Carbanionic Reactivity of the Anomeric Center in Carbohydrates

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I. Introduction

In less than the last two decades a fundamentally new role of carbohydrates in living organisms[1] has emerged: conjugates of oligosaccharides with proteins or lipids proved to be the major information carriers between cells and their surroundings.[2−4] The need for these specific substances in quantities larger than isolable from biological sources in order to thoroughly understand their biological functions has brought about the renaissance of synthetic carbohydrate chemistry.[5−8] A quest for compounds which can mimic the above natural substances by way of similar structure and/or biological action (the so-called mimetics) has also arisen and stimulated elaboration

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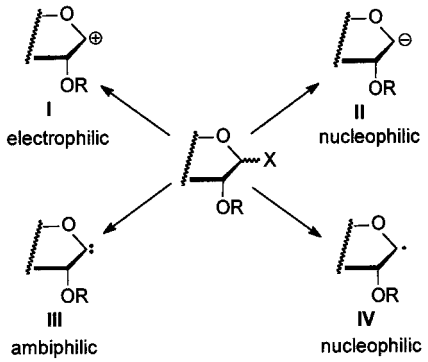
Graduating as a Chemist from the Lajos Kossuth University of Debrecen in 1978, László Somsák completed his Ph.D. degree with Professors István Farkas and the late Rezsö Bognár and received his degree at the same University in 1983. In 1990–91 he worked in Lyon (France) as a CNRS "poste rouge" fellow with G. Descotes and J.-P. Praly. He was the recipient of an Alexander von Humboldt Research Fellowship in Darmstadt (Germany) in 1992–93 as a guest of F. W. Lichtenthaler. Currently he holds the position of Associate Professor at the University of Debrecen, and for the period of 1999–2002 he has been a Széchenyi Professor of Organic Chemistry. In 1999 he was awarded the George Oláh Medal and Prize of the Hungarian Academy of Sciences. His research interests comprise radical-mediated transformations of carbohydrates, application of metal- and metal-complex-induced reactions to sugars, investigation of anomerically bifunctional monosaccharide derivatives, synthesis of *C*-glycosyl compounds and glycals, and the use of these methodologies for the preparation of glycomimetics, especially inhibitors of glycosidase and glycogen phosphorylase enzymes.

Scheme 1



of novel preparative procedures in carbohydrate synthesis.[5,6,9−11] The need for analogues of oligosaccharides resistant to hydrolytic/enzymatic cleavage is supported by drug discovery.[12] The use of carbohydrates as chiral building blocks in natural product synthesis is also an increasingly challenging area of contemporary synthetic organic chemistry.[13,14] All these efforts in chemistry and biology tend to converge in establishing a new discipline, namely, glycoscience.[15]

The chemistry of the anomeric center which is one of the most important domains of carbohydrate chemistry has been dominated by the "natural" electrophilic reactivity of the anomeric carbon for a long time.[13] Mechanistically this can be characterized by the involvement of a more or less stabilized glycosylium ion **I** (Scheme 1). Disregarding some sporadic early examples, the appearance and extensive use of methods for umpolung of the anomeric center date back to the 1980s. Anomeric carbanions[16−18] **II** and radicals[18a,b] **IV** behave as nucleophiles, and anomeric carbenes[18c−e] **III** may also react in that way.

The aim of this article is to review the chemistry of anomeric species with carbanionic character in the broadest sense, i.e., to survey compounds and reactions characterized by a carbon−metal bond at the anomeric center. Synthetically these transformations lead mainly (but not exclusively) to *C*-glycosyl derivatives[18a,19−33,33a] as well as glycals (1,4- or 1,5-anhydro-2-deoxy-ald-1-enitols).[34−37] Both types of carbohydrate derivatives are extremely important as mimics of biologically relevant sugars and also as building blocks in carbohydrate and natural product syntheses.

II. Stability, Formation, and Reactivity of Glycosyl Anions

The thermodynamic stability of carbanions can be characterized by the acidity of the corresponding CH-acidic compound: the higher the acidity, the more stable the carbanion. Since no relevant data exist in the literature for anomeric CH bonds, one has to rely on simple non-carbohydrate model compounds for which acidities are collected in Table 1.

The stabilizing effects such as hybridization, conjugation, polarizability, inductive effects, etc., operating in carbanions have been discussed in detail.[38] For glycosyl anions **VI** (Scheme 2), specific features should be considered: these species are α-alkoxy-substituted secondary carbanions in a ring which also bears additional substituents (L); the carbanionic center may also carry further groups (Z) which can contribute to the stabilization. The ring oxygen having an inductive effect may provide a slight stabilization resembling in its value the one obtained when the hybridization of carbon is changed from sp^3 to sp^2. Appearance of the anion in the β-position of the ring oxygen that is in a secondary position of the ring may cause no more significant stabilization. Electronegative substituents in farther positions of the ring (L) may act weakly stabilizing. Anomeric substituents (Z) which are highly polarizable or conjugate with the carbanionic center contribute to the stabilization to a much higher extent. It is hard to estimate how the effects of the ring oxygen and these substituents are superposed; however, additivity, in accordance with other experiences,[39] is probably not to be expected as examplified by methoxyacetonitrile (Table 1). Thus, stabilities of glycosyl anions can be estimated to follow the order of stabilization exerted by the anomeric substituents (Z), which are listed in decreasing order of this capacity[40] in Scheme 2.

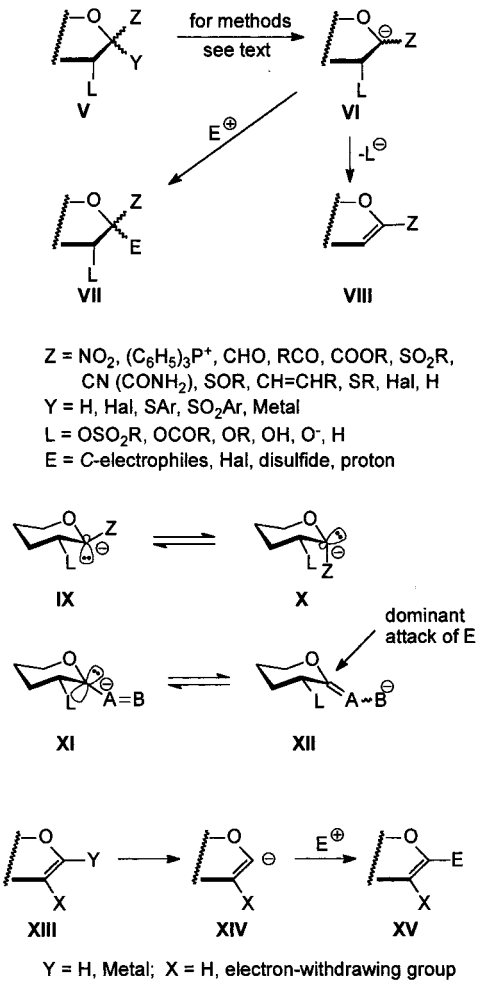
The stability of a particular glycosyl anion is reflected in properties such as the ease of its formation as well as its reactivity. Glycosyl anions have been formed by all main methods known for the preparation of carbanions:[41] (a) the more stable the anion the milder base is sufficient for its generation by deprotonating the conjugate acid (Scheme 2, **V** → **VI** Y = H, Z ≠ H); (b) less stabilized glycosyl anions are prepared by reductive metalation of suitable

Table 1. Acidities of Some C−H Bonds

compound	gas-phase acidity[a] (kcal/mol) (relative to CH_4)	pK_a (H_2O)[b]	pK_a (DMSO)[c] (relative to CH_4)
$H-CH_2-CH_3$	420.1 (−3.5)	50	
$H-CH_3$	416.6 (0)	48	56 (0)
$H-CH(CH_2)_3CH_2$	416.1 (0.5)		58[d] (−2)
$H-CH{=}CH_2$	409.4 (7.2)	44	49.5 (6.5)
$H-CH_2-OCH_3$	407.0 (9.6)		49[39] (7)
$H-CH_2-SCH_3$	393.2 (23.4)		45 (11)
$H-CH_2-CH{=}CH_2$	390.8 (25.8)		44 (12)
$H-CH_2-SC_6H_5$			42 (14)
$H-CH(CN)-CH_3$	375.0 (41.6)	25	
$H-CH_2-SO-CH_3$	373.6 (43.0)		35[39] (21)
$H-CH_2-CN$	372.9 (43.7)		31.3 (24.7)
$H-CH(CN)-OCH_3$	371.9 (44.7)		
$H-CH_2-CO_2CH_3$	371.9 (44.7)	24.5	27.5[e] (28.5)
$H-CH_2-CO-CH_3$	369.0 (47.6)	20	26.5 (29.5)
$H-CH_2-SO_2-CH_3$	365.9 (50.7)		29[39] (27)
$H-CH_2-CHO$	365.9 (50.7)	16	
$H-CH_2-SO_2-C_6H_5$	362.8 (53.8)		29[d] (27)
$H-CH_2-P^+(C_6H_5)_3$			22[f] (34)
$H-CH_2-NO_2$	356.4 (60.2)	10	17.2 (38.8)

[a] Lambert, C.; Schleyer, P. V. R. In *Methoden der organischen Chemie (Houben-Weyl)*; Hanack, M., Ed.; Georg Thieme Verlag: Stuttgart, 1993; Vol. E19d, pp 16−17. [b] March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1992; pp 250−252. [c] Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463 unless otherwise indicated. [d] Bordwell, F. G.; Drucker, G. E.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 632−635. [e] Arnett, E. M.; Harrelson Jr., J. A. *J. Am. Chem. Soc.* **1987**, *109*, 809−812. [f] Zhang, X.-M.; Bordwell, F. G. *J. Am. Chem. Soc.* **1994**, *116*, 968−972.

Scheme 2



glycosyl derivatives (**V**, Y = Hal, SAr, SO_2Ar; Z = H); (c) transmetalations (**V**, Y = Metal) are used to modify the reactivity of a particular anion. The same methods can be applied to generate an anionic center at the C-1 position of glycals (**XIII** → **XIV**) sometimes facilitated by the presence of electron-withdrawing substituents (X) in the 2-position. Other methods, e.g., carbanion formation in Michael additions, have also been reported (cf section III.A.3).

The reactivity of a glycosyl anion **VI** can be bifurcate. As a strong nucleophile, it may react with electrophiles of all types (E) to give substitution products **VII**. The stereoselectivity of this process is determined by the configuration of the anomeric anion (**IX** or **X**) or the steric availability (usually the β-face in the D-sugar series) of the conjugatively stabilized anion (**XI**, **XII**). Having a good leaving group in the β-position to the anionic center a glycosyl anion may undergo an E1cB elimination to give glycals **VIII**. These two reaction pathways are biased by the stability of the carbanion and the leaving ability of the 2-substituent L (listed in order of decreasing nucleofugality for *O*-substituents[42] in Scheme 2). With highly stabilized glycosyl anions 2-*O*-alkyl rests can survive. On the other hand, elimination of an oxide or hydride, which is known with simple carbanions,[43] has rarely been observed with glycosyl anions, presumably because of the slight stabilizing effect of the ring oxygen. Anions of type **XIV** give substitution products **XV** with electrophiles. Further manipulation of the double bond can restore or build up the desired sugar substitution pattern.

In the following sections methods for the generation of glycosyl anions are categorized according to the "strength" of the stabilizing group attached to the anomeric center of saccharide derivatives. Reactions of the anions are surveyed within a section to show eliminations first and then substitutions.

III. Generation and Reactions of Stabilized Glycosyl Anions

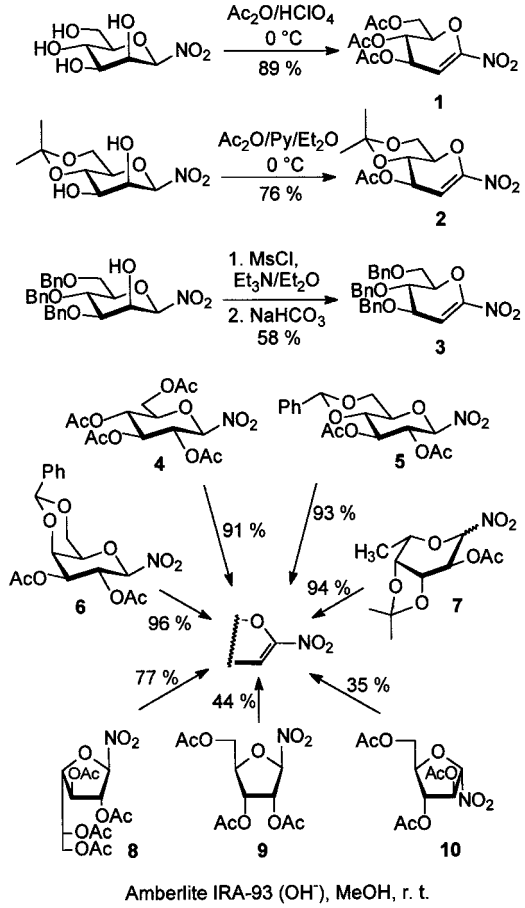
A. NO_2 as Stabilizing Group

A nitro group can be introduced at the anomeric carbon of monosaccharide derivatives by oxidative transformations of aldonolactone oximes[44] and glycosyl nitrones.[45,46]

1. 1-Nitro-glycals

The strongly electron-withdrawing nitro group can facilitate removal of the anomeric proton under mildly basic conditions. In the presence of an acetate[47] or mesylate[48] group in the 2-position, ready formation of 1-nitro-glycals **1**−**3** can be observed as shown in Scheme 3.

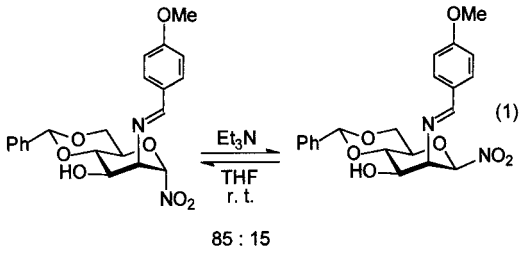
Scheme 3

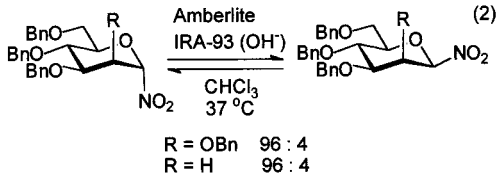


The configuration of C-2 is important: from the D-*manno* compounds (*axial* OH) the corresponding glycals **1**−**3** form already under acetylation conditions, while with D-*gluco* derivatives (*equatorial* OH) acetylation gives stable 2-acetates **4** and **5** which require somewhat stronger basic conditions for the elimination. This should be due to the antiperiplanar arrangement of the splitting moieties in the former cases which fulfill the stereoelectronic requirements for the β-elimination. The method was also applied to 1-deoxy-1-nitro derivatives of D-galactopyranose **(6)** and -furanose[47] **(8)**, L-fucopyranose[49] **(7)**, D-ribofuranose[47] **(9)**, and D-arabinofuranose[47] **(10)**.

2. Reactions of 1-Nitro-glycosyl Anions with Electrophiles

Equilibrations of 1-deoxy-1-nitro sugar derivatives[48,50] under basic conditions lead to mixtures of anomers which contain overwhelmingly the *axial* nitro derivatives (eqs 1 and 2). The anomeric effect for the nitro group was estimated to be 3.4 kcal/mol in the D-*manno* (R = OBn) and 2.4 kcal/mol in the 2-deoxy (R = H) derivatives.[48]

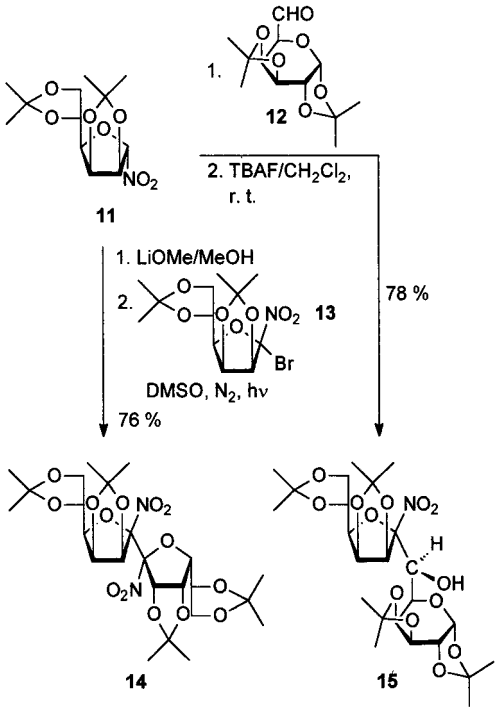




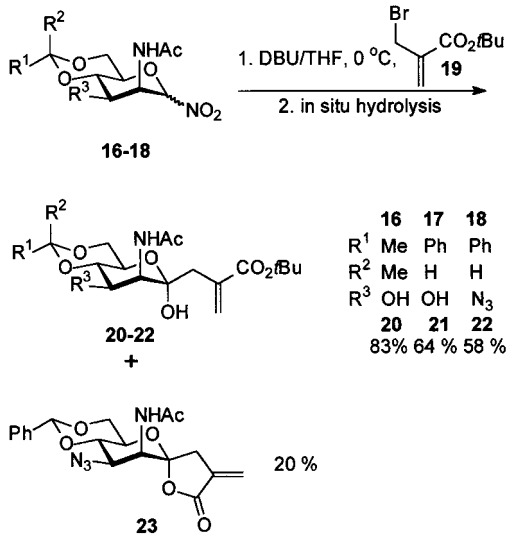
These equilibrations reveal that a 2-substituent of lower leaving ability (like an *O*-alkyl or similar group) can withstand elimination and such compounds can react with electrophiles (E) present in the reaction mixture (in the above cases E = H^+). Such reactions with various carbon electrophiles are collected in Table 2.

It is seen that even with the D-*manno* derivatives the coupled products of the Henry reaction are formed in high yields without elimination[51,52] (entries 1 and 2). The electrophile is incorporated predomi-

Scheme 4



Scheme 5



nantly from the β-face (entries 1−3). This is probably due to the strong anomeric effect of the nitro group and/or the better steric availability of the intermediate nitronate from this direction (compare Scheme 2, **XII**). Under aqueous conditions hydrolysis of the tertiary nitro group occurs readily to give the corresponding ketose derivatives[53] (entry 4). Many other nucleophilic additions of the above types have been carried out with various 1-deoxy-1-nitro-furanose compounds[52−56] (entries 6−26). Interestingly, a comparison of entries 6 and 7 with 10 and 11, respectively, shows that changing the O-5 protecting group results in opposite stereoselectivities of the nucleophilic additions.[53,54] Most important is the reaction of the anion of D-mannofuranose derivative **11** with the D-galactose-derived aldehyde **12** to give *C*-disaccharide[53] **15** (Scheme 4).

The 2-acetamido substituent is also featured by a weaker leaving ability. As a consequence, an important intermediate in a new synthesis of *N*-acetylneuraminic acid[57] (Neu5Ac) arose from the D-glucosamine derivative shown in Table 2, entry 5. Michael addition of the anions derived from *N*-acetyl-D-mannosamines **16** and **17** (Scheme 5) to **19** and subsequent β-elimination followed by hydrolysis gave **20** and **21**, respectively, which were also converted by further manipulations into Neu5Ac and its 4-epimer.[58] Similar transformations starting with the azido derivative **18** lead to **22** and **23**. From **22**, 6-amino-6-deoxysialic acid inhibitors of sialidase enzymes were synthesized.[50]

Another interesting feature of the weakly basic 1-nitro-glycosyl anions is their ability to undergo radical nucleophilic chain substitutions ($S_{RN}1$). Thus, the D-mannose-derived anion (Table 2, entry 27) reacted with 2-chloro-2-nitropropane under irradiation to give a dinitro derivative formed by coupling of two tertiary carbon centers.[59] Similarly, a highly

Scheme 6

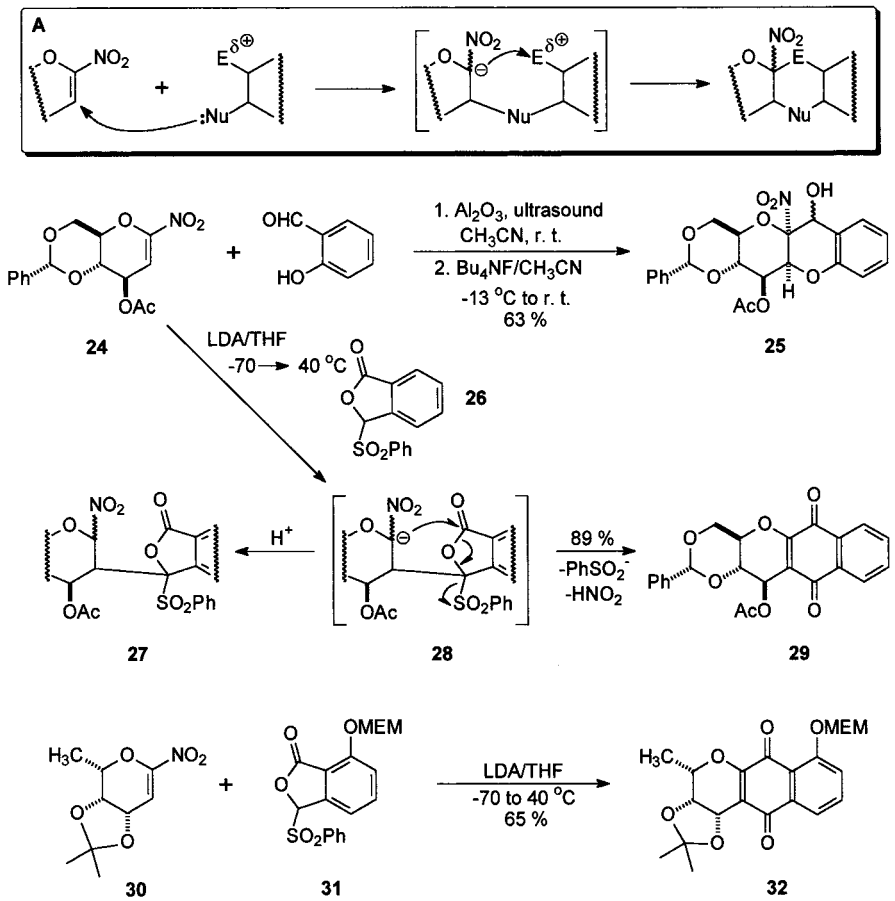


Table 2. Reactions of 1-Nitro-glycosyl Anions Obtained by Deprotonation

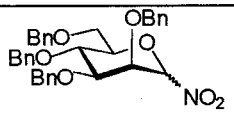
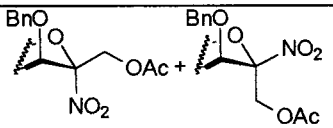
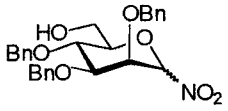
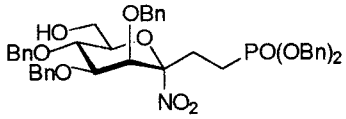
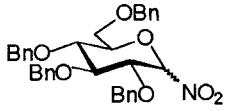
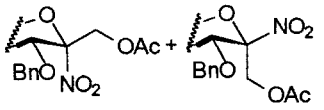
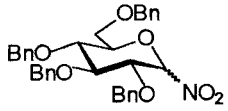
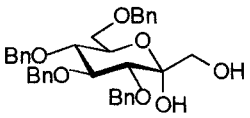
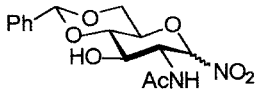
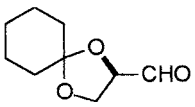
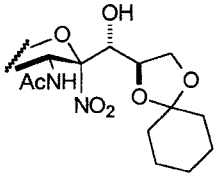
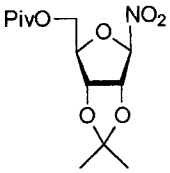
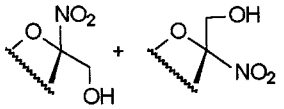
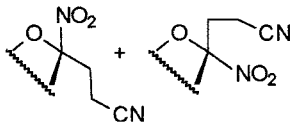
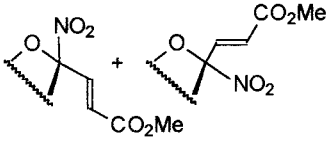
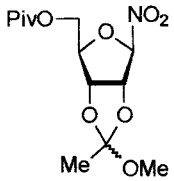
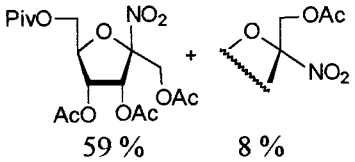
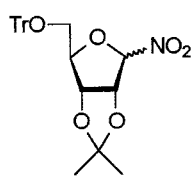
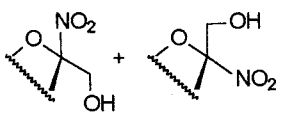
Entry	Substrate	Reaction conditions	Electrophilic partner	Product	Ref.
1.		K_2CO_3/MeOH, r. t. then acetylation	HCHO	 65 % 12 %	51
2.		Bu_4NF/THF, 0 °C → r. t	CH_2=$CHPO_3Bn_2$	 77 %	52
3.		K_2CO_3/MeOH, r. t. then acetylation	HCHO	 48 % 8 %	51
4.		Li_2CO_3/H_2O-Py 1 : 1, 60 °C, then hydrolysis	HCHO	 63 %	53
5.		Et_4NOH (cat.) DMF, r. t.		 85 %	57
6.		K_2CO_3/MeOH, r. t.	HCHO	 88 % 4 %	54
7.		Bu_4NF/CH_2Cl_2, 0 °C	CH_2=CHCN	 69 % 5 %	54
8.		Et_3N/CH_2Cl_2, −30 °C	HC≡CCO_2Me	 48 % 24 %	54
9.		K_2CO_3/MeOH, r. t and subsequent transformations	HCHO	 59 % 8 %	54
10.		K_2CO_3/MeOH, r. t.	HCHO	 2 % 74 % (5 : 95)	53

Table 2 (Continued)

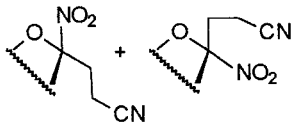
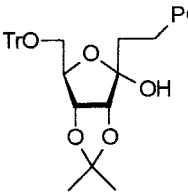
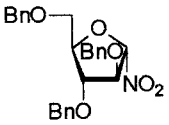
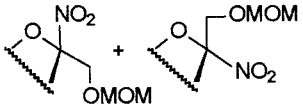
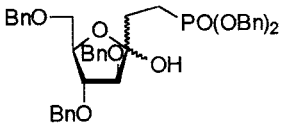
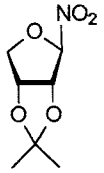
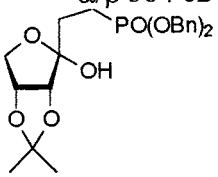
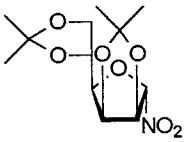
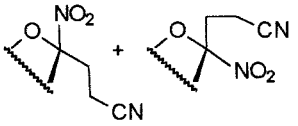
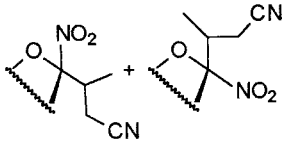
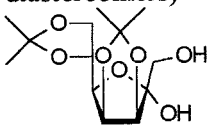
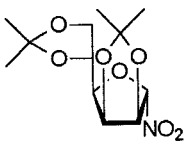
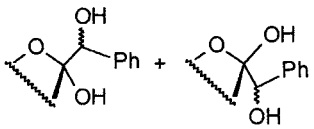
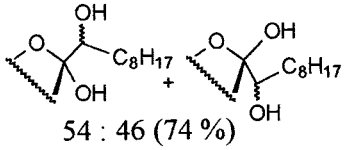
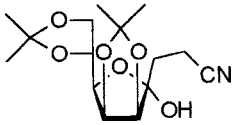
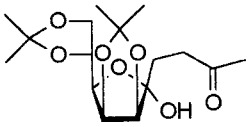
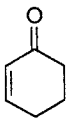
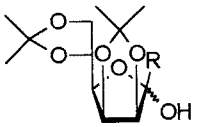
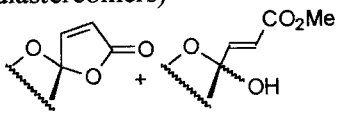
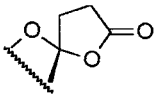
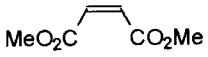
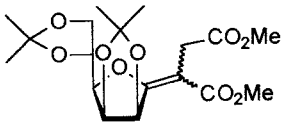
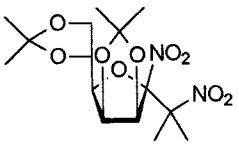
Entry	Substrate	Reaction conditions	Electrophilic partner	Product	Ref.
11.		K_2CO_3, DMSO/H_2O, 50-60 °C	CH_2=CHCN	 11 % 44 %	53
12.		Bu_4NF/THF, 0 °C	CH_2=$CHPO_3Et_2$	 87 %	55
13.		Bu_4NF/CH_2Cl_2, r. t. then formaldehyde dimethylacetal/P_2O_5	HCHO	 43 % 13 %	56
14.		Bu_4NF/THF, 0 °C → r. t. then hydrolysis	CH_2=$CHPO_3Bn_2$	 α/β 38 : 62 (83 %)	52
15.		Bu_4NF/THF, 0 °C → r. t. then hydrolysis	CH_2=$CHPO_3Bn_2$	 81 %	52
16.		Bu_4NF/THF, 0 °C → r. t	CH_2=CHCN	 60 % 7 %	53
17.		Bu_4NF/THF, 0 °C → r. t	CH_3CH=CHCN	 76 % 8 % (1 : 1 mixture of diastereomers)	53
18.		Et_4NOH/ CH_2Cl_2, r. t., then in situ hydrolysis	HCHO	 76 %	53
19.		Li_2CO_3/H_2O-Py 1 : 1, 60 °C, then hydrolysis	PhCHO	 24 % 20 %	53
20.		Li_2CO_3/H_2O-Py 1 : 1, 60 °C, then hydrolysis	$C_8H_{17}CHO$	 54 : 46 (74 %)	53

Table 2 (Continued)

Entry	Substrate	Reaction conditions	Electrophilic partner	Product	Ref.
21.		Et_4NOH/ CH_2Cl_2, r. t., then in situ hydrolysis	CH_2=CHCN	 49 %	53
22.		Bu_4NF/THF, r. t. then hydrolysis	CH_2=$CHCOCH_3$	 71 %	53
23.		Bu_4NF/THF, r. t. then hydrolysis		 R = 3-oxocyclohexyl 76 % (4 : 1 mixture of diastereomers)	53
24.		K_2CO_3, DMSO/H_2O, 50-60 °C	HC≡CCO_2Et	 50 % 17 %	53
25.		Et_4NOH/ CH_2Cl_2, r. t., then in situ hydrolysis	CH_2=$CHCO_2Me$	 63 %	53
26.		K_2CO_3, DMSO/H_2O, 50-60 °C		 48 %	53
27.		NaH, DMSO, Ar, 0 °C, hν	$(CH_3)_2C(NO_2)Cl$	 85 %	59

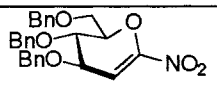
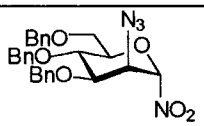
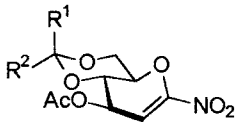
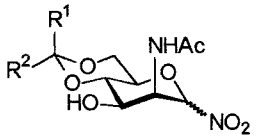
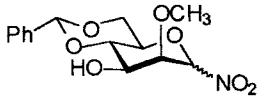
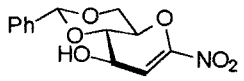
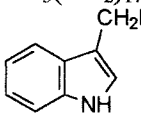
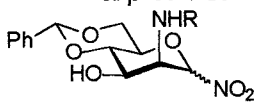
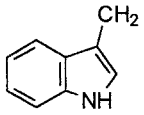
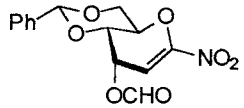
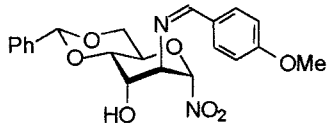
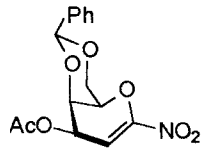
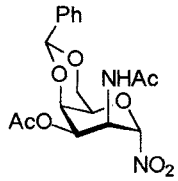
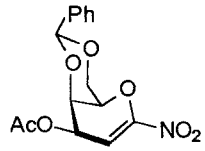
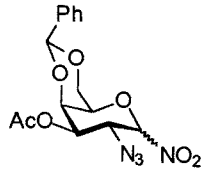
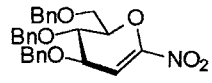
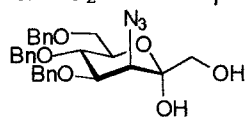
stereoselective reaction occurred between **11** and 1-bromo-1-nitro derivative **13** (Scheme 4) to give **14** in very good yield.[59]

3. Nucleophilic Additions to 1-Nitro-glycal Derivatives

The electron-deficient double bond in 1-nitro-glycal derivatives is readily attacked by nucleophiles to give Michael-type addition products. Intensively investigated were additions of *N*-nucleophiles collected in Table 3.

Due to stereoelectronic control, the incoming nucleophiles occupy an axial orientation to give precursors (entry 1) or derivatives of D-mannosamine[47] (entries 2 and 4), D-altrosamine[50] (entry 5), and D-talosamine[47] (entry 6). Since the addition of azide ion to nitro-olefins is a reversible process, the more stable D-galactosamine derivative[47] (entry 7) could also be obtained under thermodynamically controlled conditions. It was also possible to couple the addition of azide to a 1-nitro-glycal with the Henry reaction (entry 8), and thus, an α-D-*manno*-heptulopyranose derivative was prepared in high yield.[47] *O*-Nucleophiles attack also from the axial direction as exemplified by the byproducts of a Zemplén-deacetylation[47] (entry 3, see also transformation of **24** to **25** in Scheme 6). The outlined additions to 1-nitro-glycals were applied as parts of tandem reactions for the syntheses of natural products as well. The concept of this methodology is shown in Scheme 6A: the anion formed at the anomeric carbon by the addition of a nucleophile to the double bond can immediately attack an intramolecular electrophile to give a ring-closed product. According to this principle, 1-nitro-glucal **(24)** reacted with salicylaldehyde to give **25**[60] containing the pyrano[3,2-*b*][1]benzopyrane skeleton, which is constituent with natural products. Reaction of **24** with the lithium salt of sulfone **26** may give **28**

Table 3. Addition of Nucleophiles to 1-Nitro-glycal Derivatives

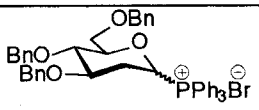
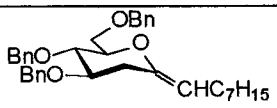
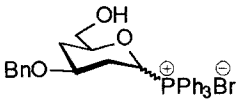
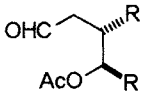
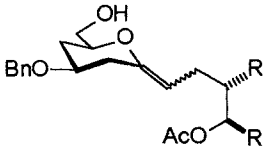
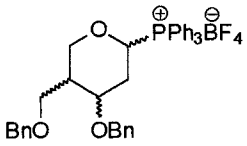
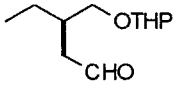
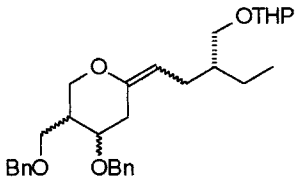
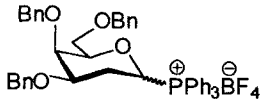
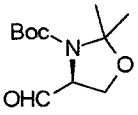
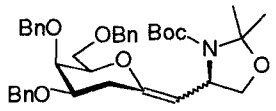
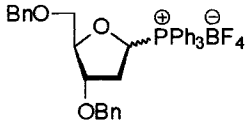
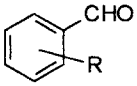
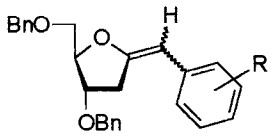
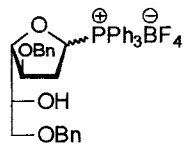
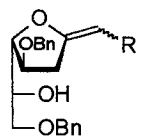
Entry	Substrate	Reaction conditions	Product	Ref.
1.		LiN_3/AcOH, DMF, 50 °C	 74 %	47
2.		NH_4OH, H_2O/THF, r. t.	 $R^1 = R^2 = CH_3$ 93 % $R^1 = H$, $R^2 = Ph$ 89 %	47
3.		NaOMe, MeOH/Et_2O, r. t.	 α/β 85 : 15 4 %	47
4.		CH_3NH_2/THF or $CH_3(CH_2)_{17}NH_2$/Py or 	 $R = CH_3$ 78 % $R = C_{18}H_{37}$ 76 % R =  70 %	47
5.		1. NH_4OH, H_2O/THF, 0 °C → r. t. 2. 4-$MeOC_6H_4CHO$	 57 %	50
6.		1. NH_4OH, H_2O/THF 2. Acetylation	 85 %	47
7.		NaN_3, HN_3/$CHCl_3$, CH_3CN, 50 °C	 α-NO_2 53 % β-NO_2 22 %	47
8.		KN_3, 18-crown-6, HCHO, CH_2Cl_2, then hydrolysis	 91 %	47

as an intermediate from which **29** could be obtained by an intramolecular nucleophilic substitution followed by a double β-elimination. Conducting the reaction at lower temperature **27** was also isolated from the mixture. A similar transformation of **30** with sulfone **31** led to the synthesis of (−)-cryptosporyn **(32)**.[49]

B. PPh_3^+ as Stabilizing Group

Anomeric phosphonium salts of sugar derivatives (cyclic ethers in general) can be prepared from glycosyl chlorides or glycoses (via the chlorides) with triphenylphosphine and from glycals or glycosides[61,62] as well as from 1,6-anhydro[66] and 1,4-anhydro

Table 4. Reactions of Glycosyl Phosphonium Salts

Entry	Substrate	Reaction conditions	Product	Ref.
1.		$C_7H_{15}CHO$ BuLi/THF/HMPT, –67 °C → r. t.	 78 %	65
2.		 BuLi/THF, –78 °C → r. t.	 R = Me R = H	66
3.		 BuLi/THF/HMPT, –67 °C → r. t.	 yield unknown	67
4.		RCHO or ArCHO	E/Z selectivities ~1 : 1 yields ~ 80 %	68
5.		BuLi/THF, –90 °C → r. t. 	 E/Z ~ 1 : 1 60 %	69
6.		 R = H, 4-OMe, 2-Cl-6-F, 4-SMe, 4-Me_2N, 4-NO_2, 2-NO_2, 4-Cl *A*) BuLi/THF, –90 °C → r. t. *B*) BuLi/THF/HMPT, –90 °C → r. t. *C*) *t*-BuOK/THF –90 °C → r. t.	 yields: 24-40 % with methods *A* and *B*, 45-58 % with method *C*; moderate E/Z selectivities	68
7.		1. BuLi, THF, –78 °C 2. RCHO, –78 → 20°C	 R = Ph E/Z = 2 : 3 66% R = *i*Pr E/Z = 2 : 3 31%	66a,b

sugars[66a,b] with triphenylphosphonium salts. For two glycosyl triphenylphosphonium tetrafluoroborates, crystal structures have also been detemined (Table 4, entries 4[63] and 6[64]).

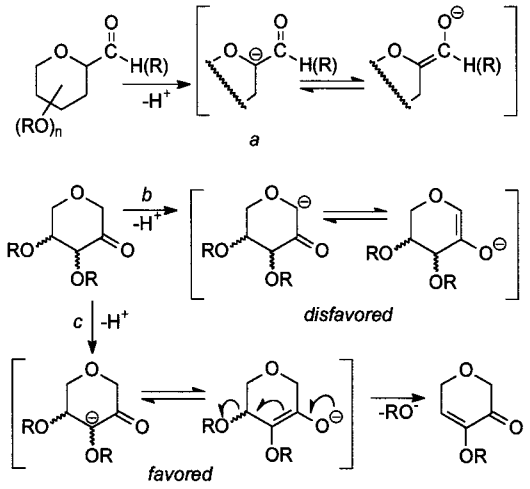
Reactions of glycosyl phosphonium salts[65–68] with aldehydes according to the Wittig protocol gave primarily *exo*-glycal derivatives collected in Table 4. Further transformations included stereoselective hy-

drogenation of the double bond to give various *C*-glycosyl compounds[65,68] (entries 1 and 6), *C*-glycosyl α-amino acid derivatives[69] (entry 5), and spiroacetalization to give bicyclic structures related to avermectins and milbemycins[66] (entry 2) as well as (−)-talaromycins[67] (entry 3). A variant of this method was used in the total synthesis of the protein phosphatase inhibitor okadaic acid.[70]

C. C=O as Stabilizing Group

A carbonyl group can be attached to the anomeric center as an *exocyclic* formyl (or keto) function or as an *endocyclic* 2-keto group. In the former case (*C*-glycosyl aldehydes: 2,5- or 2,6-anhydroaldoses), deprotonation can yield the anomeric carbanion or rather the corresponding enolate (Scheme 7, route *a*). In the

Scheme 7



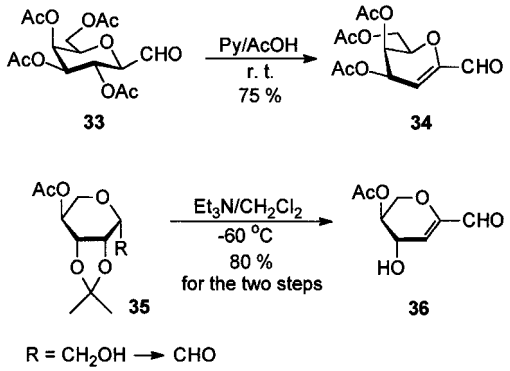
second case (glycos-2-ulose derivatives), deprotonation may occur in two positions. According to route *b*, the anomeric anion/enolate can be formed. However, proton abstraction on route *c* is the stereoelectronically favored process,[71] which can be followed by a *β*-elimination to give an enolone derivative.[72]

C-Glycosyl aldehydes can be prepared by Raney-nickel−sodium hypophosphite[73,74] or LAH[74a] reduction of glycosyl cyanides, ozonolysis of *C*-glycosyl allenes,[75] *C*-glycosyl ethenes,[76] or nitronates of *C*-glycosyl-nitromethanes,[77] periodate oxidation of *C*-D-glucopyranosyl ethylene glycols,[77a] Swern oxidation of *C*-α-D-glucopyranosyl methanol,[77b,c] as well as demasking the formyl group in 2-glycosyl-1,3-dithianes[76] or 2-glycosyl-thiazoles.[78] In some cases[76b,c,77b,c] the *C*-glycosyl aldehyde appears as a nonisolated intermediate of a synthetic sequence. A convenient method for the preparation of glycos-2-ulose derivatives is based on the hydroxylaminolysis of fully protected 2-hydroxy-glycals.[72] 1,5:3,6-Dianhydro derivatives of glycos-2-uloses were prepared to direct deprotonation at the anomeric center.[71] For use in reductive metalations, glycos-2-ulosyl bromide derivatives were synthesized most easily in one step from protected 2-hydroxy-glycals by *N*-bromosuccinimide and an alcohol.[79,80] For similar use a phenyl 1-thio-glycosid-2-ulose derivative, a starting material of higher stability, was also prepared by oxidation of phenyl 3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside.[81]

1. Deprotonation of C-Glycosyl Aldehydes

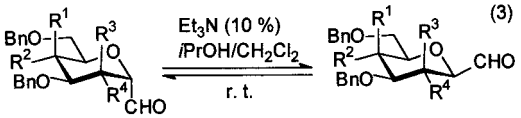
1-Formyl-glycals. In the presence of a leaving group like OAc in the 2-position as in *C*-galactosyl aldehyde **33** (Scheme 8), deprotonation under very

Scheme 8



mild conditions is easily followed by expulsion of the 2-substituent to give the corresponding galactal **34**.[74] The preparation of **34** can be performed in a one-pot procedure starting from the corresponding acetylated *β*-D-galactopyranosyl cyanide in 40% overall yield.[82] Further transformations of **34** led to glycosidase and glycosyl transferase inhibitors. Aldehyde **35** which needs not be isolated produces glycal **36**,[83] an intermediate in a new synthesis of L-ascorbic acid from D-galactose. Ready cleavage of the acetal moiety is probably due to the formation of a stable carbonyl group in the eliminating acetone, as well as to the conjugative stabilization in the α,*β*-unsaturated aldehyde.

Equilibration of *C*-Glycosyl Aldehydes. The benzyl-protected aldehydes shown in eq 3 equilibrate under mildly basic conditions.[75] Each equilibrium mixture contains mainly the anomer with a formyl group in the *β*-position, whereby the corresponding glycals derived from elimination of the 2-benzyloxy substituent also appeared as byproducts. Although percentage of the glycals was not indicated, the epimerization yield for the D-*manno* derivative was not significantly lower than those for the others despite the *axial* orientation of the 2-OBn substituent. Compared to the above glycal formations, these observations also reflect the worse nucleofugality of the benzyloxy group with respect to the acetoxy and isopropylidenyloxy moieties.



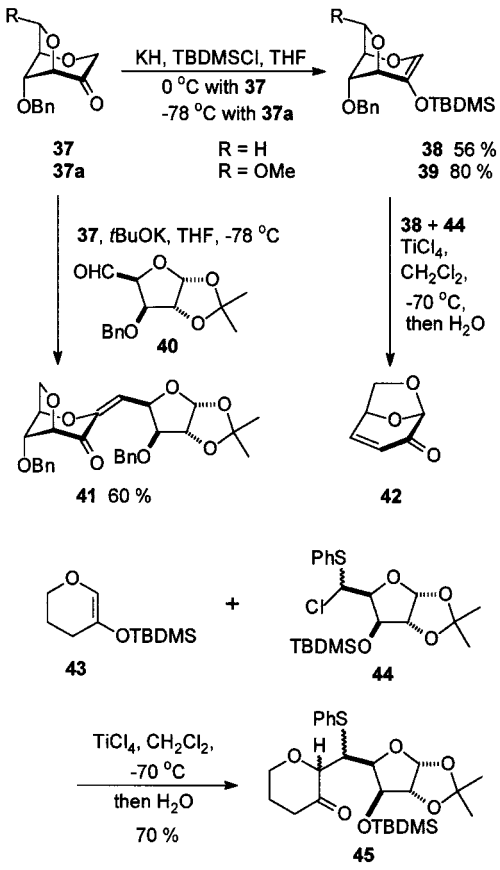
$R^1 = R^3 = H$, $R^2 = R^4 = OBn$	1 : >20	(D-*gluco*)	41 %
$R^2 = R^3 = H$, $R^1 = R^4 = OBn$	1 : 10	(D-*galacto*)	49 %
$R^1 = R^4 = H$, $R^2 = R^3 = OBn$	1 : 8	(D-*manno*)	42 %

2. Deprotonation of 1,5:3,6-Dianhydro-glycos-2-ulose Derivatives

The bicyclic derivatives **37** and **37a** deprotonate at the "anomeric" position, and the enolate formed can

be silylated to **38** and **39**,[71] respectively, as shown in Scheme 9. The enolate of **37** reacts with the D-xylose-

Scheme 9



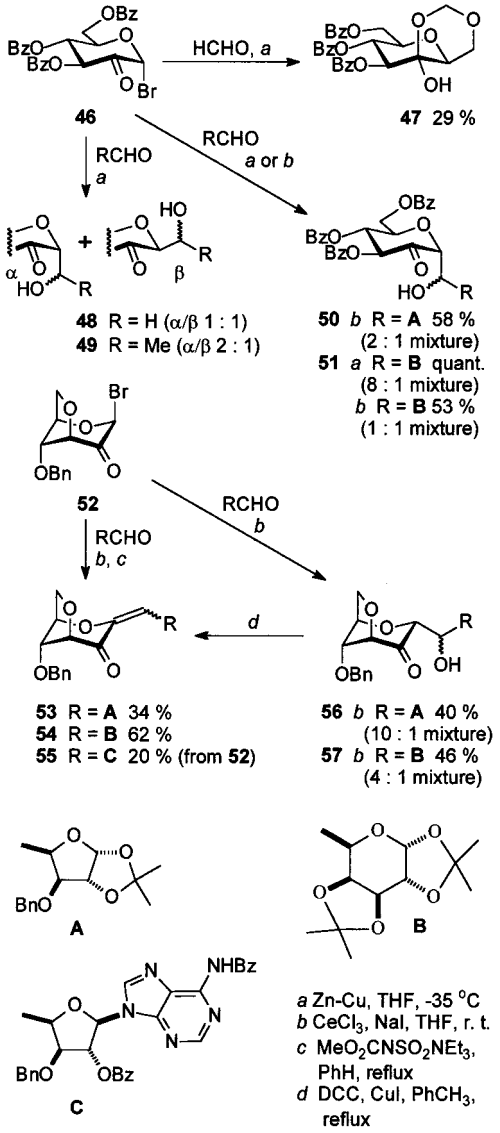
derived aldehyde **40** to give enone **41**, which is an important intermediate in the synthesis of herbicidin antibiotics.[84] To study the creation of the same skeleton, silyl-enol-ether **43** was reacted with chlorosulfide **44** and the coupled product **45** was isolated in good yield.[85] Completely unexpectedly, under the same conditions reaction of **38** afforded only 40% of levoglucosenone **42**,[85] which was formed quantitatively in the absence of **44**. The formation of **42** was also observed with other Lewis acids and could be understood in terms of a 1,3-shift of the 3,6-anhydro bridge to the anomeric position followed by β-elimination of benzyl alcohol.

3. Anions by Reductive Metalations at C-1 of Glycos-2-ulosyl Derivatives

The problem of undesired direction of deprotonation can be overcome by generating the anion/enolate via reductive removal of suitable anomeric substituents. Thus, the glycos-2-ulosyl bromide **46** (Scheme 10) can be transformed into the corresponding "anomeric" enolate by using Reformatsky conditions[86,87] (*a*) or a one electron reductant $CeCl_3$ (*b*).[87]

Coupling of the anomeric zinc−enolate with simple aldehydes results in **48** and **49** with negligible stereoselectivity. With a second formaldehyde molecule, **48**β reacts further to give the bicyclic acetal **47**.[86] It is noteworthy that the reactions of **46** with more complex, carbohydrate-derived aldehydes ste-

Scheme 10

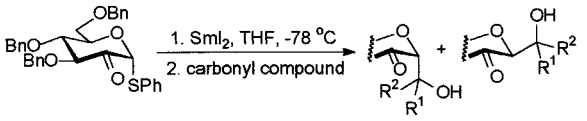


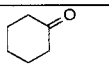
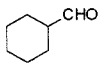
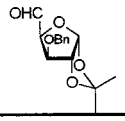
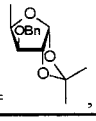
reoselectively gave the α-configurated **50** and **51** as diasteromeric mixtures.[87] The 3,6-anhydro-bridged ulosyl bromide **52** was obtained from **37** (Scheme 9) with *N*-bromosuccinimide as a source of electrophilic bromine. Reactions of **52** with complex aldehydes gave **56** and **57**, again with high stereoselectivity,[87] which may originate from the attack of the electrophile on the sterically less crowded *exo*-face of the bicyclic enolate system. The mixtures of diastereomers were dehydrated to enones **53**−**55** (single isomers but alkene geometry was not determined).

Another variant for the utilization of C-1 anions of glycos-2-ulose derivatives is based on the SmI_2-mediated coupling of a phenyl 1-thio-D-glucosid-2-ulose derivative with carbonyl compounds[81] summarized in Table 5.

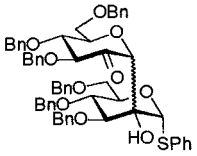
The reactivity of the samarium enolate allowed not only the use of aldehydes (entries 6 and 7), but also that of ketones (entries 1, 4, and 5) as electrophiles. While at room temperature or in the presence of added donor solvents the reaction was not very selective (entries 2 and 3), at low temperature the expected coupled products formed with high α-selec-

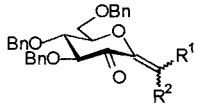
Table 5. Samarium Diiodide-Mediated Coupling of a 1-Thio-glucos-2-uloside with Carbonyl Compounds[81]



Entry	Carbonyl compound	Yield (α : β)
1.		R^1, R^2 = cyclohexyl, 87 % (79 : 21)
2.	*at room temp.*	R^1, R^2 = cyclohexyl, 19 % (55 : 45) +19 % of homocoupled product **A**
3.	*in the presence of HMPT or TMEDA*	21 % homocoupled product **A** only
4.	Me_2CO	$R^1 = R^2$ = Me, 85 % (53 : 47)
5.	Et_2CO	$R^1 = R^2$ = Et, 88 % (>90 : 10)
6.	MeCHO	R^1 = H, R^2 = Me, 75 % (>90 : 10) + 15 % dehydrated product **B**
7.		R^1 = H, R^2 = *c*-C_6H_{11}, 76 % (>90 : 10) + 24 % dehydrated product **B**
8.		R^1 = H, R^2 =  , 73 % (>90 : 10)

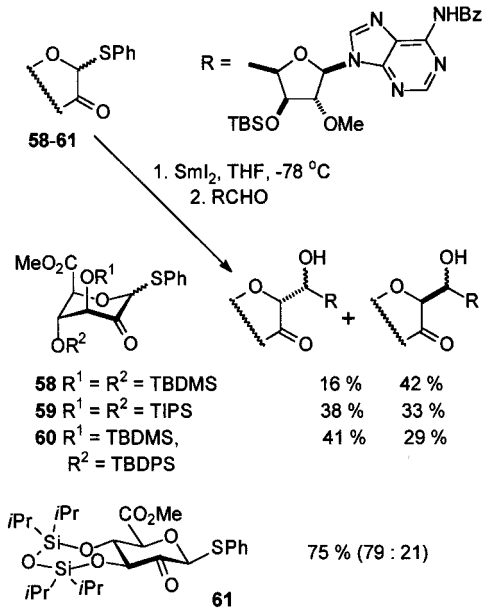
A configurations were not specified **B**





tivity and in very good yield (entry 1). In this way the benzylated analogue of the *C*-disaccharide **50** could also be prepared (entry 8). The same methodology was used to get important intermediates from uronate-derived 1-thioglycosides **58**−**61** in the first synthesis of herbicidin B summarized in Scheme 11.[88]

Scheme 11



D. COOR as Stabilizing Group

A carboxyl group can be formed at the anomeric carbon by the hydrolysis of nitrile moieties in glycosyl cyanides.[89] This transformation can also be performed in two steps: the first one is a partial hydrolysis to the carboxamide[90,91] which is then nitrosated to give the carboxylic acid.[90] Other methods use anomeric carbanions and are described in sections III.F.2, IV.B, and IV.C of this article. The carboxyl group is present at the anomeric center of such important natural products as KDO, KDN, and Neu5Ac.

1. 1,2-Eliminations from COOR-Stabilized Anomeric Anions

Under Zemplén deacetylation conditions, carboxylic ester **62** readily loses acetone to give glycal **63** (Scheme 12), which is an intermediate in the synthesis of L-ascorbic acid from D-galactose.[83] Esterification or amidation of carboxylic acid **64** with the Mukaiyama reagent gave the corresponding glycals **65** in a concomitant *β*-elimination when an excess amount of the reagents was applied.[92,93] By using 1 equiv of the reagents the expected carboxylic acid derivatives without elimination were the main products (RXH = BnOH 42%, 2-aminomethylpyridine 59%).[93] The anomeric anion can be formed by a reductive dehalogenation using zinc/pyridine (cf. sections III.E.1 and IV.A.1) from the bromocarboxylate **66** yielding the methoxycarbonyl-glycal **67** by expul-

Scheme 12

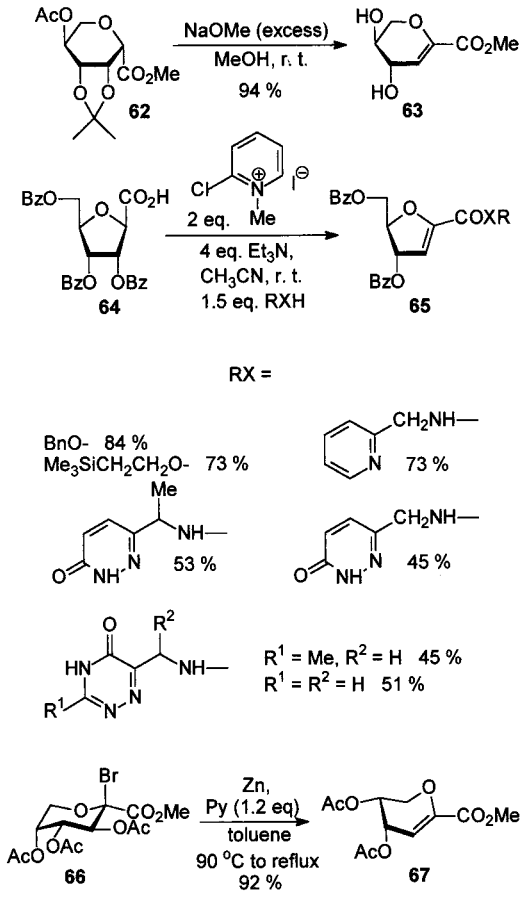


Table 6. Reactions of COOR-Stabilized Anomeric Anions/Enolates

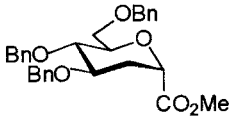
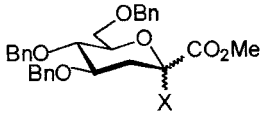
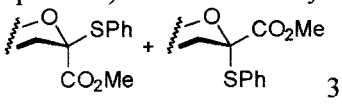
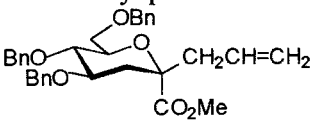
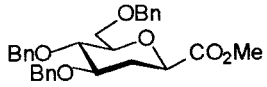
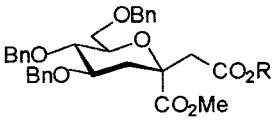
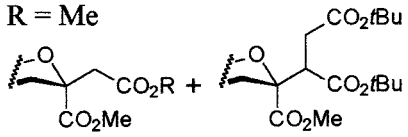
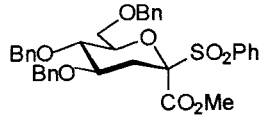
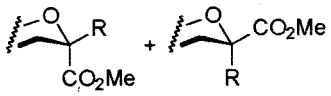
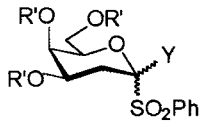
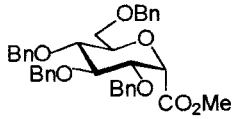
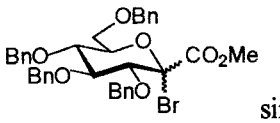
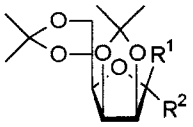
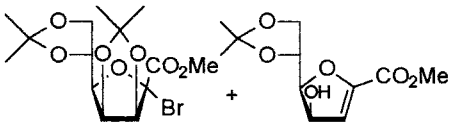
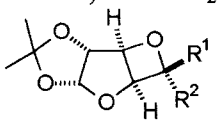
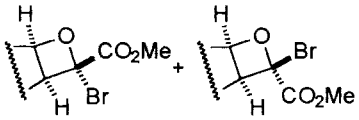
Entry	Substrate	Reaction conditions	Product	Ref.
1.		LDA/THF, −70 °C then *A)* C_2Cl_6	 X = Cl → OMe (α/β ratio not specified) overall yield 30 %	95
		B) PhSSPh	 30 %	95
		C) CH_2=$CHCH_2Br$	combined yield 62 % (1.6 : 1) from the sulfonyl precursor 	95
2.		$NaN(TMS)_2$, THF $BrCH_2CO_2R$	 50 % 48 % R = Me  R = *t*Bu 32 % 11 %	96
3.		Li-naphthalenide/THF, −75 °C then *A)* MeOH *B)* PhSSPh *C)* MeI *D)* RCl	 *A)* (R = H) 2 : 1 76 % *B)* (R = SPh) 1.6 : 1 62 % *C)* (R = Me) 3 : 5 (unassigned) 50 % *D)* (R = β-$Me_3Si(CH_2)_2OCH_2$) 70 %	97,98
4.	 Y = H → CO_2Me R' = TBDMS	Li-naphthalenide/THF, −70 °C PhSSPh	(R = SPh) 8 : 1 63 %	99
5.		$LiN[Si(CH_3)_3]_2$/THF, −78 °C CBr_4	 single anomer, configuration not determined, yield unknown	100

Table 6 (Continued)

Entry	Substrate	Reaction conditions	Product	Ref.
6.		$LiN[Si(CH_3)_3]_2$/THF, −78 °C CBr_4	 yield not indicated	101
	$R^1 = CO_2Me$, $R^2 = H$		62 %	
	$R^1 = H$, $R^2 = CO_2Me$		35 %	
7.		$LiN[Si(CH_3)_3]_2$/THF, −78 °C CBr_4		101
	$R^1 = CO_2Me$, $R^2 = H$		36 % 9 % recovery of start. mat. 35 %	
	$R^1 = H$, $R^2 = CO_2Me$		22 % 18 % recovery of start. mat. 28 %	

sion of the 2-acetoxy substituent.[94] A comparison of the above reactions with the ones in Table 6, entries 5−7, shows that the leaving ability of the 2-*O*-substituent decreases in the order *O*-acyl > *O*-isopropylidene > *O*-benzyl (*O*-alkyl) as it was similarly observed with 1-deoxy-1-nitro derivatives (section III.A.1).

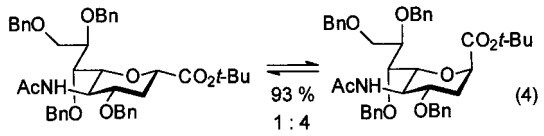
2. Reactions of COOR-Stabilized Anions with Electrophiles

Generation of benzylated 2-deoxy-1-methoxycarbonyl-D-glycopyranosyl anions can be achieved either by deprotonation[95,96] (Table 6, entries 1 and 2) or reductive desulfonylation[97−99] (entries 3 and 4). Deprotonation can also be effected with fully substituted *C*-pyranosyl-[100] (entry 5), *C*-furanosyl- (entry 6), and *C*-oxetanosyl-formates (entry 7).[101] These results show that 2-*O*-substituents of moderate nucleofugality can survive due to the anion-stabilizing ability of the ester group.

In the presence of methanol, the 2-deoxy anion/enolate gives the protonated compounds with moderate stereoselectivity (entry 3*A*).[97,98] With perhaloalkanes, anomerically halogenated products were obtained[95,100,101] (entries 1*A* and 5−7). It was reported that all attempts to brominate the β-anomer of the *C*-(α-D-glucopyranosyl)formate in entry 5 were unsuccessful.[100] This may indicate that deprotonation can depend on stereoelectronic factors[102] because the same intermediate enolate must form from both anomers. On the contrary, in the 2-deoxy series, proton removal was possible from both anomers (compare entries 1 and 2). Because of the limited number of examples among carbohydrate derivatives, this phenomenon deserves further studies. This method can be an alternative of radical-mediated halogenation reactions[103] widely used for the production of 1-substituted glycosyl halides but not applicable in the presence of benzyl protecting groups. Thioglycosides which are valuable glycosylating agents result from reactions of COOR-stabilized glycosyl anions with diphenyl-disulfide[95,97−99] (entries 1*B*, 3*B*, and 4).

The carbanionic reactivity of derivatives of ulosonic acids (KDO, KDN, and Neu5Ac) has been extensively investigated because the 2-deoxy as well as *C*-glycosyl derivatives and especially *C*-disaccharides obtainable in this way are valuable tools for glycobiologists to explore and understand the molecular biological roles of these molecules and their derivatives.

Either anomer of 2-deoxy-KDO with base-stable protecting groups **68**$\alpha\beta$ can be readily deprotonated (Table 7, entries 1−19). In the presence of sodium methoxide and methanol, the equilibrium mixture contains mainly the anomer with the methoxycarbonyl group in the *axial* position (entry 1).[104] Equilibration of a 2-deoxy-Neu5Ac derivative gave similar results[104a] (eq 4). This was attributed to the anomeric effect of that substituent and shows also that the kinetic and thermodynamic product is the same in this (and similar) transformation(s).



(4)

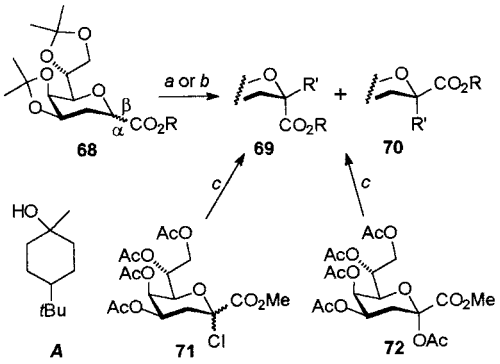
Conditions: LiN(Ch)*i*Pr, THF, aq. NH_4Cl, -50 °C

Deoxygenation at the 2-position of both KDO and Neu5Ac could be achieved by samarium diiodide-induced reductive deacetoxylation of the fully acetylated ulosonic acids **72** and **73** (Table 7, entry 21, and Table 8, entry 1, respectively).[105]

With a large variety of *C*-electrophiles many KDO-*C*-glycosyl derivatives[104,106−109] (Table 7, entries 2−18) were prepared from the isopropylidenated 2-deoxy-KDO anomers **68**$\alpha\beta$. By using diphenyl-disulfide as the electrophile, phenyl 2-thio-KDO-glycosides[110] were obtained (Table 7, entry 19).

Reaction of the enolate derived from benzyl-protected 2-deoxy-Neu5Ac with formaldehyde gave

Table 7. Reactions of KDO-Derived Anomeric Anions/Enolates



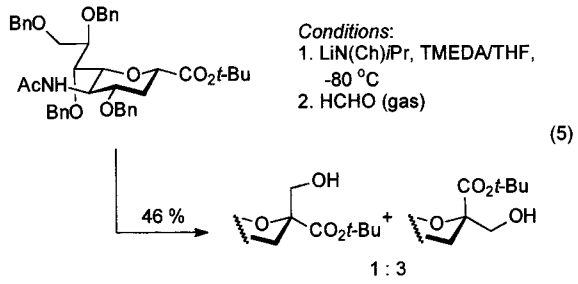
entry	substrate *conditions*	electrophile	product R	product R′	**69**:**70** (yield [%])	ref
1	**68**α*β a*	MeOH	Me	H	4:1	104
2	**68**α*β b*	$(CN)_2$	Me	CN	>95:5 (47)	104
3			Et	CN	90:10 (55)	104
4		CO_2 (then red.)	Et	CH_2OH	75:25 (46)	104
5		HCHO (gas)	Me	CH_2OH	5.1:1 (76, 15)	106
6			Et	CH_2OH	90:10 (47)	104
7		MeCOOPh	Et	MeCO	70:30 (60)	104
8		$(MeCO)_2O$	Et	MeCO	95:5 (62)	104
9		MeCOCl	Et	MeCO	85:15 (55)	104
10		MeI	Et	Me	>95:5 (50)	104
11		$HC{\equiv}CCH_2Br$	Et	$HC{\equiv}CCH_2$	90:10 (50)	104
12		$BrCH_2CO_2t$-Bu	Et	CH_2CO_2t-Bu	>95:5 (30)	104
13		$BrCH_2CO_2$-*n*-octyl	Et	CH_2CO_2-*n*-octyl	**69** (38)	107
14		$PhCH_2Br$	Me	$PhCH_2$	95:5 (67)	104
15		$CH_2{=}CHCO_2Me$	Et	$CH_2CH_2CO_2Me$	75:25 (27)	104
16	**68**α *b*	$TfOCH_2PO_3Et_2$	Et	$CH_2PO_3Et_2$	**69** (50)	107
17	**68**β *b*		Me	$CH_2PO_3Et_2$	**69** (56)	109
18	**68**α *b*	Cs_2CO_3, MeI	Me	CO_2Me	(78)	108
19	**68**β *b*	PhSSPh	Me	SPh	85:15 (51)	110
20	**71** *c*	4-*t*Bu-cyclohexanone	Me	***A***	**69** (94)	111
21	**72** *c*	$HOCH_2CH_2OH$	Me	H	**69** (93)	105

Table 8. Transformations of KDN and Neu5Ac Derivatives via C-2 Anions/Enolates (see Scheme 13)

entry	substrate	electrophile	product **79** R^1	product **79** R^2	yield	ref
1	**73**	$HOCH_2CH_2OH$			**76** + **77** 91% (1:4)	105
2	**74**	acetone	Me	Me	95%	111
3		**80** $n = 0$	from **80**	H	88%	111
4		**80** $n = 1$	from **80**	H	95%	111
5	**75**	**81**	from **81**	H	91%	111
6		4-*t*Bu-cyclohexanone	$R^1{-}R^2 = -(CH_2)_2{-}CHtBu{-}(CH_2)_2-$		96%	111
7	**83**	cyclopentanone	$R^1{-}R^2 = -(CH_2)_4-$		93%	113
8		$CH_3(CH_2)_6CHO$	$CH_3(CH_2)_6$	H	96%	113
9		**81**	from **81**	H	85%	114,115
10		**82**			**77** 81%	113
11	**84**	acetone	Me	Me	85−96%	114
12		$CH_3(CH_2)_6CHO$	$CH_3(CH_2)_6$	H	85−96%	114
13		$CH_3(CH_2)_{12}CHO$	$CH_3(CH_2)_{12}$	H	85−96%	114
14		cyclopentanone	$R^1{-}R^2 = -(CH_2)_4-$		85−96%	114
15		**80** $n = 1$	from **80**	H	unknown	114
16		**81**	from **81**	H	92%	114
17	**85**	none			**78** 92%	112
18	**86**	4-*t*Bu-cyclohexanone	$R^1{-}R^2 = -(CH_2)_2{-}CHtBu{-}(CH_2)_2-$		90%	112
19		**81**	from **81**	H	88%	112

the corresponding *C*-glycosyl methanols with preponderant formation of the axial ester[110a] (eq 5).

Application of samarium diiodide allowed anionic reactions of KDO, KDN and Neu5Ac derivatives to be performed also in the presence of base-labile acetyl protecting groups, thereby also making available more readily accessible starting materials for enolate C−C couplings. These transformations have to be carried out under Barbier conditions, i.e., the reductant should be added to a mixture of the substrate



(5)

and the electrophile. As substrates, anomeric chlorides[111,112] **71** and **74** (Table 7, entry 20; Table 8, entries 2−4) and phenyl-[112−115] (**83**−**85**; Table 8, entries 7−17) and 2-pyridyl-sulfones[111,112] (**86**; Table 8, entry 18, 19) were used. As *C*-electrophiles, simple and carbohydrate-derived (**80**, **81**) aldehydes and simple ketones could be applied. With a sugar-derived ketone (**82**), only the protonated product was formed[113] (Table 8, entry 10) because of the steric inaccessibility of the electrophilic reaction center. In the absence of an electrophile (Table 8, entry 17), the attempted radical-mediated cyclization of allylic ester **85** also failed, yielding again the protonated product **78** only.[112] After deprotection some of the Neu5Ac derivatives **79** were investigated as inhibitors of bacterial neuraminidase from *Clostridium perfringens* to show inhibitor constants in the micromolar range.[115a]

E. CN, $CONH_2$, and Heterocyclic Moieties as Stabilizing Groups

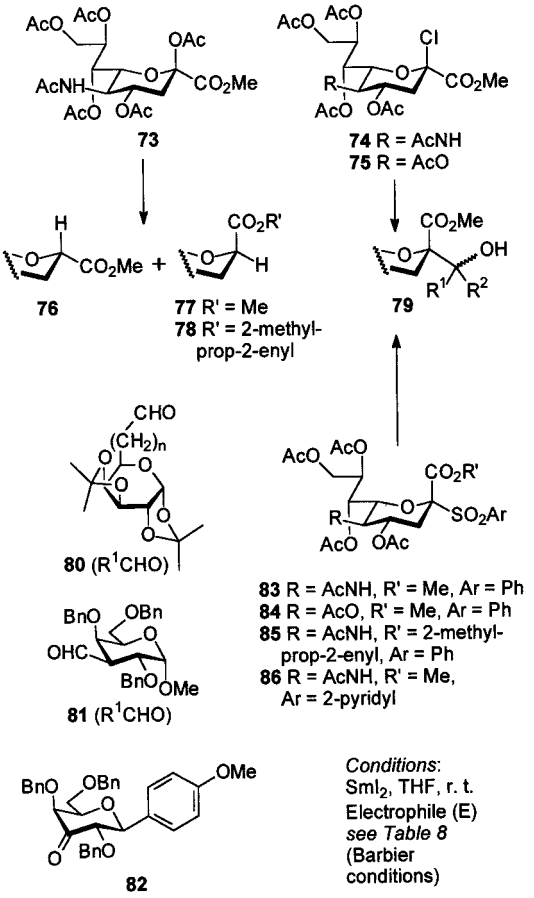
Introduction of the title groups to the anomeric carbon makes a uniform chemistry and is based on various cyanation reactions.[116] Most frequently used methods include substitution of an equatorial anomeric acetoxy or benzoyloxy group in per-*O*-acylated or otherwise protected sugars with TMSCN or displacement of an anomeric bromide by mercury(II) cyanide.[117,118] According to another efficient method, *C*-glycosyl-nitromethanes are transformed into glycosyl cyanides with phosphorus trichloride pyridine as a reagent.[119] The nitrile group in the glycosyl cyanides can be partially hydrolyzed to give the corresponding carboxamides[90,91] or subjected to cyclization reactions to give *C*-glycosyl-heterocycles.[120,121]

1. 1-Cyano-, 1-Carboxamido-, and 1-(Benzothiazol-2-yl)-glycals

Glycosyl anions leading to the title compounds were generated by deprotonations (method *a*) or reductive dehalogenations (method *b*) as summarized in Scheme 14 and Table 9.

Reactions of acetylated glycopyranosyl cyanides **87**−**91** with DBU (method *a*) gave the corresponding 1-cyano glycals in moderate to good yields.[122−124] Application of the above conditions to 2-(D-glycosyl)-benzothiazoles **98**−**100** yielded glycals **101**−**103**,[122] respectively. Similar treatment of the benzoylated analogue of **89** (Bz instead of Ac, X = H; prepared from D-xylose tetrabenzoate by the TMSCN method) gave the benzoylated **95** in 62% overall yield for the cyanation−elimination sequence.[125] The method also performed well in the furanoid series exemplified by

Scheme 13



the synthesis of **106** and **107**[126] from **104** and **105**, respectively. However, the rhamnopyranosyl cyanides **110** and **111** behaved differently under debenzoylation conditions. Only the deprotected rhamnal **112** was formed from **110**, while in the case of **111**, the deprotected nitrile **113** could also be isolated.[127] The reason for this is probably the stereoelectronically favorable arrangement of the leaving moieties in **110**, although similar dependence of the reaction on stereoelectronics was not observed in the acetylated series (compare the reaction of **87** or **88** to that of **91**). In general, the benzoylated compounds gave better results in the eliminations than their acetylated counterparts. A probable reason for this is that DBU can also induce deacetylation by removal of protons in the α position to the ester carbonyl, a step which is impossible with benzoates.[128]

Reductive eliminations by zinc−pyridine (method *b*) from the bromo derivatives **87**−**90**, **92**, **99**, and **108** (easily prepared by radical-mediated bromination[103] of glycosyl cyanides and related compounds; X = H→Br) afforded glycals **93**−**97**, **102**,[122,129,130] and **109**,[131] respectively. The yields were generally higher and the products purer as compared to those obtained by method *a*. Thus, despite the one-step longer procedure, the bromination−reductive elimination sequence can be recommended for the synthesis of these compounds. For a mechanistic discussion, see section IV.A.1. Further transformations[132] of the above derivatives lead to glycosidase enzyme inhibitors,[131,133] DHA,[123] DAHP[124,134] derivatives, which are

Scheme 14

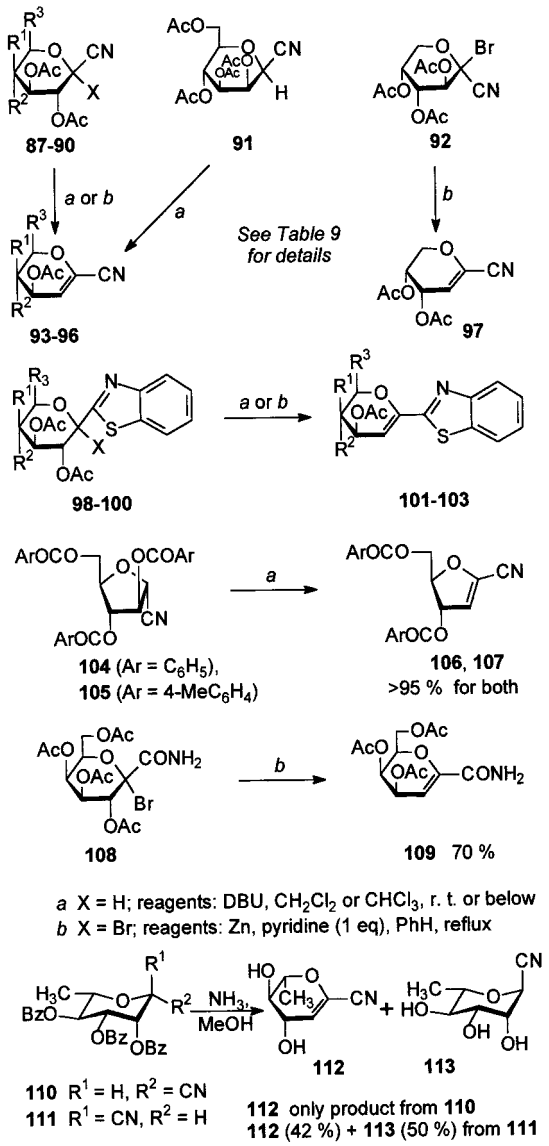


Table 9. Preparation of 1-Cyano- and 1-(Benzothiazol-2-yl)-glycals (see Scheme 14)

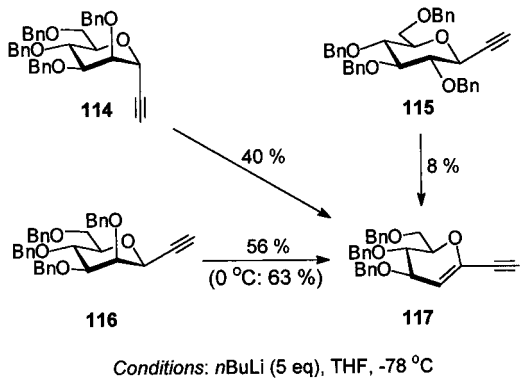
starting compd	R^1	R^2	R^3	product	yield [%] by method *a* (X = H)	*b* (X = Br)
87	H	OAc	CH_2OAc	**93**	70[134]	62[130]
88	OAc	H	CH_2OAc	**94**	40[a,122] 69[b,123]	75[129,130]
89	H	OAc	H	**95**	51[122]	78[130]
90	OAc	H	H	**96**	51[122]	72[122]
91				**93**	60[124]	
92				**97**		75[129,130]
98	H	OAc	CH_2OAc	**101**	47[122]	
99	OAc	H	CH_2OAc	**102**	77[122]	38[122]
100	H	OAc	H	**103**	57[122]	

[a] Isolated by crystallization. [b] Isolated by chromatography.

potential inhibitors of early steps in the shikimate pathway.

1-Ethynyl Glycals. Because of their constitutional similarity to 1-cyano glycals, the title compounds are mentioned in this section. CH-Acidity in the propargylic position may be sufficient for allowing deprotonation, although no acidity data could be located in the literature for propyne. Thus, *C*-glycosyl acetylenes are expected to be good precursors of 1-ethynyl glycals. This has indeed been the case demonstrated by the formation of glucal **117** from benzylated α-(**114**) and β-D-mannopyranosyl (**116**) and β-D-glucopyranosyl (**115**) acetylenes on treatment with excess butyllithium (Scheme 15). 1-Methyl-2-(β-D-

Scheme 15

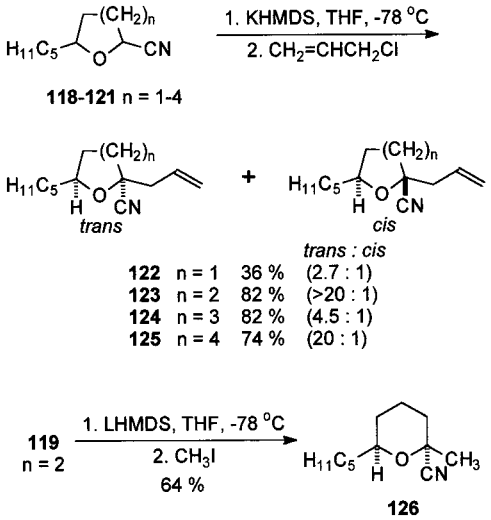


mannopyranosyl)ethyne, however, gave no glycal as did β-D-mannopyranosyl methane and benzene. On the basis of deuteration experiments, it was suggested that the reaction proceeded through an E2 rather than the expected E1cB mechanism.[135]

2. Substitutions in CN-Stabilized Anomeric Anions

To the best of our knowledge, electrophilic substitutions at anomeric anions bearing a CN group are unknown with carbohydrate derivatives. However, several examples have been published with related *O*-heterocycles, some of which are shown in Scheme 16. Deprotonation of cyclic ethers **118**−**121** and

Scheme 16

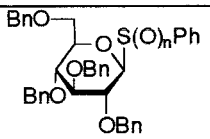
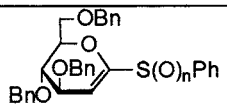
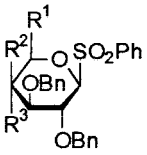
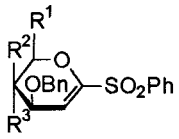
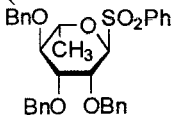
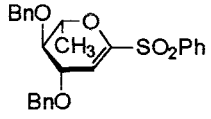
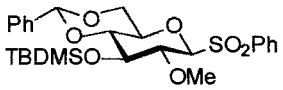
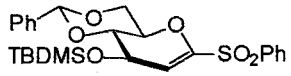
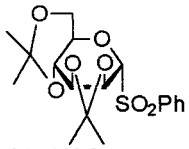
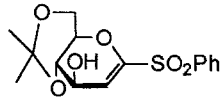
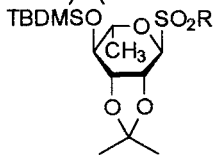
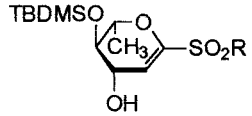
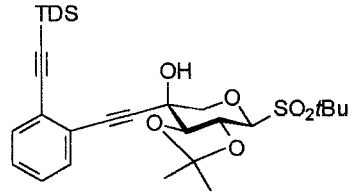
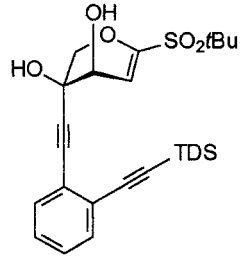
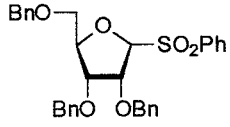
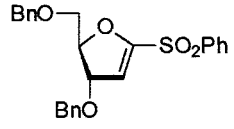


subsequent reactions with carbon electrophiles gave the substituted cyclic cyanohydrins **122**−**126** with remarkable stereoselectivity.[136,137] Further elaboration of these products by reductive decyanation (section IV.B) gave alkylated cyclic ethers.

F. SO_2R as Stabilizing Group

The sulfonyl group attached to the anomeric center can play a dual role: (a) due to its carbanion-

Table 10. Eliminations from SO_2R-Stabilized Glycosyl Anions

Entry	Substrate	Reaction conditions	Product		Ref.
1.		*A*) Na-thiophenate/ DMSO, 95 °C *B*) BaO/EtOH, reflux			140
	n = 2		n = 2	*A*) 18 % *B*) 24 %	
		C) LDA/THF, −90 °C		*C*) 89 %	139
2.	n = 1	LDA/THF, −80 °C	n = 1	80 %	145
3.		LDA/THF, −90 °C			139
	$R^1 = CH_2OBn$, $R^2 = OBn$, $R^3 = H$			91 %	
	$R^1 = H$, $R^2 = H$, $R^3 = OBn$ (also from the α-anomer)			91 %	
4.		LDA/THF, −90 °C			139
				81 %	
5.		BuLi, THF, −78 °C			141
				80 %	
6.		MeLi/THF, reflux			142
				good yield	
7.		MeLi/THF, −66 °C → r. t.			142
				R = Ph 82 % R = *t*-Bu 80 %	
8.		BuLi, THF, −78 → −40 °C			143
				77 %	
9.		BuLi, THF, −78 °C			144
				90 %	

stabilizing capacity it can facilitate removal of the anomeric proton and (b) by reductive metalation methods the group itself can be replaced by a metal. These two features can be coupled efficiently and used for stereoselective syntheses of *C*-glycosyl derivatives. This section deals with anomeric deprotonations next to a SO_2R moiety, although reductive desulfonations will also be alluded to as parts of synthetic sequences. Metalations at the sulfonyl group will be treated in detail in sections IV.A.3, IV.B.3, and IV.C.3. The anomeric sulfonyl rest can be formed by oxidation of 1-thioglycosides.[138,139]

1. 1-Sulfonyl Glycals

Synthetic methods leading to various 1-sulfonylglycals are collected in Table 10.

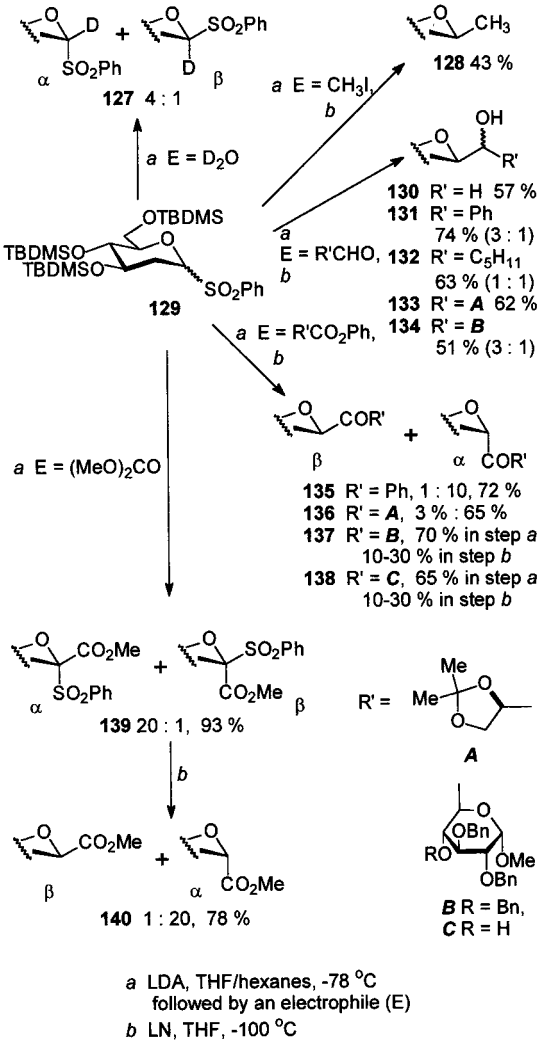
Early attempts to deprotonate benzylated glucopyranosyl phenyl sulfone with weak bases gave the glycal derivative in moderate yield[140] (entry 1*A*,*B*). The use of powerful bases, however, significantly improved the yield of this reaction[139] (entry 1*C*). The method was applicable to either anomer of variously protected anomeric sulfones, whereby *O*-alkyl[139,141] (entries 3−5) and *O*-isopropylidene[142,143] (entries 6−8) rests proved suitable leaving groups. The method performed well in the furanoid series[144] (entry 9). This elimination was also used in synthetic studies related to enediyne antibiotics[143] (entry 8). Similarly, 1-phenylsulfinyl-glucal[145] could be prepared from the corresponding sulfoxides (entry 2).

2. Substitutions with 1-Sulfonyl-glycosyl Anions

Deprotonations of 2-phenylsulfonyl-tetrahydropyran derivatives by *n*-butyllithium and ensuing reactions with several *C*-electrophiles leading to spiroketals[146] were investigated[147] and applied in the total synthesis of okadaic acid.[70]

TBDMS protection proved superior to methylation or benzylation for deprotonations of 2-deoxy-D-glucopyranosyl phenyl sulfones.[148] Quenching the lithium salt of **129** (Scheme 17) with D_2O led to the deuterated derivatives **127** with the α-sulfonyl anomer preponderating.[148] The same ratios were found with methyl- and benzyl-protected compounds, showing that attack of the electrophile is favored from the β-face of the 1-sulfonyl-glycosyl anions.

Scheme 17



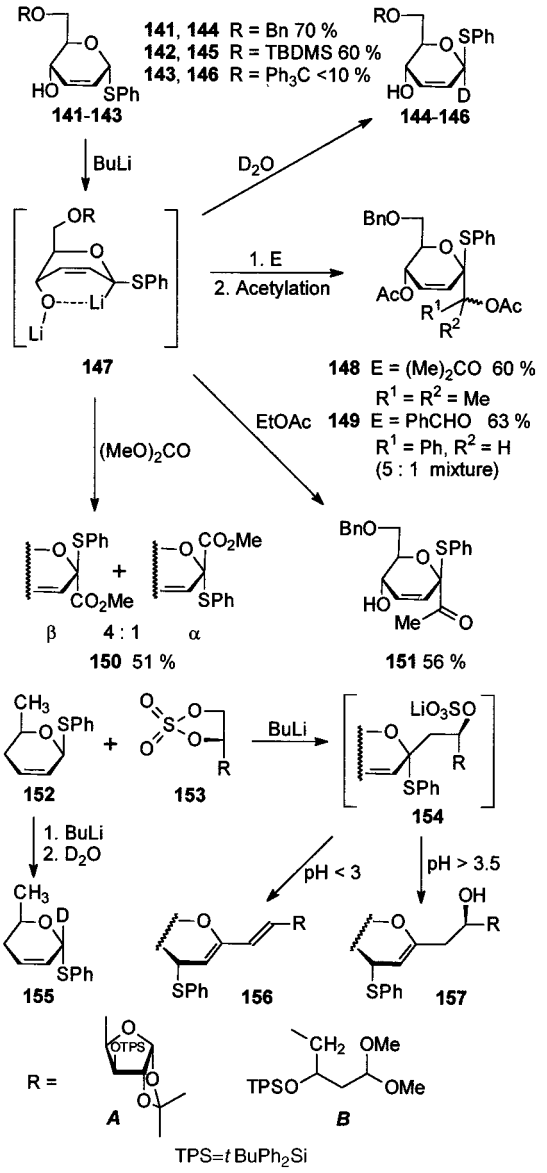
Reactions of these anions with *C*-electrophiles combined with subsequent reductive removal of the sulfonyl group by lithium naphthalenide are illustrated in Scheme 17. Alkylation with methyl iodide gave the 2-deoxy-β-D-glucopyranosyl methane **128**.[149] Reaction with formaldehyde gave the *C*-glucosyl-methanol **130** and with higher aldehydes the secondary alcohols **131**−**134**.[149] The latter ones were oxidized to β-*C*-glycosyl ketones. Reactions with simple phenyl esters gave good yields of α-*C*-glycosyl ketones[149] **135** and **136**. With more complex esters, the coupling step was efficient but the desulfonylation gave **137** and **138** only in moderate yield.[149] Dimethyl carbonate reacted with the anion of **129** to give 1-methoxycarbonyl-glycosyl sulfones **139** with excellent stereoselectivity, which on desulfonylation produced the *C*-(2-deoxy-α-D-glucopyranosyl)formate **140** as the major product.[150] Note that in a similar reaction of the benzylated analogue of **129** with dimethyl carbonate the product isolated in 73% yield was claimed to be **139**β.[97] It is seen that in the above reaction sequence, which can be performed in a one-pot procedure, either β- (with MeI, R′CHO) or α-*C*-glycosyl (with esters) derivatives can be obtained with very good stereoselectivity depending on the electrophile. For **128**−**134** this can be reasoned so that the kinetic anion formed in the desulfonylation step is configurationally stable at the applied temperature and protonation occurs from the same side as the departing α-*C*-glycosyl sulfone. On the other hand, with enolizable *C*-substituents, anomeric enolates can form during desulfonylation which are attacked by the proton from the sterically less hindered β-face to give **135**−**138** and **140**. Coupling of phenylsulfonyl-stabilized anomeric anions was also used in the enantioselective total syntheses of the marine natural products altohyrtin C (spongistatin 2)[151,152] and bryostatin 2,[153,154] exhibiting antitumor activity.

G. SPh as Stabilizing Group

The phenylthio moiety, similarly to the sulfonyl group, can facilitate deprotonation and be reductively exchanged by a metal. In the chemistry of the anomeric center, its first capacity was used in conjunction with allylic stabilization. For reductive metalations, see sections IV.A.3, IV.B.2, and IV.C.3. Suitable starting materials for deprotonations are readily obtained in a reaction of glycals with thiophenol accompanied by a Ferrier rearrangement.[155]

Deprotonation of the unsaturated phenyl thioglycosides **141**−**143** and quenching with D_2O gave the α-deuterated products **144**−**146** from which the benzylated compound **144** was obtained in the highest yield (Scheme 18). A similar thioglycoside protected by a 4,6-*O*-isopropylidene group (not shown) produced only a ring-opened compound on deprotonation. Treatment of the lithium salt of **141** with *C*-electrophiles acetone or benzaldehyde gave also α-substi-

Scheme 18

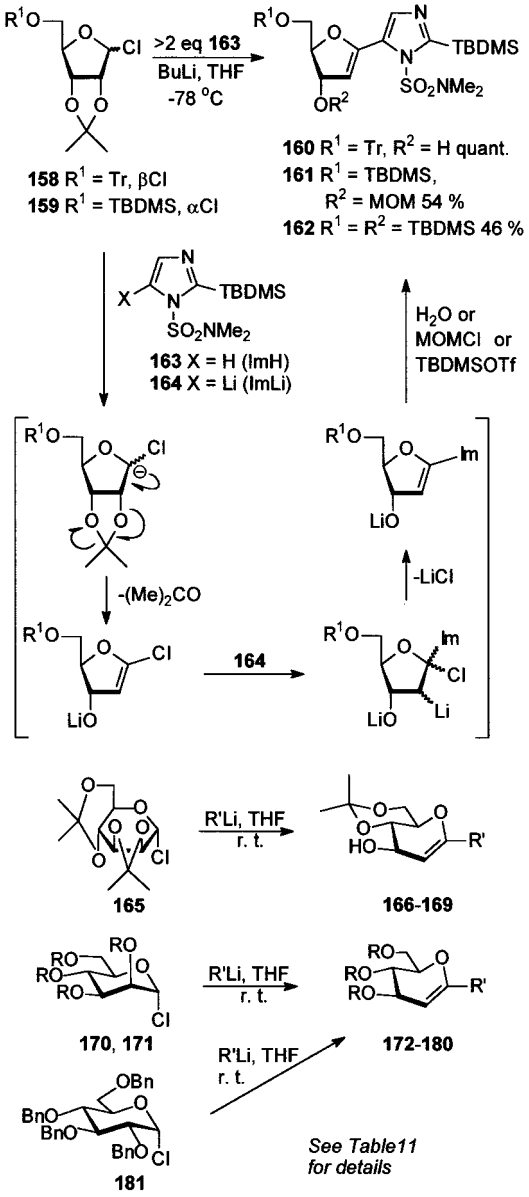


tuted products **148** and **149**, respectively. With ethyl acetate ketone **151**, with dimethyl carbonate esters **150** were obtained.[156] The exclusive (or high) α-selectivity was explained by the intermediacy of the intramolecularly complexed lithium salt **147**. The reaction of **152** with cyclic sulfates **153** (epoxides were unsuccessful) gave **156** and **157** depending on the pH of the reaction mixture.[157] The observed rearrangement was explained by a 1,3-sigmatropic migration of the phenylthio group to give the more substituted double bond. Deuteration of the lithiated **152** took place from the *β*-face without rearrangement to give **155**, thereby making it probable that other electrophiles also attack from the same side and **154** can be an intermediate of the coupling reactions. Further elaboration of products **156** and **157** lead to spiroketals,[157] which are important subunits of a variety of natural products.

H. Chlorine as Stabilizing Moiety

A synthesis of 1-*C*-substituted glycals has been worked out using glycosyl chlorides,[158] which are relatively stable and easy to prepare among anomeric halogeno derivatives. Thus, transformation (also as a one-pot procedure) of chlorides **158** and **159** with at least 2 equiv of lithiated imidazole **164** gave the substituted glycals[159] **160**−**162** (Scheme 19). Accord-

Scheme 19



ing to a mechanistic proposal,[159] **164** deprotonates the anomeric carbon which is followed by loss of an acetone. A second **164** replaces the vinylic chlorine via a tetrahedral intermediate, and a final protonation or etherification gives alcohol **160** or ethers **161** and **162**, respectively. Similarly, a variety of pyranoid glycals **166**−**169** and **172**−**180** (Table 11) were also synthesized demonstrating the generality of the method.[160] The *O*-alkyl or *O*-acetal protection seems to be a prerequisite of this transformation because reaction of acylated glycosyl halides with organolithiums gave the corresponding deprotected *C*-glycosyl compounds in a nucleophilic substitution at the anomeric carbon.[161]

Table 11. Preparation of 1-*C*-Substituted Glycals from Glycosyl Chlorides by Lithiumorganyls[160] (see Scheme 19)

substrate	product	R	R′	yield
165	**166**		Me	50%
	167		Bu	54%
	168		Ph	71%
	169		*t*-Bu	37% (0 °C, 46%)
170 R = Me	**172**	Me	Me	66%
	173	Me	Bu	50%
	174	Me	*s*-Bu	36%
	175	Me	*t*-Bu	40%
	176	Me	Ph	70%
171 R = Bn	**177**	Bn	Bu	55%
	178	Bn	Ph	72%
181	**177**	Bn	Bu	50% (at −78 °C, decomp. at 0 °C)
	178	Bn	Ph	65% (at 0 °C, no reaction at −78 °C)
	179	Bn	Me	74% (at 0 °C)
	180	Bn	*t*-Bu	35% (at 0 °C, decomp. at room temp.)

IV. Generation and Reactions of Glycosyl Anions without Stabilizing Groups

In the absence of a carbanion-stabilizing group attached to the anomeric carbon, the formation of anionic intermediates mostly rests on reductive metalation processes while transmetalations serve to modify the reactivity of these species. Substrates of the reductive metalations are glycosyl halides (bromides and chlorides), phosphates, sulfones, and 1-thioglycosides. Frequently used reducing agents are arenides (e.g., lithium or sodium naphthalenide −3.1 V in THF), alkali metals in liquid ammonia (Li −2.64 V, K −2.38 V, Na −2.25 V), or THF (Na −3.04 V),[162] transition metals (e.g., zinc in variously activated forms ca. −0.76 V in water)[163] and their complexes (e.g., $Cr^{(II)}L$ from −0.41 V (L = H_2O) in water[163] to ca. −1.3 V (L = EDTA) in aqueous medium,[164] $Ti^{III}L$), as well as lanthanoides (e.g., Sm^{II} from −1.33 to −2.05 V depending on the added HMPA (0−5 equiv, respectively) in THF).[165,166] The formal potentials listed allow one to estimate the strength of the metalating reagent. Similar data for characterizing the reactivity of the substrates are scarce: reduction peak potentials were measured[167] for some glycosyl bromides (−1.17 to −1.25 V or −1.60 to −1.92 V) and a chloride (−2.65 V or >−2.6V) on silver or mercury cathodes, respectively, in acetonitrile. Because of the wide range of the measuring conditions, these data are not directly comparable and may only roughly guide choosing the proper reagent for a given substrate. Therefore, it is better to try several or each of the reducing agents.

Elimination of the 2-substituent is a ready process in the absence of an anion-stabilizing moiety, and special methods have been devised to overcome undesired glycal formation (section IV.C). On the other hand, glycals[34−37] are one of the most valuable types of chiral starting materials[168] in syntheses easily obtained from readily available enantiopure compounds (the so-called “chiral pool”).

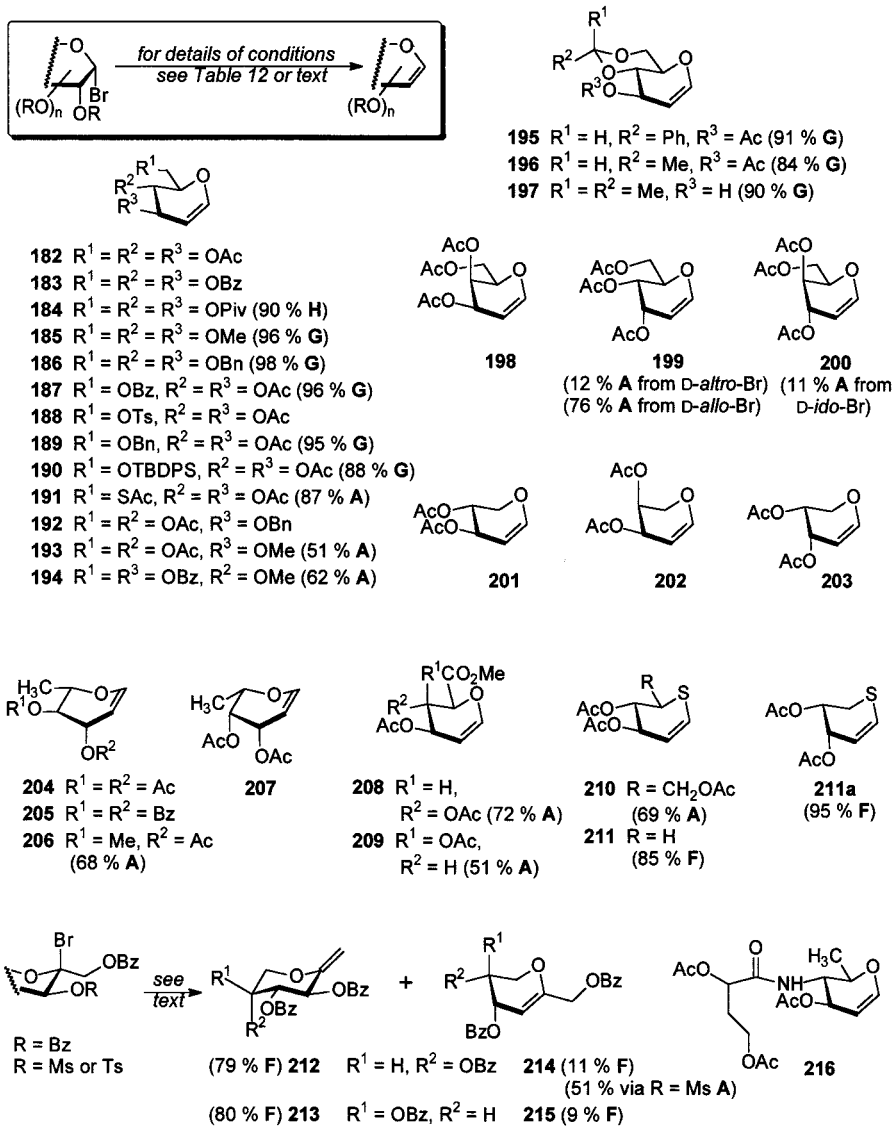
A. Preparation of Glycals

1. From Glycosyl Bromides

Acetylated glycosyl bromides are the most often used starting materials for the synthesis of a variety of glycals. The original method of preparation,[169] i.e., the reaction of acetobromoglucose with zinc dust in (buffered) aqueous acetic acid at a temperature ranging from −20 °C to room temperature,[170] has undergone countless modifications. A collection of glycals obtained by one of these protocols is presented in Scheme 20 and Table 12.

The starting glycosyl bromide can be isolated before the glycal-forming reaction. However, because acetobromosugars are rather sensitive and cannot be stored for long times after isolation, the preparation of glycals has been performed in one continuous operation.[170,171] This involves formation of a glycosyl bromide from the free sugar by acetylation and subsequent acidolysis of the anomeric acetates by hydrobromic acid, yielding a crude mixture which is directly subjected to elimination in the presence of zinc dust. In situ preparation of the starting bromide is also effected from the per-*O*-acylated or 1-*O*-acylated sugars. Various methods can be used for enhancing the activity of zinc.[172] Most frequently zinc−copper[170] or zinc−platinum[173] couples are prepared by adding copper(II) sulfate or platinic chloride, respectively, to the reaction mixture. The reaction medium (acetic acid and water in various ratios ranging from 1:1 to 9:1) is usually buffered by sodium or ammonium acetate. Illustrative results obtained by these modifications are shown under method A in Table 12. Method B is a recent update of A with respect to the formation of the glycosyl bromide from a free sugar in the one-pot procedure.[171] Method A was also applied for the preparation of D-glucals **191**,[174] **192**,[175] **193**,[176] and **194**.[177] D-Allal **199** was obtained from the D-altropyranosyl[178] as well as from the D-allopyranosyl bromide,[179] and D-gulal[178] **200** was obtained from D-idopyranosyl bromide. L-Rhamnal **206**,[180] glycals of uronic acid esters **208**[181] and **209,**[182] as well as of 5-thio-D-glucose **210**[183] were also made in this way. It is seen that depending on the sugar configuration yields of the glycals vary from excellent to poor. A reason for the low yields can be the ready solvolysis of the reactive glycosyl bromide in the applied medium; therefore, replacement of water with tetrahydrofuran[184] (method C) or the use of vitamin B-12 as a special mediator in methanol[185] (method D) providing essentially neutral conditions was suggested. Acetic acid could similarly be omitted, and high-yielding glycal formation could be achieved in aprotic media with highly reactive zinc−silver/graphite[186] (method E) or with simply activated zinc in the presence of a *N*-base[187] (method F). 1-Methylimidazole (MIM) or 4-methyl-pyridine (4-Pic) proved to be the best *N*-bases, and besides ethyl acetate benzene, tetrahydrofuran, acetone, and dichloromethane were also applicable as solvents. 5-Thioxylal[188] **211** and 5-thio-ribal[188a] **211a**, used for the synthesis of oral antithrombotic agents, as well as **216,**[189] an intermediate in the synthesis of fluorinated ligands to probe binding of antigenic determinants

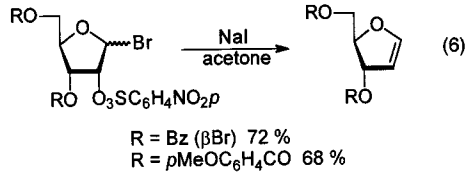
Scheme 20



of *Vibrio cholerae*, were also prepared by this last procedure.

Ketohexoses can provide *exo*- or *endo*-glycals as shown for the D-fructals **212** and **214** as well as L-sorbals **213** and **215** prepared by method F. The elimination favors formation of the exocyclic double bond also with method A giving **212** and **214** in 7:1 ratio.[190] To direct the elimination toward the *endo*-position, the leaving ability of the 3-*O*-substituent had to be enhanced by introducing 3-*O*-mesyl or 3-*O*-tosyl groups in diacetone-fructose. Subsequent exchange of protecting groups, formation of the anomeric bromide, and subjecting it to the conditions of method A gave **214** in 51% overall yield for the whole sequence, while the acetylated analogue was obtained in 53%.[190]

Attempts to get furanoid glycals by method A were less successful. The desired products could be obtained in low yields, and the main products resulted from the hydrolysis of the starting furanosyl bromides.[192] The acid-sensitive furanoid glycals could be acquired from furanosyl bromides by introducing a good leaving group in the 2-position and using sodium iodide under neutral conditions as shown in eq 6.[193,194] The method was also used for the directed preparation of *endo*-[191] (e.g., **214**) and *exo*-glycals[195] of ketoses (cf. compound **232** in Scheme 22).



(6)

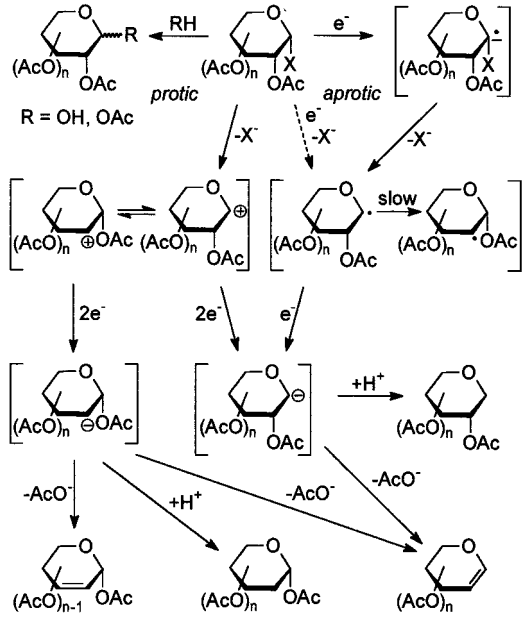
After early speculations,[196] detailed mechanistic studies on glycal formation were carried out with methods A and F in the past decade. Gas chromatographic analysis and identification of byproducts (in addition to solvolytic ones) formed in reactions of several acetobromopyranoses performed with method A revealed the intermediacy of glycosylium ions.[197] On the other hand, similar analysis showed the presence of β-D-glucose pentaacetate as the sole very minor byproduct formed from acetobromoglucose under the conditions of method F, and inhibition and trapping experiments suggested the involvement of glycosyl radicals in such reactions.[198] The most

Table 12. Preparation of Pyranoid Glycals from Glycopyranosyl Bromides (see Scheme 20)

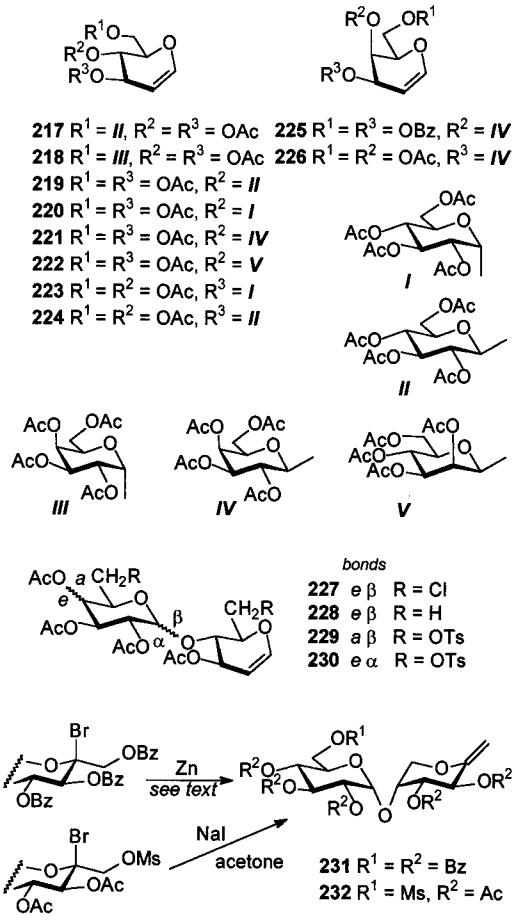
	method (yield [%] (configuration of the starting compound))								
glycal	A[169,170] Zn, AcOH−H_2O (classic)	B[171] Zn, AcOH−H_2O r.t. (improved)	C[184] Zn, THF−AcOH 9:1, 0 °C to r. t.	D[185] Zn, NH_4Cl, MeOH, Vit. B-12, r.t.	E[186] Zn−Ag/C, THF, −20 °C to r.t.	F[187] Zn, MIM, EtOAc, reflux	G[200,202] $(Cp_2Ti^{III}Cl)_2$ THF, r.t.	H[204] Cr^{II}EDTA DMF−H_2O, r.t.	I[207] Al−Hg, THF, 0 °C to r.t.
182	60−70[170,a]	98	80−90	94 (D-*gluco*) 95 (D-*manno*)	96[186]	95 187	82[200,202] 91[199] in situ[b] (D-*gluco*) 94[200,202] 87[199] in situ[b] (D-*manno*)	87	85 (D-*gluco*) 78 (D-*manno*)
183	100[c] (−10 to 0 °C)		80−90			89[187]		88	60 (D-*gluco*) 65 (D-*manno*)
188	87[d] (−5 to 0 °C)					81[187]			
198	66[173] Pt[e] r.t. 59[f] Cu (−10 to 0 °C)	58	80−90	93	87[186]	95[187]	89[200,202] 77[199] in situ[b]	71	60
201	61[g] 35[h]		80−90		92[186]	*i*−*k*	89[200, 202]	66	
202	60[l] (0−10 °C)	51	80−90			*i*,*j*			
203			80−90		90[186]	65[187] 4-Pic/PhH[m]	70[200, 202]	90	
204	80[170,a] 80[n] 93[h]	71		45			84[199] in situ[b]		82
205	79[o]								80
207	40[p] 30[q]		83		60[r]	*s* 72[t] Py/PhH	82[199] in situ		

[a] From the free sugar at −10 to 20 °C. [b] With in situ prepared reagent. [c] Lundt, I.; Pedersen, C. *Acta Chem. Scand.* **1970**, *24*, 240−246. [d] Nagabhushan, T. L. *Can. J. Chem.* **1970**, *48*, 257−261. [e] Using platinic chloride activation. [f] Using copper(II) sulfate activation: Rosenthal, A.; Read, D. *Meth. Carbohydr. Chem.* **1963**, *2*, 457−462. [g] From the free sugar at −10 °C: Weygand, F. *Methods Carbohydr. Chem.* **1962**, *1*, 182−185. [h] From the tetraacetate at 0 °C: Bartner, P.; Boxler, D. L.; Brambilla, R.; Mallams, A. K.; Morton, J. B.; Reichert, P.; Sancilio, F. D.; Surprenant, H.; Tomalesky, G.; Lukacs, G.; Olesker, A.; Thang, T. T.; Valente, L.; Omura, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1600−1622. [i] Yield unknown: Marco-Contelles, J.; Ruiz, J. *Tetrahedron Lett.* **1998**, *39*, 6393−6394. [j] Yield unknown: Pérez-Pérez, M. J.; Doboszewski, B.; Rozenski, J.; Herdewijn, P. *Tetrahedron: Asymmetry* **1995**, *6*, 973−984. [k] Yield unknown: Doboszewski, B.; Blaton, N.; Herdewijn, P. *J. Org. Chem.* **1995**, *60*, 7909−7919. [l] Humoller, F. L. *Methods Carbohydr. Chem.* **1962**, *1*, 83−88. [m] By using 4-methylpyridine in refluxing benzene. [n] From the tetraacetate at −10 °C: Iselin, B.; Reichstein, T. *Helv. Chim. Acta* **1944**, *27*, 1146−1149. [o] Hadfield, A. F.; Cunningham, L.; Sartorelli, A. C. *Carbohydr. Res.* **1979**, *72*, 93−104. [p] From the free sugar at 0 to −10 °C: El Khadem, H. S.; Swartz, D. L.; Nelson, J. K.; Berry, L. A. *Carbohydr. Res.* **1977**, *58*, 230−234. [q] From the tetraacetate at −10 °C: Iselin, B.; Reichstein, T. *Helv. Chim. Acta* **1944**, *27*, 1200−1203. [r] Yield unknown: Pudlo, P.; Thiem, J.; Vill, V. *Chem. Ber.* **1990**, *123*, 1129−1135. [s] Yield unknown: Ludewig, M.; Thiem, J. *Eur. J. Org. Chem.* **1998**, 1189−1191. [t] By using pyridine in refluxing benzene: Bajza, I. Personal communication.

Scheme 21



Scheme 22



important mechanistic conclusions are summarized for both the *protic* (method A) and the *aprotic* (method F) reaction in Scheme 21.

Formation of the glycosylium ion may be ascribed to the highly polar, ionizing, and dissociating solvent (average dielectric constant for AcOH−H_2O 1:1: $\epsilon \sim 42$) used in method A. This ion can be reduced or rearranged before reduction to give carbanionic species both at C-1 and C-2, respectively. The anomeric anion can be protonated to give the dehalogenated product or it can eliminate an acetate to give the glycal. The C-2 anion can be protonated, resulting in a 2-deoxy derivative, or eliminate an acetate, giving the glycal or a 2,3-unsaturated sugar. In the nonsolvolytic and apolar medium of method F (for the solvents used $2 < \epsilon < 7$), a (possibly dissociative) electron transfer results in the formation of glycosyl radicals which rearrange rather slowly. Therefore, a second electron transfer gives the anomeric anion exclusively. This can only get stabilized by the elimination of an acetate because protonation is impossible in the aprotic medium. It was suggested that these processes lead to a chain reaction. This can explain the usually very high purity (>95%) of the raw product from transformations by method F. It is not to be excluded that the radical pathway is operative under protic conditions as well. The considerations on solvent polarity are corroborated by the results obtained with method C (for the applied solvent mixture $\epsilon \sim 7$). The excellent yields afforded by method D may reveal that vitamin B-12 directs the reaction to proceed via radical intermediates either by an electron transfer to the substrate from a Co(I) species or by the formation of a readily homolyzable glycosyl−cobalt intermediate.

The titanium(III) species $(Cp_2TiCl)_2$ (also generated in situ by manganese)[199] is an excellent one-electron-transfer agent, and thus, it can direct the reaction to proceed via radicals (method G). The aprotic and neutral conditions allow the use of various protecting groups in highly reactive glycosyl bromides as illustrated by the high-yielding preparation of glucals **185**−**187**, **189**, **190**, and **195**−**197**.[200−202] A 2-deoxyglycosyl titanium(IV) compound was isolated as an analogue of the intermediate in the above reactions. An authoritative survey was published on the use of Ti(III) reagents in carbohydrate chemistry.[202a] The methylated glucal **185** was also obtained from the corresponding bromide with sodium naphthalenide in tetrahydrofuran in 41% yield.[203]

Chromium(II) is known to generate radicals from alkyl halides by an inner-sphere electron transfer. In aqueous medium the chromium(II)aqua complex does not react with acetobromoglucose. However, the reactivity of this ion can be enhanced (method H) by complexation, especially with ethylenediaminetetraacetic acid (EDTA) to produce glycals in excellent yields even in highly polar aqueous medium[204] ($\epsilon \sim 58$ for a DMF−H_2O 1:1 mixture). This reflects that glycal formation can be the main pathway even in a solvolytic milieu if the radical-forming step is faster than solvolysis. The intermediate glycosyl chromium(III) species have rather long lifetimes as shown by UV−vis spectroscopy.[205] The reaction of acetobromoglucose with Cr(II)TMEDA generated in situ from chromium(III) chloride with manganese was also investigated.[206]

Aluminum amalgam proved a good alternative to the zinc-based reagents illustrated under method I.[207] Electrolysis of acetobromoglucose with mercury pool electrodes in acetonitrile gave **182** quantitatively.[208] The reaction of acetobromoglucose with samarium

diiodide in tetrahydrofuran afforded **182** in 90% yield.[209,210]

Disaccharide glycals (Scheme 22) such as gentiobial **217**, melibial **218**, cellobial **219**, maltal **220**, and lactal **221** prepared by method A were surveyed.[34] Newer examples for the application of method A with di- and trisaccharides are **222**[211] (93%), **223**[212] (65%), laminaribial **224** (54%,[213] 70%[214]), a pyruvated lactal[215] (98%), the galactosylated galactals **225**[216] (88%) and **226**[217] (92%), the 6,6′-difunctionalized cellobials[218] **227** (98%) and **228** (92%), lactal **229** (65%) and maltal **230** (60%) derivatives,[219] and per-*O*-acetylated maltotrial[220] (42%). Method B gave per-*O*-acetylated maltal **220** (86%), lactal **221** (61%), and maltotrial (50%) from the appropriate free sugars.[171] From the corresponding acetobromo disaccharides were prepared cellobial **219** by methods E (83%),[186] F (75%),[187] G (91%),[199] and H (95%)[205] and maltal **220** (94%) by method G.[199] Method E gave the exocyclic glycal of leucrose **231** (42%), but this compound was obtained in 65% yield by method A. The analogous **232** was prepared by the sodium iodide protocol in 50% yield.[221] Method F was also used for the obtention of lactal[222] and maltal but yields were not indicated.[223]

2. From Glycosyl Chlorides

Glycosyl chlorides are less reactive than bromides, and from among the methods listed in the previous section, zinc−silver/graphite- and Cr(II)-based reagents are applicable/have been tested for the conversion of these starting materials into glycals. Acetylated pyranoid derivatives (Scheme 20) **182** (93%), **201** (82%), and **203** (97%) were obtained with a Cr(II)EN complex in DMF after reacetylation[224] and **182** (79%), **198** (91%), **201** (72%), **203** (90%), and **204** (61%) with Cr(II)EDTA in water−DMF[204,205] from the corresponding glycopyranosyl chlorides.

As it was seen, synthesis of furanoid glycals required special glycosyl bromides as substrates and their acid sensitivity excluded the classical Fischer−Zach procedure from the useful methods. These difficulties could be overcome by using the highly reactive zinc−silver/graphite which gave **235** and **253** (Scheme 23) in 86% and 81% yields, respectively, from easily available furanosyl chlorides.[186] Similarly activated potassium (method I in Table 13) also gave excellent yields of furanoid glycals protected at will in the 3-position, and the pyranoid compound **186** (Scheme 20) was made in 88% yield from the per-*O*-

Scheme 23

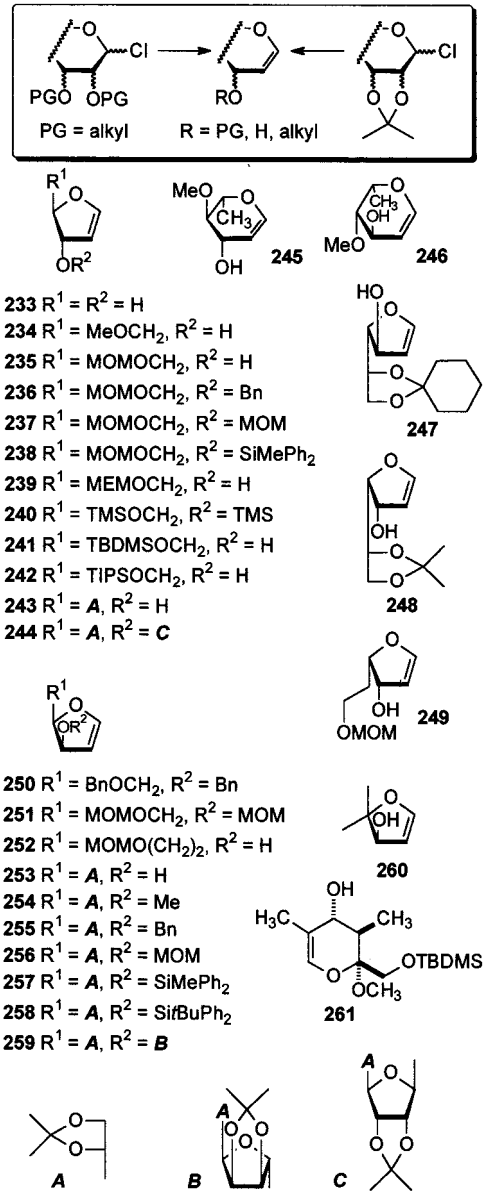
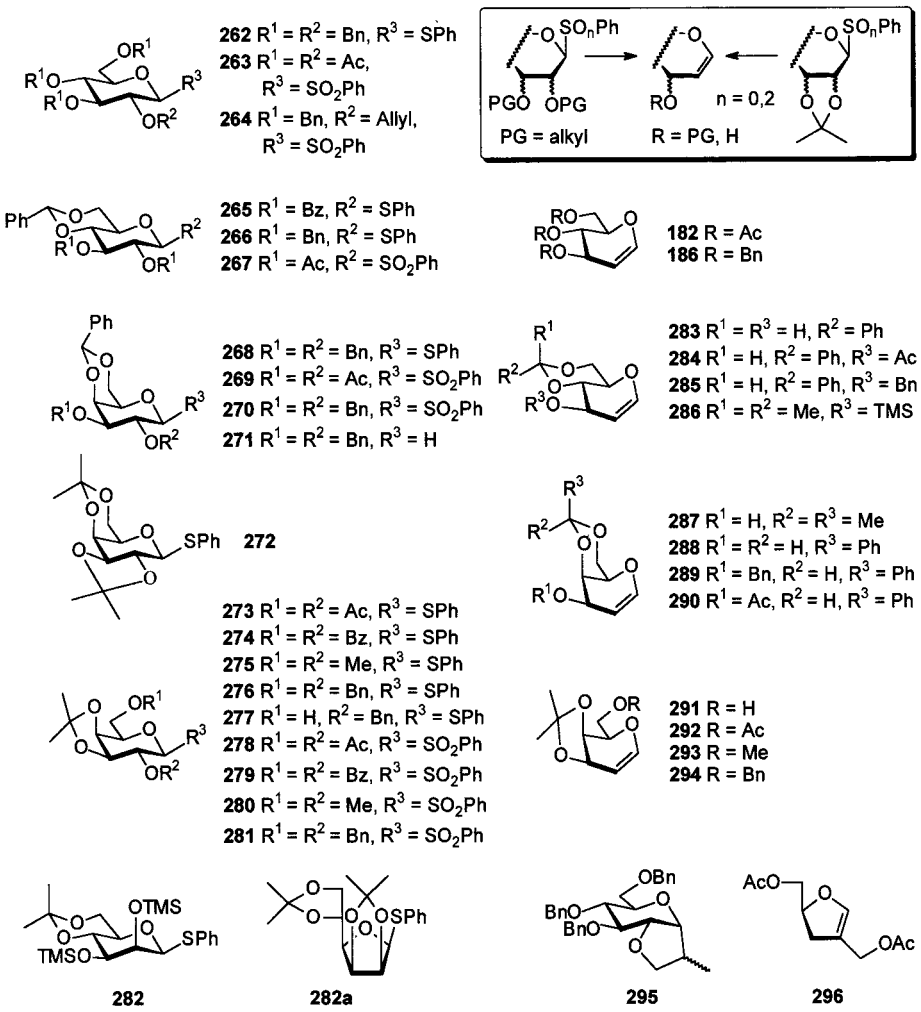


Table 13. Preparation of Furanoid Glycals from Glycosyl Chlorides (see Scheme 23)

	method	glycals prepared (%)
I[225]	C_8K, THF, 0 °C, then electrophile (R^2X)	**235** (92), **236** (86), **237** (80), **238** (90), **253** (96), **255** (84), **256** (77), **257** (90), **258** (86)
II	Na-naphthalenide, THF, r.t., then electrophile (R^2X)	**243** (54),[203,228] enantiomer-**243** (yield unknown),[a] **253** (59),[203] **253** (82, −35 °C),[227] **254** (60)[203]
III[203,228]	Na or K, THF, r. t., then electrophile (R^2X)	**244** (69), **259** (63)
IV	Li, NH_3(l), −78 °C, then electrophile (R^2X)	**233** (51),[229] **234** (75),[b] **235** (80),[226,229] **239** (65−82),[c] **240** (60),[d] **241** (65),[c] **242** (65−82),[c] **247** (68),[e] enantiomer-**247** (61),[e] **248** (76),[f] **249** (82),[g,h] **250** (yield unknown),[i] **251** (56),[j] **252** (70),[g,h] **253** (75),[226,k] **260** (79)[l]

[a] Bertrand, P.; Gesson, J.-P.; Renoux, B.; Tranoy, L. *Tetrahedron Lett.* **1995**, *36*, 4073−4076. [b] Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S.; Vanier, N. R. *Can. J. Chem.* **1979**, *57*, 1743−1745. [c] Cheng, J. C.-Y.; Hacksell, U.; Daves Jr, G. D. *J. Org. Chem.* **1985**, *50*, 2778−2780. [d] Abramski, W.; Chmielewski, M. *J. Carbohydr. Chem.* **1994**, *13*, 125−128. [e] Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 655−659. [f] Hacksell, U.; Daves Jr, G. D. *J. Org. Chem.* **1983**, *48*, 2870−2876. [g] Ireland, R. E.; Vevert, J.-P. *Can. J. Chem.* **1981**, *59*, 572−583. [h] Ireland, R. E.; Vevert, J.-P. *J. Org. Chem.* **1980**, *45*, 4259−4260. [i] El-Lagdach, A.; Diaz, Y.; Castillón, S. *Tetrahedron Lett.* **1993**, *34*, 2821−2822. [j] Obayashi, M.; Schlosser, M. *Chem. Lett.* **1985**, 1715−1718. [k] Ghosh, A. K.; McKee, S. P.; Thompson, W. J. *J. Org. Chem.* **1991**, *56*, 6500−6503. [l] Pirrung, M. C.; Lee, Y. R. *J. Am. Chem. Soc.* **1995**, *117*, 4814−4821.

Scheme 24



benzylated glucopyranosyl chloride.[225] Sodium sand in toluene at 70 °C gave **253** in 11% yield together with 9% of **259**.[203] Lithium, magnesium, zinc, or zinc−copper couple were unreactive toward acetal-protected glycofuranosyl chlorides, and transmetalation with organolithiums proved also unsuccessful.[203,226] Samarium diiodide was reported to give none of the targeted reductive elimination product **253** from the corresponding furanosyl chloride.[227] However, sodium naphthalenide (method II) gave moderate yields of the expected glycals,[203,228] which could be enhanced by lowering the reaction temperature.[227] Sodium or potassium metals (method III) furnished the disaccharide glycals **244** and **259**.[203,228] Further trials to optimize obtention of **244** from 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl chloride showed lithium, sodium, and potassium in liquid ammonia−THF (10:1 mixture) at −78 °C to give the target glycal and the product of reductive dehalogenation (1,4-anhydro-2,3:5,6-di-*O*-isopropylidene-D-mannitol) in 8:1, 11:1, and 15:1 ratios, respectively, in 75−80% yields. The use of sodium trimesitylborane in THF at −20 °C raised the above ratio to >50:1 (70%), and with LiDBB the yield was also increased to 94%. This reagent was applied to obtain **261** in 81% yield as an intermediate in the synthesis of subunits of monensin polyether antibiotics.[227] By far the most widely applied is method IV, which gives the desired furanoid glycals in good yields sometimes accompanied by small amounts (up to 20%) of reductively dehalogenated byproducts.[226,229] The latter, because of their rather unreactive nature, generally do not disturb further transformations of the main product glycals; therefore, separation can be effected in later stages of the synthesis. No byproduct was formed with the pyranoid derivatives **245** and **246** (90% yield for both). A one-pot procedure was developed starting with an acetalated 1-OH-unprotected glycose (in certain cases obtained by DIBAL reduction of the corresponding lactone as the first step in a continuous operation) to be converted into the chloride by hexamethylphosphorus triamide and carbon tetrachloride, which was then subjected to the reductive elimination conditions. Yields in Table 13 method IV mostly refer to such one-pot procedures.

3. From 1-Thioglycosides and Their S-Oxides

Because of the rather sensitive nature of glycosyl halides, the much more stable 1-thio-, 1-sulfinyl-, and 1-sulfonylglycosyl derivatives were also investigated as precursors of glycals. Preparation of these starting materials is as easy as that of the halides.[230]

Reaction of phenyl 2,3:5,6-di-*O*-isopropylidene-1-thio-β-D-mannofuranoside (**282a** Scheme 24) with potassium graphite followed by in situ silylation gave **258** (96%) (Scheme 23), and the per-*O*-benzylated **262**

(Scheme 24) lead to **186** (81%).[231] Lithium naphthalenide in THF at −78 °C transformed **262** into **186** in quantitative yield.[232] Other diversely protected 1-thioglycosides gave the corresponding glycals generally in very good yields with this reagent (Scheme 24; **265** → **283**[138,233] 86%, **266** → **285**[234] 98%, **268** → **288** 75%, **272** → **287** 85%, **273** → **291** 68% + 17% deacetylated starting material, **274** gave no glycal but mono- and didebenzoylated starting material, **275** → **293** 96%, **276** → **294** 97%, **277** → **291**[138,233] 92%, **282** → **286**[235] 68%). The same method was applied to get disaccharide glycal **297**[138,233] (Scheme 25) and the oligosaccharide derivatives **298**−**303**.[236−238]

Lithium naphthalenide was useful for achieving reductive eliminations from phenyl glycosyl sulfones as well[138,233] (Scheme 24; **270** → **289** 30% + **271** 46%, **278** → **291** 47% + **292** 41%, **279** → **291** 82%, **280** → **293** 85%, **281** → **294** 95%).

Phenyl 1-thioglucoside **262** was unreactive toward samarium diiodide even in the presence of HMPT;[209,239] however, the fully acetylated sulfone **263** furnished **182** in 98% yield under similar conditions. The samarium diiodide-mediated reductive elimination from glycosyl aryl sulfones was studied as to the effect of the protecting group and configuration in the 2-position as well as the effect of added HMPT shown in Table 14. 2-Acetoxy sulfone ***A*** (Table 14, entries 1 and 2) gave the corresponding glycal only with HMPT as a cosolvent. The fully benzylated analogue gave the glycal ***B*** and the reductively desulfonated product ***C*** (entry 3). Without HMPT, the D-*manno* phenyl sulfone ***D*** proved unreactive (entry 5) also, and a study on the effect of the aryl moiety showed 2-pyr-

Scheme 25

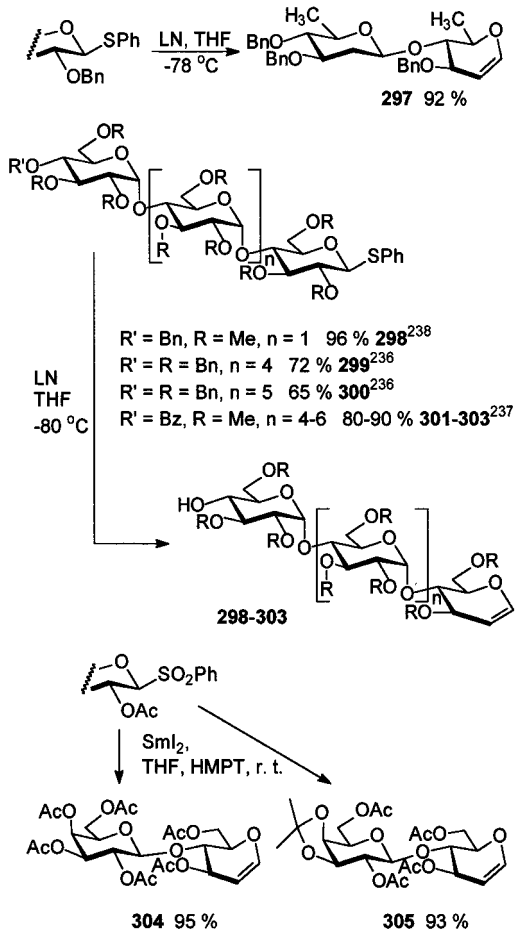
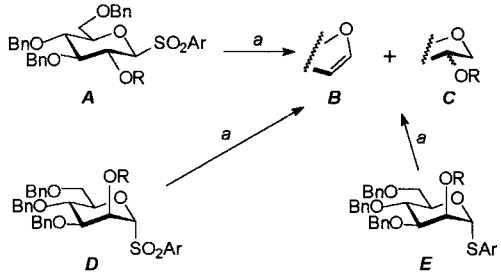


Table 14. Ratio of Elimination and Protonation with Glycosyl Samarium(III) Intermediates



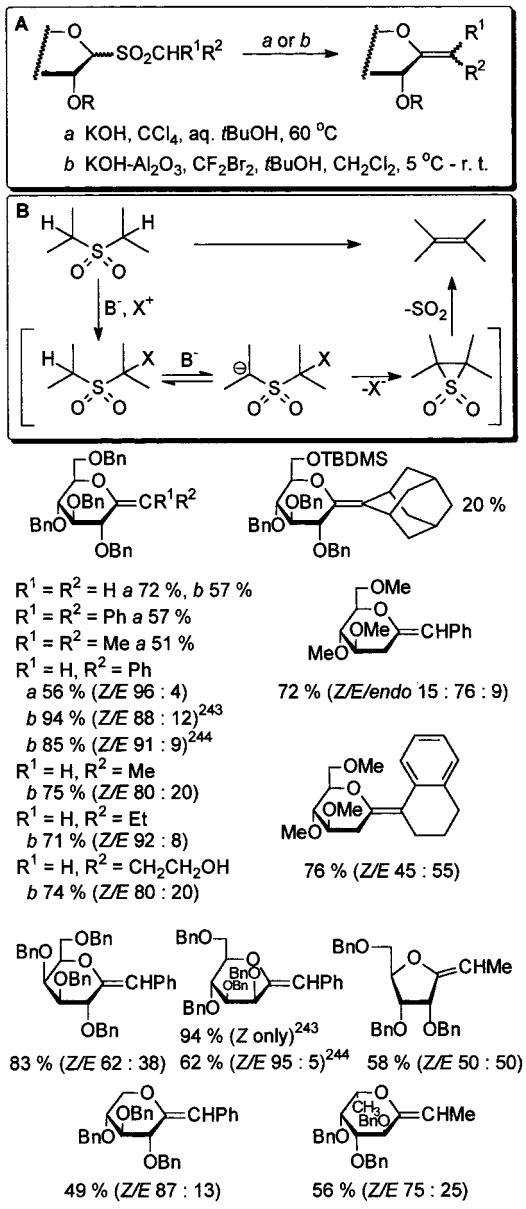
a: SmI_2, THF, r. t. with or without added HMPT (*see Table*)

entry	substrate	Ar	R	HMPT (eq)	***B*** (%)	***C*** (%)	ref
1	***A***	Ph	Ac	0	no reaction		209
2		Ph	Ac	23	96		210,239
3		Ph	Bn	23 (−40 °C)	56	33	239
4		Pyr	TMS	0	60	23	265
5	***D***	Ph	Ac	0	<5		*a*
6		2-naphthyl	Ac	0	22		*a*
7		2-pyrimidyl	Ac	0	72		*a*
8		2-(*N*-methylimidazolyl)	Ac	0	76		*a*
9		2-pyridyl	Ac	0	94		*a*,265,266
10		2-pyridyl	CO_2Bn	0	62		266,297
11		2-pyridyl	CONHPr	0	99		266,297
12		2-pyridyl	TMS	0	9	91	265,266
13	***E***	2-benzothiazolyl	Ac	0	78		*a*
14		2-pyridyl	Ac	0	64		*a*
15		2-pyridyl	TMS	0	5	71	266
16		2-pyridyl	TMS	2	65	13	266
17		2-pyridyl	TMS	4	73	9	266

[a] Skrydstrup, T.; Mazéas, D.; Elmouchir, M.; Doisneau, G.; Riche, C.; Chiaroni, A.; Beau, J.-M. *Chem. Eur. J.* **1997**, *3*, 1342−1356.

idyl sulfones to be the best substrates (entries 6−11). Heteroaryl sulfones allowed good yields to be achieved in the eliminations with 1-thiomannosides ***E*** (entries 13 and 14) also. With poor leaving groups in the 2-position, concurrent protonation occurred to give products ***C*** (entries 3, 4, 12, and 15) in surprisingly high proportion with the D-*manno* compounds. This was corroborated by the reaction of an α-D-mannopyranosyl phosphate (***D***, R = Bn, $OPO(OPh)_2$ instead of SO_2Pyr) to give glycal ***B*** (11%) and reduced product ***C*** (72%).[240] Enhancing the anionic character of the intermediate glycosyl samarium(III) species by complexation with HMPA was necessary to favor elimination from the 1-thiomannosides (entries 16 and 17). These results show an unexpectedly higher tendency to elimination from the D-*gluco* substrates as compared to the D-*manno* ones with a stereoelectronically favorable trans diaxial orientation of the leaving moieties. This feature and reactions of these intermediates with *C*-electrophiles will be discussed further in section IV.C.3.

Scheme 26

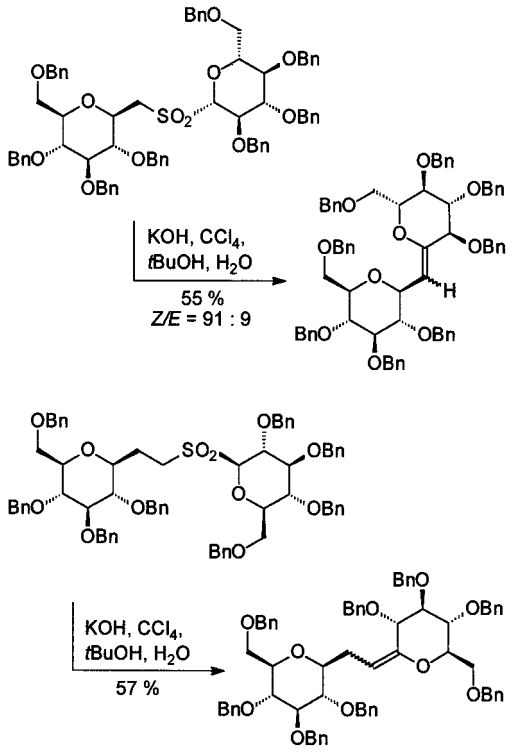


With SmI_2, sulfone **264** (Scheme 24) gave the cyclized **295** (78%) demonstrating that the transformation proceeds via radical intermediates according to the mechanism outlined in Scheme 21. A series of glycosyl phenyl sulfones were similarly converted to glycals of mono- (Scheme 24; **267** → **284** 98%, **269** → **290** 98%, **278** → **292** 98%) and disaccharides (Scheme 25: **304** and **305**) by using SmI_2.[210,239] The furanoid glycal **296** (Scheme 24) was similarly obtained from the corresponding 2-acetoxy-1-phenylsulfonyl derivative.[241]

The D-*manno* 2-pyridylsulfonyl derivative shown in Table 14 entry 9 gave the corresponding glucal **186** in 70% yield also with in situ generated $(Cp_2TiCl)_2$.[199]

Glycosyl sulfones with at least one C−H bond on the carbon attaching the "aglycon" to the sulfur atom have proved to be excellent substrates for the obtention of *exo*-glycals in a Ramberg−Bäcklund rearrangement (Scheme 26, **A**). According to the generally accepted mechanism[242] (Scheme 26, **B**) a glycosyl anion should appear in the course of the reaction; however, elimination of the 2-alkoxy substituent is disfavored. This phenomenon needs further mechanistic studies because easy expulsion of alkoxy and isopropylideneoxy substituents from the 2-position has been demonstrated (cf. section III.F.1). The method offers simple possibilities to get variously substituted *exo*-glycals including quaternary derivatives with rather good *Z* selectivities in several cases[243,244] (Scheme 26). *exo*-Glycal precursors of *C*-disaccharides[245] (Scheme 27) and the *C*-glycosyl

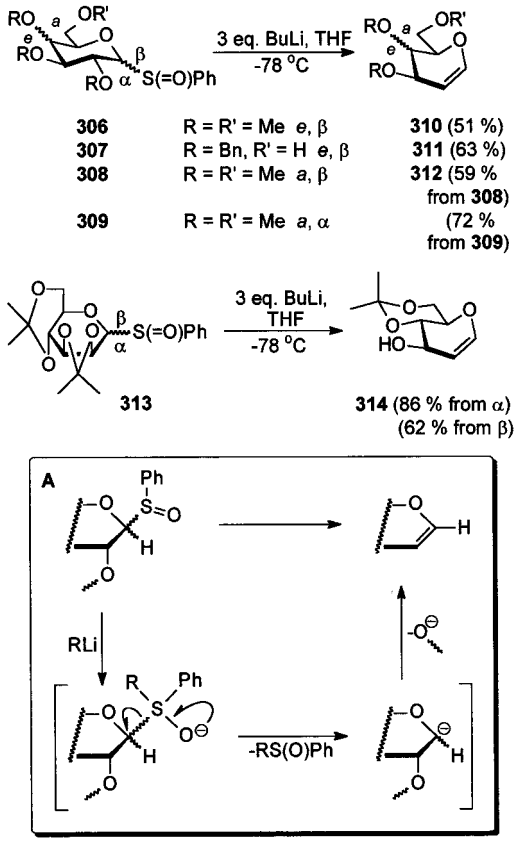
Scheme 27



derivative of daunomycin[244] were obtained by using this methodology.

Anomeric sulfoxides **306**−**309** and **313** were converted into glycals **310**−**312** and **314**, respectively, by using butyllithium (Scheme 28).[246] Phenyl-, meth-

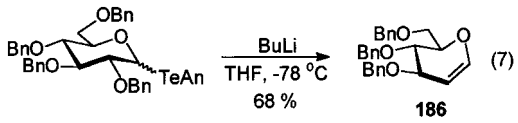
Scheme 28



yl-, and *tert*-butyllithium gave similar results. Mechanistically the transformation can be understood (Scheme 28, **A**) by an initial nucleophilic addition of the organolithium to the sulfoxide followed by a ligand-exchange reaction to give the anomeric anion, which then undergoes *β*-elimination to afford the glycal. This mechanistic explanation was proved by the reaction of a 1-deuterioglycosyl sulfoxide.[247]

4. From 1-Telluroglycosides

In an isolated example of glycal formation, an anomeric mixture of anisyl 2,3,4,6-tetra-*O*-benzyl-1-telluro-D-glucopyranosides was converted into per-*O*-benzylated glucal **186** with butyllithium in THF[248] (eq 7).

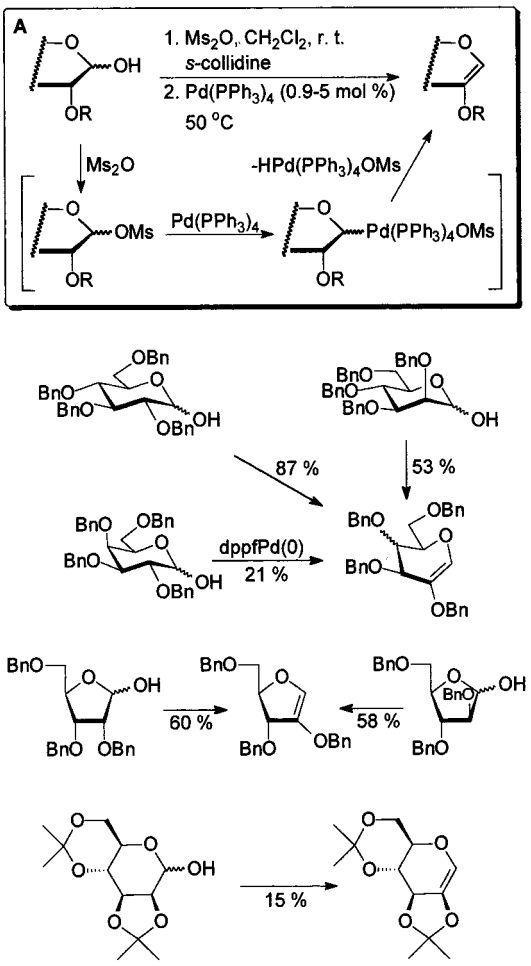


(7)

5. 2-Hydroxy-glycals from Anomeric Palladium Complexes

The methods surveyed in the preceding sections rely on the ready removal of the 2-*O*-substituent from suitably generated anomeric anionic species in an E1cb-type elimination. Metalation of the anomeric carbon with a palladium complex makes it possible to eliminate a hydride from the 2-position, thereby providing access to protected 2-hydroxy-glycals (Scheme 29). The reaction sequence starts with a conventional mesylation of the anomeric hydroxyl group (Scheme 29, **A**) followed by a treatment with a catalytic amount of a palladium(0) complex. This

Scheme 29



results in an anomeric palladium(II) species by an oxidative addition. Subsequent *β*-hydride elimination gives the glycal derivative and a palladium hydride undergoing a reductive elimination to recover the catalyst. Yields vary from low to very good, and the transformation makes available 2-hydroxy-glycals with full ether or acetal protection otherwise not easily obtained or accessible at all.[249]

6. Other Methods for Glycal Formation

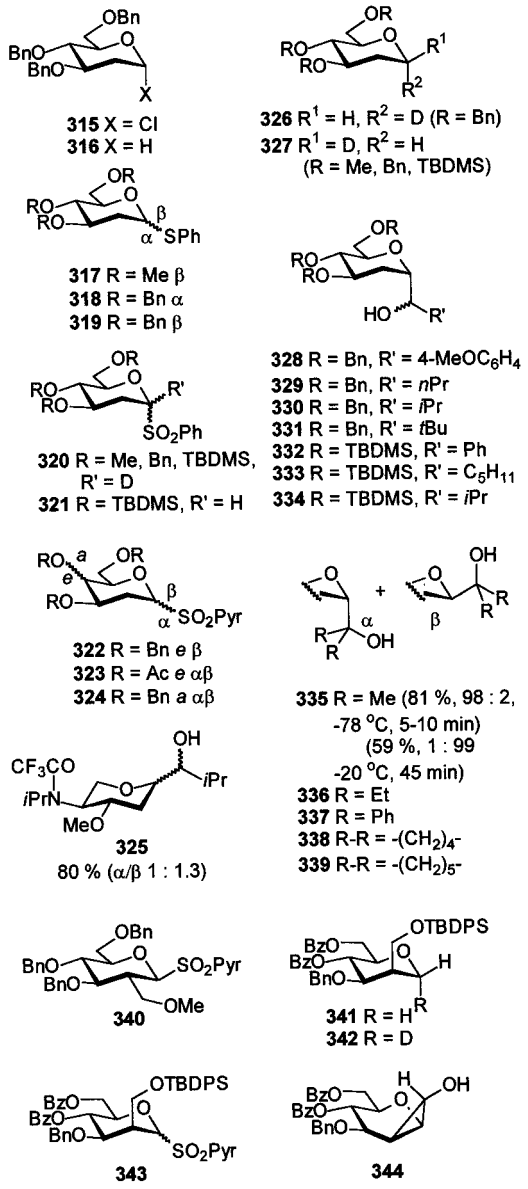
As the last review on glycals[37] is 20 years old, it may be useful to list methods of preparation for these substances which, starting from monosaccharide derivatives, utilize reactions involving no anomeric carbanions as intermediates. Radical-induced eliminations were achieved from 1-thioglycoside-2-xanthates,[138,233] 2-azido-2-deoxy-selenoglycosides,[250] a 2-phosphonooxy-1-thioglucoside,[251] a 1,2-*O*-thiocarbonyl-α-D-glucose derivative,[252] and a *C*-(1,2-dibromo-1,2-dideoxy-D-glucopyranosyl)formate.[253] A C-2 radical or anion may be the intermediate in the transformation of 1,6-anhydrohexopyranose derivatives into glycals.[254] Eliminations to form furanoid glycals were reported from 2-deoxy-pentofuranose derivatives, such as nucleosides,[255,256] 1-*O*-mesylates,[257] 1-selenoglycofuranosides,[258] 1,4-anhydro-2-deoxy-2-phenylselenyl-D-pentitols,[259] and furanose 1,2-diols.[260] Both furanoid and pyranoid glycals can be obtained by a Tipson−Cohen-type elimination applied to car-

bohydrate 1,2-diols.[260a] Glycals with aliphatic and aromatic substituents in the 1-position were prepared by olefin metathesis.[260b] D-Allal, D-gulal, and 1,5-anhydro-2,6-dideoxy-L-*ribo*-hex-1-enitol derivatives were obtained from per-*O*-acetylated D-glucal, D-galactal, and L-rhamnal, respectively.[260c]

B. 2-Deoxy-glycosyl Anions as Nucleophiles

In the absence of substituents in the 2-position of the sugar ring, formation of glycals is suppressed because expulsion of a hydride anion is mostly unfavored and the intermediate anionic species can act as a nucleophilic agent in substitution and addition reactions. Similarly, no elimination is to be expected with a 2-*C*-branching. For the generation of 2-deoxy-glycosyl anions, the corresponding anomeric chlorides, 1-thio- and 1-telluroglycosides, and sulfones were used. Glycosylstannane derivatives have also become rather popular because they can be easily transmetalated to give anomeric nucleophiles whose reactivity can be further tuned.

Scheme 30

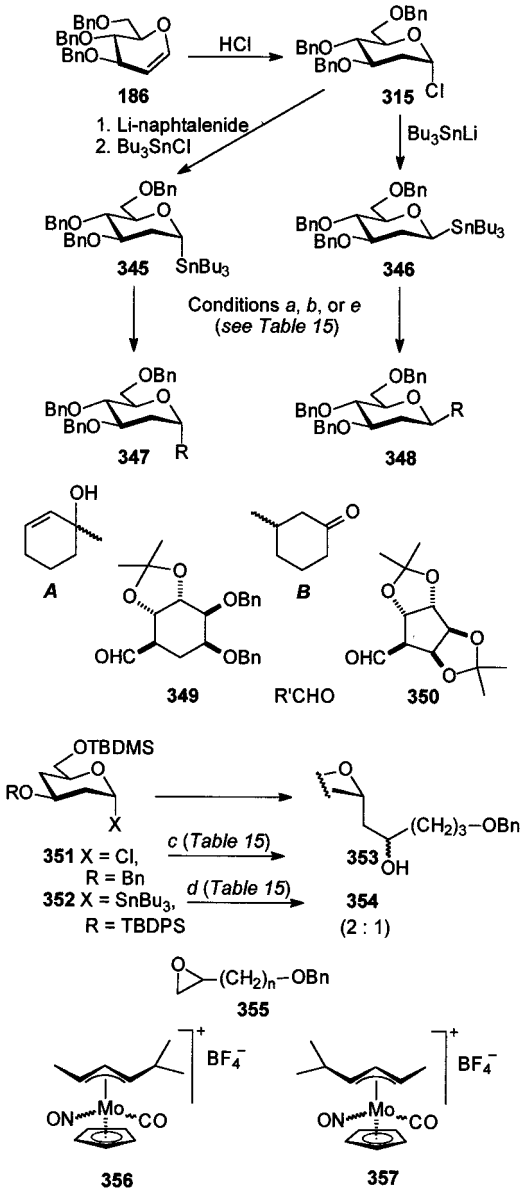


The preparation of simple α-lithio cyclic ethers was achieved from α-phenylthio derivatives with LDMAN. Their reactions with electrophiles demonstrated that the kinetic product formed from either epimer of the starting material was an axially oriented lithium salt which proved configurationally stable at the applied low temperature (−78 °C). Upon heating to −30 °C, these salts epimerized to the thermodinamically more stable equatorial derivatives giving the corresponding products with electrophiles.[261,262] 2-Cyano cyclic ethers undergo reductive decyanations with sodium or lithium in liquid ammonia at −78 °C to give the product with very good to excellent stereoselectivity in six- and eight-membered rings, but the reaction is unselective with five- and seven-membered ones.[136,137]

1. From 2-Deoxy-glycosyl Chlorides

Reductive lithiation of **315** (Scheme 30) (prepared from the per-*O*-benzylated glucal **186** as shown in Scheme 31) with lithium naphthalenide in THF at

Scheme 31

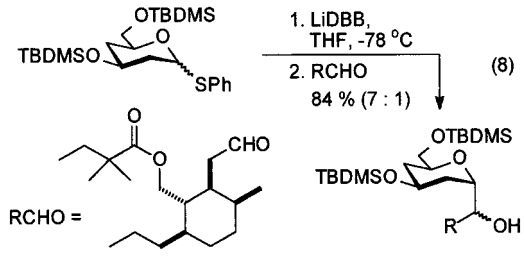


−78 °C followed by quenching with D_2O gave 80% of **326** based on **186**. Reactions of the glycosyllithium intermediate with 4-methoxybenzaldehyde and benzophenone gave **328** (65%, 3:1 diastereomeric ratio) and **337** (30% α only), respectively, in the latter case together with 30% of **316**. These findings indicated that at low temperature the intermediate lithium salt was configurationally stable and coupled with electrophiles to give the *axial* derivatives.[232]

The reactivity of **315** toward samarium diiodide in THF−HMPT (5% v/v) was investigated in the presence of carbonyl electrophiles. With cyclopentanone under Barbier conditions (a mixture of **315** and the electrophile was added to the reagent), **338** (44% α, 20% *β*), glucal **186** (11%), and **316** (10%) were obtained.[209] These figures were changed in a later publication[210] to 70%, 17%, 1%, and 4%, respectively. Under Grignard conditions (the reagent was added to **315** followed by the electrophile), the coupled product **338** formed in less than 5%, the main products being **186** and **316**.[209] The Barbier protocol afforded **336** (60% α, 13% *β*) with pentan-3-one together with some **186** and **316**. Using Grignard conditions, compounds **329** (26%, isolated as the corresponding ketone after oxidation), **186** (20%), and **316** (42%) were obtained with butanal; 2-methylpropanal gave **330** (34% isolated as the ketone); 2,2-dimethylpropanal afforded **331** (53% α) and **316** (21%).[209,210]

2. From 2-Deoxy-1-thioglycosides

Treatment of both **318** and **319** with lithium naphthalenide followed by electrophiles (D_2O, 4-methoxy-benzaldehyde, benzophenone) gave similar results as **315** affording **326**, **328**, and **337**, respectively.[232] This indicated that irrespective of the anomeric configuration of the starting material the lithium salt was formed (presumably via the more stable axial radical) as the axially oriented kinetic product. This was corroborated by the reaction of **317** with LiDBB and acetone, which gave **335** with excellent α-selectivity under kinetic conditions (−78 °C, 5−10 min), while a similar *β*-selectivity was achieved under thermodynamic conditions (−20 °C, 45 min).[263] An intermediate in the synthesis of the monocyclic analogue of compactine was similarly obtained by kinetic lithiation and subsequent coupling with an aldehyde (Equation 8).[264]



3. From 2-Deoxy-glycosyl Aryl Sulfones

Deuterated sulfones **320** resulted in single anomers **327** when treated with lithium naphthalenide in THF at −78 °C followed by hydrolysis. This was fully in keeping with experiences on the formation of axial kinetic glycosyllithiums at low temperature. Accordingly, in reactions of **321** with benzaldehyde, hexanal, 2-methylpropanal, **332** (66%, 1:1 diastereomeric ratio) and **316** (26%), **333** (45%, 3:1 ratio), **334** (59%, 2:1 ratio) were isolated, respectively.[148]

2-Pyridyl-sulfones proved good substrates for reductive samariations in the 2-deoxy-glycosyl series as well. Thus, reactions of **322**−**324** with cyclohexanone mediated by samarium diiodide in THF at room temperature under Barbier conditions (the SmI_2 solution was added to a mixture of the sulfone and cyclohexanone) gave the corresponding *C*-glycosyl cyclohexanols **339** in 82%, 88%, and 86% yields, respectively, in a 1:1 anomeric ratio for each, and **325** was obtained in a similar manner.[265,266] The 2-*C*-branched **340** furnished the corresponding *C*-glycosyl cyclohexanols **339** (73%, 4:1).[265,266] The D-*manno*-configurated **343** yielded only **341** (99%) with cyclohexanone; **342** (94%, D-incorporation 70%) was obtained in the presence of CH_3OD; and without added electrophile **344** was isolated in 99% yield. Attempted couplings of a D-*manno*-configurated "*C*-disaccharidyl" 2-pyridyl sulfone with cyclohexanone or a 2-*C*-formyl-D-mannopyranose derivative yielded only the reductively desulfonylated product in >90% yields.[267]

4. From 2-Deoxy-glycosyl Stannanes

Both anomeric stannanes **345** (70%) and **346** (85%) can be prepared from glucal **186** via the nonisolated chloride **315** as illustrated in Scheme 31. 2-Deoxyglycosyl stannanes were also prepared by addition of stannyl anions (R_3SnLi) to carbohydrate-derived 2,3-dihydro-4*H*-pyran-4-ones.[268] These compounds are stable; their anomeric configuration is well established and maintained on transmetalation by *n*-butyllithium. Further transmetalation to copper derivatives also keeps the original configuration. Therefore, these stannanes offer excellent possibilities for the preparation of *C*-glycosyl derivatives **347** and **348** in a highly stereocontrolled way. Changing the hard lithium to the soft copper tunes the reactivity of the intermediate glycosyl anion and, thus, makes the regioselectivity also controllable (compare entries 10 and 15 in Table 15 which summarizes compounds obtained by variants of this methodology).

A large variety of electrophiles were used such as D_2O (entry 1), alkyl iodide[269,270] (entry 2), aldehydes[269−271] (entries 3−6) leading also to carba-*C*-disaccharides[272] (entries 7 and 8), ketones[270] (entries 9 and 10), acid chlorides[96] (entries 11 and 12), α-*β* unsaturated ketones[273] (entries 13−15), epoxides[273a,274] **355** (entries 16−19), and cationic *π*-allyl complexes[275] **356** and **357** (entries 20 and 21). The last mentioned method was used for the preparation of an intermediate in the synthesis of salinomycin.[276]

5. From 2-Deoxy-1-telluroglycosides

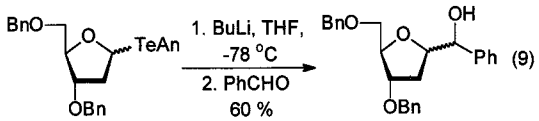
A 1-telluroglycoside also proved to be a suitable substrate for transmetalation and subsequent reac-

Table 15. 2-Deoxy-D-glucopyranosyl Derivatives from 2-Deoxy-glycosyl Stannanes 345 or 346 (see Scheme 31)

entry	electrophile	R	yield [%] (diastereomeric ratio) **347**	**348**	ref
	Conditions *a*: (1) BuLi, THF, −78 °C; (2) electrophile; (3) hydrolysis				
	H^+ from the solvent	H (**316**)			
1	D_2O	D	70	74	269,270
2	nC_4H_9I	nC_4H_9		39 + **316** (52%)	269,270
3	PhCHO	CH(OH)Ph	65 (3:1) + **316**	95 (1:1) + **316** (1−10%)	269,270
4	n-$C_5H_{11}CHO$	CH(OH)n-C_5H_{11}	74 (10:1) + **316**	80 (1:1) + **316** (16%)	269,270
5	iPrCHO	CH(OH)iPr		80 (3:1) + **316** (1−10%)	270
6	EtCHO	CH(OH)Et	72 (10:1)	68 (1.2:1)	271
7	**349** = R′CHO	R′CH(OH) from **349**	82 (16:1)		272
8	**350** = R′CHO	R′CH(OH) from **350**	74 (three aldol products)		272
9	$Me_2C{=}O$	$C(OH)Me_2$	80 + **316**	60	270
10	cyclohex-2-enone	***A***		65 (1:1)	270
11	$ClCO_2Me$	CO_2Me		53	96
12	$ClPO(OEt)_2$	$PO(OEt)_2$		26	96
	Conditions *b*: (1) BuLi, THF,; (2) $CuBr.SMe_2$, DIPS-THF; (3) electrophile; (4) $BF_3.OEt_2$ (−78 °C during the whole sequence)				
13	$CH_2{=}CHCOMe$	CH_2CH_2COMe	75	55	273
14	$Me_2C{=}CHCOMe$	CMe_2CH_2COMe	−	20	273
15	cyclohex-2-enone	***B***	64	78	273
	Conditions *c*: (1) LN, THF, −78 °C; (2) $MeOCMe_2C{\equiv}CCu$				
16	**355** n = 3	$CH(OH)(CH_2)_3OBn$	36[a] **353** (n.d.[b])		273a
	Conditions *d*: (1) BuLi, THF; (2) Cu(2-thienyl)CNLi; (3) electrophile; (4) $BF_3.OEt_2$ (−78 °C during the whole sequence)				
17	**355** n = 1	$CH(OH)CH_2OBn$	67 (n.d.[b])	50 (1:1) + glycal	274
18	**355** n = 3	$CH(OH)(CH_2)_3OBn$	71 (3:2)	63 (1:1)	274
19	**355** n = 3	$CH(OH)(CH_2)_3OBn$	71 **354** (2:1)		274
	Conditions *e*: (1) BuLi, THF; (2) $CuBr.SMe_2$, DIPS-THF; (3) electrophile; (4) CAN (−80 °C during the whole sequence)				
20	**356**	(*S*)CHMeCH=CHCHMe_2	81	49	275
21	**357**	(*R*)CHMeCH=CHCHMe_2	75	54	275

[a] Yield refers to synthetic sequence starting from the corresponding glycal. [b] Not determined.

tion with benzaldehyde to give a *C*-glycosyl derivative[248,277] as shown in eq 9.



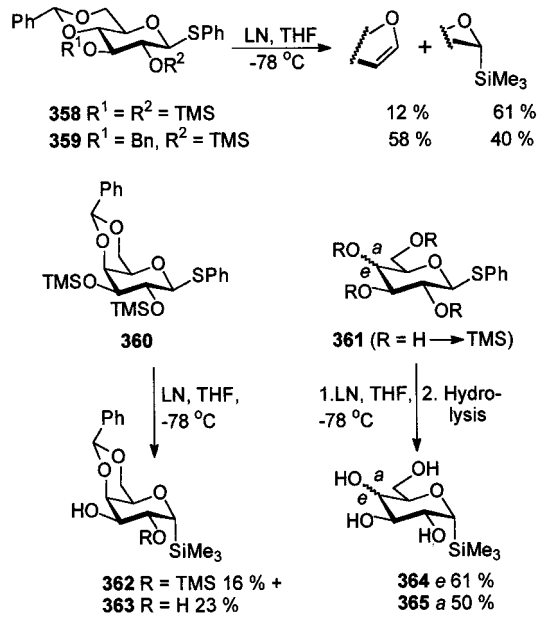
C. Glycosyl Anions with the Preservation of the 2-*O*-Substituent

In this section transformations involving glycosyl anions as reactive intermediates as well as stable and isolable glycosylmetal derivatives with full substitution pattern are collected. The latter can also be starting materials for further anionic transformations.

1. Glycosyl Silanes and Stannanes

Reductive metalation of phenyl 1-thio-2-*O*-silylglycosides with lithium naphthalenide showed that elimination yielding the corresponding glycal was the preferred pathway with the D-*manno*-configurated **282** (Scheme 24). Compounds **358**−**361** (Scheme 32) with an *equatorial* 2-*O*-silyl substituent gave partly or exlusively 1-*C*-trimethylsilyl glycosyl derivatives **362**−**365**, respectively, as results of an *O*,*C*-silyl migration. Formation of unsaturated byproducts was less preponderant with **358** than with **359**, and the glycal, although formed, was not isolated from the reaction of **360**. Good overall yields were achieved from unprotected 1-thioglycosides **361** in a per-*O*-

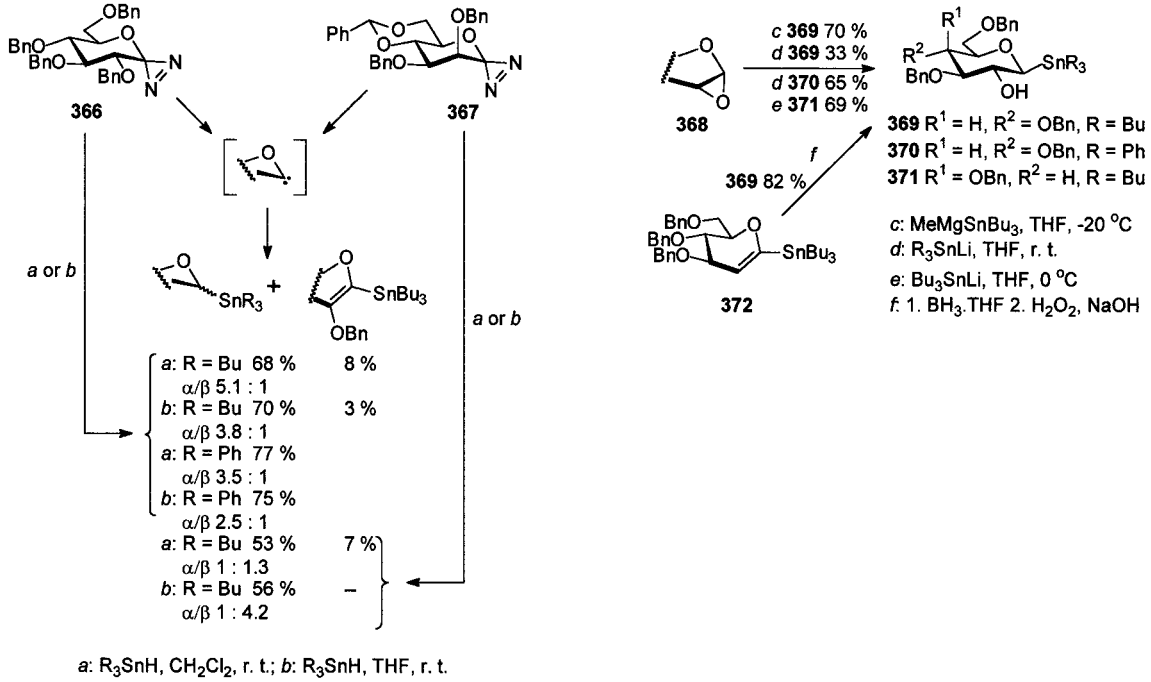
Scheme 32



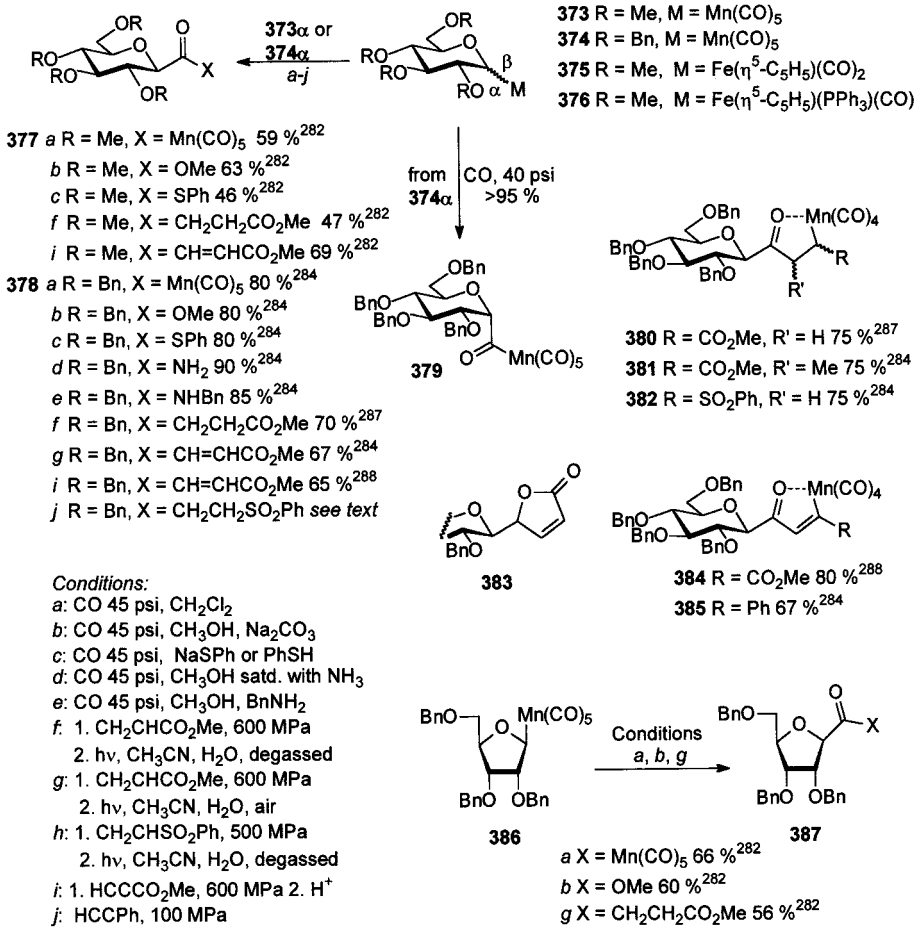
silylation, reductive metalation, hydrolysis sequence.[235] Preparation of 2-deoxy-glycosyl silanes by the addition of silyl anions to 2,3-dihydro-4*H*-pyran-4-ones was reported.[268]

Insertion of anomeric carbenes generated from glycosylidene-spiro-diazirines **366** and **367** (Scheme 33) into the tin−hydrogen bond of trialkyl- or triarylstannanes gave fully *O*-protected glycosyl stannanes.

Scheme 33

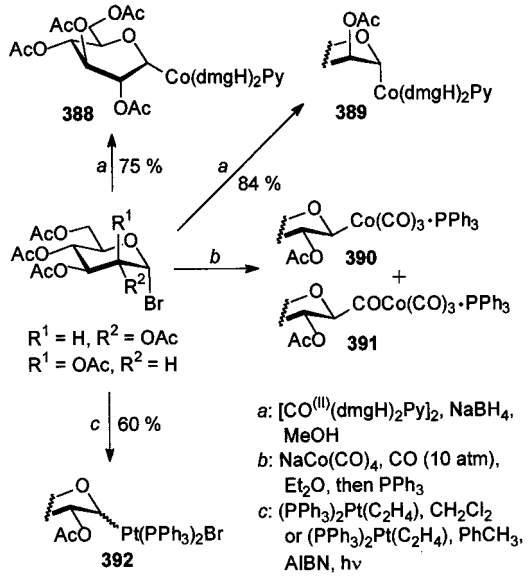


Scheme 34



The moderate stereoselectivity depended on the configuration of the carbon in the 2-position.[278] 2-*O*-Unprotected glycosyl stannanes **369**,[279] **370**,[280] and **371**[281] were obtained in reactions of the corresponding sugar epoxide **368** with tin nucleophiles. For the preparation of **369**, hydroboration−oxidation of stannyl glucal **372** was reported.[271] Such partially protected glycosyl stannanes were also prepared via 1,5-anhydro-alditol-1-id-2-*O*-ate intermediates (glycosyl dianions), and this as well as their use for the generation of glycosyl dianions will be discussed in section IV.C.4.

Scheme 35

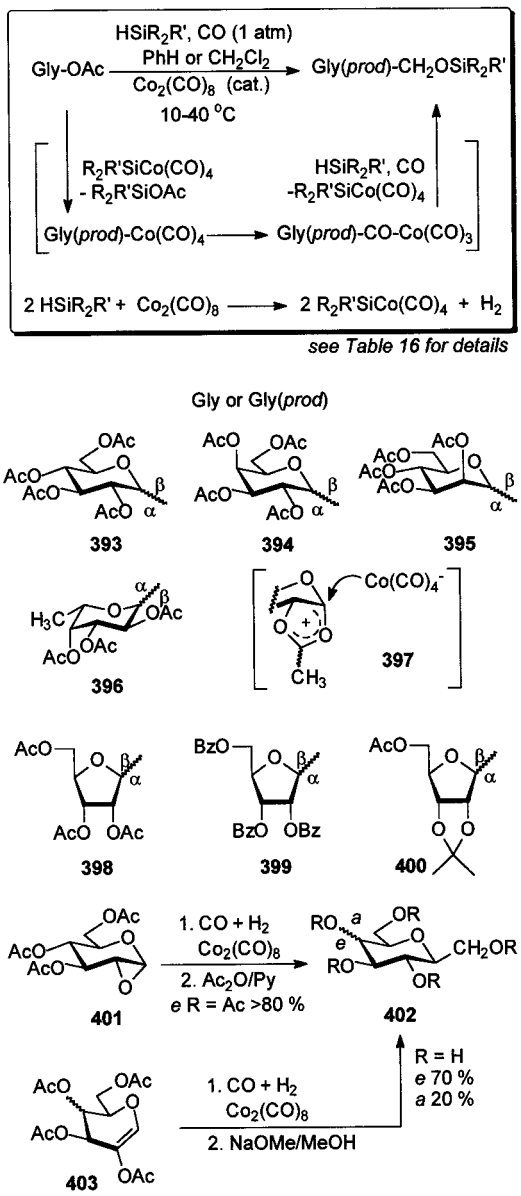


2. Glycosyl Transition-Metal Derivatives

Nucleophilic substitutions in alkylated glycosyl bromides with $NaMn(CO)_5$ in THF at −78 °C gave glycosyl manganese complexes **373***β* (75%), **374***β* (75%), and **386** (65%) (Scheme 34) as well as similar *β*-D-galactopyranosyl (75%), D-mannopyranosyl (60%, α/*β* 1:2), and D-arabinofuranosyl (70%, α/*β* 2:1) derivatives.[282,283] In the latter case the presence of tetra-*n*-butylammonium bromide changed the anomeric ratio (55%, α/*β* >98:2). Using $KMn(CO)_5$ in diethyl ether at −20 °C increased the yield of **374***β* to 93%, and with $NaMn(CO)_5$ in diethyl ether at −20 °C in the presence of tetra-*n*-butylammonium bromide a significant amount of **374**α was obtained (75%, α/*β* 3:2).[284] Glucosyl iron complex **375***β* was obtained exclusively from the corresponding glycosyl bromide with $NaFe(\eta^5\text{-}C_5H_5)(CO)_2$ in THF at −78 °C in 47% isolated yield,[285,285a] while at ambient temperature a 5:1 mixture of anomers **375***β* and **375**α was formed.[285a] A ligand exchange in **375***β* under photolytic conditions gave **376***β* (85%).[286]

Migratory insertion of carbon monoxide into the glycosyl−metal bond in **373***β*, **374***β*, and **386** gave **377***a*, **378***a*, and **387***a*, respectively.[282] This reaction was approximately seven times faster with **374**α than with **374***β*, and **379** could be separated from unreacted **374***β*. Since **379** lost carbon monoxide on gentle heating, this sequence allowed for the preparation of **374**α in pure state in 85% yield. Similarly, the otherwise unseparable anomers of D-mannopyranosyl and D-arabinofuranosyl manganese complexes were separated in an analogous fashion.[284] In the presence of alcohols, amines, or thiols, insertion of carbon monoxide was followed by nucleophilic substitutions to give carboxylic acid derivatives **377***b*,*c*, **378***b*−*e*, and **387***b*.[282,284] In the presence of additional unsaturated reagents under conditions *f*−*j*, unstable manganacycles **380**−**385** were formed which, on photolytic or protolytic decomposition, gave ketone derivatives **377***f*,*i*, **378***f*,*g*,*i*, and **387***g*[282,284,287,288] (manganacycle not shown for the latter). Photolytic demetalation of manganacycle **382** resulted in ketone **378***j* and butenolide **383** in 35% and 65% yields, respectively.[284] Iron complex **375** resisted carbon monoxide insertion.[285]

Scheme 36



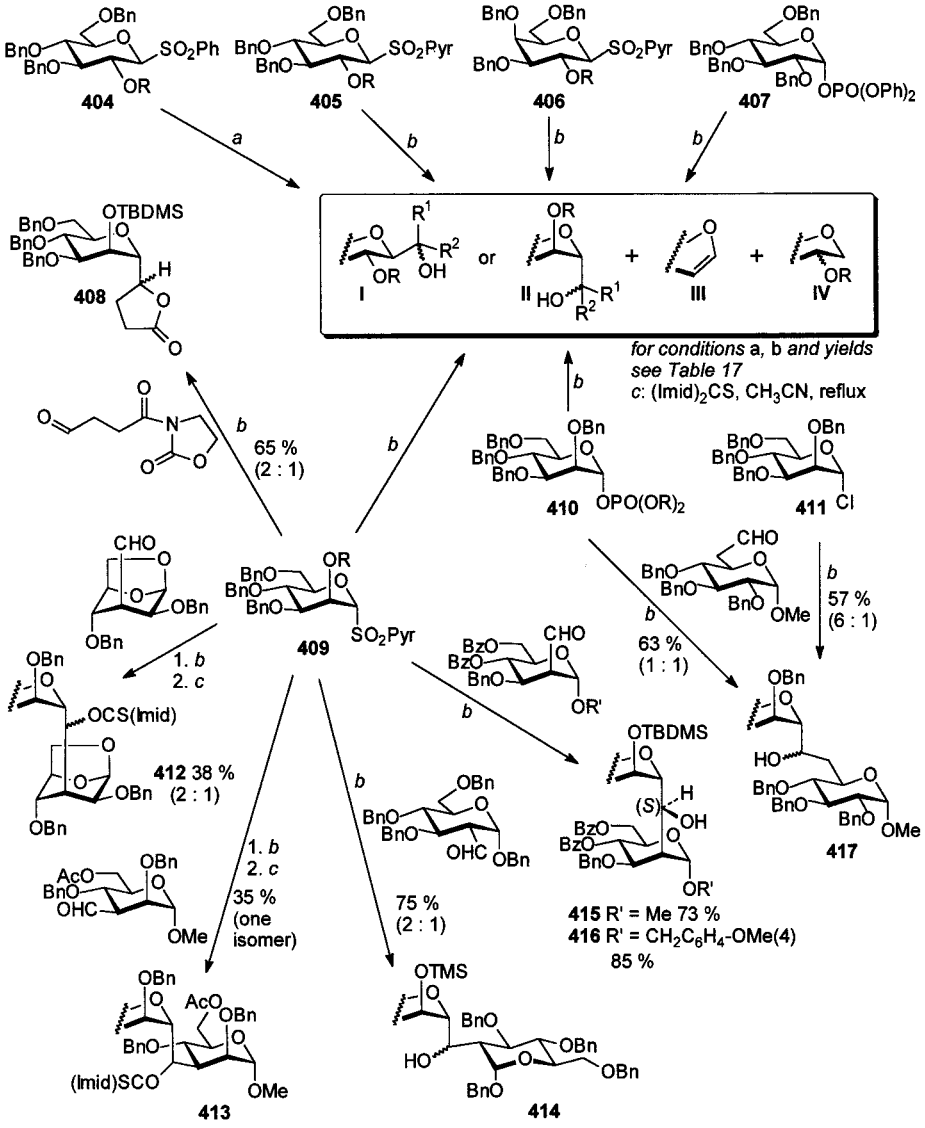
Glycosyl cobaloximes **388** and **389** were obtained from the corresponding acetobromosugars. According to the vicinal proton−proton couplings in the ^1H NMR spectra, **388** adopts a $B_{2,5}$ boat conformation while the $^4C_1$ chair is retained in **389**. Upon irradiation, **388** and **389** underwent anomerization to give the *β*-anomer in 31% and 36% yields, respectively, together with 45% tri-*O*-acetyl-D-glucal **182** reported in the first case only. These compounds are excellent precursors of glycosyl radicals; however, the formation of **182** may reveal some anionic reactivity as well.[289] Acetobromoglucose was converted into the cobalt complex **390** and the carbon monoxide insertion product **391**[290] as well as into the platinum complex **392**.[291]

Glycosyl cobalt complex intermediates appear in a catalytic synthesis of *C*-glycosyl methanols[292,293] outlined in Scheme 36 and Table 16 . Protected glycosyl acetates undergo nucleophilic substitution by a si-

Table 16. *C*-Glycosyl Silylmethanols by Cobalt-Catalyzed CO Insertion Reactions (see Scheme 36)

	yield for Gly(*prod*)-CH_2OSiR_2R' (%)			
Gly-OAc	Gly(*prod*)	R = R′ = Me	R = Et, R′ = Me	ref
393*β*	**393***β*	75	82	292
393α	**393***β*	78		292
394*β*	**394***β*	63 (PhH, 40 °C), 82 (CH_2Cl_2, 10 °C)		292
395*β*	**395***β*	51		292
395α	**395***β*	45	11% **395**α, 31% **395***β*	292
396α	**396***β*		85	294
398*β*	**398**α*β*		10% **398**α, 23% **398***β* (PhH, 30 °C) 5% **398**α, 70% **398***β* (CH_2Cl_2, 30 °C)	293
399*β*	**399***β*		75	292
400*β*	**400**α*β*		39% **398**α, 7% **398***β* (PhH, 30 °C) 27% **398**α, 7% **398***β* (CH_2Cl_2, 30 °C)	293

Scheme 37



lylated cobalt species initially formed from the applied silane and dicobalt−octacarbonyl. After a carbonyl insertion into the sugar−cobalt bond, the silylated nucleophile is reformed and the intermediate is concomitantly reduced on the action of silane and carbon monoxide to close the catalytic cycle. The method generally shows a good 1,2-trans selectivity independent of the anomeric configuration of the starting 1-*O*-acetate. This can be understood so that the initial nucleophilic attack occurs in dioxolanium ion **397** and is directed by the orientation of the 2-*O*-acyl participating group.[292] The method was applied in the synthesis of fucosyltransferase inhibitors.[294]

Fully acetylated *C*-glucosyl methanol **402***e* was obtained in an application of the oxo reaction to Brigl's anhydride **401**. The same reactions with 2-hydroxy-glycal peracetates **403** gave **402** after deacetylation. Under similar conditions, pyranoid glycals afforded 2,6-anhydro-3-deoxy-alditols (*C*-(2-deoxy-glycosyl)methanols). All these transformations

Table 17. Reactions of Glycosyl−Samarium(III) Intermediates (see Scheme 37)

entry	substrate	electrophile	products (isolated yield [%])			ref
			Conditions *a*: (substrate + electrophile) + SmI_2, THF−HMPT (5% v/v), r.t. (Barbier conditions)			
			I (R as in **404**)	**III**	**IV**	
1	**404** R = Bn	cyclopentanone	28 (R^1-R^2 = −$(CH_2)_4$−)	57	10	210
2	R = Bn	2,2-dimethylpropanal	24 (R^1 = H, R^2 = *t*Bu)	39		210
3	R = Na	2,2-dimethylpropanal	16 (R = R^1 = H, R^2 = *t*Bu)	34	27	210
			Conditions *b*: (1) (substrate + electrophile) + SmI_2, THF, r.t. (Barbier conditions)			
			I (R = H)[a]	**III**	**IV**	
4	**405** R = TMS	*n*-heptanal	43 (7:2) (R^1 = H, R^2 = *n*-hexyl)	36	−	265,266
5	R = TMS	cyclohexanone	44 (R^1-R^2 = −$(CH_2)_5$−)	37		265,266
6	R = TBDMS	cyclohexanone	57 (R^1-R^2 = −$(CH_2)_5$−)	21		265,266
7	R = TBDMS	2-methylpropanal	55 (3:2) (R^1 = H, R^2 = *i*Pr)	22		265,266
8	R = H	cyclohexanone	4 (R^1-R^2 = −$(CH_2)_5$−) + 13% α-anomer			266
9	**406** R = TMS	cyclohexanone	25 (R^1-R^2 = −$(CH_2)_5$−)	35		266
10	R = TMS	3-pentanone	31 (R^1 = R^2 = ethyl)			298
11	R = TBDMS	cyclohexanone	22 (R^1-R^2 = −$(CH_2)_5$−)	32		266
12	407	acetone	52 (R^1 = R^2 = Me	28		240
			II (R as in **409**)	**III**	**IV**	
13	**409** R = Ac	cyclohexanone		94		265 266
14	R = CO_2Bn	cyclohexanone		62		266,297
15	R = CONHPr	cyclohexanone		99		266,297
16	R = Me	cyclohexanone	78 (R^1-R^2 = −$(CH_2)_5$−)	9		266,297
17	R = Bn	cyclohexanone	81 (R^1-R^2 = −$(CH_2)_5$−)	6		265,266
18	R = MEM	cyclohexanone	45 (R^1-R^2 = −$(CH_2)_5$−)	25		266,297
19	R = THP	cyclohexanone	56 (R^1-R^2 = −$(CH_2)_5$−)	21		266,297
			II (R = H)[a]	**III**	**IV**	
20	**409** R = TMS	cyclohexanone	86 (R^1-R^2 = −$(CH_2)_5$−)	1	4	265,266
21	R = TMS	3-pentanone	80 (R^1 = R^2 = ethyl)	3		265,266
22	R = TMS	*n*-octanal	82 (9:2) (R^1 = H, R^2 = *n*-heptyl)	9		265,266
23	R = TMS	2-methylpropanal	77 (13:2) (R^1 = H, R^2 = *i*Pr)	7	−	265,266
24	R = TMS	benzaldehyde	10 (2:1) (R^1 = H, R^2 = Ph)	32	−	265,266
25	R = TBDMS	cyclohexanone	80 (R^1-R^2 = −$(CH_2)_5$−)	−	−	266,297
26	R = TBDMS	formylcyclohexane	84 (4:1) (R^1 = H, R^2 = *c*C_6H_{11})	−	−	266,297
27	R = TBDMS	*n*-nonanal	71 (5:1) (R^1 = H, R^2 = *n*-octyl)	−	−	266,297
28	R = H	cyclohexanone	13 (R^1-R^2 = −$(CH_2)_5$−) + 19% β-anomer	17		266,297
			II (R = Bn)	**III**	**IV**	
29	**410** R = Bn	none		11	72	240
30	R = Bn	*tert*-amyl alcohol		6	85	240
31	R = Ph	*tert*-amyl alcohol		*b*	83	240
32	R = Bn	cyclopentanone	81 (R^1-R^2 = −$(CH_2)_4$−)			240
33	R = Ph	cyclopentanone	85(R^1-R^2 = −$(CH_2)_4$−)			240
34	R = Bn	acetone	72 (R^1 = R^2 = Me)			240
35	R = Ph	acetone	74 (R^1 = R^2 = Me)			240
36	R = Bn	2-methylpropanal	68 (11.7:1) (R^1 = H, R^2 = *i*Pr)			240
37	R = Bn	2-methylpropanal	65 (10.2:1) (R^1 = H, R^2 = *i*Pr)			240
38	R = Bn	CO_2	56 (R^1-R^2 = O=)			240

[a] Yields refer to desilylated products obtained by TBAF treatment. [b] Not indicated.

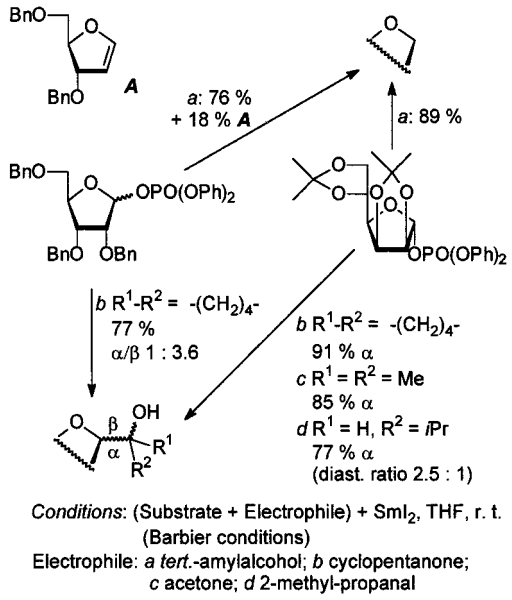
are believed to proceed through the formation of glycosyl−cobalt tetracarbonyl intermediates followed by carbonyl insertion.[295] Interestingly, rhodium-catalyzed hydroformylation of glucal derivatives gave 2-*C*-formyl compounds.[296]

3. Glycosyl Samarium(III) Intermediates

The excellent one-electron reductant samarium diiodide proved to be a valuable mediator in Barbier-type couplings of suitable saccharide derivatives and carbonyl electrophiles (Scheme 37 and Table 17). The first trials[210] with phenyl sulfone **404** showed that with a moderately nucleofugal 2-benzyloxy substituent, reasonable amounts of coupled products **I** could be obtained (entries 1 and 2). Decreasing the nucleofugality of the 2-substituent (entry 3) did not enhance the ratio of **I**. Pyridyl sulfones **405**, **406**, **409** with 2-*O*-silyl (entries 4−7, 9−11, and 20−27), 2-*O*-alkyl (entries 16 and 17), or 2-*O*-acetal (entries 18 and 19) protection needed no HMPT as a cosolvent, and, expectedly, because of the less anionic character of the intermediate, formation of the elimination product **III** was diminished[265,266,297,298] (compare Table 14 in section IV.A.3). Interestingly, with 2-*O*-silyl protection, **405** and **406** showed a higher tendency for elimination than **409**, which is contrary to the supposed *anti*-elimination (compare entries 4−7 and 9−11 to 20−27). The coupling with the electrophile occurred with exclusive 1,2-trans selectivity, and this was independent of the anomeric configuration of the starting sulfone as demonstrated by similar product distributions with either anomer of **405** (R = TMS)

and **409** (R = Bn).[266] The formation of the *C*-glycosyl derivative was not as efficient with benzaldehyde (entry 24) as with aliphatic carbonyl compounds (e.g., entries 20−23). Mechanistic possibilities were discussed in order to rationalize the above findings among others, suggesting a hitherto unknown *syn*-elimination preferred to the anti process in heteroatom-substituted organosamarium compounds; however, more experimental data would be necessary to clear all details.[266] Glycopyranosyl phosphates **407** and **410** and furanosyl derivatives shown in Scheme 38 also proved to be good substrates for reductive

Scheme 38



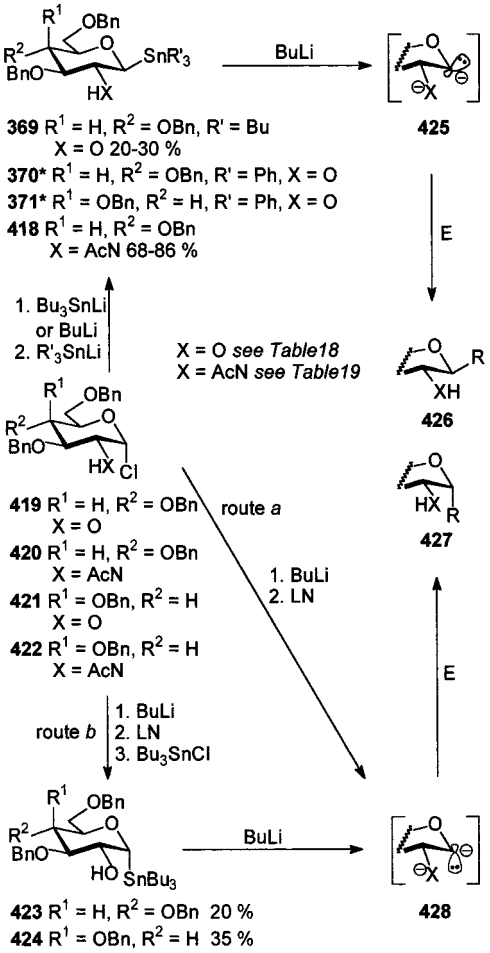
samariation and coupling with electrophilic partners (Table 17, entries 12 and 29−38) exhibiting similar selectivities as the sulfones.[240] Both pyridyl sulfone **409** and phosphate **410** of D-*manno* configuration were transformed with more complex aldehydes to give **408**[298] and *C*-disaccharides **412**, **413**,[299] **414**,[265,266] **415**, **416**,[267,297,300] **417**,[240] and the latter one was also prepared from the benzylated chloride **411**.[301]

4. 1,5-Anhydro-alditol-1-id-2-O-ates (Glycosyl Dianions) as Intermediates

Deprotonation of the 2-OH moiety makes a poor leaving group in the 2-position, and thus, another possibility is opened for the preservation of the 2-substituent in a glycosyl anion. Chain elongation in aldehydo sugar dithioacetals was performed in an analogous manner,[302] and the principle was extensively used for the preparation of various *C*-glycosyl compounds[271,280,281,303,304] (Scheme 39 and Table 18).

Glycosyl chlorides **419** and **421** unprotected at the 2-position[305] served as starting materials for the generation of dianions **428** by deprotonation and subsequent reductive lithiation (route *a*). Transformation of these chlorides into the corresponding α-D-glycosyl stannanes **423** and **424** via dianions **428** (route *b*) produced a more stable starting material, although in moderate yield, for transmetalations to

Scheme 39



*obtained from a 1,2-epoxide shown in Scheme 33

intermediates **428** with the preservation of the anomeric configuration. The following coupling reactions gave compounds **427** (Table 18). The *β*-D-glycosyl stannane **369** was formed from the deprotonated chloride and tributylstannyllithium in modest yield; therefore, **370** and **371** were prepared from 1,2-epoxides as shown in Scheme 33. Transmetalation of stannanes **369**−**371** also kept the anomeric configuration to afford anion **425**, and subsequent reactions with electrophiles gave coupled products **426** (Table 18).

Glycosyl dianions were obtained from either anomer of fucosyl sulfoxide **429** (Scheme 40), and deuteration or coupling with 2-methyl-propanal was stereospecific, maintaining the anomeric configuration of the starting material.[306] Methyllithium−lithium bromide was more efficient for the deprotonation step than *t*BuLi as shown by the higher deuteration ratio. The method was applied for the assembly of a *C*-disaccharide as well.[307]

Attempts to couple a glycosyl dianion from the fucosyl phenyl sulfone analogous to **429** with isobutyraldehyde failed, and only products from reductive desulfonylation as well as dimerization of the intermediate fucosyl radical could be isolated.[307]

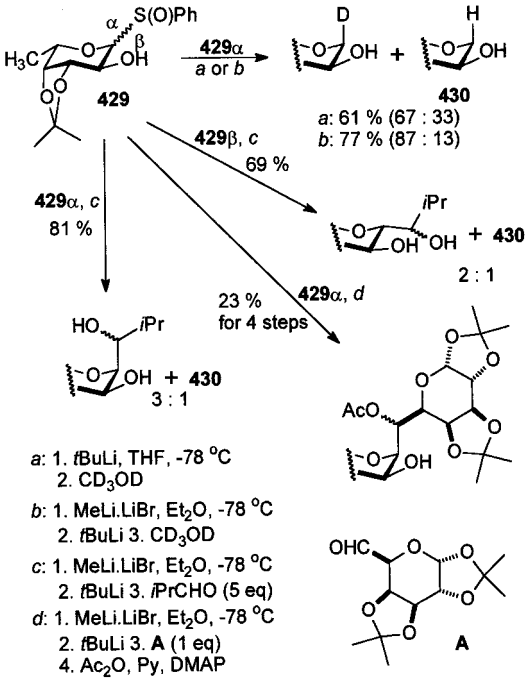
Table 18. Reactions of Glycosyl Dianions with Electrophiles (see Scheme 39)

starting compound	electrophile (E)	product **426** (X = O), R	yield [%] (diast. ratio)	ref
369	PhCHO	CH(OH)Ph	56 (1.1:1)	271
	EtCHO	CH(OH)Et	51 (1.1:1)	271
	*i*PrCHO	CH(OH)*i*Pr	50 (1.3:1)	271
370	MeOD	D	81 (+4% **427**)[a]	280
	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	50 (+50% **427**)	280
	PhCHO	CH(OH)Ph	77 (1.4:1)	280
	*i*PrCHO	CH(OH)*i*Pr	67 (1.4:1)	280
	CH_2=CHCHO	CH(OH)CH=CH_2	69 (1.5:1)	280
	PhCN[b]	COPh	84	280
	MeI[c]	Me	50	280
	Me_2SO_4	Me	77	280
	CO_2[d]	COOH	82	304
371 (R′ = Bu)	MeOD	D	83	281
	PhCHO	CH(OH)Ph	77 (1:1)	281
	*i*PrCHO	CH(OH)*i*Pr	57 (1:1)	281

starting compound	electrophile (E)	product **427** (X = O), R	yield [%] (diast. ratio)	ref
419	MeOD	D	75	303
	MeOH	H	82	303
	MeCHO	CH(OH)Me	62 (1.4:1)	303
	PhCHO	CH(OH)Ph	70 (1:1)	303
	*i*PrCHO	CH(OH)*i*Pr	59 (1:1)	303
	HCHO	CH_2OH	17	303
	MeI	Me	72	303
	CO_2[d]	COOH	57	304
421	MeOD	D	53	281
	PhCHO	CH(OH)Ph	37 (1.5:1)	281
423	PhCHO	CH(OH)Ph	30−40	271
424	MeOD	D	94	281
	PhCHO	CH(OH)Ph	77 (1:1.8)	281
	*i*PrCHO	CH(OH)*i*Pr	61 (1:1.4)	281

[a] Together with 4% of **426** (X = O, R = H). [b] Acyl chlorides proved unsuitable for acylation. [c] In the presence of 10 equiv of lithium 2-thienylcyanocuprate. [d] Followed by acetylation to give the corresponding 2-*O*-acetylated product.

Scheme 40



D. Anomeric Anions from *N*-Acyl-D-glycosamine Derivatives

The biologically very important *N*-acetyl-D-glycosamine derivatives are similarly prone to deprotonation and then formation of dianionic intermediates (Scheme 39 and Table 19) as the 2-OH-unprotected derivatives described in the previous section. The configurationally stable anomeric anions **425** and **428** (X = AcN for both) were generated from glycosaminyl chloride **420** via **418** and from **420** and **422** (route *a*), respectively. Thereby, a general methodology can be used for the preparation of otherwise not readily accessible *C*-glycosyl derivatives of *N*-acetyl-D-glucosamine[308−310] and *N*-acetyl-D-galactosamine[311] of type **426** and **427** (X = AcN for both). Generation of the dianions of *N*-acetyl-D-glycosamines from the corresponding stannane was further optimized by using methyllithium−lithium bromide for the deprotonation and butyllithium for the transmetalation step, thereby almost completely avoiding undesired reduction by a proton transfer to the anomeric anion from incompletely deprotonated amide.[312] The method was applied to assemble intermediates for various glucosamine−amino acid conjugates **431**,[313] **432**,[314] and **433**−**436**[315] shown in Scheme 41, as well as UDP−sugar mimetics as potential glycosyltransferase inhibitors.[315a]

The samarium diiodide-mediated coupling of saccharide derivatives with carbonyl electrophiles was applied in the glycosamine series as well (Scheme 42 and Table 20). Pyridyl sulfones **437** and **441** coupled with several ketones and aldehydes under Barbier conditions to give *C*-disaccharide **438**[316] and the

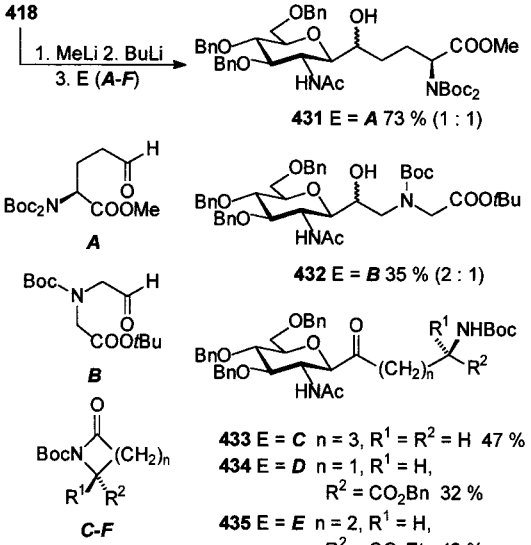
Table 19. Reactions of Glycosyl Dianions Derived from *N*-Acyl-D-glycosamines (see Scheme 39)

starting compound	electrophile (E)	product **426** (X = AcN), R	yield [%] (diast. ratio)	ref
418	MeOD	D	80	308
	PhCHO	CH(OH)Ph	80 (1.4:1)	308
	*i*PrCHO	CH(OH)*i*Pr	76 (1.6:1)	308
	CH_2=CHCHO	CH(OH)CH=CH_2	80 (1.3:1)	308
	MeCHO	CH(OH)Me	80 (1.5:1)	308
	Me_2SO_4	Me	44[a]	308
	CO_2	COOH	83	309
(X = CbzN)	CO_2	COOH	83	310
	*n*PrNCO	CONH*n*Pr	52	309

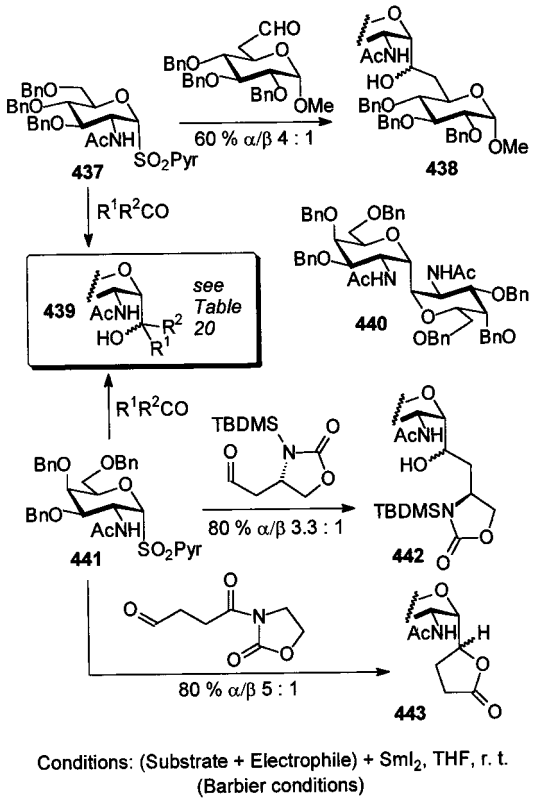
starting compound	electrophile (E)	product **427** (X = AcN), R	yield [%] (diast. ratio)	ref
420	MeOD	D	58	308
	PhCHO	CH(OH)Ph	72 (1.9:1)	308
	*i*PrCHO	CH(OH)*i*Pr	64 (2.2:1)	308
	CH_2=CHCHO	CH(OH)CH=CH_2	54 (2:1)	308
	Me_2SO_4	Me	26[a]	308
	CO_2	COOH	66[b]	315a
422	MeOD	D	75[c]	311
	PhCHO	CH(OH)Ph	72 (1.8:1)	311
	*i*PrCHO	CH(OH)*i*Pr	75 (1.6:1)	311
	CO_2	COOH	86	311
			53[d]	315a

[a] Together with a large amount (unspecified) of **426** (X = AcN, R = H). [b] Yield refers to a reaction sequence starting with benzylated, anomerically unblocked GlcNAc. [c] With 2−3% of **426** (X = AcN, R = H). [d] Yield refers to a reaction sequence starting with benzylated, anomerically unblocked GalNAc.

Scheme 41



Scheme 42

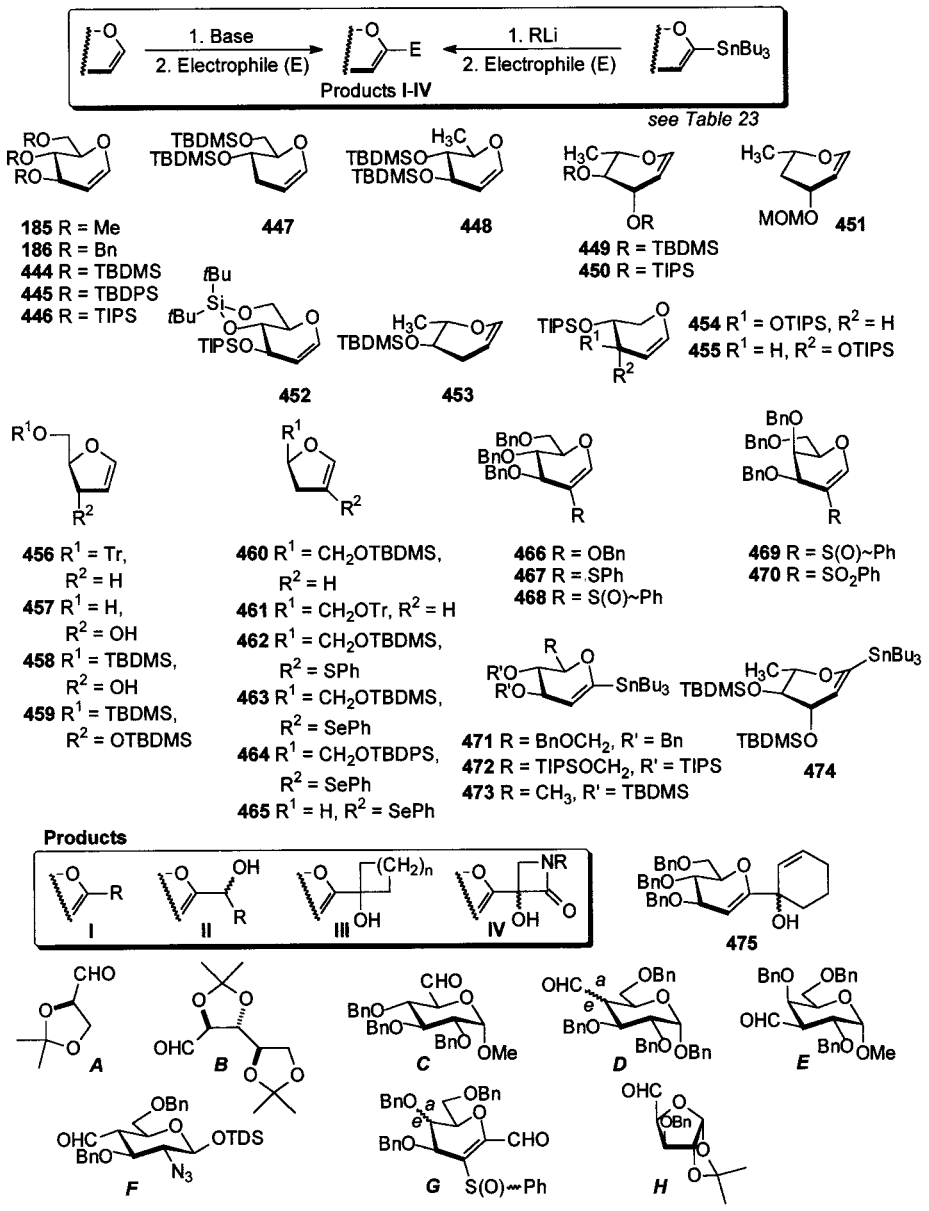


corresponding *C*-glycosyl compounds **439**,[298,316,317] **442**,[318] and **443**,[298,317] respectively. A closer investigation of the reaction of **441** in the presence of cyclohexanone showed the formation of the reductively desulfonylated product (16% not shown) and dimer **440** (9%) besides the anomeric pair of *C*-galactosides **439**. No elimination took place in this reaction to give tri-*O*-benzyl-D-galactal, which was the only product from the 2-azido- and the 2-benzylcarbamoyl derivatives (**441** N_3 or $NHCO_2Bn$ instead of AcNH, respectively). The most remarkable feature of these reactions was the (sometimes high) α-selectivity to give 1,2-cis-configurated products. This was unexpected in light of the exclusive 1,2-trans selectivity observed with 2-*O*-silyl-protected substrates (cf. section IV.C.3) and was explained by a strong chelation between the carbonyl of the 2-AcNH group and the anomeric samarium(III) preventing inversion at that center to the thermodynamically more stable equatorial isomer.[298]

Table 20. Products from *N*-acetyl-D-glycosaminyl−samarium(III) Intermediates (see Scheme 42)

		product **439**		
substrate	electrophile	yield [%] (diast. ratio)	α:β	ref
437	cyclohexanone	77 R^1-R^2 = $-(CH_2)_5-$	3.6:1	316
	3-pentanone	51 $R^1 = R^2$ = ethyl	3.3:1	316
	n-octanal	63 (4.7:1) R^1 = H, R^2 = *n*-heptyl	3.6:1	316
	formylcyclohexane	48 (>10:1) R^1 = H, R^2 = cyclohexyl	3.6:1	316
	5-benzoyloxypentanal	64 (4.3:1) R^1 = H, R^2 = 4-benzoyloxy-butyl	3:1	316
441	cyclohexanone	68 R^1-R^2 = $-(CH_2)_5-$ (see text)	10:1	298,317
	cyclopentanone	60 R^1-R^2 = $-(CH_2)_4-$	5:1	298,317
	formylcyclohexane	67 R^1 = H, R^2 = cyclohexyl	20:1	298,317
	3-pentanone	67 $R^1 = R^2$ = ethyl	10:1	298,317
	2-methylpropanal	72 (5:1) R^1 = H, R^2 = *i*Pr	12:1	298,317
	n-heptanal	69 (6:1) R^1 = H, R^2 = *n*-hexyl	9:1	298,317

Scheme 43



V. Metalation of Glycals and Ensuing Reactions

Though glycals have no real anomeric center, their double bond derived from and convertible back to sp^3 carbons offers many possibilities for various transformations. Therefore, the C-1 carbon can be regarded as a latent anomeric center in these compounds. Formation of anionic species at this position can be effected either by proton removal or transmetalation as outlined in Scheme 43. Methods for the preparation of glycals have been collected in section IV.A, and formation of tributylstannyl derivatives

Table 21. Deprotonation of Glycals as Shown by Deuterium Incorporation (see Scheme 43)

		reaction conditions			D incorporation (%) at site			
entry	substrate	solvent	base (equiv)	temp. or range (°C)	C-1 (**I**, R = D)	ratio of C-1-D/Si-D[a]		ref
1	**444**	THF	*n*BuLi	0 to 25	85[b]			319
2	**444**	THF	1.4 *t*BuLi	−78 to 0	54	2.4:1		320
3		THF	3.5 *t*BuLi	−78 to 0	92	1.2:1		320
4		THF	4.0 *t*BuLi	−78 to 0	>98	1:1.1		320
5		THF	2.7 *t*BuLi	−78 to −20	82	1.2:1		320
6		THF	2.7 *t*BuLi	−78	0			320
7		Et_2O	2.8 *t*BuLi	−78 to 0	86	1.1:1		320
8		Et_2O	3.4 *t*BuLi	−78 to 0	>98	1:1.4		320
9		THF−pentane	2.0 *t*BuLi	−78 to 0	87	1.2:1		320
10		THF−pentane	2.8 *t*BuLi	−78 to 0	>98	1:1.2		320
11	**445**	THF	6.0 *t*BuLi	−78 to 0	quant.			320
12	**446**	THF	6.0 *t*BuLi	−78 to 0	quant.			320
13	**460**	THF−pentane	*t*BuLi	−78 to −20	90			323
14	**466**	THF	*n*BuLi, *t*BuOK	−100	63[b]			324
15	**468**	THF−HMPT	LDA	−100	quant.			325
						6-*O*-TBDMS	4-*O*-TBDMS	
16	**444**	THF	3.2 *t*BuLi	−78 to 0	84	57	6	321
17		THF	4.0 *t*BuLi	−78 to 0	>98	77	11	321
18		THF	8.0 *t*BuLi	−78 to 0	>98	85	25	321
19	**449**	THF	2.2 *t*BuLi	−78 to 0	>98		3	321
20		THF	8.0 *t*BuLi	−78 to 0	>98		11	321

[a] Stands for deprotonated PG. [b] Isolated yield.

Table 22. Preparation of Tributylstannyl Glycals (see Schemes 43 and 44)

entry	substrate (Scheme 43)	reaction conditions + Bu_3SnCl	product **I** (R = $SnBu_3$) (Scheme 43) [%]	ref
1	**186** (not isolated)	*n*BuLi, *t*BuOK, THF, −78 °C	(=**471**) 55 from triacetylglucal **182**	329
2	**446**	*t*BuLi (6 equiv), THF, 0 °C	(=**472**) 71	320
3	**448**	*t*BuLi, THF−pentane, −78 °C	(=**473**) 92	336
4	**449**	*n*BuLi, *t*BuOK	(=**474**) yield unknown	337
5	**451**	*n*BuLi, *t*BuOK	yield unknown	337
6	**452**	*t*BuLi	(=**524**) 80 from triacetylglucal **182**	366
7	**456**	*t*BuLi, THF, −78 °C	(=**502**) 60	144,323
8	**457**	*t*BuLi, THF, −78 to 0 °C	3:1 **I** (=**503**)/furane[a]	144
9	**458**		(=**504**) 63[b] + SiSn	144
10	**459**		only furane[c]	144

[a] 2-Hydroxymethyl-5-tri-*n*-butylstannyl furane. [b] Together with a product stannylated in the protecting group. [c] 2-*tert*-Butyldimethylsilyloxymethyl-5-tri-*n*-butylstannyl furane.

which are substrates for transmetalations will be briefly summarized in the forthcoming section V.B.

A. Deprotonation of Glycals

The C-1 carbon of glycals lends itself for deprotonation because of the enhanced acidity of vinylic positions (cf. Table 1). Methyl- or benzyl-protected compounds **185** and **186** (Scheme 43), however, gave unsatisfactory results in reactions with normal or tertiary butyllithium at or below room temperature.[319] Although with TBDMS protection (**444**) and using normal butyllithium deuterium incorporation was reported to be rather high at C-1[319] (Table 21, entry 1), a large excess of tertiary butyllithium was necessary to completely deprotonate the C-1 position. Unfortunately, this was accompanied by the formation of α-silyl carbanions as a result of deprotonation in the methyl moieties of the protecting groups[320] (entries 2−10). A particular study showed that in addition to the C-1 vinylic position, primarily the 6-*O*-TBDMS and to a much lesser extent the 4-*O*-TBDMS groups were deprotonated while the 3-position resisted parallel deprotonation[321] (entries 16−18). This was explained by chelation of the metal by the ring oxygen and O-6, which then directed the attack of the base to the 6-*O*-TBDMS group.[322] Similar complexation involving the ring oxygen and the secondary O-4 is less favored, and even more unfavorably two secondary oxygens (O-4 and O-3) ought to be chelated for deprotonation in the 3-*O*-TBDMS group. As a confirmation of this with 6-deoxy glycals (e.g., **449**), the appearance of α-silyl carbanions was negligible[321] (entries 19 and 20). With the use of TBDPS (**445**) or especially TIPS (**446**) protection, this problem could be circumvented (entries 11 and 12). In the furanoid derivative **460**, no α-silyl carbanions were observed at a high ratio of deprotonation at C-1[323] (entry 13).

Substituents with an inductive effect in the 2-position of glycals may facilitate deprotonation at C-1. Heteroatoms in that position can also direct the attack of base toward C-1 by complexation. Trials with 2-benzyloxy-D-glucal (**466**) gave an acceptable yield on deuteration (Table 21, entry 14); however, reactions of **466** and the 2-phenylthio derivative **467** with several electrophiles resulted in low yields or conversions[324] (cf. Table 23, entries 9−11 and 25). With the more strongly electron-withdrawing 2-

Table 23. Reactions of C-1 Metalated Glycals with Electrophiles (see Scheme 43)

		reaction conditions		product (yield [%])		
entry	substrate	base	electrophile	**I**	R	ref
1	**444**	*t*BuLi, −78 to 0 °C	MeI	86	Me	319
2	**444**		CH_2=$CHCH_2I$	70	allyl	319
3	**444** or **445**	*t*BuLi, Et_2O, −40 to 0 °C, CuI (cat.)	CH_2=$CHCH_2Br$	75	allyl	331
4	**444**		CO_2	60	COOH	319
5	**444** or **445**	*t*BuLi, THF−hexane, −78 to 0 °C	PhSSPh	19 (+ SPh in a PG)	SPh	333
6	**445**	*t*BuLi, THF−pentane, −78 to 0 °C	$ClCO_2Me$	59	CO_2Me	96
7	**445**	*t*BuLi, THF−pentane, −78 to 0 °C	$ClPO(OEt)_2$	47	$PO(OEt)_2$	96
8	**447**	*t*BuLi, −50 °C	MeI	85	Me	319
9	**466**	*n*BuLi, *t*BuOK, THF, −100 °C	MeI	47	Me	324
10			$ClCO_2Me$	35	CO_2Me	324
11			MeSSMe	49	SMe	324
12	**468** (*R*)	LDA, THF, HMPT, −100 °C	DMF	(=***Ge***) 89	CHO	332
13	**469** (*R*)	LDA, THF, HMPT, −100 °C	DMF	(=***Ga***) 95	CHO	326
14	**469** (*S*)		DMF	(=***Ga***) 98	CHO	326
15	**470**	LDA, THF, HMPT, −100 °C	DMF	(=***Ga***) 94	CHO	326
16	**471**	BuLi, THF, −78 °C	MeI	88	Me	329
17				76		319
18			Me_3SiCl	92	$SiMe_3$	329
19				93		319
20	**472**	BuLi, THF, CuBr, Me_2S, −78 °C	MeI	n.i.[a] changing PG to TBDMS	Me	330
21			CH_2=$CHCH_2I$	n.i.[a]	Allyl	330
22		CH_2Cl_2, r.t.	I_2	81−85 from **446**	I (**535**)	334,335
23	**473**	CH_2Cl_2, r.t.	I_2	96	I (**534**)	336
			RCHO	**II** (diast. r.)	R	
24	**444**	*t*BuLi, −50 °C	MeCHO	96 (1:1)	Me	337
25	**467**	LDA, THF, HMPT, −100 °C	EtCHO	90 (1:1) and 50% recovery of **467** for each	Et	324
			PhCHO			
			B			
					Ph from ***B***	
26	**468**		EtCHO	90 (2:1 or 2:5)	Et	325
27			PhCHO	86 (4:1)	Ph	325
28			***B***	85 (4:1) or 65 (5:2)	from ***B***	325
29			***De***	74 (10:1)	from ***De***	341
30			***Da***	74 (10:1)	from ***Da***	341
31	**468** (*R*)		***Ge*** (*R*)	72	from ***Ge***	332
32	**469**	LDA, THF, HMPT, −100 °C	$OHCCH(OEt)_2$	76 (1:1) 60 (1:2)	$CH(OEt)_2$	338
33	**469** (*S*)		***E***	59 (one isomer)	from ***E***	342
34	**469** (*S*)		***F***	81 (1:2)	from ***F***	343
35	**469** (*R*)		***De***	90 (1:1)	from ***De***	344
36	**469** (*R*,*S*)		***Ga*** (*R*,*S*)	89 (*R*,*R*) 74 (*S*,*S*)	from ***Ga***	326
37	**471**	BuLi, THF, −78 °C	PhCHO	95 (n.i.[a])	Ph	329
38				89 (n.i.[a])		319
39			$nC_5H_{11}CHO$	62 (n.i.[a])	nC_5H_{11}	319
40			Me_2CHCHO	93 (n.i.[a])	Me_2CH	319
41			***A***	49 (1:1)	from ***A***	319
42			***C***	50 (1:1)	from ***C***	329
43			***C***	50 (1:1)	from ***C***	329
44	**472**		***H***	31 (2:1)	from ***H***	345,346
				III	n	
45	**446**	*t*BuLi, THF-pentane, −78 to 0 °C	cyclobutanone	81	1	339
46			cyclopentanone	94	2	339
47	**448**		cyclobutanone	77	1	339
48			cyclopentanone	83	2	339
49	**450**		cyclobutanone	70	1	339

Table 23 (Continued)

		reaction conditions		product (yield [%])		
entry	substrate	base	electrophile	**III**	n	ref
50			cyclopentanone	n.i.[a]	2	339
51	**453**		cyclobutanone	65	1	339
52			cyclopentanone	72	2	339
53	**454**		cyclobutanone	87	1	339
54			cyclopentanone	85	2	339
55	**455**		cyclobutanone	n.i.[a]	1	339
56			cyclopentanone	n.i.[a]	2	339
57	**471**	BuLi, THF, −78 °C	cyclohex-2-enone	**475** 77		319
58	**472**	*t*BuLi	cyclopentanone	n.i.[a]	2	340
59	**474**	*t*BuLi	cyclopentanone	n.i.[a]	2	340
				IV (diast. r.)	R	
60	**460**	*t*BuLi, THF-pentane, −78 → 10 °C	*N*-alkyl-azetidin-2,3-dione + $BF_3.OEt_2$	64 (1:1)	Bn	323
61	**461**			58 (n.i.[a])	Bn	323
62	**462**			32 (n.i.[a])	Bn	323
63	**463**			42 (n.i.[a])	Bn	323
64	**464**			79 (n.i.[a])	PMB	323
65	**465**			41 (n.i.[a])	Bn	323

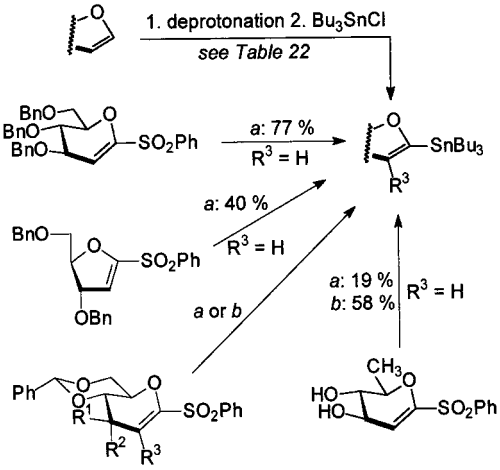
[a] Not indicated.

phenylsulfinyl group in **468**, deprotonation was quantitative[325] (Table 21, entry 15), and the 2-phenylsulfonyl rest in **470**[326] also proved to be very efficient[326] (cf. Table 23, entry 15).

B. 1-Tributylstannyl Glycals

The 1-tributylstannyl glycals (Scheme 44) are versatile substrates for carbanionic transformations.

Scheme 44



Reactions of C-1-lithiated glycals with tributyltin chloride give these compounds generally in good yields (Table 22, entries 1−6). The reaction is also effective in the furanoid series (entry 7) provided there is no leaving group in the 3-position (entry 10), because this readily eliminates to give a stannyl furane derivative. This elimination can be avoided or diminished in 3-*O*-unprotected glycals (entries 8 and 9) which produce multiple *O*,*C*-anions and hence poor nucleofuges in the 3-position.[144] 1-Tributylstannyl glycals can be very efficiently produced from easily accessible 1-phenylsulfonyl glycals (cf. section III.F.1) with tributyltin hydride by a radical-mediated substitution[141,144,319,327,328] (Scheme 44).

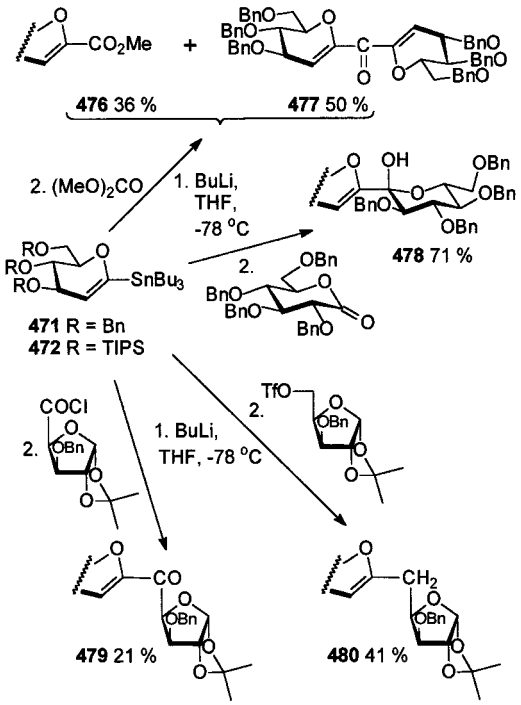
C. Reactions of C-1 Metalated Glycals with Electrophiles

Both deprotonation of glycals and transmetalation of their 1-tributylstannyl derivatives were used to generate carbanionic reagents for coupling with various electrophilic partners (Scheme 43, Table 23). The obtained compounds comprise stuctural motifs of *C*-glycosyl methanes[319,324,329,330] (entries 1, 8, 9, 16, 17, and 20), 3-(*C*-glycosyl)-propenes[319,330,331] (entries 2, 3, and 21), *C*-glycosyl aldehydes[326,332] (entries 12−15), *C*-glycosyl carboxylates[96,319,324] (entries 4, 6, 10, and **476**[319] see Scheme 45), glycosyl silanes[319,329] (entries 18 and 19), thioglycosides[324,333] (entries 5 and 11), glycosyl phosphonic acids[96] (entry 7), iodoglycals[334−336] (entries 22 and 23), *C*-glycosyl alcohols[319,323−325,329,337−340] (entries 24−28, 32, 37−41, and 45−65), and *C*-disaccharides[319,326,329,332,341−346] (entries 29−31, 33−36, 42−44, and **477**,[319] **478**,[347] **479**, **480**[345−347] shown in Scheme 45).

Several combinations of the above reaction conditions and compounds were applied in natural product syntheses. A stannyl glycal was alkylated with an alkyl bromide derivative in a synthesis of calcimycin.[348] Coupling of lithiated **474** with a bicyclic ketone in the presence of cerium(III) chloride was used in a synthesis of the forskolin nucleus.[337] An in situ prepared stannyl glycal was coupled with a γ-lactone in the total synthesis of okadaic acid.[70] An iodo-glycal obtained from a stannyl derivative with *N*-iodosuccinimide and converted to a Grignard compound after lithiation was the intermediate of a key coupling in the synthesis of altohyrtin A.[349]

An extensive study was carried out on the reactions of lithiated glycals and quinones (Scheme 46) in

Scheme 45



connection with the synthesis of *C*-aryl glycosides as constituents of natural products.[350] Thus, glycals **449**,[351−353] **459**, and **487**[354] were reacted with quinones ***A***−***E*** to give good yields of the corresponding coupled products **481** and type **483**−**485**, which were then aromatized. Both carbonyl groups of ***B***−***E*** could be used in the nucleophilic additions to afford dicoupled products **489**−**494**, and protection of the hydroxyl in the intermediate (e.g., **484** → **486**) allowed two different sugar parts to be introduced into the products (**495**, **496**).[353] With specific quinone derivatives the *C*-aryl glycoside nuclei of papulacandin and chaetiacandin antibiotics were synthesized.[355]

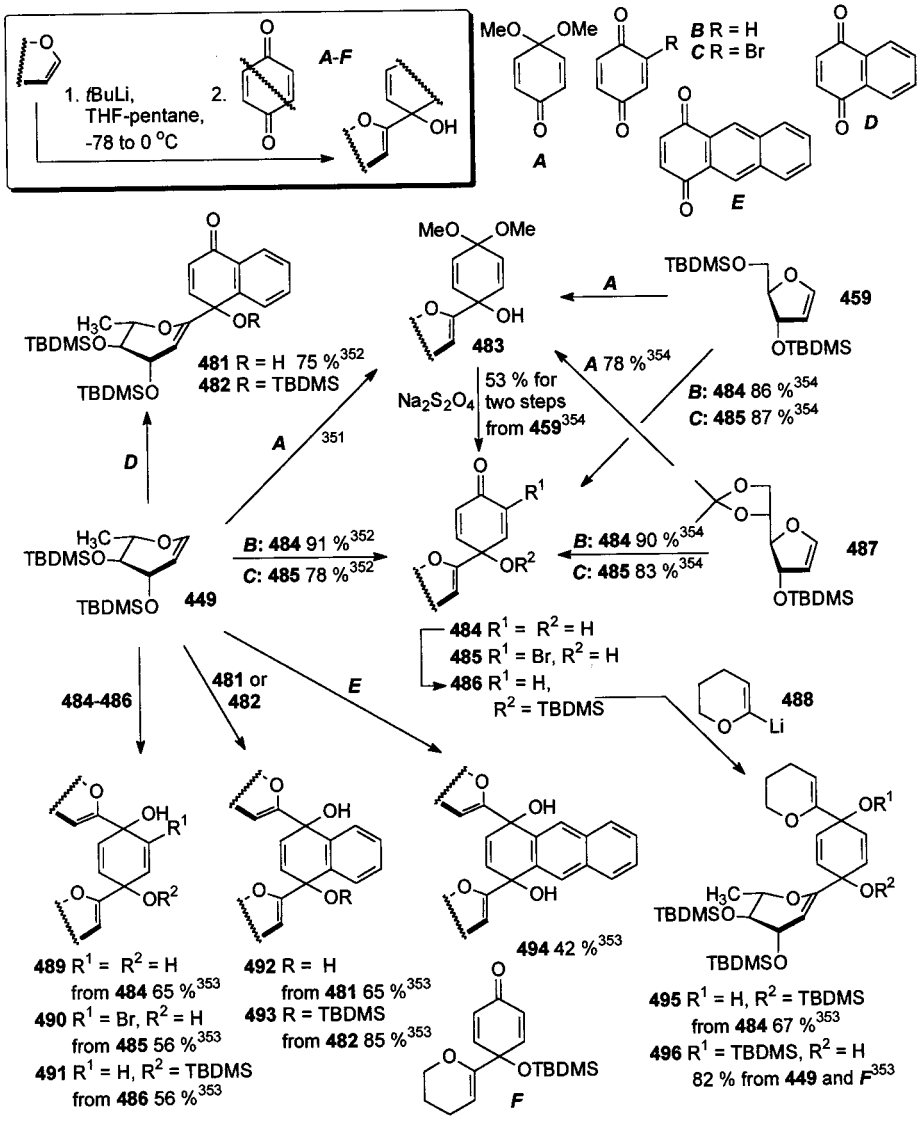
Fischer carbene complexes were prepared from lithiated glycals with transition-metal carbonyls[356,357,357a] as illustrated in Scheme 47.

D. Palladium-Catalyzed C–C Couplings with Glycal Derivatives

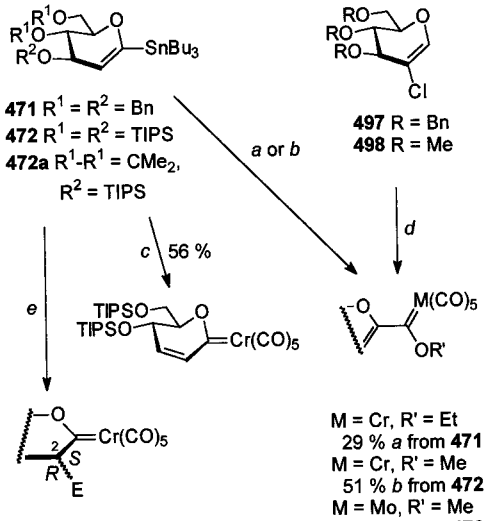
1. With Metalated Glycals

The well-known Stille coupling[357b,c] (for a general presentation see Scheme 48, **B**) and its modifications

Scheme 46



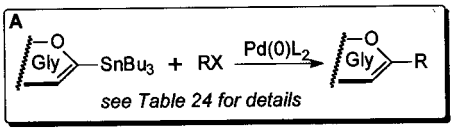
Scheme 47

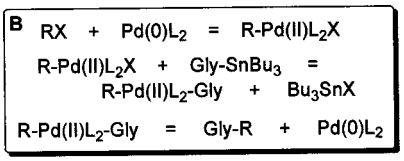


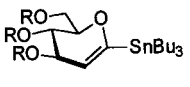
Conditions:
a: 1. BuLi, THF, -78 °C 2. $[Cr(CO)_6]$, -78 °C 3. Et_3OBF_4
b: 1. BuLi, THF-hexane, -78 °C 2. $[M(CO)_6]$, -78 °C 3. Me_3OBF_4
c: 1. BuLi, THF-hexane, -78 °C 2. $[Cr(CO)_5PPh_3]$ or $[Cr(CO)_5THF]$, -78 °C
d: 1. *s*BuLi, THF, -78 °C 2. $[Cr(CO)_6]$, -78 °C 3. Et_3OBF_4
e: 1. BuLi, THF, -78 °C 2. $[Cr(CO)_5THF]$, -78 to 0 °C 3. EX, -78 °C to r. t.

EX	2-*R*/*S*	Yield
	from **472**	
HCl	--	70 %
CF_3CO_2D	<5 : 95	64 %
$CH_2{=}CHCH_2I$	6 : 94	74 %
	from **472a**	
HCl	--	71 %
CF_3CO_2D	58 : 42	50 %
$CH_2{=}CHCH_2I$	only *S*	59 %

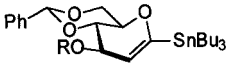
Scheme 48



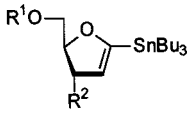




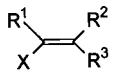
471 R = Bn
472 R = TIPS
499 R = TBDMS



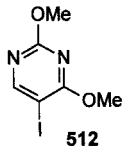
500 R = Bn
501 R = TBDMS



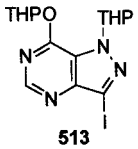
502 R^1 = Tr, R^2 = H
503 R^1 = H, R^2 = OH
504 R^1 = TBDMS, R^2 = H
505 R^1 = Bn, R^2 = OBn



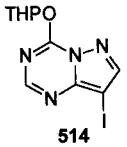
506 R^1 = Ph, R^2 = R^3 = H, X = Br
507 R^1 = R^3 = H, R^2 = Ph, X = Br
508 R^1 = Me, R^2 = H, R^3 = COOMe, X = I
509 R^1 = R^2 = H, R^3 = COOMe, X = I
510 R^1 = R^3 = H, R^2 = *n*-Bu, X = I
511 R^1 = H, R^2 = Ph, R^3 = Me, X = I



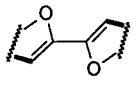
512



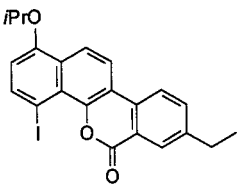
513



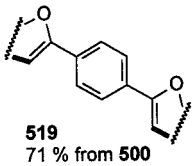
514



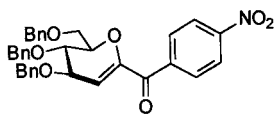
516



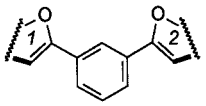
515



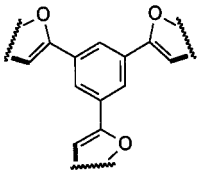
519
71 % from **500**



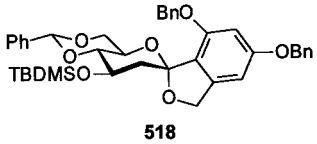
517



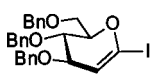
520 85 % *1* and *2* from **501**
521 79 % *1* from **501**, *2* from **500**



522 59 % from **500**



518



523

Table 24. Palladium(0)-Catalyzed Couplings of 1-Tributylstannyl Glycals (see Scheme 48)

		reaction conditions			product		
entry	substrate	catalyst	solvent reflux temp.	RX	Gly-R	dimer **516**	ref
1	**471**	$Pd(PPh_3)_4$	PhMe	PhBr	88		327,358
2		$Pd(CH_3CN)_2Cl_2$	DMF, r.t.	PhBr	48	39	327
3		$Pd(CH_3CN)_2Cl_2$	DMF, 60 °C	none		85	327
4		$Pd(PPh_3)_4$		$4\text{-}MeOC_6H_4Br$	33[a]		327
5		$Pd(PPh_3)_4$		$2,4\text{-}(BnO)_2\text{-}6\text{-}HOCH_2C_6H_2Br$	70		327
6		$Pd(PPh_3)_4$		$PhCH_2Br$	74		327,358
7		$Pd(dba)_2$		$CH_2{=}CHCH_2Br$	74		327,358
8		$Pd(CH_3CN)_2Cl_2$	$ClCH_2CH_2Cl$ r.t.	$4\text{-}NO_2C_6H_4COCl$	**517**, 70	*b*	327,358
9		$Pd(CH_3CN)_2Cl_2$	DMF	$IC{\equiv}CCH_2OH$	**523**, 75		327,358
10		$Pd(CH_3CN)_2Cl_2$	DMF, r.t.	$CH_2{=}CHBr$	33		327
11		$Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N	CH_3CN, 80 °C	**506**	10	*c*	360
12		$Pd(OAc)_2$, P(TFP)$_3$, Et_3N	CH_3CN, 80 °C		12	*c*	360
13		$Pd(OAc)_2$, $AsPh_3$, Et_3N	CH_3CN, 80 °C		28	*c*	360
14		$Pd_2(dba)_3$, CuI, $AsPh_3$	50 °C		30	*c*	360
15		$Pd(CH_3CN)_2Cl_2$	DMF, 20 °C		46	traces	360
16		$Pd(CH_3CN)_2Cl_2$	DMF, 20 °C	**507**	48	traces	360
17				**508**	67	traces	360
18				**509**	50	traces	360
19				**510**	46	traces	360
20				**511**	65	traces	360
21	**472**	$Pd(PPh_3)_4$	mesitylene	$4\text{-}CNC_6H_4Br$	66	n.m.[d]	335
22	**499**	$Pd(PPh_3)_4$	PhH	PhBr	50	n.m.[d]	335,359
23		$Pd(PPh_3)_2Cl_2$	PhH	PhBr	52	n.m.[d]	335,359
24		$Pd(PPh_3)_4$	DMF, 100 °C	PhBr	34	n.m.[d]	335,359
25		$Pd(PPh_3)_4$	THF	PhBr	70	n.m.[d]	335,359
26		$Pd(PPh_3)_2Cl_2$	PhMe	PhBr	41	12	335,359
27				$4\text{-}NO_2C_6H_4Br$	78	4	335,359
28				$4\text{-}CNC_6H_4Br$	81	8	335,359
29			100 °C	1-bromonaphthalene	59	15	335,359
30				$4\text{-}MeO_2CC_6H_4Br$	56	8	335,359
31				$4\text{-}ClC_6H_4Br$	49	8	335,359
32				$2\text{-}MeC_6H_4Br$	49	11	335,359
33				$2\text{-}AcOCH_2C_6H_4Br$	46	15	335,359
34				$2\text{-}AcOC_6H_4Br$	40	11	335,359
35				$2\text{-}BnOC_6H_4Br$	44	4	335,359
36			100 °C	$4\text{-}MeOC_6H_4Br$	30	13	335,359
37			100 °C	$2,5\text{-}(MeO)_2C_6H_3Br$	65	9	335,359
38		$Pd(PPh_3)_2Cl_2$	mesitylene	$2,4\text{-}(BnO)_2\text{-}6\text{-}AcOCH_2C_6H_2Br$	51	n.m.[d]	335
39		$Pd(PPh_3)_2Cl_2$	PhMe	$2,4\text{-}(BnO)_2\text{-}6\text{-}AcOCH_2C_6H_2Br$	49	20	362
40			PhH		85	n.m.[d]	335
41			PhMe		56	13	335
42		$Pd(PPh_3)_2Cl_2$	mesitylene	$2,4\text{-}(BnO)_2\text{-}6\text{-}TBDMSOCH_2C_6H_2Br$	66	n.m.[d]	335
43	**500**	$Pd(PPh_3)_4$	PhMe	$2\text{-}HOCH_2C_6H_4Br$	75		327,358
44				$2,4\text{-}(BnO)_2\text{-}6\text{-}HOCH_2C_6H_2Br$	73		327,358
45				$2,4\text{-}(BnO)_2\text{-}6\text{-}HOCH_2C_6H_2Br$	71	15	361
46	**501**	$Pd(PPh_3)_4$	PhMe	$2,4\text{-}(BnO)_2\text{-}6\text{-}HOCH_2C_6H_2Br$	**518**, 72	10	141
					518, 71	15	361
47				$2\text{-}HOCH_2C_6H_4Br$	73	20	361
48		$Pd(PPh_3)_4$, 7 equiv of Na_2CO_3	PhMe	$2,4\text{-}(BnO)_2\text{-}6\text{-}HOCH_2C_6H_2Br$	78	18	141,361
49				$2\text{-}HOCH_2C_6H_4Br$	76	20	361
50		$Pd(PPh_3)_4$	PhMe	$3\text{-}BrC_6H_4Br$	83		327,358
51	**502**	$Pd(OAc)_2$, $AsPh_3$	$CH_3CN{-}THF$, 40 °C	$4\text{-}MeOC_6H_4I$	59		144
52				**515**	78		144
53				**512**	66		144
54			$CH_3CN{-}THF$, 25 °C	**513**	82		144
55	**503**		CH_3CN, 40 °C	**512**	54		144
56	**504**		$CH_3CN{-}THF$, 40 °C	**514**	81		144
57	**505**		CH_3CN, 60 °C	**512**	88		144

[a] Accompanied by 37% of *C*-phenylglucal as in entry 2. [b] Formed in unknown yield. [c] Variable amounts of dimer **516** and glucal **186**. [d] Not measured.

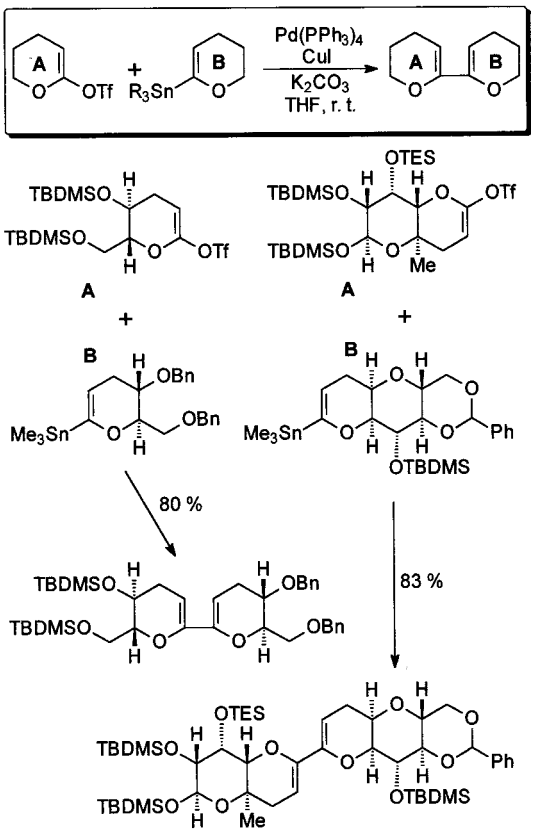
have been widely used for the preparation of intermediates, e.g., in syntheses of *C*-aryl-glycosides. Most frequently 1-tributylstannyl glycals were used as starting materials (Scheme 48, **A**).

A rich palette of palladium complexes were examined, and the best results (Table 24) were obtained with $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and $Pd(CH_3CN)_2Cl_2$.[327,335,358,359] Formation of dimers **516** was a side reaction in most cases when silylated glycals **472**, **499**, and **501** were applied (Table 24, entries 21−42 and 46−50); however, with the benzylated **471**, this could be avoided[327] (entries 1 and 4−6). On the other hand, without any coupling reagent dimer formation was the main process (entry 3). Compounds other

than aromatic halides were also applicable[327,358,360] (entries 6−8 and 10−20). The use of aromatic di- and tribromides allowed bis- and tris-*C*-glycosyl arenes **519**, **520**, and **522**, respectively, to be prepared, and it was demonstrated that different sugar units can also be introduced as in **521**.[327] *C*-Aryl glycosides related to papulacandins[141,335,361,362] (entries 5, 38, 39, 44−46, and 48), and those starting with furanoid derivatives[144] **502**−**505** (entries 51−57) were synthesized. $Pd(PPh_3)_4$-catalyzed coupling of tributylstannyl derivatives of 4,5-glycals and alkynyl bromides were applied in the total synthesis of 3-hydroxyleukotriene derivatives.[363] Failure of coupling was reported under a variety of conditions between **472** and 8-bromokalafungin, a polycyclic aromatic bromide possessing a quinone subunit.[364]

An expeditious method was developed for the cross-coupling of two different glycal units in relation to the synthesis of polyether marine natural products. Enol-triflate **A** and stannyl glycal **B** react very efficiently in the presence of palladium(0) and copper(I) to give the connected products **A**−**B** as illustrated in Scheme 49 and by five other, more complex

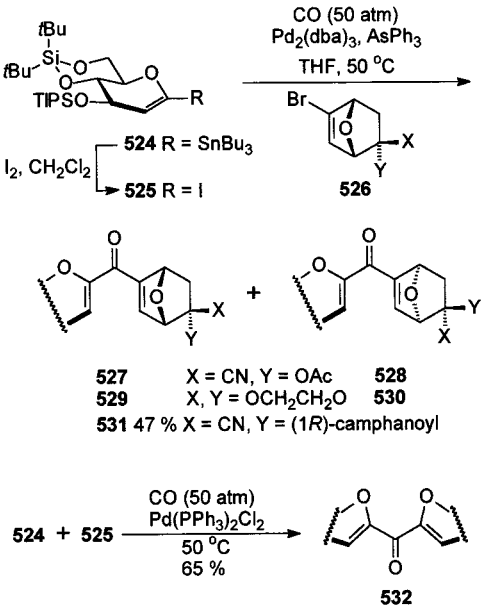
Scheme 49



examples (not shown) prepared in 70−81% yields.[365]

Under a high-pressure carbon monoxide atmosphere, a carbonylative Stille coupling could be carried out with stannyl glycal **524** to give precursors of *C*-disaccharides (Scheme 50). In the presence of specifically devised vinyl bromides **526**, diastereomeric mixtures of **527** and **528** as well as **529** and **530** were obtained in 30−55% yields. With the enantiomerically pure (1*R*)-camphanoyl derivative of **526**, ketone **531** was the isolated product. Coupling

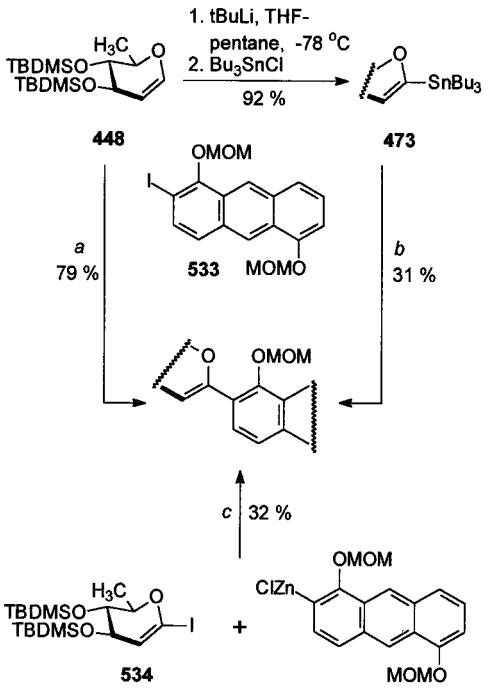
Scheme 50



of **524** with in situ generated iodoglycal **525** gave bis-*C*-glycosyl ketone **532**.[366]

In the total synthesis of vineomycinone B2 methyl ester, the coupling of glycal **448** with iodoanthracene **533** was best carried out from a zinc derivative obtained by a standard transmetalation protocol, because the corresponding stannyl glycal **473** gave only a low yield of the expected product[336,367] (Scheme 51).

Scheme 51

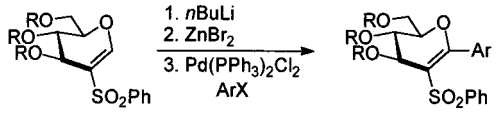


a: 1. *t*BuLi, THF-pentane, 0 °C 2. $ZnCl_2$
3. $Pd(PPh_3)_2Cl_2$ + DIBAL, THF, r. t., **533**
b: $Pd(CH_3CN)_2Cl_2$, **533**, DMF 80 °C
c: $Ni(dppp)Cl_2$, Et_2O, THF, r. t.

Transmetalation to the zinc compound of 1-lithio-2-phenylsulfonyl glycals followed by palladium-

catalyzed coupling with various aryl halides also gave good yields of the corresponding aryl glycals[368] as shown in Scheme 52.

Scheme 52



R = Me, ArX = 4-MeC_6H_4I	74 %
R = Me, ArX = 4-CNC_6H_4Br	85 %
R = Me, ArX = PyrBr	72 %
R = Bn, ArX = 4-MeC_6H_4I	70 %
R = Bn, ArX = 4-CNC_6H_4Br	80 %
R = Bn, ArX = PyrBr	73 %

2. With Iodo-glycals

In the Stille coupling of 1-tributylstannyl glycals (cf. Scheme 48) the yields were not completely satisfactory in several cases (cf. Table 24). As a possible cause of this, the slow transmetalation step to provide the Pd(II) species was reasoned that could be even more retarded by the bulky stannyl glycal.[334] Therefore, the polarity of the reaction was reversed by applying a sugar halide (**535**, Table 25) to participate in the rapid oxidative addition step followed by a slower reaction with a metalated aromatic partner.[335] This modification afforded generally better yields for the coupled products, and the best results were obtained with boronic acids (entries 4, 5, 7, 8, and 11−13) and arylzinc chlorides (entries 6, 9, 10, and 14). Vinyl glycals were also prepared in this way (entries 15 and 16). Contrary to these favorable experiences, coupling of iodoglycal **534** with a zincated anthracene derivative in the synthesis of vienomycinone B2 methyl ester (outlined in Scheme 51) gave no product with palladium catalysis while a nickel complex gave only a moderate yield of the desired compound. A further example for in situ generation and subsequent carbonylative coupling of an iodoglycal is shown in Scheme 50.

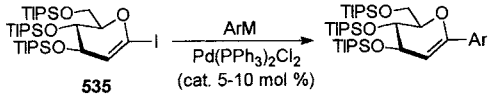
VI. Concluding Remarks

Changing the "natural" electrophilic character to nucleophilic at the anomeric carbon of carbohydrates has proven a valuable tool in synthetic carbohydrate and natural product chemistry and made possible the synthesis of structures otherwise difficult to obtain. The use of anomeric carbanionoid intermediates for umpolung of this most important reaction center assumed great importance during the last two decades. The enormous increase of activity in this field can be illustrated by the number of cited papers in three book chapters discussing the present topic published in 1995 (34[16] and 41[17] relevant citations) and 1997 (78 relevant citations).[18] The literature search for this article was ended at the end of 1999; however, some papers available from December to mid-July 2000 have been included.

Classical carbanionic routes involving strongly basic conditions have been widely applicable with base-stable protecting groups and led to highly stereoselective transformations among carbohydrates. However, the most recent trend seems to be an intensive search for more selective reagents with tunable reactivity as well as for milder and possibly neutral conditions which would also allow complicated experimental techniques to be avoided. Catalytic protocols[369] can be expected to bring new developments in enhancing the selectivity and mildness of the transformations.

Powerful new synthetic methodologies that utilize anomeric anions have paved the way for the synthesis of many biologically active compounds and natural products (e.g., inhibitors of glycoprocessing enzymes, antibiotics, antitumor and antiviral agents). Several new procedures have been elaborated for the preparation of glycals which have also expanded the scope of C-1-substituted 1,2-unsaturated glycosyl compounds. Application of these protocols resulted in the synthesis of a wealth of *C*-glycosyl derivatives and several *C*-disaccharides. The needs of glycobiologists will probably stimulate the synthesis of *C*-oligosaccharides soon. Finally, it could be pointed out that *C*-glycosyl compounds and glycals, readily available from carbohydrate precursors, are a rich source of chiral, nonracemic cyclic ethers, which are abundant in nature. They are also superb chirons[370] for general

Table 25. Palladium-Catalyzed Coupling of Iodoglucal 535 with Metalated Aromatics[334,335]



535

entry	ArM (equiv)	solvent	temp.	yield [%]
1	PhLi (4)	THF	r.t.	no reaction
2	$PhSnBu_3$ (4)	THF	reflux	20
3	PhMgBr (4)	PhMe	reflux	25
4	$PhB(OH)_2$ (4)	THF−aq Na_2CO_3	70 °C	81
5	$PhB(OMe)_2$ (4)	THF−aq Na_2CO_3	r.t.	90
6	PhZnCl (4)	THF	r.t.	90
7	4-$CNC_6H_4B(OMe)_2$ (2)	THF−aq Na_2CO_3	70 °C	90
8	4-$MeOC_6H_4B(OH)_2$ (2)	THF−aq Na_2CO_3	75 °C	81
9	4-$MeOC_6H_4ZnCl$ (4)	THF	r.t.	73
10	2-furylZnCl (4)	THF	r.t.	79
11	2-furyl$B(OMe)_2$ (2)	THF−aq Na_2CO_3	60 °C	78
12	2,5-$Cl_2C_6H_3B(OH)_2$ (2)	THF−aq Na_2CO_3	75 °C	79
13	1-naphthyl$B(OH)_2$ (2)	THF−aq Na_2CO_3	75 °C	75
14	2-MeC_6H_4ZnCl (4)	THF	r.t.	68
15	CH_2=CH$B(OMe)_2$ (4)	THF−aq Na_2CO_3	65 °C	75
16	$(CH_2$=CH$)_4Sn$ (2)	THF	reflux	67

use in a variety of syntheses of biologically relevant natural and unnatural compounds.

VII. Acknowledgment

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VIII. Abbreviations

Ac	acetyl
AIBN	azo-bis-isobutyronitrile
An	anisyl (4-methoxyphenyl)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
DAHP	3-deoxy-D-*arabino*-hept-2-ulopyranosonic acid 7-phosphate
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DHA	3-deoxy-D-*lyxo*-hept-2-ulosaric acid
DIBAL	diisobutylaluminum hydride
DIPS	diisopropylsulfide
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
dmg	dimethylglyoxime
DMSO	dimethyl sulfoxide
dppf	diphenylphosphinoferrocene
dppp	1,3-bis-diphenylphosphinopropane
EDTA	ethylenediamine tetraacetic acid
HMPT	hexamethylphosphoric acid triamide
Imid	imidazol-1-yl
KDN	3-deoxy-D-*glycero*-D-*galacto*-non-2-ulopyranosonic acid
KDO	3-deoxy-D-*manno*-oct-2-ulopyranosonic acid
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride (lithium tetrahydrido aluminat)
LDA	lithium diisopropylamide
LDMAN	lithium 1-(dimethylamino)naphthalenide
LHMDS	lithium hexamethyldisilazide
LiDBB	lithium 4,4′-di-*tert*-butylbiphenyl
LN	lithium naphthalenide
MEM	methoxyethoxymethyl
MIM	1-methylimidazole
MOM	methoxymethyl
Ms	mesyl (methanesulfonyl)
Neu5Ac	*N*-acetylneuraminic acid
PG	protecting group
Piv	pivaloyl (2,2-dimethylpropanoyl)
PMB	*p*-methoxybenzyl
Py	pyridine
Pyr	2-pyridyl
TBAF	tetrabutylammoniumfluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TDS	thexyldimethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
TPS	triphenylsilyl
Tr	trityl (triphenylmethyl)
Ts	tosyl (4-methylbenzenesulfonyl)

IX. Note Added in Proof

A catalytic cycle was developed and applied to the synthesis of glycals from glycosyl bromides and a chloride using Cp_2TiCl_2 and manganese (Hansen, T.; Daasbjerg, K.; Skrydstrup, T. *Tetrahedron Lett.* **2000**, *41*, 8645−8649).

An alternative to the mechanism shown in Scheme 21 for the formation of glycals under electrochemical conditions was proposed (Alberti, A.; Della Bona, M. A.; Macciantelli, D.; Pelizzoni, F.; Sello, G.; Torri, G.; Vismara, E. *Tetrahedron* **1996**, *42*, 10241−10248).

Radical routes to glucals from 2-bromo-2-deoxy-1-*O*-phenoxythiocarbonyl D-glucose and 2-bromo-2-deoxy-D-glucopyranosyl bromides were described (Lin, T.-S.; Yang, J.-H.; Liu, M.-C.; Zhu, J.-L. *Tetrahedron Lett.* **1990**, *31*, 3829−3832).

The olefin metathesis route was extended to prepare *C*-disaccharide glycals (Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061−6068).

The Ramberg−Bäcklund approach to *exo*-glycals was used for the synthesis of active antiproliferative *C*-glycolipids (Yang, G.; Franck, R. W.; Byun, H.-S.; Bittman, R.; Samadder, P.; Arthur, G. *Org. Lett.* **1999**, 2149−2151).

Selected examples/leading references for other methods of *exo*-glycal formation are as follows: (a) olefination of sugar lactones with Tebbe's reagent (Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett.* **1984**, *25*, 395−398; RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458−5461); (b) by dimethyltitanocene (Johnson, C. R.; Johns, B. A. *Synlett* **1997**, 1406−1408); or (c) by the Wittig methodology (Lakhrissi, Y.; Taillefumier, C.; Lakhrissi, M.; Chapleur, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 417−421 and references therein); (d) oxidation of *C*-glycosyl phenylselenyl methane followed by elimination (Lancelin, J.-M.; Pougny, J.-R.; Sinaÿ, P. *Carbohydr. Res.* **1985**, *136*, 369−374); (e) elimination from *C*-glycosyl iodomethanes (Brockhaus, M.; Lehmann, J. *Carbohydr. Res.* **1977**, *53*, 21−31. Martin, O. R.; Xie, F. *Carbohydr. Res.* **1994**, *264*, 141−146; Tatibouët, A.; Rollin, P.; Martin, O. R. *J. Carbohydr. Chem.* **2000**, *19*, 641−645). A very recent method for *exo*-glycal synthesis is based on insertion into the C-1−H bond of a carbene generated from *C*-glycosyl aldehyde tosylhydrazones (Tóth, M.; Somsák, L. *XXth Int. Carbohydr. Symp.*, Hamburg, Germany, 2000; B364, Book of Abstracts p 240).

A glucopyranosylidene carbene was inserted into the carbon−metal bond of AlR_3 (R = Me, *i*Bu) compounds to give glycosylalanes, which after hydrolysis gave mixtures of α-D-glucopyranosyl alkanes (α-D-Glcp−R) and C-1−R substituted glucals (Wenger, W.; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 1542−1560).

Reductive samariation of glycosyl iodides led to 1,2-*trans*-*C*-glycosyl compounds (Miquel, N.; Doisneau, G.; Beau, J.-M. *Chem. Commun.* **2000**, 2347−2348), and the efficiency of SmI_2-mediated *C*-glycosylation with glycosyl 2-pyridyl sulfones was enhanced by using catalytic NiI_2 to give 1,2-*trans*-diequatorial *C*-glycosyl compounds (Miquel, N.; Doisneau, G.; Beau, J.-M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*,

4111−4114). The samariation methodology was used for the synthesis of a KDO *C*-disaccharide (Koketsu, M.; Kuberan, B.; Linhardt, R. J. *Org. Lett.* **2000**, *2*, 3361−3363) and a branched *C*-trisaccharide related to α-D-Man-(1→3)-[α-D-Man-(1→6)]-D-Man to be found in the core region of asparagine-linked oligosaccharides (Mikkelsen, L. M.; Krintel, S. L.; Jiménez-Barbero, J.; Skrydstrup, T. *Chem. Commun.* **2000**, 2319−2320).

X. References

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