + Na]^+$: 1133.5417, found: 1133.5432. Analysis for $C_{66}H_{82}O_{13}Si$ (1111.47): Calcd: C, 71.32; H, 7.44. Found: C, 71.27; H, 7.43.

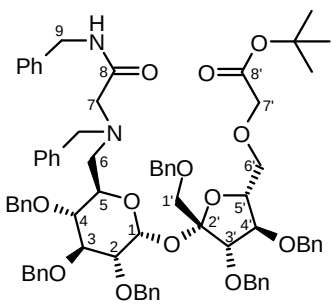
4.2.22 Synthesis of 1',2,3,3',4,4'-hexa-*O*-benzyl-6'-*O*-(2-*tert*-butoxy-2-oxoethyl)-sucrose (3.33)

Compound **3.32** (394 mg, 0.35 mmol) was desilylated with tetrabutylammonium fluoride trihydrate as above (see 4.2.3, *Procedure 1*). The product was isolated by flash chromatography (hexanes–ethyl acetate, 75:25) to afford pure compound **3.33** (251 mg, 0.25 mmol, 71%). TLC [hexanes/AcOEt (3:1)]: R_f = 0.34. Colorless oil. $[\alpha]_D{}^{20}$ = +47.7 (CH_2Cl_2). ^{1}H NMR (600 MHz): δ = 7.17–7.35 (30H, m, H-Ar), 5.74 (1H, d, $J_{1,2}$ 3.5 Hz, H-1), 4.81 (1H, d, *J* 11.3 Hz, benzylic H), 4.66 (1H, d, *J* 11.7 Hz, benzylic H), 4.61 (1H, d, *J* 11.3 Hz, benzylic H), 4.56 (1H, d, *J* 12.0 Hz, benzylic H), 4.51–4.55 (3H, m, benzylic H), 4.50 (1H, d, *J* 11.3 Hz, benzylic H), 4.49 (1H, d, *J* 11.3 Hz, benzylic H), 4.42 (1H, d, $J_{3',4'}$ 7.3 Hz, H-3'), 4.41 (1H, d, *J* 11.7 Hz, benzylic H), 4.40 (1H, d, *J* 12.4 Hz, benzylic H), 4.38 (1H, d, *J* 12.5 Hz, benzylic H), 4.15 (1H, dd, $J_{4',5'}$ 7.4 Hz, H-4'), 4.12 (1H, m, H-5'),



4.02–4.07 (2H, m, H-3, H-5), 4.00 (1H, d, $J_{7',7'}$ 16.3 Hz, H-7'), 3.95 (1H, d, H-7'), 3.73–3.80 (2H, m, 2H-6'), 3.72 (1H, d, $J_{1',1'}$ 10.9 Hz, H-1'), 3.50–3.56 (2H, m, H-4, H-6), 3.51 (1H, d, H-1'), 3.39 (1H, dd, $J_{6,6}$ 10.7 Hz, $J_{6,5}$ 1.9 Hz, H-6), 3.36 (1H, dd, $J_{2,3}$ 9.6 Hz, H-2), 1.45 (9H, s, H-^{t}Bu) ppm. ^{13}C NMR (150 MHz): δ = 169.33 ($CO_2{}^t$Bu), 138.73, 138.24, 138.04, 138.01, 137.98, 137.87 (C_{quat}, 6 × Ph), 127.47–128.40 (30C, m, C-Ph), 104.57 (C-2'), 89.35 (C-1), 83.85 (C-3'), 82.11 (C-4'), 81.43 (C_{quat}, O^{t}Bu), 79.60 (C-5'), 78.85 (C-2), 77.47 (C-4), 74.28, 73.46, 73.38, 73.06, 72.51, 71.67 (6 × OCH_2Ph), 73.43 (C-3), 72.57 (C-6'), 71.21 (C-1'), 70.04 (C-5), 69.02 (C-7'), 68.47 (C-6), 28.11 (triple intensity, 3C-^{t}Bu) ppm. HRMS (ESI) calcd for $C_{60}H_{68}O_{13}Na$ $[M + Na]^+$: 1019.4552, found: 1019.4524. Analysis for $C_{60}H_{68}O_{13}$ (997.20): Calcd: C, 72.27; H, 6.87. Found: C, 72.01; H, 6.89.

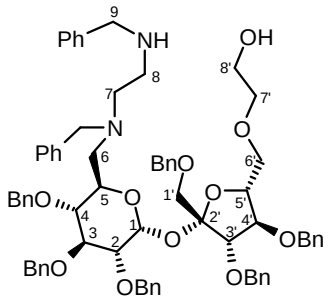
4.2.23 *N*-(2-benzyloamino-2-oxoethyl)-*N*-benzylo-6-amino-6-deoxy-1',2,3,3',4,4'-hexa-*O*-benzyl-6'-*O*-(2-*tert*-butoxy-2-oxoethyl)-sucrose (3.35)



Preparation of **3.35** was performed starting from the alcohol **3.33** (230 mg, 0.23 mmol) by tandem Swern oxidation/reductive amination as desribed previously (see 4.2.13 and 4.2.17 *Method 2*). The crude product was purificated by flash chromatography (hexanes–ethyl acetate, 90:10 to 70:30) to afford pure compound **3.35** (210 mg, 0.17 mmol, 74%). TLC [hexanes/AcOEt (3:2)]: R_f = 0.35. Colorless oil. $[\alpha]_D{}^{20}$ = +30.5 (CH_2Cl_2). ^{1}H NMR (600 MHz): δ = 7.89 (1H, t, *J* 6.0 Hz, NH), 7.08–7.33 (40H, m, H-Ar), 5.40 (1H, d, $J_{1,2}$ 3.3 Hz, H-1), 4.85 (1H, d, *J* 10.9 Hz, benzylic H), 4.80 (1H, d, *J* 11.1 Hz, benzylic H), 4.76 (1H, d, *J* 11.8 Hz, benzylic H), 4.64 (1H, d, *J* 10.9 Hz, benzylic H), 4.60 (1H, d, *J* 11.5 Hz, benzylic H), 4.43–4.54 (5H, m, H-9, 4 × benzylic H), 4.41 (1H, d, *J* 12.4 Hz, benzylic H), 4.36 (1H, d, *J* 11.1 Hz, benzylic H), 4.34 (1H, d, *J* 12.0 Hz, benzylic H), 4.33 (1H, d, $J_{3',4'}$ 7.8 Hz, H-3'), 4.18–4.24 (2H, m, H-9, H-5), 4.06–4.11 (2H, m, H-4', H-5'), 3.97 (1H, dd, $J_{3,4}$ 9.1 Hz, $J_{3,2}$ 9.7 Hz, H-3), 3.89 (1H, d, $J_{7',7'}$ 16.4 Hz, H-7'), 3.81 (1H, d, H-7'), 3.75 (1H, d, $J_{1',1'}$ 10.9 Hz, H-1'), 3.74 (1H, dd, $J_{6',6'}$ 10.1 Hz, $J_{6',5'}$ 5.0 Hz, H-6'), 3.68 (1H, dd, $J_{6',5'}$ 6.1 Hz, H-6'), 3.62 (1H, d, *J* 13.9 Hz, N-CH_2-Ph), 3.52 (1H, d, N-CH_2-Ph), 3.51 (1H, d, H-1'), 3.34 (1H, d, $J_{7,7}$ 16.7 Hz, H-7), 3.24 (1H, dd, H-2), 3.08 (1H, dd, $J_{4,5}$ 9.6 Hz, H-4), 3.07 (1H, d, H-7), 2.83 (1H, dd, $J_{6,6}$ 13.7 Hz, $J_{6,5}$ 1.8 Hz, H-6), 2.38 (1H, dd, $J_{6,5}$ 8.5 Hz, H-6), 1.42 (9H, s, 9 × H-^{t}Bu) ppm. ^{13}C NMR (150 MHz): δ = 171.12 (C-8), 169.27 (C-8'), 138.68, 138.62, 138.43, 138.23, 138.16, 138.06, 137.77, 136.87 (C_{quat}, 8 × Ph), 127.14–129.42 (40C, m, C-Ph), 105.72 (C-2'), 90.41 (C-1), 83.68 (C-3'), 83.46 (C-4'), 81.35 (C_{quat}, O^{t}Bu), 81.15 (C-3), 80.23 (C-5'),

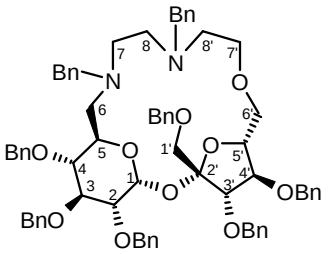
80.08 (2C, C-2, C-4), 75.40, 74.74, 73.36, 72.87, 72.14, 72.04 (6 × O*C*H$_2$Ph), 72.45 (C-6'), 70.07 (C-1'), 69.57 (C-5), 68.81 (C-7'), 58.76 (2C, C-7, N-*C*H$_2$-Ph), 55.39 (C-6), 42.87 (C-9), 28.07 (triple intensity, 3C-^{t}Bu) ppm. HRMS (ESI) calcd for $C_{76}H_{85}N_2O_{13}$ $[M + H]^+$: 1233.6052, found: 1233.6036. Analysis for $C_{78}H_{84}N_2O_{13}$ (1233.52): Calcd: C, 74.00; H, 6.86; N, 2.27. Found: C, 74.16; H, 6.99; N, 2.31.

4.2.24 *N*-(2-Benzyloaminoethyl)-*N*-benzylo-6-amino-6-deoxy-1',2,3,3',4,4'-hexa-*O*-benzyl-6'-*O*-(2-hydroxyethyl)-sucrose (3.36)



Amido ester **3.35** (186 mg, 0.15mmol) was reduced with $LiAlH_4$ (1.5 mL 1M solution in THF) in THF (20 mL) as above (see 4.2.19). The product was isolated by flash chromatography (dichloromethane–methanol, 90:10) to afford pure compound **3.36** (145 mg, 0.13 mmol, 84%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.45. Colorless oil. $[\alpha]_D^{23}$ = +38.6 (CH_2Cl_2). ^{1}H NMR (600 MHz): δ = 7.15–7.31 (40H, m, H-Ar), 5.74 (1H, d, $J_{1,2}$ 3.3 Hz, H-1), 4.90 (1H, d, *J* 10.9 Hz, benzylic H), 4.87 (1H, d, *J* 11.2 Hz, benzylic H), 4.72 (1H, d, *J* 11.5 Hz, benzylic H), 4.69 (1H, d, *J* 10.9 Hz, benzylic H), 4.63 (1H, d, *J* 11.4 Hz, benzylic H), 4.60 (1H, d, *J* 11.8 Hz, benzylic H), 4.52 (1H, d, *J* 10.6 Hz, benzylic H), 4.51 (1H, d, *J* 11.4 Hz, benzylic H), 4.50 (2H, d, *J* 10.9 Hz, benzylic H), 4.42 (1H, d, *J* 11.5 Hz, benzylic H), 4.41 (1H, d, $J_{3',4'}$ 6.8 Hz, H-3'), 4.38 (1H, d, *J* 11.8 Hz, benzylic H), 4.23 (1H, dd, $J_{4',5'}$ 7.1 Hz, H-4'), 4.19 (1H, m, H-5), 4.02 (1H, m, H-5'), 4.00 (1H, dd, $J_{3,2}$ 9.7 Hz, $J_{3,4}$ 8.8 Hz, H-3), 3.76 (1H, dd, $J_{6',6'}$ 10.8 Hz, $J_{6',5'}$ 6.1 Hz, H-6'), 3.74 (1H, d, $J_{1',1'}$ 11.1 Hz, H-1'), 3.54–3.65 (6H, m, H-6', H-1', 2H-9, Ph-C*H*$_2$-N), 3.48–3.53 (3H, m, 2H-8', H-7'), 3.44 (1H, m, H-7'), 3.42 (1H, dd, H-2), 3.34 (1H, dd, $J_{4,5}$ 9.7 Hz, H-4), 2.73 (1H, m, H-7), 2.63 (1H, m, H-6), 2.54–2.58 (2H, m, 2H-8), 2.46–2.53 (2H, m, H-6, H-7) ppm. ^{13}C NMR (150 MHz): δ = 140.28 (C_{quat}-Ph-CH_2-N), 139.18 (C_{quat}-Ph-CH_2-N), 138.83, 138.62, 138.48, 138.33, 138.16, 137.89 (C_{quat}, 6 × Ph), 129.40–126.81 (40C, m, C-Ph), 104.73 (C-2'), 89.59 (C-1), 83.71 (C-3'), 81.83 (C-4'), 81.68 (C-3), 80.21 (C-2), 79.64 (C-5'), 79.61 (C-4), 75.25, 74.43, 73.37, 72.84, 72.36, 72.21 (6 × O*C*H$_2$Ph), 73.17 (C-7'), 71.50 (C-6'), 71.39 (C-1'), 70.62 (C-5), 61.25 (C-8'), 59.39 (N-*C*H$_2$-Ph), 54.24 (C-6), 53.36 (C-7), 53.22 (C-9), 46.08 (C-8) ppm. HRMS (ESI) calcd for $C_{72}H_{81}N_2O_{11}$ $[M + H]^+$: 1149.5835, found: 1149.5847. Analysis for $C_{72}H_{80}N_2O_{11}$ (1149.45): Calcd: C, 75.24; H, 7.02; N, 2.44. Found: C, 75.29; H, 7.14; N, 2.32.

4.2.25 6,6'-[1,4-Di(azabenzyl)hexa-1,6-di-yl]-6-deoxy-1',2,3,3',4,4'-hexa-O-benzylsucrose (3.37)

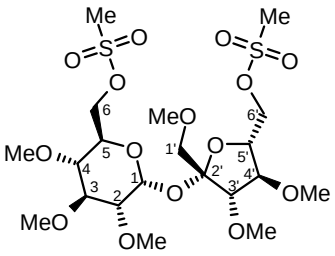


Preparation of **3.37** was performed as desribed previously (see 4.2.8) starting from amino alcohol **3.36** (127 mg, 0.11 mmol) in toluene (40 mL). The product was isolated by flash chromatography (dichloromethane–methanol, 100:0 to 90:10) to afford pure compound **3.37** (93 mg, 0.82 mmol, 74%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.48. Colorless oil. $[\alpha]_D^{22}$ = +31.3 (CH_2Cl_2). ^{1}H NMR (600 MHz): δ = 7.08–7.33 (40H, m, H-Ar), 5.71 (1H, d, $J_{1,2}$ 3.5 Hz, H-1), 4.92 (1H, d, *J* 10.8 Hz, benzylic H), 4.85 (1H, d, *J* 11.5 Hz, benzylic H), 4.74 (1H, d, *J* 12.0 Hz, benzylic H), 4.73 (1H, d, *J* 10.8 Hz, benzylic H), 4.72 (1H, d, *J* 12.0 Hz, benzylic H), 4.66 (2H, s, benzylic H), 4.63 (1H, d, *J* 11.8 Hz, benzylic H), 4.53 (1H, d, *J* 12.0 Hz, benzylic H), 4.51 (1H, d, *J* 11.5 Hz, benzylic H), 4.43–4.48 (3H, m, H-3', H-4', benzylic H), 4.35 (1H, d, *J* 12.0 Hz, benzylic H), 4.24 (1H, m, H-5), 4.05 (1H, m, H-5'), 4.01 (1H, dd, $J_{3,2}$ 9.3 Hz, $J_{3,4}$ 9.3 Hz, H-3), 3.86 (1H, dd, $J_{6',6'}$ 11.1 Hz, $J_{6',5'}$ 5.7 Hz, H-6'), 3.81 (1H, dd, $J_{6',5'}$ 2.5 Hz, H-6'), 3.68 (1H, d, $J_{1',1'}$ 10.9 Hz, H-1'), 3.46–3.58 (6H, m, H-1', H-2, 2H-7', Ph-CH_2-N), 3.39–3.44 (3H, m, H-4, Ph-CH_2-N), 2.52–2.77 (8H, m, 2H-6, 2H-7, 2H-8, 2H-8') ppm. ^{13}C NMR (150 MHz): δ = 139.82 (C_{quat}-Ph-CH_2-N), 139.03 (C_{quat}-Ph-CH_2-N), 138.85, 138.80, 138.46, 138.44, 138.19, 138.03 (C_{quat}, 6 × Ph), 129.12–126.56 (40C, m, C-Ph), 103.98 (C-2'), 88.74 (C-1), 83.49 (C-3'), 82.07 (C-3), 81.54 (C-4'), 79.74 (C-5'), 79.73 (C-2), 79.59 (C-4), 75.46, 74.55, 73.24, 72.64, 72.54, 72.50 (6 × O*C*H_2Ph), 72.28 (C-1'), 71.25 (C-6'), 70.92 (C-5), 70.70 (C-7'), 60.24 (N-*C*H_2-Ph), 59.99 (N-*C*H_2-Ph), 54.58 (C-6), 53.88, 52.12, 51.09 (C-7, C-8, C-8') ppm. HRMS (ESI) calcd for $C_{72}H_{79}N_2O_{10}$ $[M + H]^+$: 1131.5735, found: 1131.5748. Analysis for $C_{60}H_{68}O_{13}$ (1131.43): Calcd: C, 76.43; H, 6.95; N, 2.48. Found: C, 76.44; H, 6.81; N, 2.35.

1',2,3,3',4,4'-Hexa-*O*-benzyl-6,6'-di-*O*-(methylsulfonyl)sucrose (3.38) are prepared was prepared according to the literature procedure.[61]

4.2.26 Preparation of 1',2,3,3',4,4'-Hexa-*O*-methyl-6,6'-di-*O*-(methylsulfonyl) sucrose (3.39)[207]

Preparation of **3.39** was performed as desribed previously (see 4.2.12) starting from diol **3.11** (0.85 g, 2.0 mmol), Et_3N (1.12 mL, 8.0 mmol), and MsCl (0.48 mL, 6.0 mmol) in CH_2Cl_2 (40 mL). The product was isolated by flash chromatography (hexanes–ethyl acetate, 40:60) to afford pure compound **3.39** (1.05 g, 1.80 mmol, 90%). TLC (AcOEt): R_f = 0.80. Colorless oil.

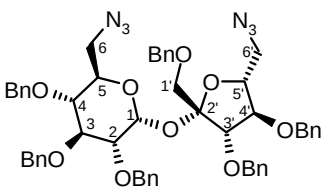


$[\alpha]_D^{21}$ = +52.5 (CH_2Cl_2). ^{1}H NMR (600 MHz): δ = 5.54 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.50 (1H, dd, $J_{6',5'}$ 7.0 Hz, $J_{6',6'}$ 11.1 Hz, H-6'), 4.48 (1H, dd, $J_{6,5}$ 2.0 Hz, $J_{6,6}$ 10.9 Hz, H-6), 4.37 (1H, dd, $J_{6',5'}$ 3.1 Hz, H-6'), 4.35 (1H, dd, $J_{6,5}$ 4.4 Hz, H-6), 4.04–4.08 (3H, m, H-3', H-5, H-5'), 3.83 (1H, dd, $J_{4',3'}$ 7.7 Hz, $J_{4',5'}$ 7.7 Hz, H-4'), 3.62 (3H, s, H-CH_3), 3.58 (3H, s, H-CH_3), 3.55 (1H, d, *J* 11.1 Hz, H-1'), 3.49 (3H, s, H-CH_3), 3.48 (3H, s, H-CH_3), 3.47 (3H, s, H-CH_3), 3.46 (1H, m, H-3), 3.41 (3H, s, H-CH_3), 3.39 (1H, d, H-1'), 3.12 (1H, dd, $J_{2,3}$ 9.6 Hz, H-2), 3.09 (1H, dd, $J_{4,3}$ 8.8 Hz, $J_{4,5}$ 10.2 Hz, H-4), 3.07 (6H, s, 6H-Ms) ppm. ^{13}C NMR (150 MHz): δ = 104.39 (C-2'), 89.19 (C-1), 84.92 (C-3'), 83.05 (C-3), 82.89 (C-4'), 81.42 (C-2), 78.91 (C-4), 77.92 (C-5'), 73.86 (C-1'), 69.92 (C-6'), 69.27 (C-5), 69.00 (C-6), 60.70, 60.56, 59.46, 58.66, 58.64, 58.61 (6 × O*C*H_3), 37.43, 37.38 (2C-Ms) ppm. HRMS (ESI) calcd for $C_{20}H_{38}O_{15}NaS_2$ $[M + Na]^+$: 605.1544, found: 605.1554. Analysis for $C_{20}H_{38}O_{15}S_2$ (582.64): Calcd: C, 41.23; H, 6.57. Found: C, 41.06; H, 6.47.

4.2.27 Synthesis of 6,6'-diazido-1',2,3,3',4,4'-hexa-*O*-benzyl-6,6'-dideoxysucrose (3.40) and 6,6'-diazido-1',2,3,3',4,4'-hexa-*O*-methyl-6,6'-dideoxysucrose (3.41)

To a solution of compound **3.38** (312 mg, 0.3 mmol) or **3.39** (175 mg, 0.3 mmol) in dry DMF (10 mL) NaN_3 (98 mg, 1.5 mmol) was added. The mixture was stirred for 12 h at 100°C and cooled to rt. Water (40 mL) and AcOEt (30 mL) were added, phases were separated, and the aqueous one extracted with AcOEt (4 × 30 mL). Combined organic solutions were washed with water (2 × 20 mL), brine (20 mL), dried, concentrated, and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 90:10 for **3.38** or 75:25 for **3.39**) to afford pure product **3.40** (241 mg, 0.26 mmol, 86%) or **3.41** (106 mg, 0.22 mmol, 74%).

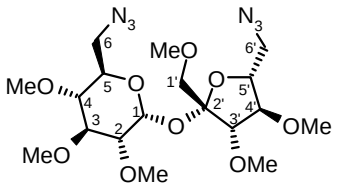
4.2.27.1 6,6'-Diazido-1',2,3,3',4,4'-hexa-*O*-benzyl-6,6'-dideoxysucrose (3.40)



TLC [hexanes/AcOEt (2:1)]: R_f = 0.76. Colorless oil. $[\alpha]_D^{23}$ = +67.3 (CH_2Cl_2). IR: ν = 3089, 3064, 3031, 2918, 2868, 2101, 1953, 1876, 1810, 1605, 1586, 1605, 1586, 1496, 1454, 1398, 1361, 1286, 1208, 1088, 1074, 1028, 1000, 942, 911, 873, 844, 736, 697 cm^{-1}. ^{1}H NMR (600 MHz): δ = 7.21–7.36 (30H, m, ArH), 5.64 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 4.91 (1H, d, *J* 10.9 Hz, benzylic H), 4.88 (1H, d, *J* 11.1 Hz, benzylic H), 4.75 (1H, d, *J* 10.9 Hz, benzylic H), 4.66 (1H, d, *J* 11.4 Hz, benzylic H), 4.63 (1H, d, *J* 11.6 Hz, benzylic H), 4.60 (1H, d, *J* 11.8 Hz, benzylic H), 4.58 (1H, d, *J* 11.6 Hz, benzylic H), 4.56 (1H, d, *J* 12.0 Hz, benzylic H), 4.55 (1H, d, *J* 11.1 Hz, benzylic H), 4.51 (1H, d, *J* 11.4 Hz, benzylic

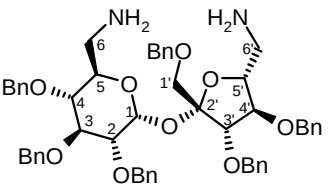
H), 4.50 (1H, d, *J* 11.8 Hz, benzylic H), 4.44 (1H, d, $J_{3',4'}$ 7.0 Hz, H-3'), 4.43 (1H, d, *J* 12.0 Hz, benzylic H), 4.02–4.10 (3H, m, H-4', H-5, H-5'), 3.94 (1H, dd, $J_{3,4}$ 9.3 Hz, $J_{3,2}$ 9.3 Hz, H-3), 3.71 (1H, d, $J_{1',1'}$ 11.1 Hz, H-1'), 3.57 (1H, dd, $J_{6',6'}$ 12.8 Hz, $J_{6',5'}$ 3.5 Hz, H-6'), 3.52 (1H, d, H-1'), 3.52 (1H, m, H-2), 3.45 (1H, dd, $J_{4,5}$ 9.7 Hz, H-4), 3.34 (1H, dd, $J_{6',5'}$ 3.2 Hz, H-6'), 3.24 (1H, dd, $J_{6,6}$ 13.1 Hz, $J_{6,5}$ 2.5 Hz, H-6), 3.16 (1H, dd, $J_{6,5}$ 4.5 Hz, H-6) ppm. ^{13}C NMR (150 MHz): δ = 138.61, 138.21, 138.05, 137.90, 137.76, 137.73 (C_{quat}, 6 × Ph), 128.46–127.58 (30C, m, C-Ph), 104.82 (C-2'), 89.90 (C-1), 83.67 (C-3'), 82.43 (C-4'), 81.47 (C-3), 79.78 (C-2), 79.24 (C-5'), 78.14 (C-4), 75.47, 74.90, 73.46, 72.99, 72.59, 72.58 (6 × O*C*H_2Ph), 71.02 (C-1'), 70.37 (C-5), 53.38 (C-6'), 51.42 (C-6) ppm. HRMS (ESI) calcd for $C_{54}H_{56}N_6O_9Na$ $[M + Na]^+$: 955.4006, found: 955.3997. Analysis for $C_{54}H_{56}N_6O_9$ (933.08): Calcd: C, 69.51; H, 6.05; N, 9.01. Found: C, 69.72; H, 6.14; N, 9.10.

4.2.27.2 6,6'-Dazido-1',2,3,3',4,4'-hexa-*O*-methyl-6,6'-dideoxysucrose (3.41)



TLC [hexanes/AcOEt (1:3)]: R_f = 0.55. Colorless oil. $[\alpha]_D^{23}$ = +74.2 (CH_2Cl_2). IR: *v* = 2983, 2932, 2830, 2100, 1445, 1375, 1286, 1237, 1186, 1148, 1098, 1016, 994, 981, 942, 867, 831 cm^{-1}. ^{1}H NMR (600 MHz): δ = 5.54 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 4.06 (1H, d, $J_{3',4'}$ 7.6 Hz, H-3'), 3.99 (1H, ddd, $J_{5,4}$ 9.9 Hz, $J_{5,6}$ 4.7 Hz, $J_{5,6}$ 2.4 Hz, H-5), 3.95 (1H, ddd, $J_{5',6'}$ 7.8 Hz, $J_{5',4'}$ 7.6 Hz, $J_{5',6'}$ 4.0 Hz, H-5'), 3.82 (1H, dd, H-4'), 3.65 (1H, dd, $J_{6',6'}$ 12.9 Hz, $J_{6',5'}$ 7.8 Hz, H-6'), 3.62 (3H, s, 3H-CH_3), 3.60 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.56 (1H, m, H-6), 3.55 (3H, s, 3H-CH_3), 3.49 (6H, s, 6H-CH_3), 3.46 (3H, s, 3H-CH_3), 3.42 (3H, s, 3H-CH_3), 3.40–3.46 (2H, m, H-3, H-6'), 3.40 (1H, d, H-1'), 3.38 (1H, dd, $J_{6,6}$ 12.9 Hz, H-6), 3.15 (1H, dd, $J_{2,3}$ 9.7 Hz, H-2), 3.05 (1H, dd, $J_{4,3}$ 9.2 Hz, H-4) ppm. ^{13}C NMR (150 MHz): δ = 104.41 (C-2'), 89.24 (C-1), 85.11 (C-3'), 84.30 (C-4'), 82.94 (C-3), 81.60 (C-2), 80.24 (C-4), 79.17 (C-5'), 73.84 (C-1'), 70.30 (C-5), 60.65, 60.53, 59.48, 58.58, 58.46, 58.44, (6 × O*C*H_3), 53.61 (C-6'), 51.85 (C-6) ppm. HRMS (ESI) calcd for $C_{18}H_{32}N_6O_9Na$ $[M + Na]^+$: 499.2128, found: 499.2130. Analysis for $C_{18}H_{32}N_6O_9$ (476.49): Calcd: C, 45.37; H, 6.77; N, 17.64. Found: C, 45.54; H, 6.79; N, 17.66.

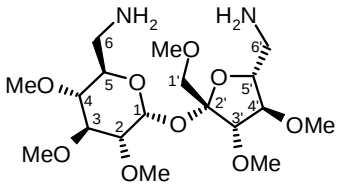
4.2.28 6,6'-Diamino-1',2,3,3',4,4'-hexa-*O*-benzyl-6,6'-dideoxysucrose (3.42)



This reaction was conducted under an argon atmosphere. To a vigorously stirred cooled (to –78 °C) solution of bis-azido compound **3.40** (150 mg, 0.16 mmol) in dry THF (10 mL), a 1M solution of $LiAlH_4$ in THF (1.3 mL) was slowly added. After 15

min, the mixture was allowed to reach room temperature and then stirred for 1 h. Excess of hydride was carefully decomposed with water (5 mL) and aqueous potassium bisulfate ($KHSO_4$, 10 mL). Ethyl acetate (20 mL) was added, the layers were separated, and the aqueous one extracted with ethyl acetate (3 × 20 mL). Combined organic solutions were dried, concentrated, and the crude product **3.42** (141 mg, 0.16 mmol, 99%) was used in the next step without further purification.

4.2.29 6,6'-Diamino-1',2,3,3',4,4'-hexa-*O*-methyl-6,6'-dideoxysucrose (3.43)



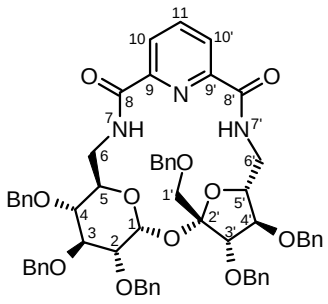
Bis-azido compound **3.41** (106 mg, 0.22 mmol) was dissolved in methanol (5 mL) and 10% palladium on activated carbon (12 mg, ~ 5 mol%) was added. The mixture was stirred under a hydrogen atmosphere overnight and then filtered through Celite. The Celite pad was additionally washed with MeOH (20 mL). Organic solutions were combined and the solvent removed under reduced pressure. The crude product **3.43** (94 mg, 0.22 mmol, 99%) was used in the next step without further purification.

4.2.30 Preparation of dilactams 3.45 and 3.46. General procedure for the synthesis of macrocyclic dilactams

This reaction was conducted under an argon atmosphere. 2,6-Pyridinedicarbonyl dichloride (**3.44**, 31 mg, 0.15 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and added dropwise to a stirred solution of di-amine **3.42** (133 mg, 0.15 mmol) or **3.43** (64 mg, 0.15 mmol) and Et_3N (63 μL, 0.45 mmol) in dry CH_2Cl_2 (40 mL) under an argone atmosphere. The mixture was stirred at room temperature for 1h, then concentrated *in vacuo* and the residue was partitioned between AcOEt (40 mL) and water (20 mL). Saturated K_2CO_3 solution (10 mL) was added, the layers were separated, and the aqueous one extracted with AcOEt (3 × 30 mL). Combined organic extracts were washed with water (20 mL) and brine (10 mL), dried, and concentrated, and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 35:65 for **3.45** or 0:100 for **3.46**) to afford pure compound **3.45** (107 mg, 0.10 mmol, 70%) or **3.46** (56 mg, 0.10 mmol, 67%).

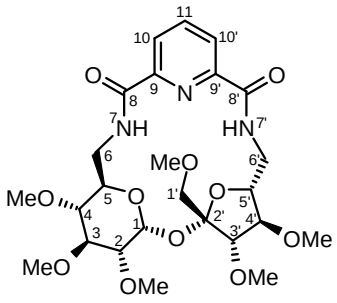
4.2.30.1 6,6'-*N*-[Pyridine-2,6-di-yl-bis(carbonylamino)]-1',2,3,3',4,4'-hexa-*O*-benzyl-6,6'-dideoxysucrose (3.45).

TLC [hexanes/AcOEt (1:2)]: R_f = 0.68. Colorless oil. $[\alpha]_D^{22}$ = +54.1 (CH_2Cl_2). IR: ν = 3403, 3088, 3063, 3030, 3007, 2920, 2870, 1683, 1570, 1530, 1497, 1453, 1402, 1360, 1305, 1238, 1209, 1157, 1072, 1028, 1003, 957, 913, 843, 750, 736, 697, 615 cm^{-1}. ^1H NMR (600 MHz):



δ = 8.37 (1H, d, $J_{7,6}$ 6.9 Hz, H-7), 8.26 (1H, d, $J_{7',6'}$ 6.9 Hz, H-7'), 8.26 (1H, d, $J_{10',11}$ 7.8 Hz, H-10'), 8.22 (1H, d, $J_{10,11}$ 7.7 Hz, H-10), 8.02 (1H, dd, H-11), 7.05–7.36 (30H, m, H-Ar), 5.61 (1H, d, $J_{1,2}$ 3.2 Hz, H-1), 4.91 (1H, d, *J* 11.0 Hz, benzylic H), 4.90 (1H, d, *J* 10.8 Hz, benzylic H), 4.84 (1H, d, *J* 11.3 Hz, benzylic H), 4.80 (1H, d, *J* 11.1 Hz, benzylic H), 4.69 (1H, d, *J* 11.4 Hz, benzylic H), 4.67 (2H, d, *J* 11.2 Hz, benzylic H), 4.42 (1H, d, *J* 11.5 Hz, benzylic H), 4.38 (1H, d, *J* 11.5 Hz, benzylic H), 4.33 (1H, d, *J* 11.2 Hz, benzylic H), 4.22–4.30 (4H, m, H-5, H-3', 2 × benzylic H), 4.15–4.21 (2H, m, H-5', H-6'), 4.06 (1H, dd, $J_{3,4}$ 9.3 Hz, $J_{3,2}$ 9.3 Hz, H-3), 4.00 (1H, ddd, $J_{6,6}$ 12.9 Hz, $J_{6,7}$ 7.4 Hz, $J_{6,5}$ 2.6 Hz, H-6), 3.88 (1H, dd, $J_{4',3'}$ 7.0 Hz, $J_{4',5'}$ 3.8 Hz, H-4'), 3.68 (1H, d, $J_{1',1'}$ 10.1 Hz, H-1'), 3.60 (1H, dd, $J_{2,3}$ 9.2 Hz, H-2), 3.57 (1H, d, H-1'), 3.45 (1H, dd, $J_{6',6'}$ 14.7 Hz, $H_{6',5'}$ 3.0 Hz, H-6'), 3.37 (1H, dd, $J_{4,5}$ 9.4 Hz, H-4), 3.02 (1H, m, H-6) ppm. ^{13}C NMR (150 MHz): δ = 163.28 (C-8'), 162.43 (C-8), 148.08, 147.56 (C-9, C-9'), 139.15 (C-11), 138.34, 138.17, 137.89, 137.74, 137.39, 137.32 (C_{quat}, 6 × Ph), 128.49–127.32 (30C, m, C-Ph), 124.00 (C-10'), 123.84 (C-10), 104.90 (C-2'), 92.07 (C-1), 83.30 (C-3'), 81.79 (C-4'), 81.54 (C-3), 80.58 (C-4), 79.93 (C-2), 78.68 (C-5'), 75.50, 75.06, 74.43, 72.99, 72.70, 72.29 (6 × O*C*H_2Ph), 73.81 (C-1'), 70.45 (C-5), 41.49 (C-6), 38.46 (C-6')ppm. HRMS (ESI) calcd for $C_{61}H_{61}N_3O_{11}Na$ $[M + Na]^+$: 1034.4204, found: 1034.4210. Analysis for $C_{61}H_{61}N_3O_{11}$ (1012.18): Calcd: C, 72.39; H, 6.07; N, 4.15. Found: C, 72.15; H, 6.10; N, 4.16.

4.2.30.2 6,6'-N-[Pyridine-2,6-di-yl-bis(carbonylamino)]-1',2,3,3',4,4'-hexa-O-methyl-6,6'-dideoxysucrose (3.46)



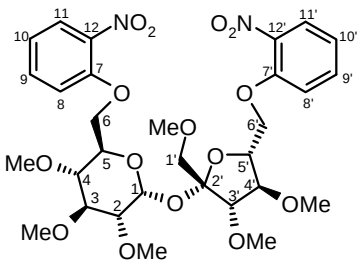
TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.56. Colorless oil. $[\alpha]_D^{22}$ = +57.3 (CH_2Cl_2). IR: *ν* = 3404, 2984, 2930, 2831, 1686, 1531, 1448, 1373, 1292, 1242, 1185, 1161, 1104, 1069, 1022, 998, 970, 926, 844, 756, 665, 646 cm^{-1}. ^{1}H NMR (600 MHz): δ = 8.60 (1H, d, $J_{7,6}$ 7.2 Hz, H-7), 8.39 (1H, d, $J_{7',6'}$ 9.9 Hz, H-7'), 8.27–8.30 (2H, m, H-10, H-10'), 8.04 (1H, dd, $J_{11,10}$ 7.7 Hz, $J_{11,10'}$ 7.7 Hz, H-11), 5.59 (1H, d, $J_{1,2}$ 3.5 Hz, H-1), 4.20 (1H, ddd, $J_{6',6'}$ 14.7 Hz, $J_{6',5'}$ 1.8 Hz, H-6'), 4.10–4.15 (3H, m, H-5, H-5', H-6), 3.81 (1H, d, $J_{3',4'}$ 2.9 Hz, H-3'), 3.63 (3H, s, 3H-CH_3), 3.61 (1H, d, $J_{1',1'}$ 10.3 Hz, H-1'), 3.60 (3H, s, 3H-CH_3), 3.56 (1H, dd, $J_{4',5'}$ 6.3 Hz, H-4'), 3.55 (3H, s, 3H-CH_3), 3.46–3.52 (3H, m, H-3, H-6', H-1'), 3.44 (3H, s, 3H-CH_3), 3.37 (3H, s, 3H-CH_3), 3.29 (3H, s, 3H-CH_3), 3.18 (1H, dd, $J_{2,3}$ 9.8 Hz, H-2), 3.10 (1H, m, H-6),

2.96 (1H, dd, $J_{4,3}$ 9.3 Hz, $J_{4,5}$ 9.3 Hz, H-4) ppm. ^{13}C NMR (150 MHz): δ = 163.35 (C-8'), 162.68 (C-8), 148.14, 147.64 (C-9, C-9'), 139.30 (C-11), 124.07, 123.95 (C-10, C-10'), 105.31 (C-2'), 91.33 (C-1), 84.65 (C-3'), 83.48 (C-4'), 83.28 (C-3), 82.67 (C-4), 82.12 (C-2), 79.28 (C-5'), 75.71 (C-1'), 69.85 (C-5), 60.86, 60.75, 59.53, 59.53, 58.17, 57.79 (6 × O*C*H$_3$), 41.49 (C-6), 38.95 (C-6') ppm. HRMS (ESI) calcd for $C_{25}H_{37}N_3O_{11}Na$ $[M + Na]^+$: 578.2326, found: 578.2328. Analysis for $C_{25}H_{37}N_3O_{11}$ (555.59): Calcd: C, 54.05; H, 6.71; N, 7.56. Found: C, 54.16; H, 6.85; N, 7.51.

4.2.31 General procedure for the synthesis of 1',2,3,3',4,4'-hexa-*O*-methyl-6,6'-di-*O*-nitrophenylsucroses (3.48a-c)[207] and 6,6'-di-*O*-cyanophenyl-1',2,3,3',4,4'-hexa-*O*-methylsucroses (3.54a–c)[240]

To a solution of compound **3.39** (291 mg, 0.5 mmol) in dry DMF (25 mL) K_2CO_3 (345 mg, 2.5 mmol) was added, followed by the corresponding nitrophenole **3.47a–c** (209 mg, 1.5 mmol) or cyanophenol **3.53a–c** (179 mg, 1.5 mmol). The mixture was stirred for 24 h at 100°C, cooled to rt, and partitioned between water (50 mL) and AcOEt (50 mL). Phases were separated and the aqueous one extracted with AcOEt (4 × 50 mL). Combined organic solutions were washed with water (2 × 30 mL), brine (30 mL), dried, and concentrated, and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 70:30 to 55:45 for nitro compounds or hexanes–ethyl acetate, 90:10 to 70:30 for cyano compounds) to afford pure product **3.48a–c** or **3.54a–c**.

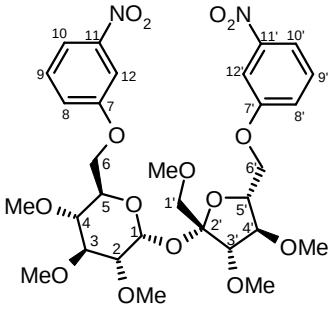
4.2.31.1 1',2,3,3',4,4'-Hexa-*O*-methyl-6,6'-di-*O*-2-nitrophenylsucrose (3.48a)



Yield: 284 mg (0.42 mmol, 85%). TLC [hexanes/AcOEt (1:2)]: R_f = 0.45. Yellowish oil. $[\alpha]_D^{21}$ = +33.2 (CH_2Cl_2). IR: ν = 2981, 2934, 2832, 1739, 1608, 1584, 1526, 1488, 1450, 1353, 1283, 1254, 1185, 1164, 1151, 1101, 1017, 1003, 983, 949, 879, 857, 818, 773, 745, 700, 663, 614, 559, 517 cm^{-1}. ^{1}H NMR (600 MHz): δ = 7.84 (1H, dd, $J_{8,9}$ 8.1 Hz, $J_{8,10}$ 1.7 Hz, H-8), 7.78 (1H, dd, $J_{8',9'}$ 8.1 Hz, $J_{8',10'}$ 1.7 Hz, H-8'), 7.51 (1H, ddd, $J_{10,11}$ 8.4 Hz, $J_{10,9}$ 7.5 Hz, $J_{10,8}$ 1.7 Hz, H-10), 7.37 (1H, ddd, $J_{10',11'}$ 8.3 Hz, $J_{10',9'}$ 7.4 Hz, $J_{10',8'}$ 1.7 Hz, H-10'), 7.12 (1H, dd, $J_{11,10}$ 8.4 Hz, $J_{11,9}$ 0.8 Hz, H-11), 7.12 (1H, dd, $J_{11',10'}$ 8.4 Hz, $J_{11',9'}$ 0.8 Hz, H-11'), 7.03 (1H, ddd, $J_{9,8}$ 8.1 Hz, $J_{9,10}$ 7.5 Hz, $J_{9,11}$ 0.9 Hz, H-9), 6.98 (1H, ddd, $J_{9',8'}$ 8.1 Hz, $J_{9',10'}$ 7.5 Hz, $J_{9',11'}$ 0.9 Hz, H-9'), 5.55 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 4.31–4.37 (2H, m, 2H-6'), 4.21–4.27 (3H, m, H-5', 2H-6), 4.15 (1H, m, H-5), 4.07 (1H, d, $J_{3',4'}$ 6,8 Hz, H-3'), 3.92 (1H, dd, $J_{4',5'}$ 6.4 Hz,

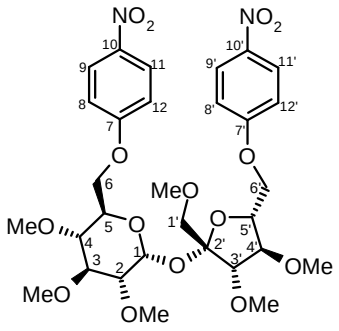
H-4'), 3.65 (1H, d, $J_{1',1'}$ 11.1 Hz, H-1'), 3.60 (3H, s, 3H-CH_3), 3.52 (3H, s, 3H-CH_3), 3.49 (4H, m, H-3, 3H-CH_3), 3.46 (3H, s, 3H-CH_3), 3.45 (3H, s, 3H-CH_3), 3.42 (1H, d, H-1'), 3.41 (3H, s, 3H-CH_3), 3.37 (1H, dd, $J_{4,5}$ 10.0 Hz, $J_{4,3}$ 9.1 Hz, H-4), 3.17 (1H, dd, $J_{2,3}$ 9.7 Hz, H-2) ppm. ^{13}C NMR (150 MHz): δ = 152.29 (C-7), 152.00 (C-7'), 140.26 (C-12'), 140.01 (C-12), 134.13 (C-10), 133.86 (C-10'), 125.65 (C-8), 125.42 (C-8'), 120.74 (C-9'), 120.59 (C-9), 115.52 (C-11'), 115.01 (C-11), 104.94 (C-2'), 89.95 (C-1), 85.77 (C-3'), 84.54 (C-4'), 83.04 (C-3), 81.39 (C-2), 78.92 (C-4), 78.68 (C-5'), 73.35 (C-1'), 71.16 (C-6'), 69.72 (C-5), 68.94 (C-6), 60.46, 60.41, 59.46, 58.71, 58.45, 58.26 (6 × O*C*H$_3$) ppm. HRMS (ESI) calcd for $C_{30}H_{40}N_2O_{15}$ $[M + H]^+$: 691.2321, found: 691.2341. Analysis for $C_{30}H_{40}N_2O_{15}$ (668.66): Calcd: C, 53.89; H, 6.03; N, 4.19. Found: C, 53.78; H, 6.08; N, 4.22.

4.2.31.2 1',2,3,3',4,4'-Hexa-*O*-methyl-6,6'-di-*O*-3-nitrophenylsucrose (3.48b)



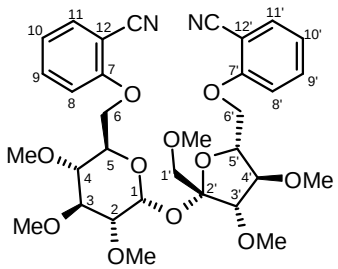
Yield: 301 mg (0.45 mmol, 90%). TLC [hexanes/AcOEt (1:2)]: R_f = 0.45. Yellowish solid, m.p. 120 °C. $[\alpha]_D^{21}$ = +58.0 (CH_2Cl_2). IR: ν = 3098, 2925, 2832, 2065, 1750, 1620, 1581, 1531, 1485, 1450, 1414, 1351, 1320, 1289, 1246, 1184, 1151, 1099, 1022, 995, 939, 892, 875, 863, 815, 801, 757, 738, 672, 620, 585, 558 cm^{-1}. ^{1}H NMR (600 MHz): δ = 7.79 (1H, d, $J_{10,9}$ 8.1 Hz, H-10), 7.75 (1H, d, $J_{10',9'}$ 8.1 Hz, H-10'), 7.74 (1H, s, H-12), 7.71 (1H, s, H-12'), 7.40 (1H, dd, $J_{9,8}$ 8.3 Hz, H-9), 7.33 (1H, dd, $J_{9',8'}$ 8.3 Hz, H-9'), 7.23 (1H, d, H-8), 7.21 (1H, d, H-8'), 5.62 (1H, d, $J_{1,2}$ 3.8 Hz, H-1), 4.38 (1H, dd, $J_{6',6'}$ 10.0 Hz, $J_{6',5'}$ 6.5 Hz, H-6'), 4.27 (1H, dd, $J_{6',5'}$ 4.0 Hz, H-6'), 4.19–4.25 (4H, m, H-5, H-5', 2H-6), 4.13 (1H, d, $J_{3',4'}$ 7.5 Hz, H-3'), 4.02 (1H, dd, $J_{4',5'}$ 7.5 Hz, H-4'), 3.63 (3H, s, 3H-CH_3), 3.62 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.53 (3H, s, 3H-CH_3), 3.52 (3H, s, 3H-CH_3), 3.51 (1H, m, H-3), 3.50 (3H, s, 3H-CH_3), 3.45 (1H, d, H-1'), 3.45 (3H, s, 3H-CH_3), 3.44 (3H, s, 3H-CH_3), 3.23 (1H, dd, $J_{4,5}$ 9.3 Hz, $J_{4,3}$ 9.3 Hz, H-4), 3.17 (1H, dd, $J_{2,3}$ 9.7 Hz, H-2) ppm. ^{13}C NMR (150 MHz): δ = 159.18 (C-7), 159.10 (C-7'), 149.13 (C-11), 149.07 (C-11'), 130.01 (C-9), 129.80 (C-9'), 121.88 (C-8'), 121.40 (C-8), 115.99 (C-10, C-10'), 109.01 (C-12), 108.76 (C-12'), 104.42 (C-2'), 89.37 (C-1), 85.26 (C-3'), 83.82 (C-4'), 83.23 (C-3), 81.65 (C-2), 79.46 (C-4), 78.61 (C-5'), 73.73 (C-1'), 69.78 (C-5), 69.68 (C-6'), 68.11 (C-6), 60.73, 60.56, 59.42, 58.66, 58.53, 58.47 (6 × O*C*H$_3$) ppm. HRMS (ESI) calcd for $C_{30}H_{40}N_2O_{15}Na$ $[M + Na]^+$: 691.2321, found: 691.2308. Anal. calcd. for $C_{30}H_{40}N_2O_{15}$ (668.66): C, 53.89; H, 6.03; N, 4.19. Found: C, 54.04; H, 5.92; N, 4.28.

4.2.31.3 1',2,3,3',4,4'-Hexa-*O*-methyl-6,6'-di-*O*-4-nitrophenylsucrose (3.48c)



Yield: 284 mg (0.42 mmol, 88%). TLC [hexanes/AcOEt (1:2)]: R_f = 0.53. Yellow oil. $[\alpha]_D^{21}$ = +84.9 (CH_2Cl_2). IR: ν = 3115, 3084, 2984, 2934, 2833, 2451, 1738, 1608, 1594, 1515, 1499, 1452, 1423, 1375, 1343, 1299, 1265, 1173, 1150, 1110, 1101, 1020, 983, 862, 846, 752, 690, 657, 630, 576, 531, 499 cm^{-1}. ^1H NMR (600 MHz): δ = 8.20 (2H, d, $J_{9,8}$ 9.3 Hz, H-9, H-11), 8.11 (2H, d, $J_{9',8'}$ 9.3 Hz, H-9', H-11'), 6.99 (2H, d, H-8, H-12), 6.69 (2H, d, H-8', H-12'), 5.62 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.37 (1H, dd, $J_{6',6'}$ 10.2 Hz, $J_{6',5'}$ 6.4 Hz, H-6'), 4.18–4.28 (5H, m, H-6', 2H-6, H-5, H-5'), 4.11 (1H, d, $J_{3',4'}$ 7.5 Hz, H-3'), 3.95 (1H, dd, $J_{4',5'}$ 7.4 Hz, H-4'), 3.63 (3H, s, 3H-CH_3), 3.62 (1H, d, $J_{1',1'}$ 11.4 Hz, H-1'), 3.53 (3H, s, 3H-CH_3), 3.50 (3H, s, 3H-CH_3), 3.50 (1H, m, H-3), 3.45 (3H, s, 3H-CH_3), 3.446 (3H, s, 3H-CH_3), 3.44 (1H, d, H-1'), 3.43 (3H, s, 3H-CH_3), 3.22 (1H, dd, $J_{4,5}$ 9.3 Hz, $J_{4,3}$ 9.2 Hz, H-4), 3.17 (1H, dd, $J_{2,3}$ 3.7 Hz, H-2) ppm. ^{13}C NMR (150 MHz): δ = 163.62, 163.60 (C-7, C-7'), 141.83, 141.74 (C-10, C-10'), 126.01 (C-9, C-11), 125.84 (C-9', C-11'), 114.01 (C-8, C-12), 114.53 (C-8', C-12'), 104.57 (C-2'), 89.54 (C-1), 85.39 (C-3'), 83.65 (C-4'), 83.25 (C-3), 81.70 (C-2), 79.42 (C-4), 78.48 (C-5'), 73.66 (C-1'), 69.72 (C-6'), 69.55 (C-5), 68.18 (C-6), 61.00, 60.65, 59.48, 58.75, 58.54, 58.40 (6 × O*C*H_3) ppm. HRMS (ESI) calcd for $C_{30}H_{40}N_2O_{15}Na$ $[M + Na]^+$: 691.2321, found: 691.2316. Analysis for $C_{30}H_{40}N_2O_{15}$ (668.66): Calcd: C, 53.89; H, 6.03; N, 4.19. Found: C, 53.71; H, 6.21; N, 3.96.

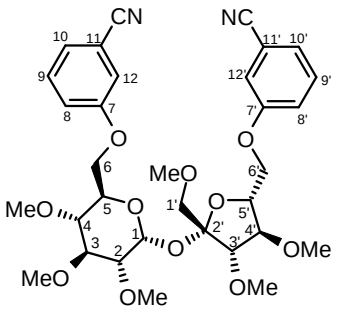
4.2.31.4 6,6'-Di-*O*-(2-cyanophenyl)-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.54a)



Yield: 255 mg (0.41 mmol, 81%). TLC [hexanes/AcOEt (1:2)]: R_f = 0.47. Colorless oil. $[\alpha]_D^{24}$ = +55.9 (CH_2Cl_2). IR: ν = 2983, 2934, 2832, 2228, 1741, 1599, 1581, 1494, 1449, 1374, 1292, 1261, 1185, 1164, 1102, 1045, 1018, 983, 879, 835, 757, 667, 566, 497 cm^{-1}. ^1H NMR (600 MHz): δ = 7.55 (1H, dd, *J* 7.7 Hz, *J* 1.7 Hz, H-8), 7.53 (1H, dd, *J* 7.5 Hz, *J* 1.7 Hz, H-8'), 7.51 (1H, ddd, *J* 8.4 Hz, *J* 7.6 Hz, *J* 1.6 Hz, H-10), 7.37 (1H, ddd, *J* 8.5 Hz, *J* 7.6 Hz, *J* 1.7 Hz, H-10'), 6.99–7.07 (3H, m, H-11, H-11', H-9), 6.95 (1H, dd, *J* 7.6 Hz, *J* 7.6 Hz, H-9'), 5.59 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.32–4.38 (2H, m, 2H-6'), 4.23–4.27 (3H, m, H-5', 2H-6), 4.18 (1H, m, H-5), 4.09 (1H, d, $J_{3',4'}$ 6.7 Hz, H-3'), 3.90 (1H, dd, $J_{4',5'}$ 6.1 Hz, H-4'), 3.66 (1H, d, $J_{1',1'}$ 11.1 Hz, H-1'), 3.60 (3H, s, 3H-CH_3), 3.54 (3H, s, 3H-CH_3), 3.51 (1H, dd, $J_{3,2}$ 9.7 Hz, $J_{3,4}$ 9.1 Hz, H-

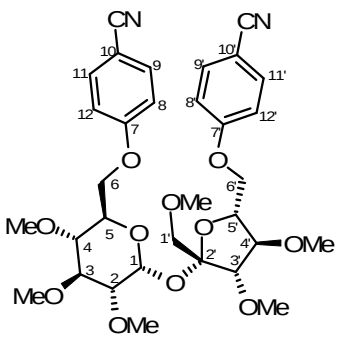
3), 3.49 (3H, s, 3H-CH_3), 3.47 (3H, s, 3H-CH_3), 3.46 (3H, s, 3H-CH_3), 3.43 (1H, d, H-1'), 3.42 (3H, s, 3H-CH_3), 3.34 (1H, dd, $J_{4,5}$ 10.0 Hz, H-4), 3.16 (1H, dd, H-2) ppm. ^{13}C NMR (150 MHz): δ = 160.49 (C-7), 160.33 (C-7'), 134.33 (C-10), 134.15 (C-10'), 133.82 (C-8), 133.82 (C-8'), 121.13 (C-9), 121.01 (C-9'), 116.40 (C-12'), 116.30 (C-12), 112.87 (C-11), 112.79 (C-11'), 104.98 (C-2'), 102.33 (*C*N), 102.25 (*C*N), 90.02 (C-1), 85.88 (C-3'), 84.92 (C-4'), 83.12 (C-3), 81.46 (C-2), 79.16 (C-4), 78.83 (C-5'), 73.30 (C-1'), 70.42 (C-6'), 69.71 (C-5), 68.52 (C-6), 60.63, 60.47, 59.51, 58.75, 58.55, 58.46 (6 × O*C*H_3) ppm. HRMS (ESI) calcd for $C_{32}H_{40}N_2O_{11}Na$ $[M + Na]^+$: 651.2524, found: 651.2525. Analysis for $C_{32}H_{40}N_2O_{11}$ (628.68): Calcd: C, 61.14; H, 6.41; N, 4.46. Found: C, 61.23; H, 6.34; N, 4.57.

4.2.31.5 6,6'-Di-*O*-(3-cyanophenyl)-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.54b)



Yield: 265 mg (0.42 mmol, 84%). TLC [hexanes/AcOEt (1:2)]: R_f = 0.51. Colorless oil. $[\alpha]_D^{22}$ = +56.3 (CH_2Cl_2). IR: ν = 3075, 2982, 2933, 2831, 2231, 1741, 1597, 1579, 1483, 1432, 1328, 1291, 1265, 1185, 1148, 1101, 1017, 983, 873, 790, 756, 682, 616, 517, 475 cm^{-1}. ^{1}H NMR (600 MHz): δ = 7.36 (1H, dd, *J* 7.8 Hz, *J* 8.0 Hz, H-9), 7.28 (1H, dd, *J* 7.8 Hz, *J* 8.2 Hz, H-9'), 7.24 (1H, d, *J* 7.6 Hz, H-10), 7.20 (1H, d, *J* 7.4 Hz, H-10'), 7.12–7.17 (3H, m, H-8, H-12, H-12'), 7.11 (1H, dd, *J* 8.2 Hz, *J* 2.3 Hz, H-8'), 5.60 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.29 (1H, m, H-6'), 4.12–4.23 (5H, m, H-5, H-5', 2H-6, H-6'), 4.11 (1H, d, $J_{3',4'}$ 7.6 Hz, H-3'), 3.97 (1H, dd, $J_{4',5'}$ 7.3 Hz, H-4'), 3.64 (3H, s, 3H-CH_3), 3.61 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.53 (3H, s, 3H-CH_3), 3.51 (3H, s, 3H-CH_3), 3.49 (1H, m, H-3), 3.47 (3H, s, 3H-CH_3), 3.44 (3H, s, 3H-CH_3), 3.43 (3H, s, 3H-CH_3), 3.43 (1H, d, H-1'), 3.22 (1H, dd, *J* 10.2 Hz, *J* 8.9 Hz, H-4), 3.16 (1H, dd, $J_{2,3}$ 9.7 Hz, H-2) ppm. ^{13}C NMR (150 MHz): δ = 158.74 (C-7), 158.65 (C-7'), 130.47 (C-9), 130.26 (C-9'), 124.83 (C-10), 124.76 (C-10'), 119.90 (C-8), 119.84 (C-8'), 118.51 (C-11), 118.51 (C-11'), 117.48 (C-12'), 117.39 (C-12), 113.30 (*C*N), 113.16 (*C*N), 104.39 (C-2'), 89.39 (C-1), 85.34 (C-3'), 83.79 (C-4'), 83.21 (C-3), 81.64 (C-2), 79.47 (C-4), 78.53 (C-5'), 73.70 (C-1'), 69.66 (C-5), 69.30 (C-6'), 67.80 (C-6), 60.76, 60.58, 59.42, 58.65, 58.47, 58.43 (6 × O*C*H_3) ppm. HRMS (ESI) calcd for $C_{32}H_{40}N_2O_{11}Na$ $[M + Na]^+$: 651.2524, found: 651.2522. Analysis for $C_{32}H_{40}N_2O_{11}$ (628.68): Calcd: C, 61.14; H, 6.41; N, 4.46. Found: C, 61.29; H, 6.61; N, 4.34.

4.2.31.6 6,6'-Di-*O*-(4-cyanophenyl)-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.54c)



Yield: 258 mg (0.41 mmol, 82%). TLC [hexanes/AcOEt (1:2)]: R_f = 0.54. Colorless oil. $[\alpha]_D^{24}$ = +75.8 (CH_2Cl_2). IR: ν = 2983, 2933, 2831, 2225, 1606, 1575, 1509, 1453, 1419, 1374, 1302, 1259, 1173, 1150, 1100, 1019, 983, 836, 755, 724, 684, 548 cm^{-1}. ^1H NMR (600 MHz): δ = 7.59 (2H, d, *J* 9.0 Hz, H-9, H-11), 7.50 (2H, d, *J* 9.0 Hz, H-9', H-11'), 6.98 (2H, d, *J* 9.0 Hz, H-8, H-12), 6.94 (2H, d, *J* 9.0 Hz, H-8', H-12'), 5.60 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.32 (1H, m, H-6'), 4.14–4.22 (5H, m, H-5, 2H-6, H-5', H-6'), 4.10 (1H, d, $J_{3',4'}$ 7.5 Hz, H-3'), 3.93 (1H, dd, $J_{4',5'}$ 7.3 Hz, H-4'), 3.62 (3H, s, 3H-CH_3), 3.61 (1H, d, $J_{1',1'}$ 10.8 Hz, H-1'), 3.52 (3H, s, 3H-CH_3), 3.49 (3H, s, 3H-CH_3), 3.49 (1H, dd, $J_{3,2}$ 9.7 Hz, $J_{3,4}$ 8.9 Hz, H-3), 3.435 (3H, s, 3H-CH_3), 3.432 (3H, s, 3H-CH_3), 3.427 (1H, d, H-1'), 3.418 (3H, s, 3H-CH_3), 3.20 (1H, dd, $J_{4,5}$ 9.7 Hz, H-4), 3.15 (1H, dd, H-2) ppm. ^{13}C NMR (150 MHz): δ = 161.92, 161.89 (C-7, C-7'), 134.11 (C-8, C-12), 133.93 (C-8', C-12'), 119.03, 118.94 (C-10, C-10'), 115.33 (C-9', C-11'), 115.27 (C-9, C-11), 104.54 (*C*N), 104.50 (C-2'), 104.36 (*C*N), 89.46 (C-1), 85.35 (C-3'), 83.64 (C-4'), 83.24 (C-3), 81.70 (C-2), 79.47 (C-4), 78.49 (C-5'), 73.68 (C-1'), 69.51 (C-5), 69.33 (C-6'), 67.78 (C-6), 60.78, 60.63, 59.46, 58.72, 58.51, 58.39 (6 × O*C*H_3) ppm. HRMS (ESI) calcd for $C_{32}H_{40}N_2O_{11}Na$ $[M + Na]^+$: 651.2524, found: 651.2538. Analysis for $C_{32}H_{40}N_2O_{11}$ (628.68): Calcd: C, 61.14; H, 6.41; N, 4.46. Found: C, 61.16; H, 6.55; N, 4.31.

4.2.32 General procedure for the syntheses of 6,6'-di-*O*-aminophenyl-1',2,3,3',4,4'-hexa-*O*-methylsucroses (3.49a-c)[207]

A mixture of bis-nitro compound **3.48a–c** (200 mg, 0.3 mmol), and 10% palladium on activated carbon (16 mg, ~ 5 mol%) in AcOEt–EtOH (10 mL/10 mL) was stirred under a hydrogen atmosphere overnight. It was then filtered through Celite which was additionally washed with AcOEt (50 mL). Organic solutions were combined and the solvent removed under reduced pressure and the resulting residue was purified by flash chromatography (hexanes–ethyl acetate, 70:30 to 20:80) to afford pure compound **3.49a-c**.

4.2.32.1 6,6'-Di-*O*-2-aminophenyl-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.49a)

Yield: 171 mg (0.28 mmol, 94%). TLC [hexanes/AcOEt (1:2)]: R_f = 0.27. Colorless oil. $[\alpha]_D^{24}$ = +70.9 (CH_2Cl_2). IR: ν = 3459, 3364, 3208, 2983, 2933, 2830, 1737, 1617, 1597, 1507, 1459, 1374, 1341, 1280, 1219, 1148, 1100, 1020, 1004, 983, 959, 883, 851, 742, 565 cm^{-1}. ^1H

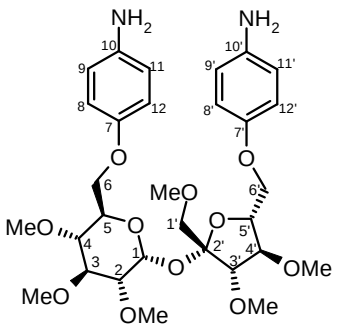
NMR (600 MHz): δ = 6.82 (1H, dd, *J* 1.1 Hz, *J* 7.8 Hz, H-Ar), 6.80 (1H, dd, *J* 1.2 Hz, *J* 6.2 Hz, H-Ar), 6.68–6.77 (4H, m, 4H-Ar), 6.57–6.63 (2H, m, 2H-Ar), 5.93 (1H, d, $J_{1,2}$ 3.9 Hz, H-1), 4.39 (1H, dd, $J_{4',5'}$ 8.2 Hz, $J_{4',3'}$ 8.5 Hz, H-4'), 4.34 (1H, dd, $J_{6',5'}$ 2.4 Hz, $J_{6',6'}$ 10.8 Hz, H-6'), 4.25 (1H, m, H-5), 4.22 (1H, dd, $J_{6,5}$ 3.1 Hz, $J_{6,6}$ 10.3 Hz, H-6), 4.10–4.14 (2H, m, H-3', H-6), 4.08 (1H, dd, $J_{6',5'}$ 7.3 Hz, H-6'), 4.40 (1H, m, H-5'), 3.63 (3H, s, 3H-CH_3), 3.57 (1H, d, $J_{1',1'}$ 10.8 Hz, H-1'), 3.52 (3H, s, 3H-CH_3), 3.51 (3H, s, 3H-CH_3), 3.49 (1H, dd, $J_{3,2}$ 9.7 Hz, $J_{3,4}$ 9.0 Hz, H-3), 3.46 (1H, d, H-1'), 3.44 (3H, s, 3H-CH_3), 3.41 (3H, s, 3H-CH_3), 3.39 (3H, s, 3H-CH_3), 3.37 (1H, dd, $J_{4,5}$ 9.2 Hz, H-4), 3.22 (1H, dd, H-2) ppm. ^{13}C NMR (150 MHz): δ = 146.39, 145.89 (C-7, C-7'), 137.23, 136.54 (C-12, C-12'), 121.65, 121.60, 118.52, 117.27, 115.25, 114.88, 112.25, 111.39 (8C-Ar), 103.67 (C-2'), 87.87 (C-1), 84.93 (C-3'), 83.24 (C-3), 81.34 (C-4'), 81.20 (C-2), 79.45 (C-4), 78.45 (C-5'), 75.52 (C-1'), 70.02 (C-5), 67.08 (C-6, C-6'), 60.79, 60.58, 59.53, 58.72, 58.61, 57.81 (6 × O*C*H_3) ppm. HRMS (ESI) calcd for $C_{30}H_{44}N_2O_{11}Na$ $[M + Na]^+$: 631.2837, found: 631.2822. Analysis for $C_{30}H_{44}N_2O_{11}$ (608.69): Calcd: C, 59.20; H, 7.29; N, 4.60. Found: C, 59.36; H, 7.39; N, 4.51.

4.2.32.2 6,6'-Di-*O*-3-aminophenyl-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.49b)

Yield: 175 mg (0.29 mmol, 96%). TLC [hexanes/AcOEt (1:3)]: R_f = 0.20. Yellow solid, m.p. 51 °C. $[\alpha]_D^{21}$ = +65.6 (CH_2Cl_2). IR: ν = 3457, 3366, 3237, 2983, 2934, 2831, 1622, 1602, 1496, 1454, 1331, 1291, 1192, 1160, 1099, 1016, 992, 982, 832, 758, 688 cm^{-1}. ^{1}H NMR (600 MHz): δ = 7.05 (1H, dd, $J_{9,8}$ 8.0 Hz, $J_{9,10}$ 8.1 Hz, H-9), 6.96 (1H, dd, $J_{9',8'}$ 8.0 Hz, $J_{9',10'}$ 8.0 Hz, H-9'), 6.35 (1H, ddd, $J_{8,9}$ 8.2 Hz, $J_{8,12}$ 2.2 Hz, $J_{8,10}$ 0.6 Hz, H-8), 6.30 (1H, ddd, $J_{8',9'}$ 8.0 Hz, $J_{8',12'}$ 2.2 Hz, $J_{8',10'}$ 0.6 Hz, H-8'), 6.28 (1H, ddd, $J_{10,9}$ 8.0 Hz, $J_{10,12}$ 2.2 Hz, $J_{10,8}$ 0.6 Hz, H-10), 6.24 (1H, dd, $J_{12,8}$ 2.2 Hz, $J_{12,10}$ 2.2 Hz, H-12), 6.21 (1H, ddd, $J_{10',9'}$ 8.0 Hz, $J_{10',12'}$ 2.2 Hz, $J_{10',8'}$ 0.6 Hz, H-10'), 6.18 (1H, dd, $J_{12',8'}$ 2.2 Hz, $J_{12',10'}$ 2.2 Hz, H-12'), 5.59 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.27 (1H, dd, $J_{6',6'}$ 10.0 Hz, $J_{6',5'}$ 6.5 Hz, H-6'), 4.13–4.19 (2H, m, H-5, H-5'), 4.08–4.13 (3H, m, H-3', H-6, H-6'), 4.05 (1H, dd, $J_{6,6}$ 10.3 Hz, $J_{6,5}$ 4.7 Hz, H-6), 3.98 (1H, dd, $J_{4',3'}$ 7.6 Hz, $J_{4',5'}$ 7.6 Hz, H-4'), 3.66 (4H, br s, 4H-NH_2), 3.63 (3H, s, 3H-CH_3), 3.60 (1H, d, $J_{1',1'}$ 10.9 Hz, H-1'), 3.53 (1H, dd, $J_{3,2}$ 9.6 Hz, $J_{3,4}$ 9.0 Hz, H-3), 3.503 (3H, s, 3H-CH_3), 3.502 (3H, s, 3H-CH_3), 3.47 (3H, s, 3H-CH_3), 3.44 (3H, s, 3H-CH_3), 3.421 (1H, d, H-1'), 3.418 (3H, s, 3H-CH_3), 3.26 (1H, dd, $J_{4,5}$ 10.1 Hz, H-4), 3.16 (1H, dd, H-2) ppm. ^{13}C NMR (150 MHz): δ =

159.96 (C-7), 159.88 (C-7'), 147.83, 147.78 (C-11, C-11'), 130.13 (C-9), 129.97 (C-9'), 108.12 (C-10), 107.82 (C-10'), 105.01 (C-8'), 104.75 (C-8), 104.11 (C-2'), 101.60 (C-12), 101.39 (C-12'), 89.23 (C-1), 85.16 (C-3'), 84.06 (C-4'), 83.19 (C-3), 81.65 (C-2), 79.72 (C-4), 78.96 (C-5'), 73.77 (C-1'), 69.75 (C-5), 68.97 (C-6'), 66.94 (C-6), 60.71, 60.50, 59.37, 58.56, 58.55, 58.46 (6 × O*C*H$_3$) ppm. HRMS (ESI) calcd for $C_{30}H_{44}N_2O_{11}Na$ $[M + Na]^+$: 631.2837, found: 631.2849. Analysis for $C_{30}H_{44}N_2O_{11}$ (608.69): Calcd: C, 59.20; H, 7.29; N, 4.60. Found: C, 58.96; H, 7.18; N, 4.52.

4.2.32.3 6,6'-Di-*O*-4-aminophenyl-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.49c)



Yield: 166 mg (0.27 mmol, 91%). TLC [hexanes/AcOEt (1:2)]: R_f = 0.25. White solid, m.p. 179 °C. $[\alpha]_D^{25}$ = +73.0 (CH_2Cl_2). IR: ν = 3439, 3353, 3229, 2981, 2933, 2830, 1628, 1512, 1456, 1374, 1329, 1294, 1273, 1236, 1184, 1151, 1098, 1018, 982, 823, 771, 517 cm^{-1}. ^{1}H NMR (600 MHz): δ = 6.75 (2H, d, $J_{8,9}$ 8.8 Hz, H-8, H-12), 6.73 (2H, d, $J_{8',9'}$ 8.8 Hz, H-8', H-12'), 6.62 (2H, d, H-9, H-11), 6.53 (2H, d, H-9', H-11'), 5.63 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 4.20 (1H, dd, $J_{6',6'}$ 9.9 Hz, $J_{6',5'}$ 6.2 Hz, H-6'), 4.11–4.15 (2H, m, H-5, H-5'), 4.04–4.10 (3H, m, H-3', H-6, H-6'), 4.03 (1H, dd, $J_{6,6}$ 10.5 Hz, $J_{6,5}$ 4.1 Hz, H-6), 3.97 (1H, dd, $J_{4',3'}$ 7.6 Hz, $J_{4',5'}$ 7.4 Hz, H-4'), 3.66 (4H, br s, 4H-NH_2), 3.62 (3H, s, 3H-CH_3), 3.61 (1H, d, $J_{1',1'}$ 10.8 Hz, H-1'), 3.50 (1H, dd, $J_{3,2}$ 9.7 Hz, $J_{3,4}$ 9.1 Hz, H-3), 3.496 (3H, s, 3H-CH_3), 3.491 (3H, s, 3H-CH_3), 3.45 (3H, s, 3H-CH_3), 3.431 (1H, d, H-1'), 3.429 (3H, s, 3H-CH_3), 3.41 (3H, s, 3H-CH_3), 3.31 (1H, dd, $J_{4,5}$ 9.9 Hz, H-4), 3.18 (1H, dd, H-2) ppm. ^{13}C NMR (150 MHz): δ = 152.08 (C-7), 151.93 (C-7'), 140.16, 140.13 (C-10, C-10'), 116.33 (2C, C-9, C-11), 116.32 (2C, C-9', C-11'), 115.83 (4C, C-8, C-12, C-8', C-12'), 104.22 (C-2'), 89.33 (C-1), 85.32 (C-3'), 84.21 (C-4'), 83.21 (C-3), 81.68 (C-2), 79.58 (C-4), 79.07 (C-5'), 73.84 (C-1'), 69.93 (C-6'), 69.90 (C-5'), 67.62 (C-6), 60.74, 60.50, 59.42, 58.60, 58.54, 58.38 (6 × O*C*H$_3$) ppm. HRMS (ESI) calcd for $C_{30}H_{44}N_2O_{11}Na$ $[M + Na]^+$: 631.2837, found: 631.2861. Analysis for $C_{30}H_{44}N_2O_{11}$ (608.69): Calcd: C, 59.20; H, 7.29; N, 4.60. Found: C, 58.95; H, 7.17; N, 4.39.

4.2.33 General procedure for the syntheses of 6,6'-di-*O*-[4-(aminomethyl)phenyl]-1',2,3,3',4,4'-hexa-*O*-methylsucroses (3.55a–c)[240]

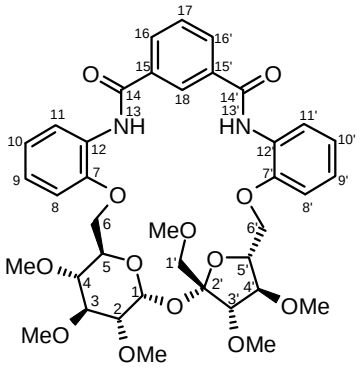
This reaction was conducted under an argon atmosphere. To a cooled to 0 °C solution of compound **3.54a–c** (215 mg, 0,34 mmol) in dry THF (30 mL), $LiAlH_4$ (93 mg, 2.45 mmol) was added slowly within 5 min. The mixture was stirred for 1 h at 60°C and cooled to room

temperature. Excess of hydride was carefully decomposed with water (10 mL) and aqueous potassium bisulfate ($KHSO_4$, 40 mL). Ethyl acetate (50 mL) was added, the layers were separated and the aqueous one was extracted with ethyl acetate (3 × 40 mL). Combined organic solutions were dried, concentrated, and the crude product was ready for next transformations without purification.

4.2.34 Syntheses of dilactams 3.51a–e, 3.52a–e,[207] 3.56a–c, 3.57a–c[240]

Preparation of these dilactams was performed as desribed previously (see 4.2.30) starting from isophthaloyl or 2,6-pyridinedicarbonyl dichlorides (**3.50** or **3.44**, respectively) (35 mg, 0.17 mmol), di-amine **3.49a–c** (103 mg, 0.17 mmol) or **3.55a–c** (108 mg, 0.17 mmol) and Et_3N (71 μL, 0.51 mmol). The products were isolated by flash chromatography (hexanes–ethyl acetate, 70:30 to 10:90).

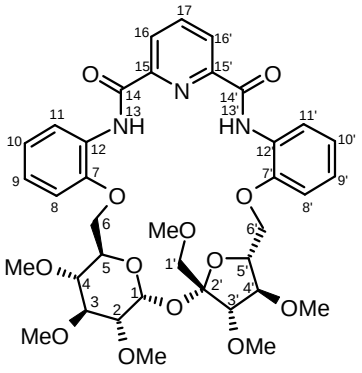
4.2.34.1 6,6'-*O*-{[Benzene-1,3-di-yl-bis(carbonylamino)]-2,2'-diphenyl}-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.51a).



Yield: 97 mg (0.13 mmol, 77%). TLC [hexanes/AcOEt (1:2)]: R_f = 0.40. White solid, m.p. 191 °C. $[\alpha]_D^{24}$ = +59.5 (CH_2Cl_2). IR: ν = 3387, 3065, 2983, 2933, 2831, 1676, 1601, 1526, 1491, 1457, 1400, 1373, 1331, 1291, 1252, 1204, 1188, 1136, 1099, 1016, 998, 939, 751 cm^{-1}. ^1H NMR (600 MHz): δ = 9.00 (1H, s, H-13), 8.89 (1H, s, H-13'), 8.51 (1H, br s, H-11'), 8.46 (1H, d, *J* 7.2 Hz, H-11), 8.32 (1H, d, *J* 7.8 Hz, H-16), 8.24 (1H, d, *J* 7.7 Hz, H-16'), 8.14 (1H, s, H-18), 7.69 (1H, dd, *J* 7.7 Hz, *J* 7.7 Hz, H-17), 7.15 (1H, dd, *J* 8.1 Hz, *J* 1.2 Hz, H-8), 7.07–7.13 (3H, m, H-9, H-10, H-10'), 7.03–7.07 (2H, H-8', H-9'), 5.22 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 4.39–4.47 (3H, m, 2H-6, H-6'), 4.27–4.32 (2H, m, H-4', H-6'), 4.18 (1H, m, H-5), 4.13 (1H, m, H-5'), 4.04 (1H, d, $J_{3',4'}$ 8.1 Hz, H-3'), 3.53 (3H, s, 3H-CH_3), 3.40 (3H, s, 3H-CH_3), 3.37 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.36 (1H, dd, $J_{3,4}$ 8.8 Hz, H-3), 3.252 (3H, s, 3H-CH_3), 3.246 (3H, s, 3H-CH_3), 3.19 (3H, s, 3H-CH_3), 3.16 (1H, d, H-1'), 3.04 (3H, s, 3H-CH_3), 2.88 (1H, dd, $J_{2,3}$ 9.8 Hz, H-2), 2.81 (1H, dd, $J_{4,5}$ 10.5 Hz, H-4) ppm. ^{13}C NMR (150 MHz): δ = 165.02 (C-14'), 164.23 (C-14), 148.76 (C-7), 146.54 (C-7'), 135.84 (C-15'), 135.32 (C-15), 132.58 (C-16), 132.25 (C-16'), 129.98 (C-17), 129.52 (C-12'), 128.48 (C-12), 124.59 (C-10), 124.16 (C-10'), 122.76 (C-9), 122.42 (C-18), 121.74 (C-9'), 121.45 (C-11), 120.56 (C-11'), 113.86 (C-8'), 113.26 (C-8), 104.43 (C-2'), 88.69 (C-1), 83.32, 83.30 (C-3, C-4'), 81.87 (C-3'), 81.45 (C-2), 79.67 (C-4), 74.40 (C-5'), 74.15 (C-1'), 70.91 (C-6'), 70.12

(C-5), 68.97 (C-6), 60.54, 60.44, 59.49, 58.25, 58.13, 54.93 (6 × O*C*H$_3$) ppm. HRMS (ESI) calcd for $C_{38}H_{46}N_2O_{13}Na$ [M + Na]$^+$: 761.2892, found: 761.2927. Anal. calcd. for $C_{38}H_{46}N_2O_{13}$ (738.80): C, 61.78; H, 6.28; N, 3.79%. Found: C, 61.89; H, 6.46; N, 3.67.

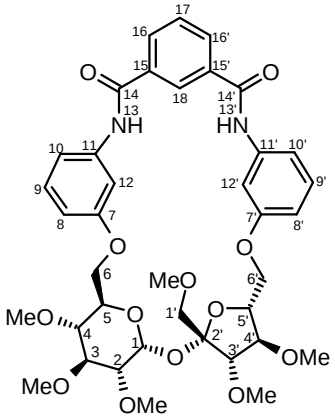
4.2.34.2 6,6'-*O*-{[Pyridine-2,6-di-yl-bis(carbonylamino)]-2,2'-diphenyl}-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.52a)



Yield: 98 mg (0.13 mmol, 78%). TLC [hexanes/AcOEt (1:2)]: R_f = 0.40. White solid, m.p. 228 °C. $[\alpha]_D^{23}$ = +83.4 (CH_2Cl_2). IR: ν = 3375, 2982, 2933, 2829, 1690, 1599, 1532, 1483, 1457, 1401, 1376, 1326, 1292, 1247, 1221, 1204, 1150, 1134, 1102, 1074, 1044, 1022, 992, 949, 751 cm^{-1}. ^{1}H NMR (600 MHz): δ = 10.48 (1H, s, H-13), 9.83 (1H, s, H-13'), 8.51 (1H, dd, $J_{11,10}$ 8.1 Hz, $J_{11,9}$ 1.5 Hz, H-11), 8.47 (2H, m, H-16, H-16'), 8.28 (1H, d, $J_{11',10'}$ 7.5 Hz, H-11'), 8.13 (1H, dd, J 7.6 Hz, J 7.8 Hz, H-17), 7.07–7.15 (5H, m, H-8, H-8', H-9, H-9', H-10'), 7.01 (1H, ddd, $J_{10,9}$ 7.7 Hz, $J_{10,8}$ 1.2 Hz, H-10), 5.41 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.55 (1H, ddd, $J_{5,4}$ 10.2 Hz, $J_{5,6}$ 9.1 Hz, $J_{5,6}$ 1.5 Hz, H-5), 4.33–4.38 (3H, m, H-6, 2H-6'), 4.23 (1H, dd, $J_{6,6}$ 12.7 Hz, $J_{6,5}$ 9.1 Hz, H-6), 4.10 (1H, dd, $J_{4',3'}$ 7.4 Hz, $J_{4',5'}$ 7.5 Hz, H-4'), 4.00 (1H, m, H-5'), 3.89 (1H, d, H-3'), 3.59 (3H, s, 3H-CH$_3$), 3.46 (1H, dd, $J_{3,2}$ 9.6 Hz, $J_{3,4}$ 8.7 Hz, H-3), 3.41 (1H, d, $J_{1',1'}$ 10.8 Hz, H-1'), 3.39 (3H, s, 3H-CH$_3$), 3.37 (3H, s, 3H-CH$_3$), 3.28 (3H, s, 3H-CH$_3$), 3.27 (1H, d, H-1'), 3.25 (3H, s, 3H-CH$_3$), 3.15 (3H, s, 3H-CH$_3$), 2.87 (1H, dd, H-2), 2.71 (1H, dd, H-4) ppm. ^{13}C NMR (150 MHz): δ = 161.8 (C-14'), 161.01 (C-14), 149.87 (C-7'), 149.68 (C-15'), 149.62 (C-15), 148.93 (C-7), 139.36 (C-17), 127.76 (C-12), 127.59 (C-12'), 125.46, 125.22 (C-16, C-16'), 125.00 (C-9'), 124.24 (C-9), 122.61 (C-11'), 121.87 (C-10'), 121.27 (C-10), 119.81 (C-11), 114.26 (C-8'), 112.72 (C-8), 104.19 (C-2'), 88.04 (C-1), 85.00 (C-3'), 82.94 (C-3), 82.56 (C-4'), 81.23 (C-2), 80.78 (C-4), 79.35 (C-5'), 74.60 (C-1'), 71.03 (C-6), 70.48 (C-6'), 70.34 (C-5), 60.59, 60.34, 59.35, 58.37, 57.68, 57.61 (6 × O*C*H$_3$) ppm. HRMS (ESI) calcd for $C_{37}H_{45}N_3O_{13}Na$ [M + Na]$^+$: 762.2845, found: 762.2852. Anal. calcd. for $C_{37}H_{45}N_3O_{13}$ (739.78): C, 60.07; H, 6.13; N, 5.68%. Found: C, 60.04; H, 6.14; N, 5.65.

4.2.34.3 6,6'-*O*-{[Benzene-1,3-di-yl-bis(carbonylamino)]-3,3'-diphenyl}-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.51b)

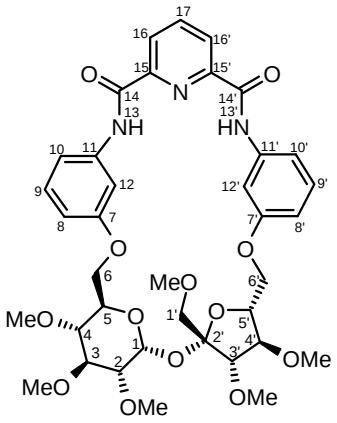
Yield: 72 mg (0.10 mmol, 57%). TLC [hexanes/AcOEt (1:2)]: R_f = 0.46. White solid, m.p. 274 °C. $[\alpha]_D^{24}$ = +50.1 (DMSO). IR: ν = 3247, 3148, 3070, 2976, 2929, 2828, 1651, 1604,



1545, 1498, 1454, 1422, 1347, 1317, 1289, 1262, 1197, 1185, 1154, 1101, 1053, 1022, 998, 984, 962, 934, 913, 873, 846, 753, 706, 684 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, 80 °C): δ = 9.89 (1H, s, H-13), 9.86 (1H, s, H-13'), 8.56 (1H, s, H-18), 8.06 (1H, d, $J_{16',17}$ 7.7 Hz, H-16'), 8.02 (1H, d, $J_{16,17}$ 7.7 Hz, H-16), 7.94 (1H, d, $J_{10',9'}$ 7.9 Hz, H-10'), 7.67 (1H, dd, H-17), 7.61 (1H, br s, H-10), 7.25 (1H, dd, $J_{9',8'}$ 8.2 Hz, $J_{9',10'}$ 8.2 Hz, H-9'), 7.23 (1H, dd, $J_{9,8}$ 8.2 Hz, H-9), 7.20 (1H, dd, $J_{12,8}$ 2.0 Hz, $J_{12,10}$ 1.7 Hz, H-12), 7.05 (1H, br s, H-12'), 6.74 (1H, dd, $J_{8,9}$ 8.2 Hz, H-8), 6.68 (1H, dd, $J_{8',9'}$ 8.2 Hz, $J_{8',12'}$ 2.2 Hz, H-8'), 5.45 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.20–4.25 (2H, m, H-6', H-6), 4.15 (1H, dd, $J_{6,6}$ 10.2, H-6), 4.10 (1H, ddd, $J_{5,4}$ 9.7 Hz, $J_{5,6}$ 2.7 Hz, $J_{5,6}$ 2.7 Hz, H-5), 3.99–4.05 (2H, m, H-5', H-6'), 3.95 (1H, d, $J_{3',4'}$ 5.7 Hz, H-3'), 3.76 (1H, dd, H-4'), 3.57 (1H, d, $J_{1',1'}$ 10.9 Hz, H-1'), 3.51 (3H, s, 3H-CH_3), 3.47 (3H, s, 3H-CH_3), 3.46 (3H, s, 3H-CH_3), 3.43 (1H, dd, H-3), 3.41 (1H, d, H-1'), 3.399 (3H, s, 3H-CH_3), 3.397 (3H, s, 3H-CH_3), 3.38 (1H, m, H-4), 3.37 (3H, s, 3H-CH_3), 3.15 (1H, dd, $J_{2,3}$ 9.2 Hz, H-2) ppm. ^{13}C NMR (150 MHz, DMSO-d_6, 80 °C): δ = 164.59 (C-14), 163.69 (C-14'), 158.47 (C-7), 157.96 (C-7'), 139.92 (C-11), 139.90 (C-11'), 134.23, 133.65 (C-15, C-15'), 130.60 (C-16), 130.38 (C-16'), 129.42 (C-9), 129.33 (C-9'), 128.91 (C-17), 127.00 (C-18), 112.40 (C-8), 112.40 (C-10), 112.06 (C-8'), 111.49 (C-10'), 106.66 (C-12), 104.21 (C-2'), 103.74 (C-12'), 89.25 (C-1), 84.71 (C-4'), 84.35 (C-3'), 82.46 (C-3), 80.78 (C-2), 78.75 (C-4), 77.77 (C-5'), 72.51 (C-1'), 68.68 (C-5), 68.40 (C-6'), 67.48 (C-6), 59.26, 59.07, 58.37, 57.70, 57.28, 57.21 (6 × OCH_3) ppm. HRMS (ESI) calcd for $C_{38}H_{46}N_2O_{13}Na$ $[M + Na]^+$: 761.2892, found: 761.2914. Anal. calcd. for $C_{38}H_{46}N_2O_{13}$ (738.80): C, 61.78; H, 6.28; N, 3.79%. Found: C, 61.94; H, 6.42; N, 3.57.

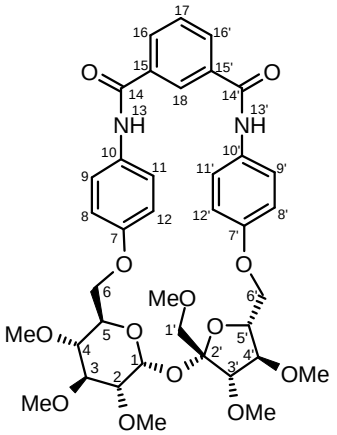
4.2.34.4 6,6'-*O*-{[Pyridine-2,6-di-yl-bis(carbonylamino)]-3,3'-diphenyl}-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.52b)

Yield: 78 mg (0.11 mmol, 62%). TLC [hexanes/AcOEt (1:2)]: R_f = 0.47. White solid, m.p. 272 °C. $[\alpha]_D^{23}$ = +86.2 (CH_2Cl_2). IR: ν = 3500, 3307, 3072, 2930, 2829, 1669, 1609, 1561, 1539, 1498, 1456, 1431, 1387, 1330, 1294, 1277, 1260, 1199, 1188, 1156, 1100, 1021, 998, 984, 958, 869, 840, 778, 755, 704, 681 cm^{-1}. ^{1}H NMR (600 MHz): δ = 9.84 (1H, s, H-13'), 9.69 (1H, s, H-13), 8.41 (2H, d, $J_{16,17}$ = $J_{16',17}$ = 7.7 Hz, H-16, H-16'), 8.12–8.16 (3H, m, H-10, H-10', H-17), 7.30–7.36 (2H, m, H-9, H-9'), 6.85 (1H, dd, $J_{8',9'}$ 8.2 Hz, $J_{8',10'}$ 1.8 Hz, H-8'), 6.75 (1H, dd, $J_{8,9}$ 8.2 Hz, $J_{8,10}$ 2.0 Hz, H-8), 6.68 (1H, br s, H-12'), 6.55 (1H, br s, H-12),



5.61 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.25–4.32 (2H, m, H-5, H-6'), 4.11–4.23 (4H, m, 2H-6, H-5', H-6'), 4.01 (1H, d, $J_{3',4'}$ 5.3 Hz, H-3'), 3.78 (1H, dd, $J_{4',5'}$ 5.9 Hz, H-4'), 3.74 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.65 (3H, s, 3H-CH_3), 3.60 (1H, dd, $J_{3,2}$ 9.3 Hz, $J_{3,4}$ 9.2 Hz, H-3), 3.56 (3H, s, 3H-CH_3), 3.55 (3H, s, 3H-CH_3), 3.48 (3H, s, 3H-CH_3), 3.47 (1H, d, H-1'), 3.45 (3H, s, 3H-CH_3), 3.44 (1H, m, H-4), 3.42 (3H, s, 3H-CH_3), 3.29 (1H, dd, H-2) ppm. ^{13}C NMR (150 MHz): δ = 160.44, 160.23 (C-14, C-14'), 159.37 (C-7'), 158.83 (C-7), 148.32, 148.27 (C-15, C-15'), 140.12 (C-17), 138.34 (C-11), 138.22 (C-11'), 130.92, 130.83 (C-9, C-9'), 125.20, 125.03 (C-16, C-16'), 114.34 (C-8'), 112.05, 112.01, 111.87 (C-8', C-10, C-10'), 105.52 (C-2'), 104.99 (C-12'), 104.01 (C-12), 90.04 (C-1), 85.21 (C-3'), 85.03 (C-4'), 83.16 (C-3), 81.52 (C-2), 79.74 (C-4), 78.83 (C-5'), 72.84 (C-1'), 69.46 (C-5), 69.09 (C-6), 68.49 (C-6'), 60.80, 60.56, 59.22, 58.86, 58.17, 58.06 (6 × O*C*H_3) ppm. HRMS (ESI) calcd for $C_{37}H_{45}N_3O_{13}Na$ $[M + Na]^+$: 762.2845, found: 762.2840. Anal. calcd. for $C_{37}H_{45}N_3O_{13}$ (739.78): C, 60.07; H, 6.13; N, 5.68%. Found: C, 60.21; H, 6.18; N, 5.60.

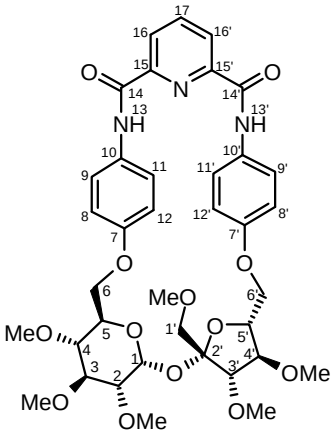
4.2.34.5 6,6'-*O*-{[Benzene-1,3-di-yl-bis(carbonylamino)]-4,4'-diphenyl}-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.51c)



Yield: 23 mg (0.03 mmol, 18%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.67. White solid, m.p. 239 °C. $[\alpha]_D^{23}$ = +63.5 (CH_2Cl_2). IR: ν = 3518, 3239, 3137, 3072, 2928, 2830, 1659, 1644, 1608, 1549, 1521, 1450, 1413, 1383, 1328, 1286, 1237, 1162, 1147, 1102, 1018, 1005, 982, 952, 832, 752 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, 80 °C): δ = 9.51 (1H, s, NH), 9.37 (1H, s, NH), 7.79 (1H, d, $J_{16',17}$ 7.2 Hz, H-16'), 7.66 (1H, d, $J_{16,17}$ 7.2 Hz, H-16), 7.45 (1H, t, J 7.7 Hz, H-17), 7.35 (1H, s, H-18), 7.02 (4H, br s, H-9, H-11, H-9', H-11'), 6.83 (4H, d, J 8.4 Hz, H-8, H-12, H-8', H-12'), 5.34 (1H, d, $J_{1,2}$ 3.2 Hz, H-1), 3.99–4.06 (3H, m, H-6, 2H-6'), 3.92–3.99 (3H, m, H-3', H-6, H-5'), 3.89 (1H, d, $J_{5,4}$ 9.7 Hz, H-5), 3.73 (1H, dd, $J_{4',3'}$ 7.4 Hz, $J_{4',5'}$ 7.4 Hz, H-4'), 3.48 (3H, s, 3H-CH_3), 3.46 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.42 (3H, s, 3H-CH_3), 3.37 (9H, br s, 9H-CH_3), 3.36 (1H, d, H-1'), 3.35 (3H, s, 3H-CH_3), 3.33 (1H, dd, $J_{3,4}$ 9.4 Hz, $J_{3,2}$ 9.2 Hz, H-3), 3.23 (1H, dd, H-4), 3.06 (1H, m, H-2) ppm. ^{13}C NMR (150 MHz, DMSO-d_6, 80 °C): δ = 166.11, 166.68 (C-14, C-14'), 155.88, 155.40 (C-7, C-7'), 133.73, 133.64 (C-15, C-15'),

132.12, 131.88 (C-10, C-10'), 130.69, 129.51 (C-16, C-16'), 128.17 (C-17), 128.14 (C-18), 125.54 (2C), 1223.20 (2C), 114.89 (2C),114.50 (2C), (C-8, C-8', C-9, C9', C-11, C-11', C-12, C-12'), 103.58 (C-2'), 88.79 (C-1), 83.91 (C-3'), 83.39 (C-4'), 82.20 (C-3), 80.63 (C-2), 78.25 (C-4), 78.13 (C-5'), 73.30 (C-1'), 70.54 (C-6'), 69.57 (C-5), 66.38 (C-6), 59.16, 59.09, 58.43, 57.61, 57.27, 57.27 (6 × O*C*H$_3$) ppm. HRMS (ESI) calcd for $C_{38}H_{46}N_2O_{13}Na$ [M + Na]$^+$: 761.2892, found: 761.2929. Anal. calcd. for $C_{38}H_{46}N_2O_{13}$ (738.80): C, 61.78; H, 6.28; N, 3.79%. Found: C, 61.62; H, 6.36; N, 3.70.

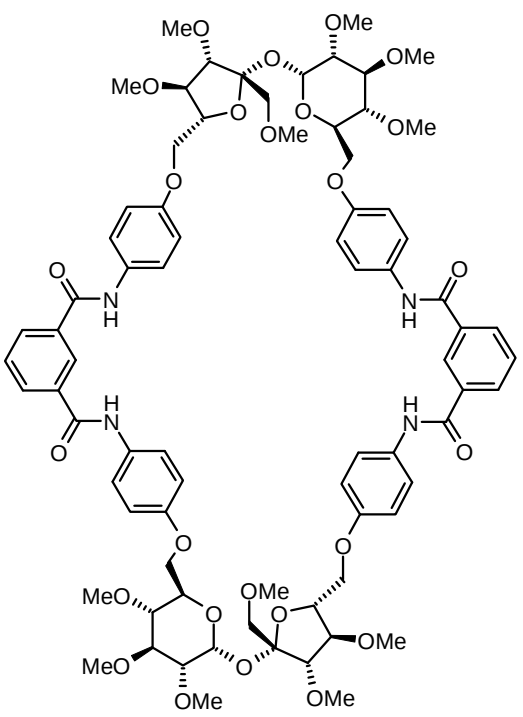
4.2.34.6 6,6'-*O*-{[Pyridine-2,6-di-yl-bis(carbonylamino)]-4,4'-diphenyl}-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.52c)

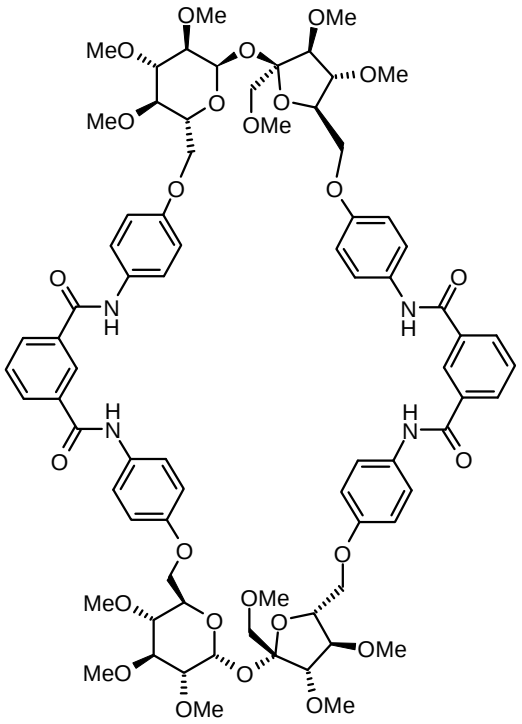


Yield: 29 mg (0.04 mmol, 23%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.73. White solid, m.p. 231 °C. $[\alpha]_D^{22}$ = +81.3 (CH_2Cl_2). IR: ν = 3507, 3333, 3242, 3006, 2981,2928, 2854, 2832, 1662, 1588, 1571, 1528, 1514, 1456, 1420, 1381, 1288, 1240, 1150, 1101, 1020, 1002, 983, 836, 755 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6, 110 °C): δ = 9.30 (1H, s, NH), 8.98 (1H, s, NH), 8.10–8.18 (3H, m, H-16, H-16', H-17), 7.09–7.16 (4H, m, H-Ar), 6.84–6.89 (4H, m, H-Ar), 5.36 (1H, d, $J_{1,2}$ 3.5 Hz, H-1), 3.80–4.08 (7H, m), 3.68 (1H, dd, *J* 7.0 Hz, *J* 7.0 Hz), 3.48 (3H, s, 3H-CH_3), 3.47 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.41 (3H, s, 3H-CH_3), 3.39 (3H, s, 3H-CH_3), 3.38 (3H, s, 3H-CH_3), 3.35 (3H, s, 3H-CH_3), 3.35 (1H, d, H-1'), 3.34 (3H, s, 3H-CH_3), 3.33 (1H, m), 3.23 (1H, dd, *J* 9.1 Hz, *J* 9.7 Hz, H-4), 3.07 (1H, dd, $J_{2,3}$ 9.6 Hz, H-2) ppm. HRMS (ESI) calcd for $C_{37}H_{45}N_3O_{13}Na$ [M + Na]$^+$: 762.2845, found: 762.2855. Analysis for $C_{37}H_{45}N_3O_{13}$ (739.78): Calcd: C, 60.07; H, 6.13; N, 5.68. Found: C, 59.99; H, 6.41; N, 5.46.

4.2.34.7 Macrocyclic dilactams 3.51d and 3.51e

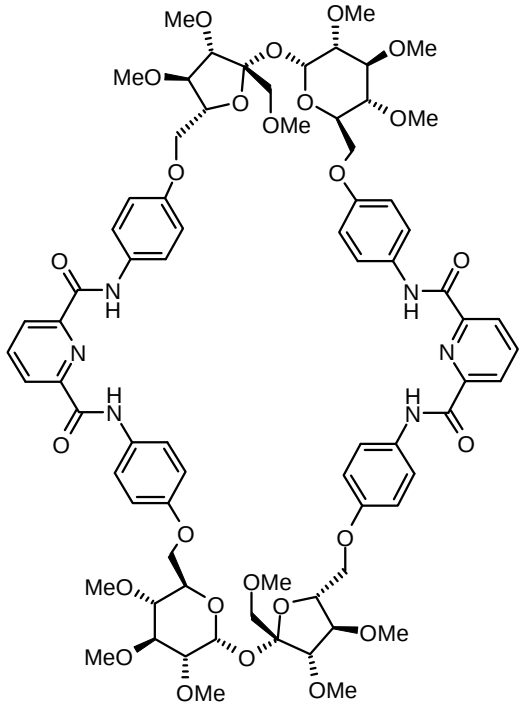
Yield: 78 mg (0.11 mmol, 62%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.65. ^{1}H NMR (600 MHz): δ = 10.22 (2H, s, NH), 10.20 (2H, s, NH), 10.15 (2H, s, NH), 10.13 (2H, s, NH), 8.38 (3H, br s, H-isophthalic), 8.35 (1H, s, H-isophthalic), 8.05 (2H, d, *J* 7.7 Hz, H-Ar), 8.03 (2H, d, *J* 7.8 Hz, H-Ar), 7.95–8.01 (4H, m, H-Ar), 7.70 (4H, d, *J* 8.8 Hz, H-Ar), 7.68 (4H, d, *J* 9.0 Hz, H-Ar), 7.60 (1H, t, *J* 7.6 Hz, H-isophthalic), 7.53 (2H, t, *J* 7.7 Hz, H-isophthalic), 7.45–7.49 (8H, m, H-Ar), 7.43 (1H, t, *J* 7.6 Hz, H-isophthalic), 6.92–6.98 (8H, m, H-Ar), 6.77 (8H, d, *J* 8.9 Hz, H-Ar), 5.41 (4H, m), 4.24–4.34 (4H, m), 3.98–4.13 (24H, m), 3.91–3.96

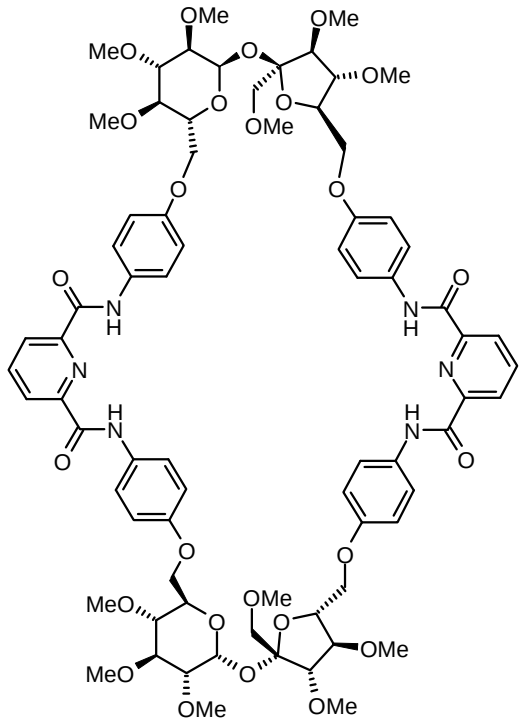




(4H, m), 3.43–3.52 (52H, m), 3.30–3.42 (32H, m), 3.14–3.20 (4H, m), 3.11 (4H, dd, *J* 6.0 Hz, *J* 3.4 Hz) ppm. MS (ESI) 1499.5 {[M($C_{76}H_{92}N_4O_{26}$) + Na]$^+$}.

4.2.34.8 Macrocyclic dilactams 3.52d and 3.52e

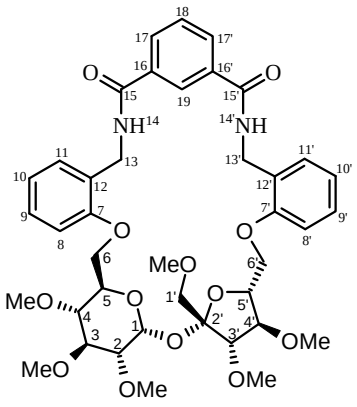




Yield: 68 mg (0.09 mmol, 54%). TLC [AcOEt/MeOH/H_2O (45:5:3)]: R_f = 0.69. ^{1}H NMR (600 MHz): δ = 9.35 (2H, s, NH), 9.24 (2H, s, NH), 9.18 (2H, s, NH), 9.09 (2H, s, NH), 8.41 (2H, dd, *J* 7.7 Hz, *J* 0.6 Hz, H-pyridine), 8.20 (2H, d, *J* 7.8 Hz, H-pyridine), 8.03 (2H, d, *J* 7.7

Hz, H-pyridine), 7.97 (1H, t, 7.7 Hz, H-pyridine), 7.94 (2H, t, *J* 7.8 Hz, H-pyridine), 7.81 (2H, dd, *J* 7.7 Hz, *J* 0.8 Hz, H-pyridine), 7.76 (1H, t, *J* 7.7 Hz, H-pyridine), 7.42–7.48 (12H, m, H-Ar), 7.37 (4H, d, *J* 8.9 Hz, H-Ar), 6.92 (4H, d, *J* 8.9 Hz, H-Ar), 6.84 (4H, d, *J* 8.8 Hz, H-Ar), 6.79 (4H, d, *J* 8.8 Hz, H-Ar), 6.78 (4H, d, *J* 8.8 Hz, H-Ar), 5.58 (4H, m), 4.26–4.35 (4H, m), 4.19–4.26 (8H, m), 4.14–4.19 (6H, m), 4.08–4.14 (6H, m), 3.95–4.03 (6H, m), 3.90 (2H, dd, *J* 6.9 Hz, *J* 7.3 Hz), 3.84 (2H, d, *J* 8.8 Hz), 3.67 (6H, s, 3H-CH_3), 3.65 (6H, s, 3H-CH_3), 3.59 (6H, s, 3H-CH_3), 3.58 (6H, s, 3H-CH_3), 3.51–3.58 (32H, m), 3.41–3.51 (32H, m), 3.32 (2H, dd, *J* 9.3 Hz, *J* 9.8 Hz), 3.27 (2H, dd, *J* 9.5 Hz, *J* 3.5 Hz), 3.20 (2H, dd, *J* 9.7 Hz, *J* 3.6 Hz) ppm. ^{13}C NMR (150 MHz): δ = 160.78 (2C), 160.46 (2C), 160.36 (2C), 159.99 (2C), 155.93 (2C), 155.83 (2C), 155.72 (2C), 155.42 (2C), 149.00 (2C), 148.97 (2C), 148.61 (2C), 147.95 (2C), 139.11 (2C), 139.05, 139.00, 131.01 (2C), 130.48 (2C), 130.47 (2C), 130.41 (2C), 125.33 (2C), 124.92 (2C), 124.67 (2C), 124.44 (2C), 121.90 (4C), 121.08 (4C), 120.98 (4C), 120.80 (4C), 115.42 (4C), 115.39 (4C), 115.10 (4C), 114.96 (4C), 104.06 (2C), 103.87 (2C), 89.57 (2C), 88.97 (2C), 85.86 (2C), 84.89 (2C), 84.68 (2C), 84.68 (2C), 83.40 (2C), 83.34 (2C), 81.76 (2C), 81.64 (2C), 79.48 (2C), 78.99 (2C), 78.86 (2C), 78.84 (2C), 74.19 (2C), 73.80 (2C), 70.09 (2C), 69.84 (2C), 69.67 (2C), 69.69 (2C), 67.08 (2C), 66.24 (2C), 60.79 (2C), 60.71 (2C), 60.55 (2C), 60.37 (2C), 59.41 (2C), 59.41 (2C), 59.24 (2C), 58.91 (2C), 58.80 (2C), 58.73 (2C), 58.50 (2C), 58.47 (2C) ppm. MS (ESI) 1501.6 {[M($C_{74}H_{90}N_6O_{26}$) + Na]$^+$}.

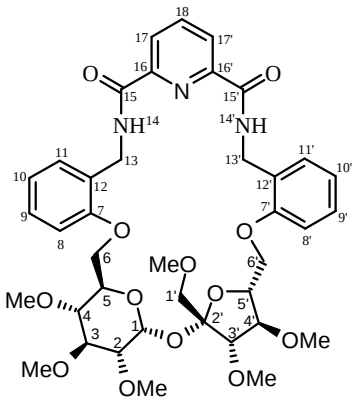
4.2.34.9 6,6'-*O*-{[Benzene-1,3-di-yl-bis(carbonylaminomethyl)]-2,2'-diphenyl}-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.56a)



Yield: 84 mg (0.11 mmol, 64%). TLC (AcOEt): R_f = 0.35. White solid, m.p. 134 °C. $[\alpha]_D^{22}$ = +78.8 (CH_2Cl_2). IR: ν = 3347, 3064, 2982, 2933, 2830, 1658, 1603, 1590, 1526, 1495, 1451, 1359, 1318, 1293, 1250, 1186, 1161, 1100, 1049, 1017, 1004, 982, 941, 882, 825, 753, 710, 593, 527 cm^{-1}. ^{1}H NMR (600 MHz): δ = 8.01–8.05 (2H, m, H-17, H-17'), 7.57 (1H, s, H-19), 7.52 (1H, t, *J* 7.7 Hz, H-18), 7.32 (1H, d, *J* 7,3 Hz, H-8'), 7.26-7.31 (3H, m, H-8', H-9, H-9'), 6.92–6.96 (2H, m, H-10, H-10'), 6.90 (1H, d, *J* 8.5 Hz, H-11'), 6.85 (1H, br s, H-14), 6.74 (1H, d, *J* 8.0 Hz, H-11), 6.66 (1H, br s, H-14'), 4.72–4.77 (2H, m, H-13, H-13'), 4.59 (1H, d, $J_{1,2}$ 3.3 Hz, H-1), 4.51 (1H, dd, *J* 13.8 Hz, *J* 6.2 Hz, H-13), 4.45 (1H, dd, *J* 13.6 Hz, *J* 6.5 Hz, H-13'), 4.27 (1H, dd, $J_{6',6'}$ 9.9 Hz, $J_{6',5'}$ 2.3 Hz, H-6'), 4.14–4.20 (2H, m, H-5', H-6), 4.08 (1H, d, $J_{3',4'}$ 7.4 Hz, H-

3'), 3.93–3.97 (2H, m, H-5, H-6'), 3.76 (1H, dd, $J_{6,6}$ 10.0 Hz, $J_{6,5}$ 1.5 Hz, H-6), 3.70 (1H, dd, $J_{4',5'}$ 7.5 Hz, $J_{4',3'}$ 7.5 Hz, H-4'), 3.56 (3H, s, H-CH_3), 3.47 (3H, s, H-CH_3), 3.46 (1H, m, H-3), 3.440 (3H, s, H-CH_3), 3.435 (3H, s, H-CH_3), 3.40–3.43 (2H, m, H-1', H-4), 3.39 (3H, s, H-CH_3), 3.23 (3H, s, H-CH_3), 3.14 (1H, d, $J_{1',1'}$ 11.2 Hz, H-1'), 2.75 (1H, dd, $J_{2,3}$ 9.5 Hz, H-2) ppm. ^{13}C NMR (150 MHz): δ = 166.96 (C-15), 166.75 (C-15'), 156.85 (C-7'), 156.81 (C-7), 135.53, 135.42 (C-16, C-16'), 131.21, 130.87 (C-17, C-17'), 131.09 (C-8), 130.84 (C-8'), 129.43, 129.31 (C-9, C-9'), 129.16 (C-18), 127.05 (C-12'), 125.73 (C-12), 123.80 (C-19), 121.72 (C-10'), 121.10 (C-10), 112.51 (C-11'), 110.99 (C-11), 104.37 (C-2'), 90.41 (C-1), 84.70 (C-3'), 84.09 (C-4'), 82.72 (C-3), 81.31 (C-2), 78.59 (C-4), 77.87 (C-5'), 73.53 (C-1'), 70.95 (C-6'), 70.25 (C-5), 66.07 (C-6), 60.67, 60.33, 59.67, 58.87, 58.04, 57.99 (6 × O*C*H_3), 41.53 (C-13), 40.94 (C-13') ppm. HRMS (ESI) calcd for $C_{40}H_{50}N_2O_{13}Na$ $[M + Na]^+$: 789.3205, found: 789.3228. Analysis for $C_{40}H_{50}N_2O_{13}$ (766.85): Calcd: C, 62.65; H, 6.57; N, 3.69. Found: C, 62.75; H, 6.68; N, 3.52.

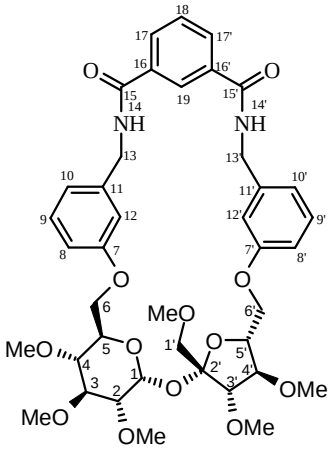
4.2.34.10 6,6'-*O*-{[Pyridine-2,6-di-yl-bis(carbonylaminomethyl)]-2,2'-diphenyl}-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.57a)



Yield: 88 mg (0.11 mmol, 67%). TLC (AcOEt): R_f = 0.37. White solid, m.p. 96 °C. $[\alpha]_D^{22}$ = +163.1 (CH_2Cl_2). IR: ν = 3537, 3403, 3303, 3064, 2984, 2933, 2831, 1735, 1674, 1602, 1590, 1528, 1494, 1452, 1360, 1289, 1278, 1244, 1186, 1161, 1149, 1101, 1051, 1017, 1003, 983, 945, 878, 844, 754, 683, 647, 609, 564 cm^{-1}. ^{1}H NMR (600 MHz): δ = 8.48 (1H, dd, $J_{14',13'}$ 4.3 Hz, $J_{14',13'}$ 7.3 Hz, H-14'), 8.34–8.37 (2H, m, H-17, H-17'), 8.22 (1H, dd, $J_{14,13}$ 4.1 Hz, $J_{14,13}$ 7.6 Hz, H-14), 8.02 (1H, t, J 7.8 Hz, H-18), 7.39 (1H, dd, $J_{11,10}$ 7.5 Hz, $J_{11,9}$ 1.6 Hz, H-11), 7.30 (1H, dd, $J_{11',10'}$ 7.6 Hz, $J_{11',9'}$ 1.6 Hz, H-11'), 7.23–7.29 (2H, m, H-9, H-9') 6.99 (1H, dd, $J_{8',9'}$ 8.2 Hz, $J_{8',10'}$ 0.8 Hz, H-8'), 6.93 (1H, ddd, $J_{10,9}$ 7.4 Hz, $J_{10,8}$ 0.9 Hz, H-10), 6.88 (1H, ddd, $J_{10',9'}$ 7.4 Hz, H-10'), 6.99 (1H, dd, $J_{8,9}$ 8.2 Hz, H-8), 5.35 (1H, d, $J_{1,2}$ 3.4 Hz, H-1), 4.85 (1H, dd, $J_{13',13'}$ 14.4 Hz, H-13'), 4.78 (1H, dd, $J_{13,13}$ 14.2 Hz, H-13), 4.69 (1H, dd, H-13'), 4.61 (1H, dd, H-13), 4.34 (1H, dd, $J_{6',6'}$ 10.2 Hz, $J_{6',5'}$ 3.1 Hz, H-6'), 4.22 (1H, m, H-5') 4.11 (1H, d, $J_{3',4'}$ 6.9 Hz, H-3'), 4.01–4.07 (2H, m, H-5, H-6), 3.98 (1H, dd, $J_{6',5'}$ 7.7 Hz, H-6'), 3.86 (1H, dd, $J_{4',5'}$ 6.9 Hz, H-4'), 3.76 (1H, d, $J_{6,6}$ 9.2 Hz, H-6), 3.57 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.52 (3H, s, H-CH_3), 3.48 (1H, dd, $J_{3,2}$ 9.6 Hz, $J_{3,4}$ 9.0 Hz, H-3), 3.460 (3H, s, H-CH_3), 3.457 (3H, s, H-CH_3), 3.450 (3H, s, H-CH_3), 3.42 (3H, s, H-CH_3), 3.41 (1H, d, H-1'), 3.32 (1H, dd, $J_{4,5}$ 9.6 Hz, H-4),

3.25 (3H, s, H-CH_3), 2.81 (1H, dd, H-2) ppm. ^{13}C NMR (150 MHz): δ = 163.38 (C-15'), 163.12 (C-15), 156.67 (C-7), 156.64 (C-7'), 148.98, 148.89 (C-16, C16'), 138.83 (C-18), 130.72 (C-11), 130.02 (C-11'), 129.03 (C-9), 128.71 (C-9'), 128.34 (C-12'), 126.42 (C-12), 124.74 (C-17), 124.74 (C-17'), 122.67 (C-10'), 121.43 (C-10), 114.94 (C-8'), 112.44 (C-8), 104.92 (C-2'), 89.89 (C-1), 84.85 (C-3'), 84.19 (C-4'), 82.81 (C-3), 81.88 (C-2), 79.03 (C-4), 78.69 (C-5'), 73.65 (C-1'), 72.06 (C-6'), 70.26 (C-5), 67.30 (C-6), 60.48, 60.42, 59.54, 58.50, 58.38, 58.03 (6 × O*C*H_3), 39.65 (C-13), 38.14 (C-13') ppm. HRMS (ESI) calcd for $C_{39}H_{49}N_3O_{13}Na$ $[M + Na]^+$: 790.3158, found: 790.3165. Analysis for $C_{39}H_{49}N_3O_{13}$ (767.84): Calcd: C, 61.01; H, 6.49; N, 5.47. Found: C, 60.80; H, 6.57; N, 5.52.

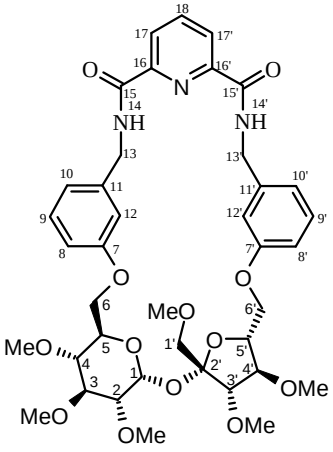
4.2.34.11 6,6'-*O*-{[Benzene-1,3-di-yl-bis(carbonylaminomethyl)]-3,3'-diphenyl}-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.56b)



Yield: 82 mg (0.11 mmol, 63%). TLC (AcOEt): R_f = 0.36. White solid, m.p. 111 °C. $[\alpha]_D^{22}$ = +59.8 (CH_2Cl_2). IR: ν = 3333, 2981, 2931, 2830, 1654, 1599, 1586, 1535, 1487, 1448, 1358, 1290, 1267, 1237, 1183, 1151, 1100, 1056, 1017, 997, 983, 956, 876, 755, 691, 622 cm^{-1}. ^{1}H NMR (600 MHz): δ = 7.97–8.01 (2H, m, H-17, H-17'), 7.91 (1H, s, H-19), 7.52 (1H, dd, $J_{17,18}$ 7.8 Hz, $J_{17',18'}$ 7.8 Hz, H-18), 7.24 (1H, dd, $J_{11,10}$ 7.8 Hz, $J_{11,12}$ 7.9 Hz, H-9), 7.19 (1H, dd, $J_{11',10'}$ 7.8 Hz, $J_{11',12'}$ 8.0 Hz, H-9'), 6.97 (1H, s, H-12), 6.91 (1H, d, H-10'), 6.87–6.89 (2H, m, H-12', H-10), 6.82–6.86 (2H, m, H-8, H-8'), 6.69 (1H, dd, $J_{14',13'}$ 5.6 Hz, $J_{14',13'}$ 5.6 Hz, H-14'), 6.64 (1H, dd, $J_{14,13}$ 5.6 Hz, $J_{14,13}$ 5.6 Hz, H-14), 5.70 (1H, d, $J_{1,2}$ 3.8 Hz, H-1), 4.65 (2H, m, H-13, H-13'), 4.50 (1H, dd, $J_{13,13}$ 14.7 Hz, H-13), 4.42 (1H, dd, $J_{13',13'}$ 14.5 Hz, H-13'), 4.12–4.23 (4H, m, H-5, H-6, 2 × H-6'), 4.06–4.12 (1H, m, H-5'), 4.09 (1H, d, $J_{3',4'}$ 8.0 Hz, H-3'), 4.03 (1H, br d, $J_{6,6}$ 9.1 Hz, H-6), 3.97 (1H, dd, $J_{4',5'}$ 8.0 Hz, H-4'), 3.61 (3H, s, H-CH_3), 3.58 (1H, d, $J_{1',1'}$ 10.9 Hz, H-1'), 3.49 (3H, s, H-CH_3), 3.48 (1H, dd, $J_{3,2}$ 9.6 Hz, $J_{3,4}$ 9.3 Hz, H-3), 3.45 (3H, s, H-CH_3), 3.42 (1H, d, H-1'), 3.41 (6H, s, H-2CH_3), 3.40 (3H, s, H-CH_3), 3.36 (1H, dd, $J_{4,5}$ 9.6 Hz, H-4), 3.21 (1H, dd, H-2) ppm. ^{13}C NMR (150 MHz): δ = 166.71 (C-15), 166.34 (C-15'), 159.20 (C-7), 159.01 (C-7'), 139.63 (C-11), 139.28 (C-11'), 134.69, 134.56 (C-16, C-16'), 130.78 (2C, C-17, C-17'), 129.79 (C-9'), 129.77 (C-9), 129.39 (C-18), 124.05 (C-19), 121.64 (C-10'), 120.80 (C-10), 115.13 (C-8'), 114.48 (C-12), 113.75 (C-12'), 112.49 (C-8), 104.15 (C-2'), 88.69 (C-1), 85.02 (C-3'), 83.17 (C-3), 83.03 (C-4'), 81.29 (C-2), 79.14 (C-4), 78.08 (C-5'), 74.83 (C-1'), 69.66 (C-5), 68.95 (C-6'), 66.30 (C-6), 60.65, 60.46, 59.41, 58.59,

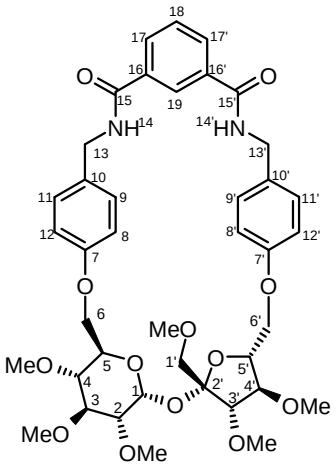
58.39, 58.03 (6 × O*C*H$_3$), 44.25 (C-13'), 43.95 (C-13) ppm. HRMS (ESI) calcd for $C_{40}H_{50}N_2O_{13}Na$ $[M + Na]^+$: 789.3202, found: 789.3214. Analysis for $C_{40}H_{50}N_2O_{13}$ (766.85): Calcd: C, 62.65; H, 6.57; N, 3.69. Found: C, 62.47; H, 6.46; N, 3.74.

4.2.34.12 6,6'-*O*-{[Pyridine-2,6-di-yl-bis(carbonylaminomethyl)]-3,3'-diphenyl}-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.57b)



Yield: 86 mg (11 mmol, 66%). TLC (AcOEt): R_f = 0.39. White solid, m.p. 125 °C. $[\alpha]_D^{22}$ = +61.6 (CH_2Cl_2). IR: ν = 3317, 2980, 2930, 2831, 1679, 1661, 1599, 1586, 1532, 1488, 1448, 1358, 1312, 1287, 1271, 1237, 1180, 1148, 1101, 1057, 1038, 1019, 1002, 982, 876, 844, 755, 682, 647, 623 cm^{-1}. ^{1}H NMR (600 MHz): δ = 8.34–8.38 (2H, m, H-17, H-17'), 8.04 (1H, dd, $J_{17,18}$ 7.8 Hz, $J_{17',18'}$ 7.8 Hz, H-18), 7.90 (1H, dd, $J_{14',13'}$ 5.1 Hz, $J_{14',13'}$ 6.6 Hz, H-14'), 7.85 (1H, dd, $J_{14,13}$ 5.6 Hz, $J_{14,13}$ 5.6 Hz, H-14), 7.25 (1H, dd, $J_{11,10}$ 7.5 Hz, $J_{11,12}$ 7.9 Hz, H-9), 7.10 (1H, dd, $J_{11',10'}$ 7.9 Hz, $J_{11',12'}$ 7.9 Hz, H-9'), 6.92 (1H, d, H-10), 6.91 (1H, d, H-10'), 6.81–6.89 (4H, m, H-8, H-8', H-12, H-12'), 5.59 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.70 (1H, dd, $J_{13',13'}$ 14.7 Hz, H-13'), 4.61 (1H, dd, $J_{13,13}$ 14.7 Hz, H-13), 4.58 (1H, dd, H-13), 4.44 (1H, dd, H-13'), 4.27 (1H, m, H-6'), 4.21 (1H, ddd, $J_{5,4}$ 10.1 Hz, $J_{5,6}$ 3.9 Hz, $J_{5,6}$ 1.6 Hz, H-5), 4.10–4.17 (3H, m, H-5', H-6, H-6'), 4.08 (1H, d, $J_{3',4'}$ 7.7 Hz, H-3'), 4.05 (1H, dd, $J_{6,6}$ 10.2 Hz, H-6), 3.90 (1H, dd, $J_{4',5'}$ 7.7 Hz, H-4'), 3.64 (3H, s, H-CH$_3$), 3.58 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.52 (1H, dd, $J_{3,2}$ 9.4 Hz, $J_{3,4}$ 9.2 Hz, H-3), 3.50 (3H, s, H-CH$_3$), 3.48 (3H, s, H-CH$_3$), 3.45 (3H, s, H-CH$_3$), 3.41 (3H, s, H-CH$_3$), 3.41 (1H, d, H-1'), 3.34 (3H, s, H-CH$_3$), 3.29 (1H, dd, H-4), 3.19 (1H, dd, H-2) ppm. ^{13}C NMR (150 MHz): δ = 163.14 (C-15'), 163.08 (C-15), 159.16 (C-7), 158.93 (C-7'), 148.63, 148.54 (C-16, C-16'), 139.25 (C-11'), 139.13 (C-11), 139.13 (C-18), 129.96 (C-9), 129.92 (C-9'), 125.17, 125.14 (C-17, C-17'), 121.11 (C-10), 120.84 (C-10'), 114.41 (C-8'), 114.17 (C-12), 113.74 (C-12'), 112.95 (C-8), 104.07 (C-2'), 89.93 (C-1), 84.93 (C-3'), 83.61 (C-4'), 83.23 (C-3), 81.51 (C-2), 79.45 (C-4), 78.37 (C-5'), 74.19 (C-1'), 69.70 (C-5), 69.23 (C-6'), 66.77 (C-6), 60.69, 60.47, 59.34, 58.53, 58.41, 58.22 (6 × O*C*H$_3$), 43.66 (C-13), 43.63 (C-13') ppm. HRMS (ESI) calcd for $C_{39}H_{49}N_3O_{13}Na$ $[M + Na]^+$: 790.3158, found: 790.3125. Analysis for $C_{39}H_{49}N_3O_{13}$ (767.84): Calcd: C, 61.01; H, 6.49; N, 5.47. Found: C, 60.93; H, 6.51; N, 5.19.

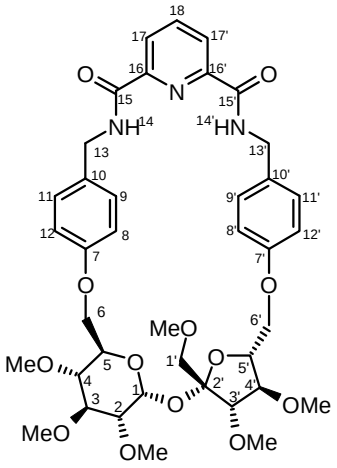
4.2.34.13 6,6'-*O*-{[Benzene-1,3-di-yl-bis(carbonylaminomethyl)]-4,4'-diphenyl}-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.56c)



Yield: 93 mg (0.12 mmol, 71%). TLC (AcOEt): R_f = 0.35. White solid, m.p. 144 °C. $[\alpha]_D^{24}$ = +58.2 (CH_2Cl_2). IR: ν = 3301, 3064, 2982, 2931, 2831, 1649, 1613, 1586, 1542, 1514, 1455, 1422, 1359, 1319, 1300, 1248, 1160, 1101, 1024, 983, 951, 824, 754, 700, 603, 580 cm^{-1}. ^1H NMR (600 MHz): δ = 7.88 (1H, d, $J_{17,18}$ 7.8 Hz, H-17), 7.85 (1H, d, $J_{17',18}$ 7.6 Hz, H-17'), 7.56 (1H, s, H-19), 7.45 (1H, dd, H-18), 7.22 (2H, d, $J_{9,8}$ 8.5 Hz, H-9, H-11), 7.07 (2H, d, $J_{9',8'}$ 8.5 Hz, H-9', H-11'), 6.91 (2H, d, H-8, H-12), 6.78 (2H, d, H-8', H-12'), 6.61 (1H, br s, NH), 6.56 (1H, br s, NH), 5.55 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.45 (1H, dd, $J_{13,13}$ 13.9 Hz, $J_{13,14}$ 5.2 Hz, H-13), 4.39 (1H, dd, $J_{13',13'}$ 13.8 Hz, $J_{13',14'}$ 6.7 Hz, H-13'), 4.35–4.39 (2H, m, H-13, H-6'), 4.32 (1H, dd, $J_{13',14'}$ 4.8 Hz, H-13'), 4.28 (1H, m, H-5), 4.20 (1H, ddd, $J_{5',4'}$ 8.3 Hz, $J_{5',6'}$ 6.7 Hz, $J_{5',6'}$ 3.3 Hz, H-5'), 4.14 (1H, d, $J_{3',4'}$ 7.8 Hz, H-3'), 4.13 (1H, m, H-6), 4.09 (1H, dd, $J_{6,6}$ 9.8 Hz, $J_{6,5}$ 5.3 Hz, H-6), 4.05 (1H, dd, $J_{6',6'}$ 9.9 Hz, $J_{6',5'}$ 3.3 Hz, H-6'), 4.03 (1H, dd, $J_{4',3'}$ 8.0 Hz, H-4'), 3.65 (3H, s, H-CH_3), 3.57 (1H, d, $J_{1',1'}$ 11.0 Hz, H-1'), 3.56 (3H, s, H-CH_3), 3.56 (1H, m, H-3), 3.541 (3H, s, H-CH_3), 3.535 (3H, s, H-CH_3), 3.48 (3H, s, H-CH_3), 3.44 (3H, s, H-CH_3), 3.42 (1H, d, H-1'), 3.26 (1H, dd, $J_{4,3}$ 9.2 Hz, $J_{4,5}$ 9.8 Hz, H-4), 3.18 (1H, dd, $J_{2,3}$ 9.6 Hz, H-2) ppm. ^{13}C NMR (150 MHz): δ = 167.25 (C-15'), 166.87 (C-15), 158.47 (C-7), 158.42 (C-7'), 134.88 (C-16), 134.88 (C-16'), 131.03 (C-17), 130.99 (C-17'), 130.48 (C-10), 129.80 (C-10'), 129.71 (C-18), 129.71 (2C, C-9, C-11), 128.59 (2C, C-9', C-11'), 123.88 (C-19), 114.80 (2C, C-8', C-12'), 114.71 (2C, C-8, C-12), 103.74 (C-2'), 88.89 (C-1), 84.64 (C-3'), 83.72 (C-4'), 83.28 (C-3), 81.68 (C-2), 79.84 (C-4), 78.89 (C-5'), 74.22 (C-1'), 69.77 (C-5), 69.44 (C-6'), 67.69 (C-6), 60.71, 60.50, 59.38, 58.82, 58.69, 58.44 (6 × OCH_3), 43.72 (C-13), 43.39 (C-13') ppm. HRMS (ESI) calcd for $C_{40}H_{50}N_2O_{13}Na$ $[M + Na]^+$: 789.3202, found: 789.3203. Analysis for $C_{40}H_{50}N_2O_{13}$ (766.85): Calcd: C, 62.65; H, 6.57; N, 3.69. Found: C, 62.83; H, 6.53; N, 3.50.

4.2.34.14 6,6'-*O*-{[Pyridine-2,6-di-yl-bis(carbonylaminomethyl)]-4,4'-diphenyl}-1',2,3,3',4,4'-hexa-*O*-methylsucrose (3.57c)

Yield: 97 mg (0.13 mmol, 74%). TLC (AcOEt): R_f = 0.37. White solid, m.p. 115 °C. $[\alpha]_D^{21}$ = +28.4 (CH_2Cl_2). IR: ν = 3330, 2982, 2932, 2831, 1671, 1613, 1585, 1535, 1514, 1449, 1363,



1301, 1287, 1248, 1151, 1100, 1023, 1003, 984, 949, 879, 827, 753, 677, 646, 603, 582 cm^{-1}. ^{1}H NMR (600 MHz): δ = 8.35 (1H, dd, $J_{16,17}$ 7.8 Hz, $J_{16,16'}$ 1.2 Hz, H-16), 8.32 (1H, dd, $J_{16',17}$ 7.8 Hz, H-16'), 8.05 (1H, dd, H-17), 7.69 (1H, dd, *J* 4.6 Hz, *J* 5.4 Hz, N-H), 7.63 (1H, dd, *J* 4.6 Hz, *J* 4.8 Hz, N-H), 7.26 (2H, d, *J* 8.7 Hz, H-9, H-11), 7.02 (2H, d, *J* 8.7 Hz, H-9', H-11'), 6.93 (2H, d, *J* 8.7 Hz, H-8', H-12'), 6.73 (2H, d, *J* 8.7 Hz, H-8, H-12), 5.52 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.67 (1H, dd, *J* 5.5 Hz, *J* 14.2 Hz, H-13), 4.57 (1H, dd, *J* 5.9 Hz, *J* 14.9 Hz, H-13'), 4.53 (1H, dd, $J_{6',5'}$ 6.8 Hz, $J_{6',6'}$ 10.0 Hz, H-6'), 4.46 (1H, dd, *J* 4.2 Hz, *J* 14.9 Hz, H-13'), 4.42 (1H, dd, *J* 4.1 Hz, *J* 14.2 Hz, H-13), 4.34 (1H, ddd, $J_{5,6}$ 1.3 Hz, $J_{5,6}$ 6.6 Hz, $J_{5,4}$ 10.3 Hz, H-5), 4.24 (1H, ddd, $J_{5',6'}$ 3.2 Hz, $J_{5',4'}$ 7.6 Hz, H-5'), 4.22 (1H, dd, $J_{6,6}$ 9.6 Hz, H-6), 4.15 (1H, dd, $J_{4',3'}$ 7.9 Hz, H-4'), 4.12 (1H, d, H-3'), 4.10 (1H, dd, H-6), 4.08 (1H, dd, H-6'), 3.65 (3H, s, H-CH_3), 3.58 (6H, s, H-CH_3), 3.57 (1H, d, $J_{1',1'}$ 11.0Hz, H-1'), 3.55 (4H, m, H-3, H-CH_3), 3.47 (3H, s, H-CH_3), 3.45 (3H, s, H-CH_3), 3.40 (1H, d, H-1'), 3.15 (1H, dd, $J_{2,3}$ 9.6 Hz, H-2), 3.13 (1H, dd, $J_{4,3}$ 8.7 Hz, H-4) ppm. ^{13}C NMR (150 MHz): δ = 162.90, 162.77 (C-14, C-14'), 158.49, 158.42 (C-7, C-7'), 148.59, 148.43 (C-15, C-15'), 139.23 (C-17), 129.70 (C-9, C-11), 129.61, 129.11 (C-10, C-10'), 128.17 (C-9', C-11'), 124.81, 124.76 (C-16, C-16'), 114.92 (C-8, C-12), 114.70 (C-8', C-12'), 103.71 (C-2'), 88.70 (C-1), 84.51 (C-4'), 83.70 (C-3'), 83.34 (C-3), 81.73 (C-2), 80.20 (C-4), 79.01 (C-5'), 73.99 (C-1'), 69.93 (C-5), 69.42 (C-6'), 68.06 (C-6), 60.68, 60.47, 59.34, 58.91, 58.75, 58.42 (6 × O*C*H_3), 43.66, 43.06 (C-13, C-13') ppm. HRMS (ESI) calcd for $C_{39}H_{49}N_3O_{13}Na$ $[M + Na]^+$: 790.3158, found: 790.3196. Analysis for $C_{39}H_{49}N_3O_{13}$ (767.84): Calcd: C, 61.01; H, 6.49; N, 5.47. Found: C, 61.23; H, 6.55; N, 5.36.

4.3 Determination of the stability constants of sucrose-based aza-crown ether complexes with chiral ammonium cations.

4.3.1 General procedure for the titration experiments:

A solution of the receptor in 0.5 mL of the respective solvent ($CDCl_3$ for the experiments with phenylethylammonium chlorides; $CDCl_3$-CD_3OD or DMSO-d_6 for methyl ester amino acid hydrochloride) was prepared (concentration given separately for each experiment). The NMR spectrum was recorded. Subsequently small portions of a guest were added to the solution. After each addition of the ammonium salt the NMR spectrum was recorded. The change of the shift of the signal of the anomeric proton of sucrose (at δ ~ 5.5 ppm) was followed. The

additions of the guest were continued until constant value of the chemical shift of H-1 (anomeric). The value of the shift of the signal was then plotted against the concentration of the guest in solution. A curve was fitted to the plot, using the empirical equation described by Fielding[63] with the application of the program Origin. The parameters: K_a (association constant) and $\Delta\delta_{max}$ (the difference in chemical shifts between that observed in the host-guest complex and that observed in the host molecule) were determined by fitting the data to the equation

$$\Delta\delta = \frac{\left\{C_H + C_G + \frac{1}{K_a} - \sqrt{((C_H + C_G + \frac{1}{K_a})^2 - 4C_H C_G)}\right\}\Delta\delta_{max}}{2C_H}$$

where δ is an experimentally measured chemical shift; Δδ is the measured change in chemical shift (upon addition of guest species) referenced to that of the uncomplexed host; C_H and C_G are the total concentrations of the host and guest, respectively.

The results are summarized in Tables 4.1–4.26. Additional labels are used: V_G is added volume of the solution of the guest at the measuring point; ΔΔδ is the measured change in chemical shift (upon addition of guest species) referenced to that chemical shift in preceding measuring.

This methodology can be used for the 1:1 complexes. If the method is applied successfully (the error of the Ka determination is not very high) the stoichiometry of the complex does not have to be additionaly proven by preparation of the Job plot.

4.3.2 Determination of the binding constants of macrocycle 3.19a–f complexes with *S*- or *R*-PEA · HCl in $CDCl_3$

Table 4.1 Determination of the binding constant of the complex of 6,6'-(3-azabenzylpenta-1,5-di-yl)-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19a**) with *S*(-)-phenylethylammonium chloride in $CDCl_3$.

C_H = 0.023314 mol/L						
No	V_G, μL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,426	0	0
2	10	0,00419	0,18	5,379	-0,047	-0,047
3	20	0,00822	0,37	5,3675	-0,0115	-0,0585
4	30	0,0121	0,55	5,36	-0,0075	-0,066
5	40	0,01584	0,73	5,3565	-0,0035	-0,0695

6	50	0,01943	0,92	5,351	-0,0055	-0,075
7	70	0,02625	1,28	5,3465	-0,0045	-0,0795
8	100	0,03563	1,83	5,341	-0,0055	-0,085
9	140	0,04676	2,57	5,338	-0,003	-0,088
10	190	0,05887	3,48	5,334	-0,004	-0,092
11	250	0,07126	4,58	5,331	-0,003	-0,095
$K = 69.79 \pm 7.27\ M^{-1}$ $\Delta\delta_{max} = - 0.1109 \pm 0.0016$						

Table 4.2 Determination of the binding constant of the complex of 6,6'-[3-aza(4-methoxy-benzyl) penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19b**) with *S*(-)-phenylethyl-ammonium chloride in $CDCl_3$.

$C_H = 0.0211$ mol/L						
No	V_G, μL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,421	0	0
2	10	0,00464	0,22	5,363	-0,058	-0,058
3	20	0,0091	0,43	5,345	-0,018	-0,076
4	30	0,01339	0,63	5,338	-0,007	-0,083
5	40	0,01753	0,83	5,332	-0,006	-0,089
6	50	0,02151	1,02	5,328	-0,004	-0,093
7	70	0,02906	1,38	5,323	-0,005	-0,098
8	80	0,03263	1,55	5,321	-0,002	-0,1
9	90	0,03609	1,71	5,32	-0,001	-0,101
10	110	0,04267	2,02	5,318	-0,002	-0,103
11	130	0,04882	2,31	5,316	-0,002	-0,105
12	150	0,0546	2,59	5,314	-0,002	-0,107
13	180	0,06263	2,97	5,312	-0,002	-0,109
14	220	0,07229	3,43	5,312	0	-0,109
$K = 140.19 \pm 9.83\ M^{-1}$ $\Delta\delta_{max} = - 0.1195 \pm 0.0009$						

Table 4.3 Determination of the binding constant of the complex of 6,6'-[3-aza(pyridine-2-yl-methyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19c**) with *S*(-)-phenylethyl-ammonium chloride in $CDCl_3$.

C_H = 0.018595 mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,415	0	0
2	4	0,0017	0,09	5,4055	-0,0095	-0,0095
3	8	0,00337	0,18	5,396	-0,0095	-0,019
4	12	0,00501	0,27	5,386	-0,01	-0,029
5	16	0,00663	0,36	5,38	-0,006	-0,035
6	20	0,00822	0,44	5,3755	-0,0045	-0,0395
7	25	0,01018	0,55	5,372	-0,0035	-0,043
8	30	0,0121	0,65	5,369	-0,003	-0,046
9	35	0,01399	0,75	5,366	-0,003	-0,049
10	40	0,01584	0,85	5,3645	-0,0015	-0,0505
11	45	0,01765	0,95	5,363	-0,0015	-0,052
12	50	0,01943	1,05	5,3615	-0,0015	-0,0535
13	60	0,0229	1,23	5,3595	-0,002	-0,0555
14	70	0,02625	1,41	5,358	-0,0015	-0,057
15	85	0,03106	1,67	5,3565	-0,0015	-0,0585
16	100	0,03563	1,92	5,3555	-0,001	-0,0595
17	120	0,04138	2,23	5,354	-0,0015	-0,061
18	150	0,04933	2,65	5,3535	-0,0005	-0,0615
19	200	0,06108	3,28	5,353	-0,0005	-0,062
$K = 316.7 \pm 32.2\ M^{-1}$ $\Delta\delta_{max} = - 0.0657 \pm 0.0007$						

Table 4.4 Determination of the binding constant of the complex of 6,6'-[3-aza(pyridine-2-ylmethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19c**) with *R*(-)-phenylethyl-ammonium chloride in $CDCl_3$.

C_H = 0.018595 mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,416	0	0
2	4	0,00174	0,09	5,431	0,015	0,015

3	8	0,00346	0,19	5,439	0,008	0,023
4	12	0,00514	0,28	5,443	0,004	0,027
5	16	0,00681	0,37	5,446	0,003	0,03
6	20	0,00844	0,45	5,447	0,001	0,031
7	25	0,01045	0,56	5,449	0,002	0,033
8	30	0,01242	0,67	5,4505	0,0015	0,0345
9	35	0,01436	0,77	5,451	0,0005	0,035
10	40	0,01626	0,87	5,452	0,001	0,036
11	45	0,01812	0,97	5,4525	0,0005	0,0365
12	50	0,01995	1,07	5,454	0,0015	0,038
13	60	0,02352	1,26	5,4555	0,0015	0,0395
14	70	0,02695	1,45	5,4565	0,001	0,0405
15	85	0,03189	1,72	5,4585	0,002	0,0425
16	100	0,03658	1,97	5,46	0,0015	0,044
17	120	0,04248	2,28	5,462	0,002	0,046
18	150	0,05065	2,72	5,4635	0,0015	0,0475
19	200	0,06271	3,37	5,4655	0,002	0,0495
$K = 67.25 \pm 5.76\ M^{-1}$ $\Delta\delta_{max} = 0.0580 \pm 0.0008$						

Table 4.5 Determination of the binding constant of the complex of 6,6'-[3-aza(prop-2-en-1-yl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19d**) with *S*(-)-phenylethyl-ammonium chloride in $CDCl_3$.

$C_H = 0.02318$ mol/L						
No	V_G, μL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,411	0	0
2	5	0,00251	0,11	5,362	-0,049	-0,049
3	10	0,00498	0,21	5,3175	-0,0445	-0,0935
4	15	0,00739	0,32	5,2895	-0,028	-0,1215
5	20	0,00976	0,42	5,275	-0,0145	-0,136
6	25	0,01208	0,52	5,264	-0,011	-0,147
7	30	0,01436	0,62	5,256	-0,008	-0,155
8	40	0,0188	0,81	5,246	-0,01	-0,165
9	50	0,02307	1,00	5,2395	-0,0065	-0,1715

10	65	0,02919	1,26	5,2345	-0,005	-0,1765
11	80	0,035	1,51	5,229	-0,0055	-0,182
12	100	0,04229	1,82	5,226	-0,003	-0,185
13	120	0,04911	2,12	5,226	0	-0,185
14	150	0,05856	2,53	5,226	0	-0,185
$K = 426 \pm 42\ M^{-1}$ $\Delta\delta_{max} = - 0.1947 \pm 0.0016$						

Table 4.6 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-2-oxoethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19e**) with *S*(-)-phenylethyl-ammonium chloride in $CDCl_3$.

$C_H = 0.00888$ mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,409	0	0
2	5	0,00251	0,06	5,36	-0,049	0,049
3	10	0,00498	0,11	5,3065	-0,0535	0,1025
4	15	0,00739	0,17	5,2745	-0,032	0,1345
5	20	0,00976	0,22	5,25	-0,0245	0,159
6	25	0,01208	0,28	5,233	-0,017	0,176
7	30	0,01436	0,33	5,2205	-0,0125	0,1885
8	35	0,0166	0,38	5,215	-0,0055	0,194
9	40	0,0188	0,43	5,209	-0,006	0,2
10	45	0,02095	0,48	5,204	-0,005	0,205
11	50	0,02307	0,53	5,2	-0,004	0,209
12	55	0,02515	0,57	5,196	-0,004	0,213
13	60	0,02719	0,62	5,193	-0,003	0,216
14	65	0,02919	0,66	5,192	-0,001	0,217
15	70	0,03116	0,71	5,1915	-0,0005	0,2175
16	80	0,035	0,80	5,191	-0,0005	0,218
17	90	0,03871	0,88	5,19	-0,001	0,219
18	100	0,04229	0,96	5,1885	-0,0015	0,2205
19	110	0,04576	1,04	5,188	-0,0005	0,221
20	130	0,05236	1,19	5,187	-0,001	0,222
21	150	0,05856	1,33	5,186	-0,001	0,223

22	170	0,06438	1,47	5,1855	-0,0005	0,2235
23	200	0,0725	1,65	5,1855	0	0,2235
$K = 623 \pm 47\ M^{-1}$ $\Delta\delta_{max} = - 0.2309 \pm 0.0011$						

Table 4.7 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *S*(-)-phenylethyl-ammonium chloride in $CDCl_3$.

$C_H = 0.00568$ mol/L						
No	V_G, μL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,411	0	0
2	5	0,00212	0,08	5,383	-0,028	-0,028
3	7	0,00295	0,11	5,372	-0,011	-0,039
4	9	0,00378	0,14	5,36	-0,012	-0,051
5	11	0,0046	0,17	5,3515	-0,0085	-0,0595
6	13	0,00542	0,20	5,346	-0,0055	-0,065
7	15	0,00623	0,23	5,341	-0,005	-0,07
8	18	0,00743	0,28	5,3345	-0,0065	-0,0765
9	22	0,00901	0,34	5,3275	-0,007	-0,0835
10	25	0,01018	0,38	5,325	-0,0025	-0,086
11	30	0,0121	0,45	5,3205	-0,0045	-0,0905
12	35	0,01399	0,52	5,3175	-0,003	-0,0935
13	40	0,01584	0,59	5,3155	-0,002	-0,0955
14	50	0,01943	0,73	5,313	-0,0025	-0,098
15	65	0,02459	0,92	5,3105	-0,0025	-0,1005
16	80	0,02949	1,10	5,3075	-0,003	-0,1035
17	100	0,03563	1,33	5,3075	0	-0,1035
18	120	0,04138	1,55	5,3075	0	-0,1035
$K = 732 \pm 69\ M^{-1}$ $\Delta\delta_{max} = - 0.1078 \pm 0.0008$						

4.3.3 Determination of the binding constants of receptor 3.19f complexes with amino acid methyl ester hydrochlorides in $CDCl_3$-CD_3OD (80:20)

Table 4.8 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *D*-alanine methyl ester hydrochloride in $CDCl_3$-CD_3OD (80:20).

C_H = 0.00639 mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,436	0	0
2	5	0,00213	0,17	5,486	0,05	0,05
3	10	0,00422	0,34	5,524	0,038	0,088
4	15	0,00626	0,50	5,554	0,03	0,118
5	20	0,00825	0,66	5,57	0,016	0,134
6	25	0,01021	0,81	5,581	0,011	0,145
7	30	0,01212	0,97	5,586	0,005	0,15
8	35	0,01399	1,12	5,588	0,002	0,152
9	40	0,01583	1,26	5,589	0,001	0,153
10	45	0,01763	1,41	5,59	0,001	0,154
11	50	0,01939	1,55	5,592	0,002	0,156
12	60	0,02281	1,82	5,594	0,002	0,158
13	80	0,02927	2,33	5,595	0,001	0,159
14	100	0,03526	2,81	5,594	-0,001	0,158
$K = 1655 \pm 164\ M^{-1}$ $\Delta\delta_{max} = 0.1629 \pm 0.0009$						

Table 4.9 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *L*-alanine methyl ester hydrochloride in $CDCl_3$-CD_3OD (80:20).

C_H = 0.00639 mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,439	0	0
2	5	0,00215	0,17	5,478	0,039	0,039
3	10	0,00425	0,34	5,519	0,041	0,08
4	15	0,0063	0,50	5,546	0,027	0,107
5	20	0,00831	0,66	5,564	0,018	0,125

6	25	0,01028	0,82	5,573	0,009	0,134
7	30	0,01221	0,97	5,58	0,007	0,141
8	35	0,0141	1,12	5,584	0,004	0,145
9	40	0,01595	1,27	5,587	0,003	0,148
10	45	0,01776	1,42	5,589	0,002	0,15
11	50	0,01953	1,56	5,5905	0,0015	0,1515
12	60	0,02298	1,83	5,594	0,0035	0,155
13	80	0,02949	2,35	5,597	0,003	0,158
14	100	0,03552	2,83	5,598	0,001	0,159
$K = 821 \pm 51\ M^{-1}$ $\Delta\delta_{max} = 0.1657 \pm 0.0012$						

Table 4.10 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *D*-valine methyl ester hydrochloride in $CDCl_3$-CD_3OD (80:20).

$C_H = 0.0082$ mol/L						
No	V_G, μL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,437	0	0
2	5	0,00118	0,07	5,46	0,023	0,023
3	10	0,00235	0,15	5,483	0,023	0,046
4	20	0,0046	0,29	5,528	0,045	0,091
5	30	0,00677	0,43	5,5675	0,0395	0,1305
6	40	0,00886	0,56	5,591	0,0235	0,154
7	50	0,01087	0,69	5,5965	0,0055	0,1595
8	60	0,01282	0,81	5,598	0,0015	0,161
9	70	0,01469	0,93	5,599	0,001	0,162
10	80	0,0165	1,04	5,6	0,001	0,163
11	100	0,01993	1,26	5,6	0	0,163
12	120	0,02315	1,46	5,6	0	0,163
13	150	0,0276	1,74	5,6	0	0,163
14	200	0,03417	2,16	5,6	0	0,163
15	250	0,03987	2,52	5,6	0	0,163
$K = 14737 \pm 991\ M^{-1}$ $\Delta\delta_{max} = 0.1637 \pm 0.0002$						

Table 4.11 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *L*-valine methyl ester hydrochloride in $CDCl_3$-CD_3OD (80:20).

C_H = 0.0082 mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,437	0	0
2	5	0,00118	0,07	5,459	0,022	0,022
3	10	0,00235	0,15	5,482	0,023	0,045
4	20	0,0046	0,29	5,526	0,044	0,089
5	30	0,00677	0,43	5,567	0,041	0,13
6	40	0,00886	0,56	5,591	0,024	0,154
7	50	0,01087	0,69	5,596	0,005	0,159
8	60	0,01282	0,81	5,597	0,001	0,16
9	70	0,01469	0,93	5,598	0,001	0,161
10	80	0,0165	1,04	5,599	0,001	0,162
11	100	0,01993	1,26	5,599	0	0,162
12	120	0,02315	1,46	5,6	0,001	0,163
13	150	0,0276	1,74	5,6	0	0,163
14	200	0,03417	2,16	5,6	0	0,163
15	250	0,03987	2,52	5,6	0	0,163
$K = 14385 \pm 1500\ M^{-1}$ $\Delta\delta_{max} = 0.1631 \pm 0.0003$						

Table 4.12 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *D*-phenylglycine methyl ester hydrochloride in $CDCl_3$-CD_3OD (80:20).

C_H = 0.01238 mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,432	0	0
2	10	0,00163	0,08	5,4535	0,0215	0,0215
3	20	0,00321	0,16	5,474	0,0205	0,042
4	30	0,00474	0,24	5,4935	0,0195	0,0615
5	35	0,00548	0,28	5,504	0,0105	0,072
6	40	0,00622	0,31	5,513	0,009	0,081

7	45	0,00694	0,35	5,522	0,009	0,09
8	50	0,00765	0,39	5,531	0,009	0,099
9	60	0,00904	0,46	5,548	0,017	0,116
10	70	0,01039	0,52	5,563	0,015	0,131
11	80	0,0117	0,59	5,5755	0,0125	0,1435
12	100	0,01421	0,72	5,59	0,0145	0,158
13	120	0,01658	0,84	5,594	0,004	0,162
14	150	0,01989	1,00	5,596	0,002	0,164
15	180	0,02296	1,16	5,597	0,001	0,165
16	210	0,02579	1,30	5,5975	0,0005	0,1655
17	250	0,02926	1,48	5,598	0,0005	0,166
$K = 5508 \pm 488\ M^{-1}$ $\Delta\delta_{max} = 0.1675 \pm 0.0005$						

Table 4.13 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *L*-phenylglycine methyl ester hydrochloride in $CDCl_3$-CD_3OD (80:20).

$C_H = 0.01238$ mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,433	0	0
2	10	0,00163	0,08	5,454	0,021	0,021
3	20	0,00321	0,16	5,475	0,021	0,042
4	30	0,00474	0,24	5,495	0,02	0,062
5	35	0,00548	0,28	5,506	0,011	0,073
6	40	0,00622	0,31	5,516	0,01	0,083
7	45	0,00694	0,35	5,524	0,008	0,091
8	50	0,00765	0,39	5,534	0,01	0,101
9	60	0,00904	0,46	5,55	0,016	0,117
10	70	0,01039	0,52	5,566	0,016	0,133
11	80	0,0117	0,59	5,579	0,013	0,146
12	100	0,01421	0,72	5,592	0,013	0,159
13	120	0,01658	0,84	5,595	0,003	0,162
14	150	0,01989	1,00	5,596	0,001	0,163
15	180	0,02296	1,16	5,597	0,001	0,164

16	210	0,02579	1,30	5,597	0	0,164
17	250	0,02926	1,48	5,597	0	0,164
$K = 4017 \pm 350\ M^{-1}$ $\Delta\delta_{max} = 0.1696 \pm 0.0006$						

Table 4.14 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *D*-phenylalanine methyl ester hydrochloride in $CDCl_3$-CD_3OD (80:20).

$C_H = 0.01416$ mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,437	0	0
2	10	0,00364	0,26	5,477	0,04	0,04
3	20	0,00713	0,50	5,515	0,038	0,078
4	30	0,0105	0,74	5,55	0,035	0,113
5	40	0,01374	0,97	5,576	0,026	0,139
6	50	0,01686	1,19	5,587	0,011	0,15
7	60	0,01987	1,40	5,592	0,005	0,155
8	70	0,02278	1,6!	5,594	0,002	0,157
9	80	0,02558	1,81	5,595	0,001	0,158
10	100	0,03091	2,18	5,596	0,001	0,159
11	120	0,0359	2,54	5,597	0,001	0,16
12	150	0,0428	3,02	5,597	0	0,16
13	200	0,05299	3,74	5,597	0	0,16
$K = 3834 \pm 151\ M^{-1}$ $\Delta\delta_{max} = 0.16142 \pm 0.00021$						

Table 4.15 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *L*-phenylalanine methyl ester hydrochloride in $CDCl_3$-CD_3OD (80:20).

$C_H = 0.01416$ mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,437	0	0
2	10	0,00364	0,26	5,477	0,04	0,04
3	20	0,00713	0,50	5,515	0,038	0,078
4	30	0,0105	0,74	5,547	0,032	0,11

5	40	0,01374	0,97	5,575	0,028	0,138
6	45	0,01531	1,08	5,582	0,007	0,145
7	50	0,01686	1,19	5,587	0,005	0,15
8	60	0,01987	1,40	5,592	0,005	0,155
9	70	0,02278	1,61	5,5935	0,0015	0,1565
10	80	0,02558	1,81	5,5945	0,001	0,1575
11	100	0,03091	2,18	5,595	0,0005	0,158
12	120	0,0359	2,54	5,597	0,002	0,16
13	150	0,0428	3,02	5,597	0	0,16
14	200	0,05299	3,74	5,597	0	0,16
$K = 3392 \pm 223\ M^{-1}$ $\Delta\delta_{max} = 0.16145 \pm 0.00042$						

4.3.4 Determination of binding constants of receptor 3.19f complexes with amino acid methyl ester hydrochlorides in DMSO-d_6

Table 4.16 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *D*-alanine methyl ester hydrochloride in DMSO-d_6.

$C_H = 0.0144$ mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,43	0	0
2	10	0,00358	0,25	5,432	0,002	0,002
3	20	0,00703	0,49	5,4335	0,0015	0,0035
4	30	0,01034	0,72	5,435	0,0015	0,005
5	40	0,01353	0,94	5,436	0,001	0,006
6	50	0,01661	1,15	5,437	0,001	0,007
7	60	0,01957	1,36	5,438	0,001	0,008
8	80	0,0252	1,75	5,4395	0,0015	0,0095
9	100	0,03045	2,11	5,4405	0,001	0,0105
10	120	0,03536	2,46	5,4415	0,001	0,0115
11	150	0,04216	2,93	5,443	0,0015	0,013
12	200	0,0522	3,62	5,4445	0,0015	0,0145
$K = 32.36 \pm 2.21\ M^{-1}$ $\Delta\delta_{max} = 0.0245 \pm 0.0008$						

Table 4.17 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *L*-alanine methyl ester hydrochloride in DMSO-d_6.

C_H = 0.0144 mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,4285	0	0
2	10	0,00358	0,25	5,431	0,0025	0,0025
3	20	0,00703	0,49	5,4345	0,0035	0,006
4	30	0,01034	0,72	5,4365	0,002	0,008
5	40	0,01353	0,94	5,4385	0,002	0,01
6	50	0,01661	1,15	5,4405	0,002	0,012
7	60	0,01957	1,36	5,4425	0,002	0,014
8	80	0,0252	1,75	5,445	0,0025	0,0165
9	100	0,03045	2,11	5,448	0,003	0,0195
10	120	0,03536	2,46	5,45	0,002	0,0215
11	150	0,04216	2,93	5,4525	0,0025	0,024
12	200	0,0522	3,62	5,4565	0,004	0,028
$K = 16.24 \pm 1.21\ M^{-1}$ $\Delta\delta_{max} = 0.0650 \pm 0.0030$						

Table 4.18 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *D*-valine methyl ester hydrochloride in DMSO-d_6.

C_H = 0.0144 mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,4295	0	0
2	10	0,00298	0,21	5,4335	0,004	0,004
3	20	0,00585	0,41	5,437	0,0035	0,0075
4	25	0,00724	0,50	5,4385	0,0015	0,009
5	30	0,00861	0,60	5,4405	0,002	0,011
6	35	0,00995	0,69	5,4411	0,0006	0,0116
7	40	0,01127	0,78	5,4423	0,0012	0,0128
8	45	0,01256	0,87	5,443	0,0007	0,0135

9	50	0,01383	0,96	5,4441	0,0011	0,0146
10	60	0,0163	1,13	5,4457	0,0016	0,0162
11	80	0,02098	1,46	5,4475	0,0018	0,018
12	100	0,02535	1,76	5,449	0,0015	0,0195
13	125	0,03042	2,11	5,45005	0,00105	0,02055
14	150	0,0351	2,44	5,4507	0,00065	0,0212
$K = 301 \pm 28\ M^{-1}$ $\Delta\delta_{max} = 0.0243 \pm 0.0004$						

Table 4.19 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *L*-valine methyl ester hydrochloride in DMSO-d_6.

$C_H = 0.0144$ mol/L						
No	V_G, μL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,4295	0	0
2	10	0,00298	0,21	5,4333	0,0038	0,0038
3	20	0,00585	0,41	5,4368	0,0035	0,0073
4	25	0,00724	0,50	5,4383	0,0015	0,0088
5	30	0,00861	0,60	5,4395	0,0012	0,01
6	35	0,00995	0,69	5,4415	0,002	0,0112
7	40	0,01127	0,78	5,442	0,0005	0,0125
8	45	0,01256	0,87	5,4431	0,0011	0,0136
9	50	0,01383	0,96	5,444	0,0009	0,0145
10	60	0,0163	1,13	5,4455	0,0015	0,016
11	80	0,02098	1,46	5,4477	0,0022	0,0182
12	100	0,02535	1,76	5,4492	0,0015	0,0197
13	125	0,03042	2,11	5,4505	0,0013	0,021
14	150	0,0351	2,44	5,4511	0,0006	0,0216
$K = 206 \pm 7\ M^{-1}$ $\Delta\delta_{max} = 0.0262 \pm 0.0002$						

Table 4.20 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *D*-phenylglycine methyl ester hydrochloride in DMSO-d_6.

C_H = 0.01237 mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,429	0	0
2	10	0,00301	0,24	5,437	0,008	0,008
3	20	0,00591	0,48	5,4435	0,0065	0,0145
4	30	0,0087	0,70	5,449	0,0055	0,02
5	40	0,01139	0,92	5,452	0,003	0,023
6	45	0,01269	1,03	5,454	0,002	0,025
7	50	0,01398	1,13	5,456	0,002	0,027
8	60	0,01647	1,33	5,458	0,002	0,029
9	70	0,01888	1,53	5,46	0,002	0,031
10	85	0,02234	1,81	5,4625	0,0025	0,0335
11	100	0,02562	2,07	5,465	0,0025	0,036
12	120	0,02975	2,40	5,467	0,002	0,038
13	150	0,03548	2,87	5,469	0,002	0,04
14	200	0,04392	3,55	5,472	0,003	0,043
$K = 145 \pm 10\ M^{-1}$ $\Delta\delta_{max} = 0.0509 \pm 0.0010$						

Table 4.21 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *L*-phenylglycine methyl ester hydrochloride in DMSO-d_6.

C_H = 0.01237 mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,428	0	0
2	10	0,0031	0,25	5,4365	0,0085	0,0085
3	20	0,00608	0,49	5,441	0,0045	0,013
4	30	0,00895	0,72	5,4456	0,0046	0,0176
5	40	0,01172	0,95	5,45	0,0044	0,022
6	45	0,01306	1,06	5,452	0,002	0,024
7	50	0,01438	1,16	5,453	0,001	0,025

8	60	0,01695	1,37	5,455	0,002	0,027
9	70	0,01943	1,57	5,458	0,003	0,03
10	85	0,02299	1,86	5,46	0,002	0,032
11	100	0,02637	2,13	5,462	0,002	0,034
12	120	0,03062	2,47	5,464	0,002	0,036
13	150	0,03651	2,95	5,467	0,003	0,039
14	200	0,0452	3,65	5,471	0,004	0,043
$K = 101 \pm 10\ M^{-1}$ $\Delta\delta_{max} = 0.0535 \pm 0.0017$						

Table 4.22 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *D*-phenylalanine methyl ester hydrochloride in DMSO-d_6.

$C_H = 0.01237$ mol/L						
No	V_G, μL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,428	0	0
2	10	0,00299	0,24	5,436	0,008	0,008
3	20	0,00587	0,47	5,441	0,005	0,013
4	30	0,00863	0,70	5,447	0,006	0,019
5	40	0,0113	0,91	5,4505	0,0035	0,0225
6	45	0,0126	1,02	5,4515	0,001	0,0235
7	50	0,01387	1,12	5,453	0,0015	0,025
8	60	0,01634	1,32	5,4555	0,0025	0,0275
9	70	0,01873	1,51	5,458	0,0025	0,03
10	85	0,02216	1,79	5,46	0,002	0,032
11	100	0,02542	2,05	5,462	0,002	0,034
12	120	0,02952	2,39	5,464	0,002	0,036
13	150	0,0352	2,85	5,4655	0,0015	0,0375
14	200	0,04358	3,52	5,468	0,0025	0,04
$K = 162 \pm 11\ M^{-1}$ $\Delta\delta_{max} = 0.04695 \pm 0.0008$						

Table 4.23 Determination of the binding constant of the complex of 6,6'-[3-aza(2-methoxy-ethyl)penta-1,5-di-yl]-1',2,3,3',4,4'-hexa-*O*-benzylsucrose (**3.19f**) with *L*-phenylalanine methyl ester hydrochloride in DMSO-d_6.

C_H = 0.01237 mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,4305	0	0
2	10	0,00302	0,24	5,4375	0,007	0,007
3	20	0,00592	0,48	5,4435	0,006	0,013
4	30	0,00871	0,70	5,4485	0,005	0,018
5	40	0,0114	0,92	5,452	0,0035	0,0215
6	45	0,01271	1,03	5,4535	0,0015	0,023
7	50	0,01399	1,13	5,455	0,0015	0,0245
8	60	0,01649	1,33	5,4575	0,0025	0,027
9	70	0,0189	1,53	5,4595	0,002	0,029
10	85	0,02237	1,81	5,462	0,0025	0,0315
11	100	0,02566	2,07	5,4635	0,0015	0,033
12	120	0,02979	2,41	5,466	0,0025	0,0355
13	150	0,03552	2,87	5,468	0,002	0,0375
14	200	0,04398	3,55	5,471	0,003	0,0405
$K = 127 \pm 6\ M^{-1}$ $\Delta\delta_{max} = 0.0491 \pm 0.0007$						

4.3.5 Determination of the binding constants of complexes of receptors 3.31 and 3.37 with *S*- or *R*-PEA · HCl in $CDCl_3$

Table 4.24 Determination of the binding constant of the complex of 6,6'-[3,5-di(azabenzyl)-hexa-1,6-di-yl]-6'-deoxy-1',2,3,3',4,4'-hexa-O-benzylsucrose (**3.31**) with *S*(-)-phenylethyl-ammonium chloride in $CDCl_3$.

C_H = 0.0095 mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,482	0	0
2	5	0,00205	0,11	5,472	-0,01	-0,01
3	10	0,00407	0,21	5,4595	-0,0125	-0,0225
4	15	0,00604	0,32	5,452	-0,0075	-0,03

5	20	0,00798	0,42	5,443	-0,009	-0,039
6	25	0,00988	0,52	5,437	-0,006	-0,045
7	30	0,01174	0,62	5,433	-0,004	-0,049
8	35	0,01357	0,71	5,429	-0,004	-0,053
9	40	0,01537	0,81	5,427	-0,002	-0,055
10	50	0,01886	0,99	5,425	-0,002	-0,057
11	60	0,02223	1,17	5,423	-0,002	-0,059
12	80	0,02861	1,51	5,421	-0,002	-0,061
13	100	0,03457	1,82	5,419	-0,002	-0,063
14	120	0,04015	2,11	5,418	-0,001	-0,064
15	150	0,04787	2,52	5,417	-0,001	-0,065
16	200	0,05927	3,12	5,416	-0,001	-0,066
$K = 522 \pm 33\ M^{-1}$ $\Delta\delta_{max} = - 0.0678 \pm 0.0006$						

Table 4.25 Determination of the binding constant of the complex of 6,6'-[1,4-di(azabenzyl)-hexa-1,6-di-yl]-6-deoxy-1',2,3,3',4,4'-hexa-O-benzylsucrose (**3.37**) with *S*(-)-phenylethyl-ammonium chloride in $CDCl_3$.

C_H = 0.0130 mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,7065	0	0
2	5	0,00172	0,13	5,698	-0,0085	-0,0085
3	10	0,00341	0,26	5,69	-0,008	-0,0165
4	15	0,00506	0,39	5,682	-0,008	-0,0245
5	20	0,00669	0,51	5,676	-0,006	-0,0305
6	25	0,00828	0,64	5,67	-0,006	-0,0365
7	30	0,00984	0,76	5,666	-0,004	-0,0405
8	40	0,01288	0,99	5,659	-0,007	-0,0475
9	50	0,0158	1,22	5,653	-0,006	-0,0535
10	65	0,02	1,54	5,647	-0,006	-0,0595
11	80	0,02397	1,85	5,643	-0,004	-0,0635
12	100	0,02897	2,23	5,639	-0,004	-0,0675
13	120	0,03364	2,59	5,638	-0,001	-0,0685
14	140	0,03802	2,93	5,636	-0,002	-0,0705

15	170	0,0441	3,39	5,634	-0,002	-0,0725
16	200	0,04966	3,8	5,632	-0,002	-0,0745
$K = 309 \pm 23\ M^{-1}$ $\Delta\delta_{max} = - 0.0796 \pm 0.0009$						

Table 4.26 Determination of the binding constant of the complex of 6,6'-[1,4-Di(azabenzyl)-hexa-1,6-di-yl]-6-deoxy-1',2,3,3',4,4'-hexa-O-benzylsucrose (**3.37**) with *R*(+)-phenylethyl-ammonium chloride in $CDCl_3$.

$C_H = 0.0130$ mol/L						
No	V_G, µL	C_G, mol/L	C_G/C_H	δ, ppm	ΔΔδ, ppm	Δδ, ppm
1	0	0	0	5,7065	0	0
2	5	0,00217	0,17	5,698	-0,0085	-0,0085
3	10	0,0043	0,33	5,689	-0,009	-0,0175
4	15	0,00639	0,49	5,684	-0,005	-0,0225
5	20	0,00844	0,65	5,678	-0,006	-0,0285
6	25	0,01045	0,80	5,672	-0,006	-0,0345
7	30	0,01242	0,96	5,668	-0,004	-0,0385
8	40	0,01626	1,25	5,659	-0,009	-0,0475
9	50	0,01995	1,54	5,653	-0,006	-0,0535
10	65	0,02525	1,94	5,649	-0,004	-0,0575
11	80	0,03027	2,33	5,645	-0,004	-0,0615
12	100	0,03658	2,82	5,641	-0,004	-0,0655
13	120	0,04248	3,27	5,638	-0,003	-0,0685
14	140	0,04801	3,70	5,635	-0,003	-0,0715
15	170	0,05569	4,29	5,634	-0,001	-0,0725
16	200	0,06271	4,83	5,632	-0,002	-0,0745
$K = 131 \pm 6\ M^{-1}$ $\Delta\delta_{max} = - 0.0852 \pm 0.0009$						

Supplementary

Results presented in this work were published in:

1. M. A. Potopnyk, P. Cmoch, S. Jarosz Short synthesis of diamide-linked sucrose macrocycles, Org. Lett., 2012, 14, 16, 4258–4261.
2. M. A. Potopnyk, B. Lewandowski, S. Jarosz Novel sucrose-based macrocyclic receptors for enantioselective recognition of chiral ammonium cations, Tetrahedron: Asymmetry, 2012, 23, 20–21, 1474–1479.
3. M. A. Potopnyk, S. Jarosz An efficient synthesis of novel sucrose-containing dilactams Monatsh. Chem., 2013, 144, 437–443.
4. M. A. Potopnyk, S. Jarosz "Sweet" sucrose macrocycles via a "click chemistry" // Click Chemistry in Glycoscience: New Developments and Strategies (Ed. Zbigniew J. Witczak, Roman Bielski), Wiley, 2013, 235–250.
5. M. A. Potopnyk, S. Jarosz "Synthesis and complexing properties of 'unsymmetrical' sucrose-based receptors", Eur. J. Org. Chem, 2013, *accepted*.

They were presented also on coferences:

1. M. A. Potopnyk, B. Lewandowski, S. Jarosz "New sucrose macrocycle", poster, 18th International Conference on Organic Synthesis, Bergen, Norway, 1-6.08.2010.
2. M. A. Potopnyk, B. Lewandowski, S. Jarosz "Synthesis of new sucrose macrocycle", poster, 3rd EuCheMS Chemistry Congress, Nuremberg, Germany, 29.08.–2.09.2010.
3. M. A. Potopnyk, S. Jarosz "New macrocyclic sucrose derivatives", poster, 9th Polish Symposium on the Organic Chemistry, Warsaw, 6-9.04.2011.
4. M. A. Potopnyk, S. Jarosz "New aza crown ethers with sucrose scaffold", poster, 12th Tetrahedron symposium, Sitges, Spain, 21-24.06.2011.
5. M. A. Potopnyk, S. Jarosz "Synthesis of new aza crown ethers with sucrose scaffold", poster, 17th European Symposium on Organic Chemistry, Crete, Greece, 10-15.07.2011.
6. M. A. Potopnyk, S. Jarosz "Synthesis macrocyclic dilactams containing the sucrose subunit and isophtalic or 2,6-pyridinedicarbonate amides", poster, 13th Tatrahedron symposium, Amsterdam, the Netherlands, 26–29.06.2012.

During the PhD I was also involved in other activities which are not in cluded in the Thesis. The results were disclosed in publications:

1. M. A. Potopnyk, P. Cmoch, M. Cieplak, A. Gajewska, S. Jarosz The synthesis of higher carbon sugars: a study on the rearrangement of higher sugar allylic alcohols, Tetrahedron: Asymmetry, 2011, 22, 7, 780–786.
2. S. Jarosz, M. Nowogródzki, Marta Magdycz, M. A. Potopnyk Carbobicyclic sugar mimics // Carbohydrate chemistry: Vol. 37, Chemical and biological approaches, The Chemical Society/The Royal Society of Chemistry (UK), 2011, 303–325.

as well as the conference communications:

1. M. A. Potopnyk, S. Jarosz, M. Cieplak, A. Gajewska "Rearrangement of higher sugar allylic alcohols", poster, 22th Conference on Advances In Organic Synthesis, Karpacz, 8-12.07.2009.
2. M. A. Potopnyk, S. Jarosz, M. Cieplak, A. Gajewska "Rearrangement of higher sugar allylic alcohols", poster, 52th Polish Chemical Society and Polish Association of Chemical Engineers Congress, Łódź, Poland, 12-16.09. 2009.
3. P. Cmoch, M. A. Potopnyk, W. Schilf, M. Cieplak, A. Gajewska, S. Jarosz "Study of products of sugar allylic alcohols rearrangement by nuclear magnetic resonance (NMR)", poster, 9th Polish Symposium on the Organic Chemistry, Warsaw, 6-9.04.2011.

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