Regio- and Stereoselective Transformations of Sucrose at the Terminal Positions

Sławomir Jarosz*[a] and Mateusz Mach[a]

Dedicated to Professor Marek Chmielewski on the occasion of his 60th birthday

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Chemistry of sucrose emphasizing regio- and stereoselective transformations performed at the terminal positions (C-1′ and/or C-6 and/or C-6′) is reviewed. 2,2′,3,3′,4-Penta-*O*-benzyl sucrose is proposed as particularly useful substrate for the preparation of modified derivatives such as amines, uronic acids, crown ether analogues with incorporated sucrose backbone, and so-called "higher sucroses", i.e. compounds elongated at either "end" by up to 9 carbon atoms. Application of benzyl protecting groups makes possible synthesis of free sucrose analogues by simple removing of the protecting groups by hydrogenolysis without affecting the very labile glycosidic bond.

[a] Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44, 01-224 Warszawa, Poland
E-mail: sljar@icho.edu.pl

Professor Slawomir Jarosz was born in Warsaw in 1952. In 1974 he received an M.Sc. in organic chemistry from Warsaw University, working with Professor Jerzy T. Wrobel. In 1979 he obtained his Ph.D. (under Professor Aleksander Zamojski) working on the asymmetric Paterno-Büchi reaction. He then spent a year as a post-doc with Professor Bert Fraser-Reid (1980−1981) at the University of Waterloo (Canada) and the University of Maryland (USA). In 1988−1989 he spent a year as a visiting scientist at Duke University (Durham NC, USA). In 1990 he defended his habilitation (D.Sc.) and in 1999 was promoted to a full professor. Currently he is head of a research group at the Institute of Organic Chemistry, Polish Academy of Sciences in Warsaw. He is a co-author of about 90 papers. His main interest includes carbohydrates, stereoselective synthesis, organometallic and radical chemistry.

Dr. Mateusz Mach was born in Lezajsk, Poland in 1971. He received his M.Sc. in chemistry from Jagiellonian University in Cracow, Poland in 1995, with Dr. Janusz Sepiol. In May 2000 he received his Ph.D. from the Institute of Organic Chemistry, Polish Academy of Sciences in Warsaw under the supervision of Professor Slawomir Jarosz. In 2001 he spent one year as a postdoctoral fellow at the Natural Products and Glycotechnology Research Institute in Raleigh, NC, USA, directed by Professor Bertram Fraser-Reid.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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1. Introduction

Sucrose (**1**) − β-D-fructofuranosyl-α-D-glucopyranoside − is commercially available in large quantities; its annual production exceeds 120 million tons. The purity of the commercially available disaccharide is so high that it may be used as a reagent for chemical transformations without any additional purification. This raw material is also very cheap; it is truly the cheapest optically pure compound available from natural sources (less than 0.50 Euro/kg). Besides in the food industry, sucrose is also used in other areas, such as the synthesis of non-metabolized sweeteners, biotechnology, and fermentation. Investigations into the preparation of surfactants and liquid crystals containing sucrose backbones have been carried out; the synthesis of biodegradable polymers and chiral synthons is also of great interest.[1−3]

Although sucrose is produced in large quantities and in very pure form from beat or cane, the presence of its derivatives in other sources in nature is not particularly in evidence. Only a limited number of papers deals with isolation of such compounds. Most probably this is connected with the methods used for isolation of organic material from plants. Only when pre-purification processes are performed under neutral or basic conditions is there a chance of isolating sucrose derivatives. Hydrolysis of the glycosidic linkage occurs readily even under very slightly acidic conditions, and only degradation products can be characterized. There are, however, some examples of the isolation of more complex derivatives. Mostly these are oligosaccharides containing the sucrose moiety in the molecule.[4] As examples of derivatives containing non-carbohydrate unit(s), compounds **2** and **3** − isolated from *Anodendron affine* − may be mentioned (Figure 1).[5]

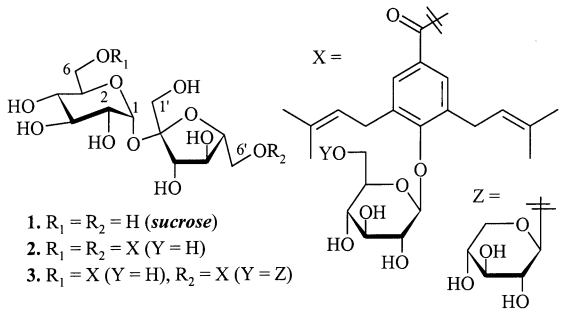


Figure 1. Sucrose and its derivatives isolated from natural sources

Two main strategies should be considered for transformations of sucrose. The first involves changing the carbohydrate backbone entirely, either by hydrolysis of the glycosidic bond and/or by transformation of the saccharide ring(s). The second leaves the sucrose backbone intact, with only slight modifications (such as oxidation at different positions, dehydration, inversion of configurations at particular centers, etc.). The chemistry and applications of this important disaccharide have been described in several reviews.[2,6−8] Although sucrose is available in large quantities from plants, its complex structure has for years been a challenge to synthetic chemists; several syntheses of this disaccharide have been accomplished to date.[9] This review is focused mainly on those transformations that *do not destroy* the disaccharide moiety, with the emphasis on those reactions in which the primary hydroxy groups are involved. Such derivatives of sucrose modified at the terminal positions may possess interesting biological properties.[10]

2. Physicochemical Properties of Sucrose

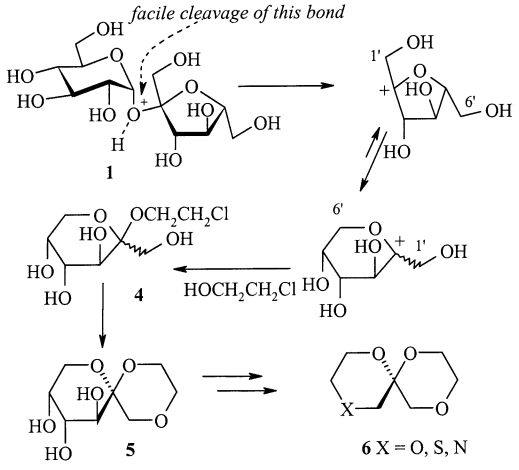
Sucrose, a colorless, crystalline substance {m.p. 182−183 °C, $[\alpha]_D$ = +69 (c = 1.0; H_2O)},[11] is hardly soluble in organic solvents, because of the presence of eight hydroxy groups. Only its solubility in polar solvents such as DMSO, DMF, and pyridine is acceptable for practical use. Structural studies in the solid phase have shown that two hydrogen bonds exist in the sucrose molecule, the first between 6′-OH and the pyranose ring oxygen atom and the second between 1′-OH and the oxygen atom in the C(2)OH moiety.[12] The sucrose molecule is stable in basic media, but is very sensitive towards acids; 0.1% methanolic hydrogen chloride induces complete cleavage of the glycosidic bond within 30 min at room temperature.[13]

The eight hydroxy groups in sucrose have similar reactivities. Only differentiation between the primary and secondary ones may be done conveniently, by reaction with bulky reagents. Of the primary groups, the most reactive are 6-OH and 6′-OH,[6] the least reactive being the neopentyl-like 1′-OH.

3. Transformations of Sucrose with Destruction of the Sugar Backbone

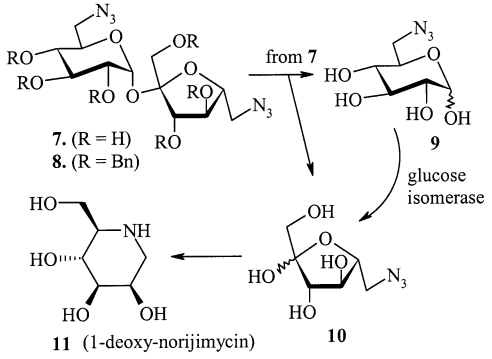
Reactions performed on sucrose may proceed either with destruction of the sucrose backbone or with its preservation. This review focuses on those transformations that preserve the disaccharide skeleton without any significant changes and only selected, most representative, examples of the former methodology are presented.

Cleavage of the glycosidic bond in sucrose occurs very easily, and great care usually has to be taken to keep the molecule unchanged. However, this property may in some cases be useful for synthetic purposes. An excellent example of such an approach was provided by Hough[14,15] (Scheme 1). Treatment of sucrose (**1**) with acidic 2-chloroethanol affords 2′-chloroethylfructose (**4**), which crystallizes out of the reaction mixture. The internal cyclization of **4**, easily performed with base, provides compound **5**, which is a convenient substrate for the preparation of spiro derivatives such as **6** (Scheme 1).[15]



Scheme 1. Transformation of sucrose with destruction of the sugar backbone

Another example of such a transformation was presented by Stütz. Starting from known 6,6′-diazido-6,6′-dideoxysucrose (**7**; for preparation see next chapter), he was able to prepare[16] 1-deoxynojirimycin (**11**; Scheme 2), a natural inhibitor of several mannosidases. Similarly, a partially protected derivative of norijimycin has been obtained from 1′,2,3,3′,4,4′-hexa-*O*-benzyl-6,6′-diazido-6,6′-dideoxysucrose (**8**).[17] Both rings of sucrose (furanosyl or pyranosyl) can be selectively cleaved, either with lead tetraacetate (cleavage of the furanose ring only) or with sodium periodate (glucose part), to give the corresponding dialdehydes.[18]



Scheme 2. Synthesis of 1-deoxy-nojirimycin from sucrose

4. Transformations of Sucrose without Destruction of the Sugar Backbone

The eight hydroxy groups of sucrose have similar reactivities, and only the primary groups can reasonably easily be differentiated from the secondary ones, through the application of bulky reagents. The secondary groups may be also differentiated from one another, although not so easily. Since this review is focused mostly on transformations (protection, substitutions, etc.) involving the primary hydroxy groups, reactions performed *only* on secondary hydroxy groups are not dealt with. In addition, the esterification of free sucrose to provide "statistical" mixtures of mono-, di-, and triprotected (and more) derivatives that might find industrial application as, for example, emulsifiers (an elegant study on the regioselectivity of acylation of sucrose with fatty acid chlorides in water was presented recently by Descotes and co-workers[3]) is not included in this article.

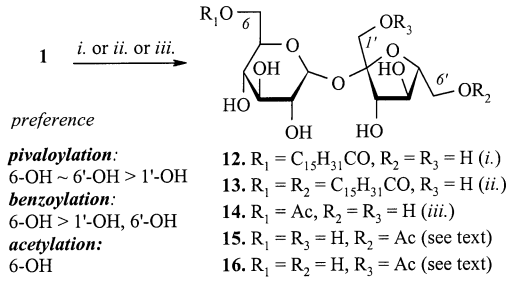
4.1. Reactions Performed at the Terminal Positions of Free Sucrose

The primary hydroxy groups may be protected with ester- or ether-forming reagents, involved in formation of acetal(s), or converted into other moieties such as chlorides, azides, etc. All these transformations are presented in this chapter. Most transformations reported here are those performed on free sucrose.

4.1.1. Differentiation of the Primary Hydroxy Groups by Esterification Reactions

The hydroxy groups of sucrose can to some extent be differentiated by ester-forming reagents. The pivaloylation of free sucrose may serve as an example of differentiation of the OH groups. For treatment with bulky pivaloyl chloride, the reactivity can be described as 6-OH ≈ 6′-OH > 1′-OH (and further 3′-OH > 2-OH > 3-OH > 4-OH).[15] The Mitsunobu reaction[19] is a convenient method for selective acylation. Such a process performed on free sucrose affords 6,1′,6′-triesters or 6,6′-diesters,[20] establishing the reactivity of hydroxy groups as 6-OH ≈ 6′-OH >1′-OH > secondary OH groups.

Several interesting esters of sucrose (including derivatives of fatty acids, such as **12** or **13**) have been prepared by this method (Scheme 3).[21] The reactivity of the primary hydroxy groups towards benzoyl chloride is different, the order being 6-OH > 1′-OH and 6′-OH.[22]

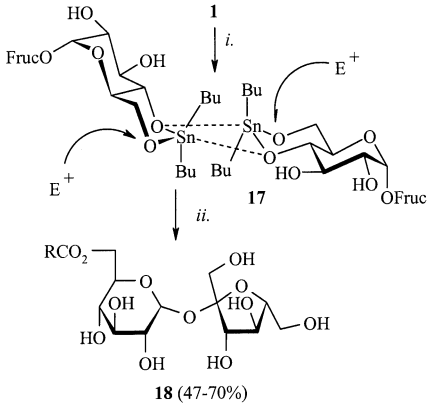


Scheme 3. *i.* TPP, DIAD (1.4 equiv.), DMF, $C_{15}H_{31}COOH$ (1.2 equiv.); *ii.* TPP, DIAD (2.8 equiv.), DMF, $C_{15}H_{31}COOH$ (2.4 equiv.); *iii.* Ac_2O, py, −40 °C

Some special techniques permit the preparation of selectively acylated sucrose derivatives in acceptable yields. Thus, acetylation of free sucrose with acetic anhydride in pyridine at low temperature (−40 °C) affords 6-*O*-acetylsucrose (**14**),[23] while regioisomeric 6′-*O*-acylsucroses (**15**) can be obtained by the action of 3-acyl-5-methyl-1,3,4-thiadiazole-2(3*H*)-thiones on sucrose in the presence of strong organic bases (DABCO).[24] Enzymatic acylation of sucrose select-

ively protects the neopentyl-like 1′-OH to give 1′-*O*-acyl sucroses (**16**; Scheme 3).[25] The position of acylation in sucrose can be usually detected by high-resolution NMR. It has been reported, however, that regioisomers of sucrose can also be differentiated by mass spectrometry.[26]

Activation of hydroxy groups with tin species for acylation is now a well-established method in carbohydrate chemistry.[27] Di-*n*-butyltin oxide forms stannylene acetals with diols, which are attacked with high regioselectivity by appropriate electrophiles. This selectivity is usually much better than that observed on simple treatment of a diol only with 1 equiv. of the corresponding electrophilic reagent. The application of the tin method in sucrose chemistry is shown in Scheme 4. When sucrose is treated with 1 equiv. of Bu_2SnO, the stannylene acetal **17** is formed (as a dimer) and is further attacked by 1 equiv. of the corresponding electrophile (acyl chloride, anhydride, etc.) to afford the monoprotected derivatives[28] **18**. The polymer-bound stannyl reagent was also recently applied for selective acetylation of the C-6 position of sucrose.[29]

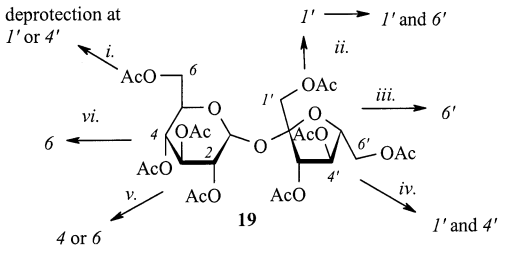


Scheme 4. *i.* nBu_2SnO (1 equiv.), MeOH, 65 °C, 3 h; *ii.* RCOX (1 equiv.), DMF, TEA, room temp., 48 h

Treatment of sucrose with *p*-toluenesulfonyl chloride affords 6,6′-di-*O*-tosylsucrose, which can be isolated chromatographically in 18% yield.[30] Treatment with modified (2,4,6-trialkyl)sulfonylating agents allows the trisulfonylated sucroses, easily purified without use of chromatographic methods, to be obtained in 50% yield.[30,31] The bulkiness of the reagent is not always necessary for good regioselectivity. For example, the mono- and disulfates can be obtained from free sucrose in a heterogenic reaction with SO_3·DMF adduct in 75% and 8% yields, respectively,[32] although the octasulfate is also very easy to prepare. This, however, is rather an exception.

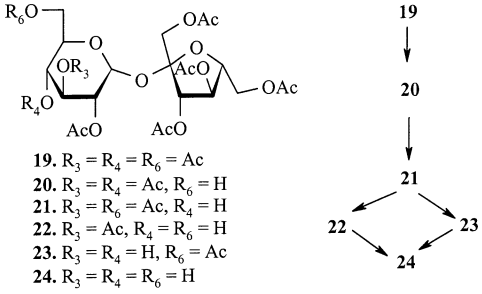
4.1.2. Methods for the Preparation of Sucrose Derivatives with Selectively Protected Primary Hydroxy Groups by Enzymatic Approaches

Another method for the preparation of sucroses with selectively blocked positions consists of the enzymatic deacetylation of octa-*O*-acetylsucrose (**19**). The use of different enzymes enables derivatives with specific free hydroxy groups[33] to be prepared (Scheme 5).



Scheme 5. Enzymatic deprotection of octa-*O*-acetylsucrose; *i.* lipase Candida (*Candida cylindracea*); *ii.* alkylase or protease N; *iii.* chymotrypsin; *iv.* lipase MY (*Candida cylindracea*); *v.* lipase AP6 (*Aspergillus niger*); *vi.* lipase OF (*Candida cylindracea*)

One of the best-known enzymes is lipase OF.[34] This enzyme selectively deprotects the hydroxy groups located in the "glucose part" of **19**. First, the least-hindered 6-OAc group is attacked to afford **20**; *migration* of an acetyl group from the C-4 to the C-6 position then provides compound **21**. The latter may undergo further deacetylation to form **22**. The group at the C-3 position is also sensitive towards the enzyme to some extent, as may be deduced from small amounts of compound **23** isolated from the post-reaction mixture. Pentaaceate **24** is the final product of this enzymatic deacetylation (Scheme 6).[34]



Scheme 6. Deacetylation of octa-*O*-acetylsucrose with lipase OF

Another useful method consists of the combination of enzymatic and chemical transformations.[24] When a mixture of regioisomers is formed in chemical transformations, enzymes may be applied to remove the undesired side products.

4.1.3. Acetalization Reactions Involving the Primary Hydroxy Groups

Because of the presence of several diol groups in the molecule (which contains eight hydroxy groups in total) it is possible to couple these with acetal-producing reagents.

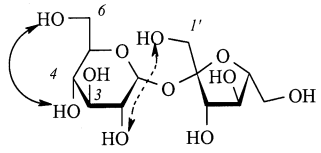
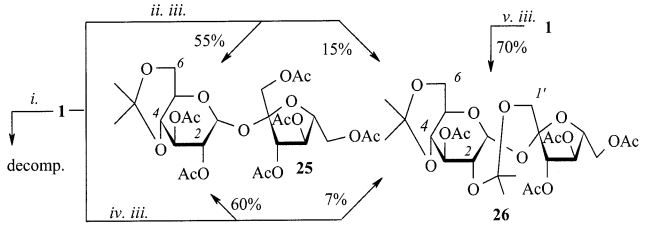


Figure 2. Preferred positions for acetalization of sucrose

Typical acetalization tendencies are shown schematically in Figure 2. It was found that the reactivities of the 4-OH and 6-OH groups were higher than those of the hydroxy groups located at the C-1′ and C-2 positions.[6]

A good example demonstrating the specific character of sucrose chemistry is shown in Scheme 7. Under standard acetalization conditions − catalysis with strong mineral acid − complete decomposition of the starting material is noted (conditions *i.* in Scheme 7). Use of a milder acid and large excess of acetalizing reagent (dimethoxypropane) at room temperature provides monoacetal **25** in good yield (conditions *ii.*). Even better yields can be obtained with 2-methoxypropene in the presence of molecular sieves (*iv.*). In both variations, significant amounts of the diacetal **26** are formed. The latter may be obtained as the sole product through the action on sucrose of an excess of 2-methoxypropene at elevated temperature (*v.* in Scheme 7).[35,36] Deprotection of the 4,6-acetal in **26** provides − in moderate yields − the monoacetal with the functionality at the 1′,2-position.[37]



Scheme 7. *i.* acetone, H^+; *ii.* DMF, dimethoxypropane (14 equiv.), TsOH, 80 min, room temp.; *iii.* Ac_2O, py; *iv.* dry DMF, MS (3 Å), 2-methoxypropene (1.3 equiv.), TsOH, 40 min, 70 °C; *v.* as in *iv.* except 2-methoxypropene (5 equiv.)

In the presence of benzaldehyde, its dimethyl acetal, or (dibromomethyl)benzene, sucrose is converted − in moderate yields (28−35%) − only into the 4,6-acetal **27**, which can be isolated after acetylation and purified by crystallization.[35,38] Analogously, 4,6-methylidenesucrose[39] (**28**) and the corresponding mono-4,6-acetals **29** and **30**, derived from β-citral or α- or β-ionone, may be prepared directly from sucrose in high yields (Figure 3).[40]

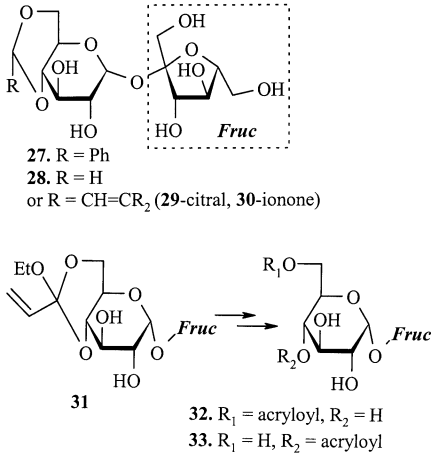
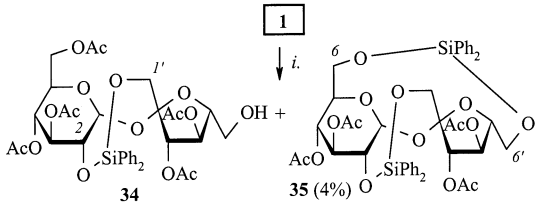


Figure 3. Derivatization of sucrose at the C-4, C-6 positions

Similar coupling of the 6-OH and 4-OH positions (although the process is chemically different) can be achieved by treatment of sucrose with ethyl orthoacrylate; this provides compound **31**, easily converted into 6-*O*- and 4-*O*-monoacryloyl sucroses (**32** and **33** respectively; Figure 3).[41] The presence of an unsaturated moiety in compounds **29**−**33** opens a route to sucrose-based homo- and copolymers.

However, as always, there are exceptions from the general rules shown in Figure 2; one of these is presented in

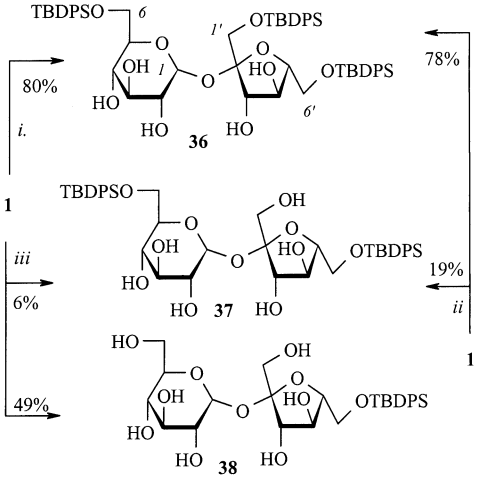


Scheme 8. *i.* Ph_2SiCl_2 then Ac_2O

Scheme 8. Treatment of sucrose with dichlorodiphenylsilane afforded monoacetal **34**, and − rather surprisingly − compound **35**, containing a twelve-membered acetal ring.[42]

4.1.4. Reactions between the Primary Hydroxy Groups and Bulky Ether-Forming Reagents

It is fairly easy to differentiate the primary hydroxy groups from secondary ones with the aid of the bulky ether-forming reagents triphenylmethyl (trityl) and silyl chlorides. An excellent reagent for this purpose is *tert*-butyldiphenylsilyl chloride (TBDPSCl), which, used in excess, protects the primary OH groups, forming the triether **36**. Significant regioselectivity is observed in differentiation of the primary groups with this reagent[43] (Scheme 9). It is worth noting that *the 6′-OH functional group is much more reactive* than the 6-OH towards TBDPSCl. Thus, a 49% yield of the 6′-*O*-protected derivative **38** was obtained by treatment of sucrose with 1.1 equiv. of *tert*-butyldiphenylsilyl chloride.



Scheme 9. *i.* Py, DMAP, TBDPSCl (4.6 equiv.), 55−60 °C, 24 h; *ii.* Py, DMAP, TBDPSCl (3 equiv.), 55−60 °C, 24 h; *iii.* Py, DMAP, TBDPSCl (1.1. equiv.), room temp., 4 h

Less selective is *tert*-butyldimethylsilyl chloride (TBDMSCl); 6,6′-di-*O*-*tert*-butyldimethylsilylsucrose can be prepared in 46% yield, together with the trisilylated derivative (13%).[44] All these silylated derivatives can be peracetylated; however, removal of the silyl protecting groups from such derivatives with fluoride ion usually causes a migration of the acetate from the O-4 to the O-6 position[43,44] (Figure 4). It is also found that these silyl groups are labile in strongly basic media.[45]

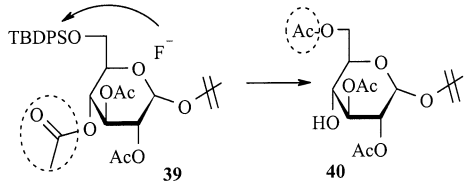
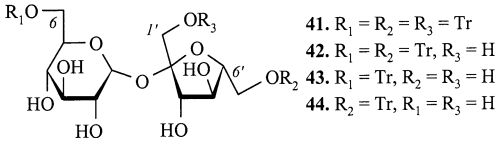


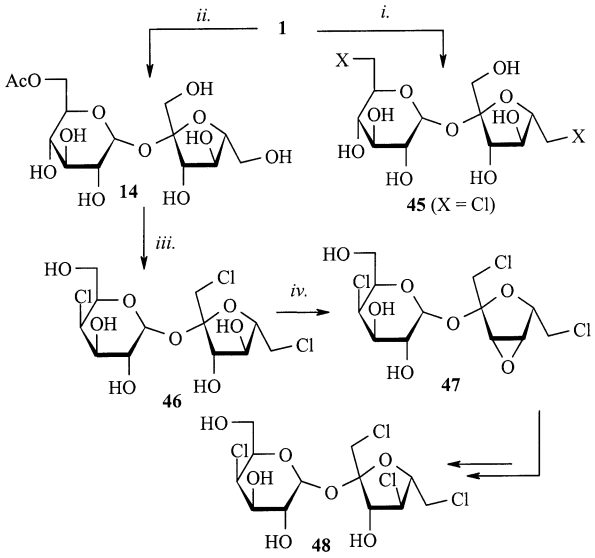
Figure 4. Migration of the acetate group from the C-4 to the C-6 position during deprotection of 6-*O*-silylsucroses

Another reagent that can also easily distinguish between the primary and secondary groups − and which is much cheaper than silanes − is triphenylmethyl chloride. Treatment of sucrose with an excess (3.6 equiv.) of trityl chloride at slightly elevated temperatures provides 1′,6,6′-tri-*O*-tritylsucrose (**41**) as the only product in 79% yield.[46] The same process is more selective at 20 °C and also affords − besides **41** − a 30% yield of 6,6′-di-*O*-tritylsucrose (**42**).[47] It was recently found that slight modifications to the original procedure could increase the yield of **42** to 50%.[48] If this reaction is performed with 2.0 equiv. of TrCl, a mixture of the mono- (**43** and **44**) and ditritylated (**42**) derivatives is formed, but the overall yield decreases to 36%.[49] If 1.2 equiv. is used, a mixture of monotritylated derivatives **43** (at the C-6 position) and **44** (at C-6′) is formed in almost equal amounts but in only 20% overall yield.[50] Trityl protecting groups, unlike their silyl counterparts, are stable under basic conditions.



4.1.5. Miscellaneous Reactions Performed at the Terminal Positions of Free Sucrose

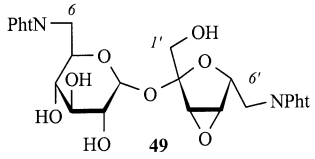
One of the most useful processes for conversion of alcohols into halides (mostly chlorides) is the Appel reaction.[51] Treatment of free sucrose with the Appel reagent (Ph_3P, CCl_4) affords 71% of 6,6′-dichloro-6,6′-dideoxysucrose (**45**, Scheme 10); this procedure is so convenient that it is now included in the excellent textbook "*Methods in Carbohydrate Chemistry*".[52] Other dihalosucroses (**45**; X = Br, I) are also available by treatment with modified Appel or Garegg reagents.[53]



Scheme 10. *i.* Ph_3P, CCl_4 (6.1 equiv.), 70 °C, 30 min; *ii.* ref.[23]; *iii.* SO_2Cl_2/py, then deacetylation; *iv.* Ph_3P, DEAD

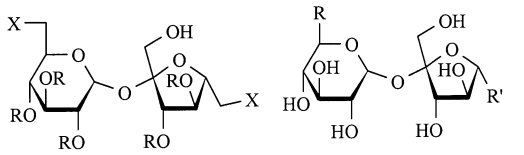
On treatment with sulfuryl chloride/pyridine,[53,54] 6-*O*-acetylsucrose[23] (**14**) is converted into so-called "sucralose" (1′,4,6′-trideoxy-1′,4,6′-trichloro-*galacto*sucrose, **46**), a compound 650 times sweeter than sucrose.[15,55] Treatment of this derivative with triphenylphosphane and diethyl azodicarboxylate affords epoxide **47**, from which the tetrachloro derivative **48** can be obtained[15] (Scheme 10). Other chlorodeoxysucroses (both 1′- and 6′-mono-, 1′,6′-di-) and *galacto*-sucroses (4-mono-, 1′,4-di-, 1′,4,6′-tri-, or 1′,4,4′,6′-tetra-) are also available.[15]

Treatment of the free sucrose with phthalimide under Mitsunobu conditions affords modified derivative **49**, in which the primary 6-OH and 6′-OH groups are replaced with phthalimide moieties, while the secondary ones at the C-3′ and C-4′ positions are converted into an epoxide.[56] It is worth noting that, under these conditions, the secondary OH group is more reactive than the primary, neopentyl-like 1′-OH. Activation of 4′-OH followed by intramolecular attack of the 3′-OH provides the corresponding epoxide **49**.



The 6,6′-dideoxy-6,6′-diazidosucrose (**7**), already mentioned in chapter 3 (Scheme 2), can conveniently be prepared from the dichlorosucrose **45** by S_N2 displacement of the chlorine atoms with azides; benzylation of this compound provides the hexa-*O*-benzyl derivative **8**.[16,17]

Oxidation of the primary hydroxy groups with oxygen on platinum catalyst occurs predominantly at the C-6 and C-6′ positions and affords a mixture of mono- and diuronic acid (**50**, **51**, and **52**), although in very low yields.[57]

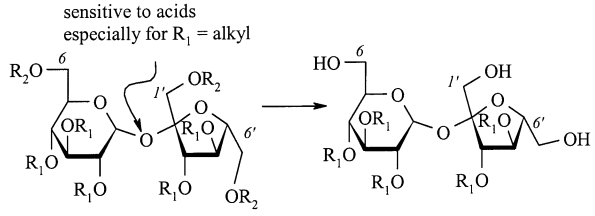


45. X = Cl, R = H
7. X = N_3, R = H
8. X = N_3, R = Bn

50. R = CH_2OH, R' = COOH
51. R = COOH, R' = CH_2OH
52. R = R' = COOH

4.2. Reactions Performed at the Terminal Positions of Partially Blocked Sucrose

For regioselective transformation of sucrose at either terminal position, protection of all the secondary hydroxy groups is required. This may be achieved by placing temporary, but stable, protecting groups on the primary groups (**53** in Figure 5; R_1 = H, R_2 = Tr or SiR_3), subsequent protection of the secondary ones (**53**; R_1 = alkyl, acyl, R_2 = SiR_3 or Tr), and final deprotection of the primary functions (**53**; R_1 = acyl, alkyl, R_2 = H). The problem lies in the preservation of the very labile glycosidic bond in the last step. This bond is very sensitive towards acids, especially when R_1 = alkyl. For R_1 = acyl, mild acids may be used for removal of temporary protecting groups from the primary positions, which allows the preparation of disaccharides such as penta-*O*-benzoylsucrose[58] (**54**) or its pentaacetyl analogue[58] **55**. However, a *migration* of the acetyl group from the C-4 to C-6 position is observed under these acidic conditions, which significantly lowers the yield of the desired derivative **55**.[58]



41. R_1 = H, R_2 = Tr
53. *see text*
56. R_1 = CH_3, R_2 = Tr
57. R_1 = Bn, R_2 = Tr

54. R_1 = COPh
55. R_1 = $COCH_3$
59. R_1 = CH_3
60. R_1 = Bn

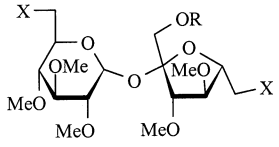
Figure 5. Derivatization of sucrose at the C-4, C-6 positions

Ester groups at the secondary positions are also inconvenient for other reasons. Such protecting groups would not survive the conditions applied in many reactions, such as reduction with $LiAlH_4$ or addition of Grignard reagents at the modified primary positions. Much more valuable are the alkyl protecting groups, which are stable under these conditions. Furthermore, temporary protection with trityl groups is more convenient than with silyl moieties, as the former are more stable under the conditions used in alkylation of secondary groups (base/alkyl halide) and, of course, much cheaper. The trityl groups are usually removed by mild acidic hydrolysis; much less common is a reductive procedure (H_2/Pd or Li/NH_3).

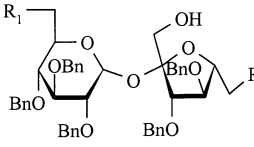
Penta-*O*-methylsucrose (**59**) was prepared from tri-*O*-tritylsucrose (**41**) by methylation of the secondary hydroxy groups (→ **56**) followed by *reductive* removal of the temporary trityl protecting groups[59] (Figure 5). The (more convenient) treatment with acid was avoided, because of the possible hydrolysis of the glycosidic bond. Compound **59**, with the methyl groups located on the secondary hydroxy groups, may be used *only as a model*. Some manipulations can be performed at the terminal positions, but deprotection in the final step (removal of five methyl groups) is not yet possible. Benzyl protecting groups in place of the methyl ones would be much more convenient.

Standard benzylation of **41** (NaH/BnBr) affords the fully protected derivative **57**. Because of the sensitivity of the benzyl groups towards the reductive conditions, the trityl groups cannot be removed as in **56**, but treatment of **57** with an acid under strictly controlled rigorous conditions provided the penta-*O*-benzylsucrose (**60**) in 50% yield without significant cleavage of the glycosidic bond[60] (Figure 5).

Synthesis of sucrose derivatives with all their secondary hydroxy groups protected as stable ethers opens a route to differentiation of the terminal OH groups and preparation of compounds modified at the C1′, C-6, or C-6′ positions. Some model reactions have been performed on penta-*O*-methylsucrose (**59**). This compound was converted into hexa-*O*-methyl derivative **63** by conversion of the 6- and 6′-OH groups into dihalide **61** (by the action of triphenylphosphane and carbon tetrachloride), followed by etherification of the remaining 1′-OH (→ **62**), and subsequent regeneration of a diol function by means of an S_N2 displacement of chlorine atoms with cesium acetate, followed by hydrolysis.[59] Treatment of **63** with methacryloyl chloride afforded unsaturated diester **64**.[61]



59. R = H, X = OH
61. R = H, X = Cl
62. R = Me, X = Cl
63. R = Me, X = OH
64. R = Me, X = CH_2=C(Me)CO_2-



60. R_1 = R_2 = OH
65 R_1 = OH, R_2 = Opiv
65a. R_1 = R_2 = Opiv
66. R_1 = R_2 = Cl

Although some model reactions, allowing study of the regioselectivity of the transformation of sucrose at the terminal positions, can be performed with **59** (or **63**), potential applications of these derivatives for the synthesis of analogues

of sucrose are not clear. Deprotection of the hydroxy groups cannot be done without destroying the sugar backbone.

4.2.1. Differentiation of the Primary Hydroxy Groups in Penta-*O*-benzylsucrose

A much more promising compound for the preparation of sucrose analogues is undoubtedly the penta-*O*-benzylsucrose (**60**), provided that the primary positions at C1′, C6, and C6′ can be distinguished from each other. Treatment of **60** with 1 equiv. of bulky pivaloyl chloride preferentially afforded the 6′-protected derivative **65**, although in low yield (30%).[62] If the hydroxy groups in **60** are activated with tri-*n*-butyltin oxide, the yield of **65** increases to 45%. However, small amounts of the 6,6′-diprotected derivative **65a** are isolated in both cases.[62] From these experiments, the following reactivity pattern (towards acylation) can be assigned to the primary hydroxy groups in 2,3,4,3′,4′-penta-*O*-benzylsucrose (**60**): 6′-OH > 6-OH >> 1′-OH.[62] This selectivity is different to that observed for free sucrose activated with tin species, in which the 6-OH is preferentially protected.[28,29]

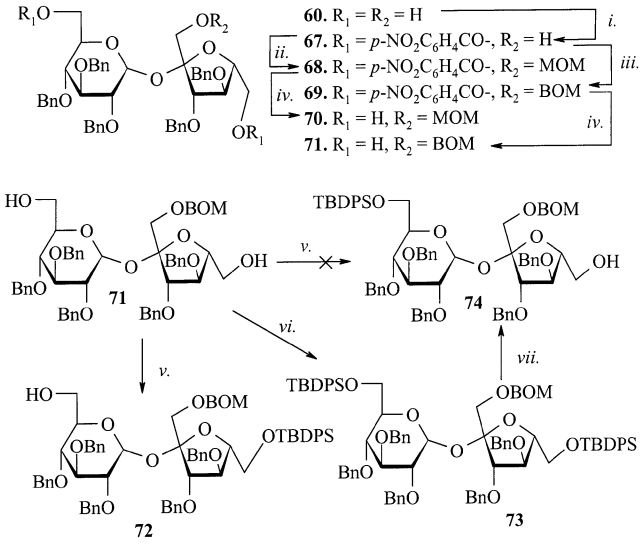
Chlorination (Ph_3P/CCl_4) of **60** is not as selective as for free sucrose. 6,6′-Dichloro-6,6′-dideoxy-2,3,3′4,4′-penta-*O*-benzylsucrose (**66**) was obtained in only 38% yield, because of the formation of the trichlorinated derivative.[63]

It was found that the primary hydroxy groups in **60** can be distinguished fairly easily by use of the methodology presented in Scheme 11. Treatment of the triol **60** with *p*-nitrobenzoic acid under Mitsunobu conditions protects the most reactive hydroxy groups at the C-6 and C-6′ positions to afford the monoalcohol **67** with the 1′-OH free.[64] This group can be blocked as either a methoxymethyl or a benzyloxymethyl ether (**68**[64] or **69**,[65] respectively). Removal of temporary protecting groups from 6-OH and 6′-OH affords diols **70**[64] and **71**,[65] respectively. Treatment of the diol **71** with 1 equiv. of *tert*-butyldiphenylsilyl chloride affords 80% of the C-6′-protected derivative **72**, together with small amounts of the diprotected compound **73**. *No formation* of the monoprotected regioisomer **74** was noted (Scheme 11).[65]

This compound can, however, be obtained in 68% yield by *selective deprotection* at the C-6′ position of the disilylated derivative **73** (which may be obtained in 95% yield by treatment of **71** with an excess of TBDPSCl).[65] Thus, all three sucrose monoalcohols (**67**, **72**, and **74**) are available through this simple methodology. *tert*-Butyldimethylsilyl chloride (TBDMS) has also been used for differentiation between 6-OH and 6′-OH in the methoxymethyl ether **70**; the yields of the corresponding monoprotected derivatives were, however, slightly lower.[64]

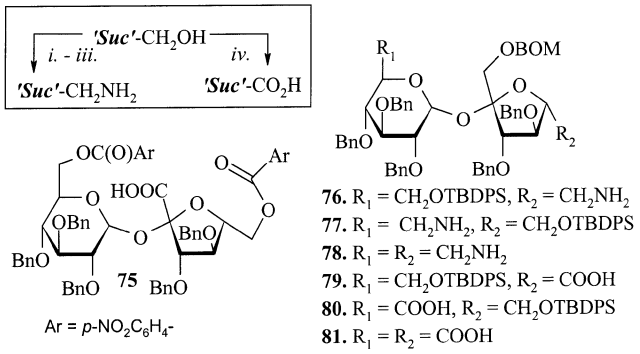
4.2.2. Functionalization of Terminal Positions in Partially Protected Sucrose

The availability of selectively protected sucrose monoalcohols and the diol (with the 6-OH and 6′-OH groups free) opened a route to various derivatives such as amines and



Scheme 11. *i.* TPP, DEAD, *p*-nitrobenzoic acid, py, room temp., 73%; *ii.* MOMCl, *i*Pr_2NEt, 63%; *iii.* BOMCl, py, 80%; *iv.* MeONa, MeOH/THF, 62% for **70**, 72% for **71**; *v.* TBDPSCl (1 equiv.), CH_2Cl_2, DMAP, *i*Pr_2NEt, 80%; *vi.* TBDPSCl (3 equiv.) DMF, NAH, 95%; *vii.* HF·py, 68%

uronic acids, which could be now prepared in good yields. Thus, alcohols **67**, **72**, and **74**, and the diol **71** were converted into mesylates and then treated with sodium azide in DMF. It was possible to obtain the corresponding azides at all positions except C-1′ (presumably for steric reasons) and to convert them into amines **76**−**78**[66] by means of a Staudinger reaction (Scheme 12).

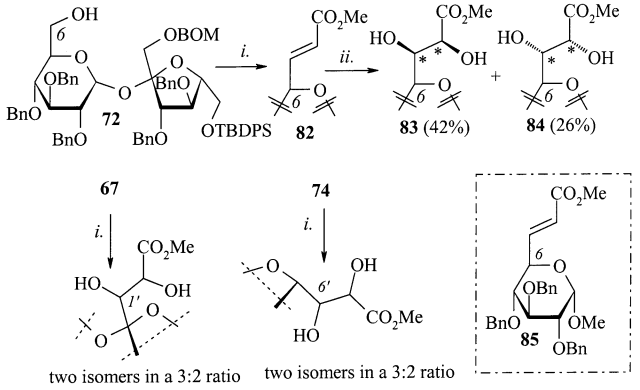


Scheme 12. *i.* MsCl, py; *ii.* NaN_3, DMF; *iii.* TPP, benzene, reflux 2−3 h, then H_2O reflux 2 h; *iv.* a. Swern oxidation, b. Jones oxidation or $Bu_4N(MnO_4)$

Contrary to previous results,[57] sucrose uronic acids are readily available from partially protected disaccharide. Oxidation of the corresponding sucrose alcohols with the Swern reagent, followed by the Jones reagent or tetrabutylammonium permanganate afforded acids **75**, **79**−**81** in good yields.[66]

Wittig-type homologation by two carbon atoms at either terminal position, followed by subsequent functionalization of the resulting double bond (an application of the Brimacombe[67] methodology to sucrose), provides a good example

of the synthetic potential of such selectively blocked sucrose derivatives.[65] The principle is presented in Scheme 13.



Scheme 13. *i.* 1. Swern oxidation; 2. $Ph_3P{=}CHCO_2Me$; *ii.* OsO_4, NMO

Monoalcohol **72**, with the 6-OH group free, was oxidized to an aldehyde with the Swern reagent[68] and treated with $Ph_3P{=}CHCO_2Me$. The resulting α,β-unsaturated ester **82** was *cis*-hydroxyated with osmium tetraoxide (catalytic version[69]) to afford the two stereoisomeric diols **83** and **84** in good chemical yield, but with significantly low stereoselectivity.[65] This result was very surprising, since osmylation of the similar compound D-glucose derivative **85** had proceeded with very high selectivity (10:1).[70] Functionalization of sucrose at the C-1′ or C-6′ positions was also possible, but again the stereoselectivity of the osmylation of the double bond was surprisingly low.[65] One of the big problems encountered in the synthesis of such homologated sucroses was determination of the configuration at the newly created chiral centers. X-ray assignment or chemical correlation are not always possible, so other methods are required. It was found that the configuration of the *vic*-diols derived from sucrose can safely be assigned by application of CD spectroscopy.[65]

Homologation of sucrose by more than two carbon atoms at either terminal position can also be conveniently performed by applying the methodology presented in Figure 6, originally developed during synthesis of higher carbon sugars.[71]

The basic idea consists of the coupling of sucrose (***Suc***−CH_2OH) and monosaccharide (***Sug***−CH_2OH) molecules with incorporation of one additional carbon atom, followed by funtionalization of the resulting enone system. The two approaches shown in Figure 6 provide regioisomeric higher sucrose enones. The first approach (***a.*** in Figure 6) requires oxidation of the corresponding sucrose monoalcohol (**67** or **72** or **74**) to the aldehyde, followed by treatment with an appropriate sugar phosphonate (sugar phosphoranes can also be used, but their preparation is not as convenient as that of phosphonates[71]). An example of functionalization of sucrose at either terminal position by a seven carbon atom unit (phosphonate **86**[72] derived from diacetonogalactose) is presented in Scheme 14. The higher sucrose enones **87**−**89** were prepared in good yields.[73] Application of other phosphonates afforded products with different functionality at the terminal positions.[73] The alternative version of a coupling (***b.*** in Figure 6) − sugar aldehyde **90** and sucrose phosphonate **91** − provided regioisomer **92** (Scheme 14).[73]

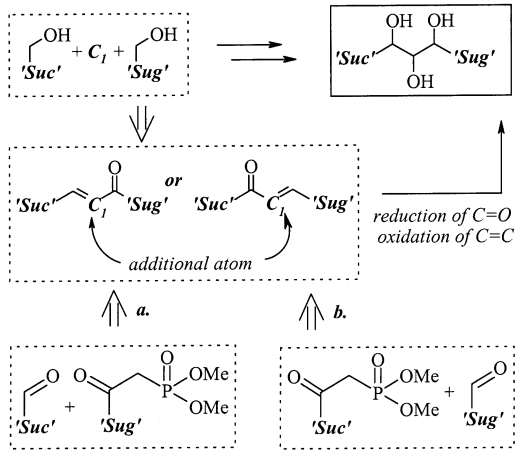
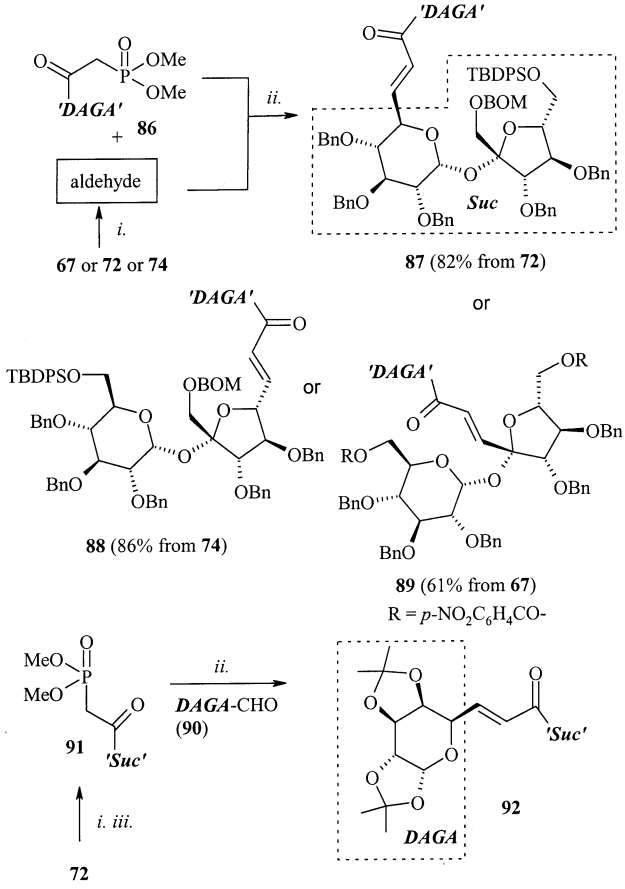


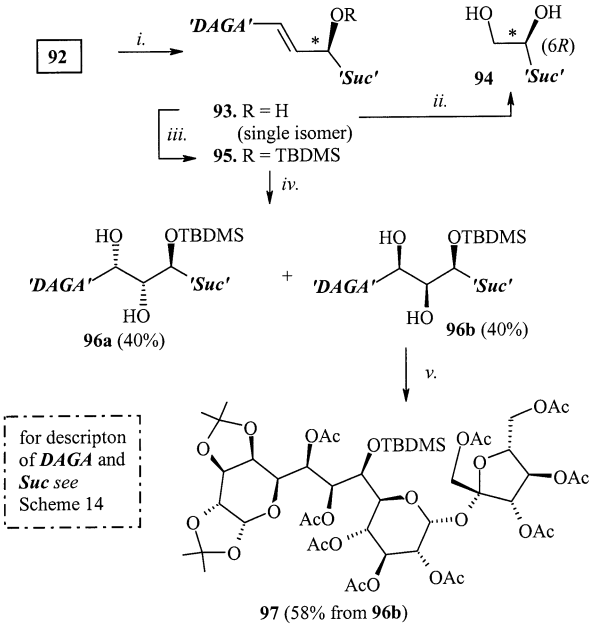
Figure 6. Synthetic plan for the preparation of higher analogues of sucrose



Scheme 14. *i.* Swern oxidation; *ii.* K_2CO_3, 18-crown-6, toluene, room temp.; *iii.* 1. Jones oxidation, 2. CH_2N_2, 3. $MeP(O)(OMe)_2$, BuLi

The synthetic potential of these compounds for the preparation of fully functionalized sucrose derivatives is shown in Scheme 15. One of the protected sucroses − higher enone

92 – was stereoselectively reduced with zinc borohydride to provide the allylic alcohol **93**. The (*R*) configuration at the newly created chiral carbinol center (which is consistent with the model proposed by us for reduction of higher sugar enones of the D-*gluco* configuration[74]) was assigned from the CD spectrum of the diol **94** obtained from **93** in two simple steps.[73] Again, it is worth pointing to the usefulness of CD spectroscopy for determination of the configurations of such complex molecules.



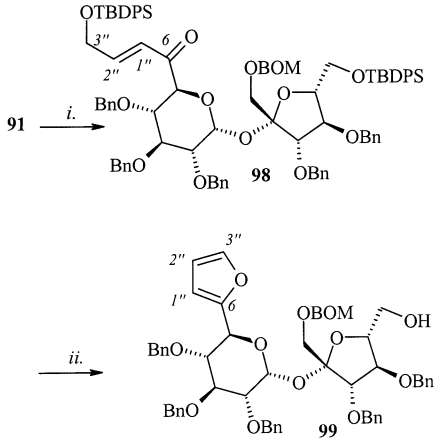
Scheme 15. *i.* $Zn(BH_4)_2$, Et_2O, 0 °C, 83%; *ii.* 1. O_3, CH_2Cl_2/MeOH, −78 °C, 2. $NaBH_4$, 68%; *iii.* TBDMSCl, DMAP, imidazole, DMF, 90 °C, 88%; *iv.* OsO_4 (cat.), NMO; *v.* 1. Na/NH_3, −78 °C, 30 min, 2. Ac_2O, py

Compound **93** was protected as the *tert*-butyldimethylsilyl ether **95** and the double bond was osmylated to give two diols **96a** and **96b** in *equal amounts*.[73] This is again a very strange result, because – according to Kishis's rule[75] – the stereoselectivity should be high, as both oxygen functions flanking the double bond act in the same direction. Deprotection of the sucrose backbone in one of the diastereoisomers (**96b**) was achieved conveniently with sodium in liquid ammonia; all the benzyl protecting groups and the TBDPS functionality were removed under these conditions.[73]

Phosphonate **91** was also used for the preparation of the more complex derivative **99**, in which the C-6 position was converted into 2-furyl ring[66] (Scheme 16). This process involved a Wittig-type coupling of **91** with *O*-*tert*-butyldiphenylsilylglycolaldehyde, followed by treatment of resulting enone **98** with a HF·py complex, which removed the silyl protecting groups and induced cyclization to **99**.[66]

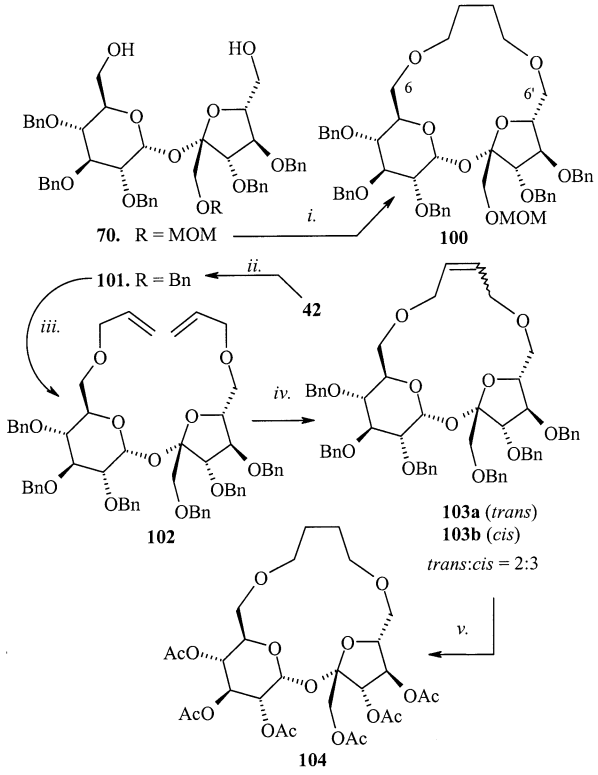
4.2.3. Synthesis of Macrocycles with Incorporated Sucrose Backbones

The C-6 and C-6′ "ends" in free sucrose are close to one another (see Figure 1). It was found that they are also close



Scheme 16. *i.* K_2CO_3, toluene, room temp., 18-crown-6, OHC−CH_2OTBDPS; *ii.* HF/py

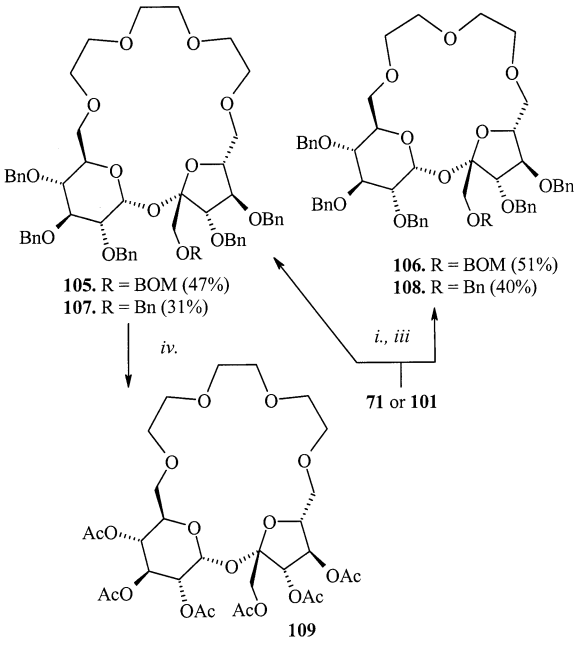
together in partially protected sucroses such as **70** (or **71** or **101**) and could be coupled together by (at least) a C_4 bridge. Thus, compound **100** was obtained by means of a Williamson coupling of the diol **70** with *n*-butylene diiodide (Scheme 17); treatment with *n*-propylene diiodide gave only the monoprotected derivatives (at the C-6 or the C-6′ positions).[76] This four-carbon atom bridge – this being the minimum length required to connect the C-6 and C-6′-ends – can be also installed[76] by metathesis[77] (Scheme 17).



Scheme 17. *i.* NaH, THF, $ICH_2CH_2CH_2CH_2I$, (21%); *ii.* NaH, DMF, BnBr, then $HOAcH_2O$, ref.[48]; *iii.* AllBr, NaH, DMF (75%); *iv.* Grubbs' catalyst, CH_2Cl_2, room temp. (78%); *v.* H_2/Pd, then Ac_2O/py (37%)

The diallyl derivative **102**, easily prepared from hexa-*O*-benzylsucrose **101**,[48] was treated with Grubbs' catalyst in dichloromethane at room temperature to afford both cyclic olefins **103a** (*trans*) and **103b** (*cis*) in a 2:3 ratio.[76] Removal of all benzyl protecting groups with simultaneous reduction of the double bond and subsequent acetylation of the hexaol provided the macrocyclic acetate **104** in good yield.[76]

These results also pointed at the possibility of synthesizing the crown ether type analogues of sucrose. Diols **71** and **101** were treated under basic conditions with ditosylates derived from polyethylene glycols. The corresponding macrocycles **105**−**108** were obtained in acceptable yields.[48] It was possible to remove all protecting groups from **107** by simple hydrogenation, and the free macrocyclic analogue (isolated as hexaacetate **109**) was obtained in quantitative yield[76] (Scheme 18).



Scheme 18. *i.* NaH, THF, room temp. 30 min; *ii.* $Ts(OCH_2CH_2)_3OTs$ (1.2 equiv.), room temp. 6 h; *iii.* $Ts(OCH_2CH_2)_2OTs$ (1.2 equiv.), room temp., 6 h; *iv.* H_2, Pd/C, then Ac_2O/py DMAP

5. Conclusion

Sucrose may be converted into a wide variety of useful precursors, which may be prepared either from free or from partially protected disaccharides. The latter is more convenient, since modifications of such derivatives can be performed with high degrees of regioselectivity. Benzyl groups are the best protecting groups for protection of all secondary hydroxy groups (and possibly the 1′-OH). The primary ones can be differentiated, permitting the preparation of the three possible sucrose monoalcohols with one free terminal hydroxy group (at C-1′, C-6, or C-6′). The diol with the 6- and 6′-OH positions unprotected is also available in good yield. Each terminal position can be selectively converted into an amine function (with the exception of C-1′) and uronic acid. Wittig-type methodology provides higher sucroses homologated by two or seven (or nine; see ref.[73]) carbon atoms at either terminal position.

The sucrose diols with the 6- and 6′-OH groups free (and the others protected with the functions easily removable under neutral conditions) have been converted into macrocyclic derivatives containing sucrose backbones. In addition, crown ether-type analogues based on sucrose can also be obtained. It is worth noting that these derivatives *can be deprotected without cleavage of the glycosidic bond.* This feature opens up a convenient route to a variety of analogues of sucrose in a free form, which can be used for biological screening or for further advanced studies.

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