New reactions and intermediates involving the anomeric center

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<u>Abstract</u> - The chemistry of new carbohydrate derivatives, involving the anomeric center and leading to glycosyl carbanions, radicals, radical anions, oxonium ions and to glycosylidene carbenes is presented.
Derivatives generated on the way to 1-nitroaldoses involve hydroximolactones, halonitroso ethers and halonitro ethers. Hydroximolactones form spiro-isoxazolidines and some of their carbamates are enzyme inhibitors. Halonitroso ethers are reactive and diastereoselective dienophiles. Halonitro ethers form C,C bonds via radical anions. Nitroaldose-derived carbanions undergo 1,2- and 1,4-additions. In the products, the nitro group can be replaced by HO, RO, H, nucleobases and alkyl groups. Nitroaldoses form 1-nitroglycals. 1,4-addition of O-, N- and C-nucleophiles to 1-nitroglycals generate C(2) substituted carbanions which may react, inter- or intramolecularly, to chain-elongated or annelated products.
The newly prepared alkoxydiaziridines (1-hydraziglycoses) rearrange to glyconolactone hydrazones and are oxidized to 1-aziglycoses, which react via glycosylidene carbenes. O-Benzylated 1-aziglycoses react preferentially with acidic hydroxy compounds to yield glycosides in a reaction which appears insensitive to steric hindrance and which allows regioselective glycosidations. Proton transfer to glycosylidene carbenes is evidenced by the formation of C-aryl glycosides as byproducts, of orthoesters from O-acylated and of oxazolidines from 2-acetamido derivatives. 1,2-*trans* O-arylglycosides are the main products from phenols. Participation of a C(2)-benzyloxy group is postulated and evidenced by the glycosidation of 1-azi-1,2-dideoxyglycoses. Spiro-cyclopropanes are formed from O-alkylated and from O-acylated 1-aziglycoses. Reaction with Ph₂PH yields glycosylphosphines and, hence, phosphine oxides.

INTRODUCTION

The concepts of transition states and of reactive intermediates form the most comprehensive basis for classifying and rationalizing chemical reactions; the concept of reactive intermediates is also at the root of a powerful heuristic principle for the invention of new synthetic reactions.
The chemistry of carbohydrates - enantiomerically pure, polyfunctional compounds of a very diverse degree of complexity, and partners in the primary and secondary metabolism - still requires synthetic methods to increase the versatility of carbohydrates as "chirons", to use the gradually changing properties of their isomers in the study of reaction mechanisms, and to synthesize products for solving biochemical problems. The invention of such methods may be based upon the design of appropriate carbohydrate derivatives for the generation of reactive intermediates such as carbocations, carbanions, radical anions, radical cations, radicals and carbenes. I report on our research on derivatives for generating glycosyl carbanions and glycosylidene carbenes.

### GLYCOSYL CARBANIONS AND 1-DEOXY-1-NITROALDOSES

To be useful for the generation of *glycosyl carbanions*, the derivatives, serving as precursors, should possess a functional group at the anomeric centre which allows deprotonation under sufficiently mild conditions to avoid elimination. Also, substitution of this functional group by other functional groups or by a (second) carbon substituent should be possible. The nitro group and, accordingly, 1-deoxy-1-nitroaldoses - the only C-nitro derivatives (ref. 1) which had not be prepared - appeared appropriate. Indeed, only the 2-deoxy derivatives of the subsequently examined glycosyl sulfones (ref. 2), the glycosyl-lithium compounds (ref. 3), and -phosphonium salts (ref. 4) are useful for the generation of glycosyl carbanions, as are the vinyllithium compounds derived from glycals (ref. 5). Glycosyl manganese compounds (ref. 6a,b) and the zinc-enolates from anhydro-uloses (ref. 6c,d) do not have this shortcoming and may prove useful for a complementary formation of C,C bonds at the anomeric center (ref. 6).
The questions related to the synthetic potential of 1-nitrosugars are indicated in *Scheme 1*. *Glycosyl carbanions* (2 and 4) may be generated by deprotonation of 1 or by *Michael* addition to 1-C-nitroglycals 3, which should be available from 2-O-acyl nitroaldoses. Reaction with electrophiles should lead to 5, in which the "tertiary" nitro group may act as a leaving group. The resulting *glycosyl cations* 6 should, in their turn, react with nucleophiles to 7. The versatility of the nitro group (ref. 1) should also allow the generation of *radicals* and *radical anions* and thus bond formation with radicals and with one-electron donors.
Two methods are available for the synthesis of 1-nitroaldoses. Both use aldose oximes as starting material. In the preferred one (ref. 7), an oxime such as 12 or 15 reacts via the tautomeric, cyclic hydroxylamine with p-nitrobenzaldehyde to a glycosyl nitrone (13, 16) which is ozonolysed to the desired nitro ether (14, 17), as illustrated in *Scheme 2* for protected and unprotected glucopyranose. Acylation of 17 and elimination opens a way to 1-C-nitroglycals such as 18. In the second one (ref. 8), the oxime is oxidised to a hydroximolactone (19, 20). Halogenation leads to a halonitroso ether 21 and, by further oxidation, to a halonitro ether 22, which is reduced to the nitroaldose. The equatorial

orientation of the nitro group in **14** and **17** is ultimately determined by the the equatorial orientation of the hydroxylamino group in the thermodynamically preferred anomer of the cyclic tautomers of **12** and **15**. The nitro group has a normal and, in $CHCl_3$, a strong anomeric effect (ref. 9a).

Scheme 1
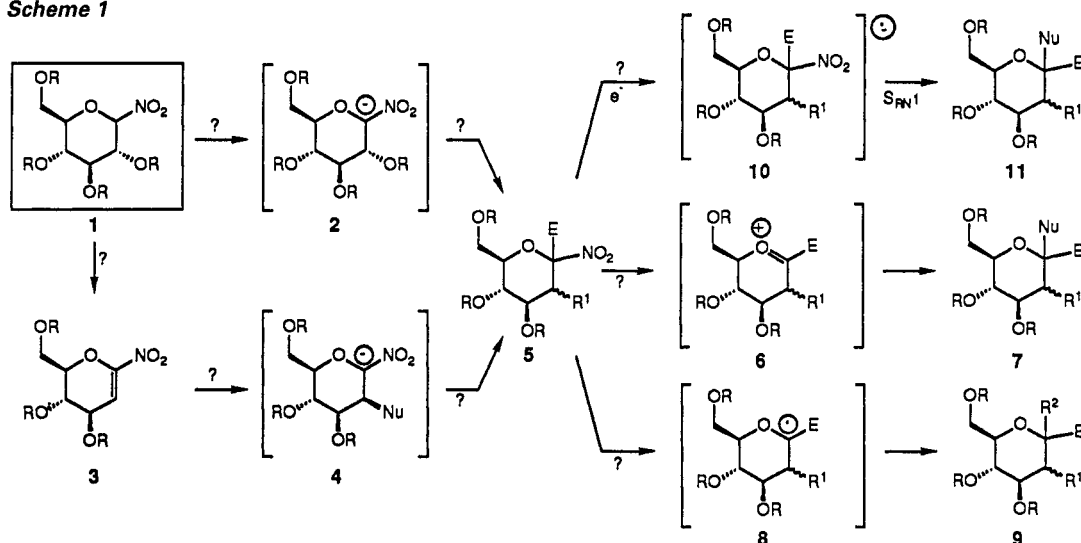
Thus, in addition to the desired nitroaldoses and nitroglycals, four new types of monosaccharide derivatives have been obtained, viz. glycosyl nitrones (ref. 9b), hydroximolactones, halonitroso ethers and halonitro ethers. Hydroximolactones are precursors of glycosylidene derived carbenes (see below). Two of their N-phenyl carbamoyl derivatives are good to excellent inhibitors of β-D-glycosidases; **23** acting on emulsin (ref. 10) (and on glycogen phosphorylase b (ref. 11)) and **24** on N-acetylglucosaminidases (ref.12). In a tandem *Michael* addition-1,3-dipolar cycloaddition sequence, **19** and **25** lead to *spiro*-isoxazolidines, e.g. to **26** (6 isomers) from **25** (ref. 13), and thus to higher-carbon sugars. *Yokoyama and Yamada* have isomerized a *ribo*-hydroximolactone to the corresponding acyclic nitrile oxide and trapped it with dimethyl acetylenedicarboxylate (ref. 14). The halonitroso ether **27** is a very reactive dienophile, yielding enantiomerically highly enriched 1,2-oxazines from 1,3-dienes, e.g. **28** (98%, e.e.> 95%) from ethyl sorbate (ref. 15). Halonitro ethers undergo radical chain reactions with weakly basic carbanions (ref. 16). The products are again higher-carbon sugars, such as the dodecadiulose derivative **30**, obtained from **28** and **29**. Thus, each one of these new derivatives has proven useful beyond its originally intended function as an intermediate in the preparation of nitroaldoses.

Scheme 2
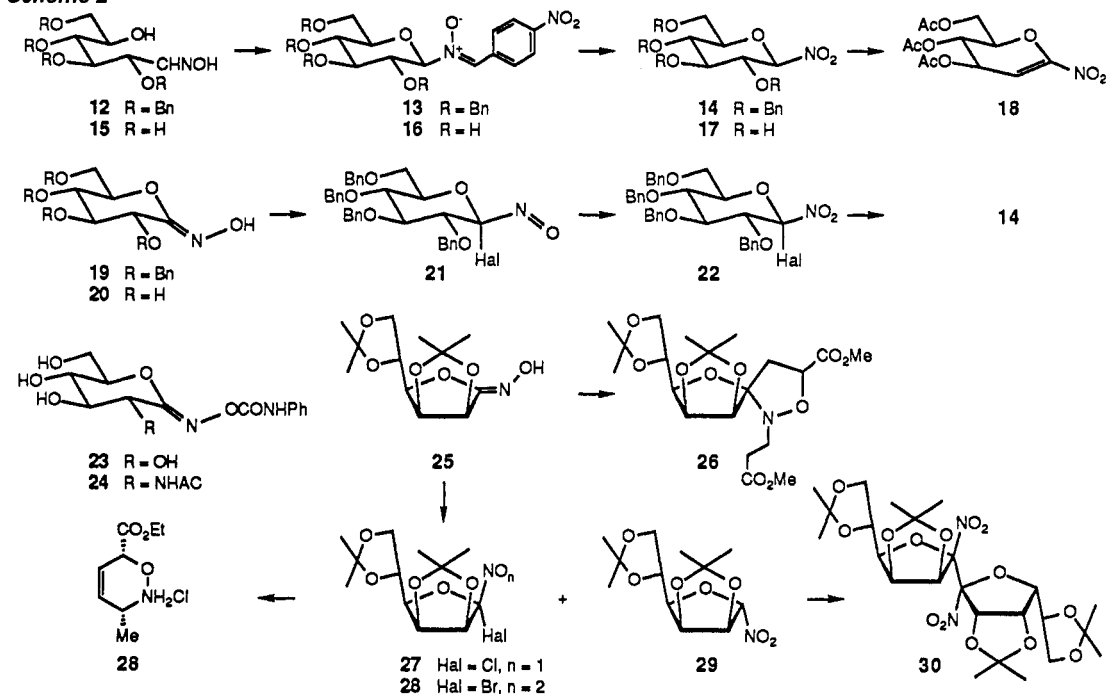
In the following, I highlight the various aspects of reactivity which are layed out in *Scheme 1*. Nitroaldoses readily form C,C bonds under conditions of the *Henry* or of the *Michael* reaction, leading to chain-elongated products *(Scheme*

3). This is illustrated by the reaction of the nitroribose **31** with formaldehyde, followed by acetylation. The psicofuranose **32** was isolated in 89% together with small amounts of its anomer. *Michael* addition of **31** with acrylonitrile yielded the *ribo*-heptulose derivative **33** and its anomer (74%) in a ratio of 14:1 (ref. 17).
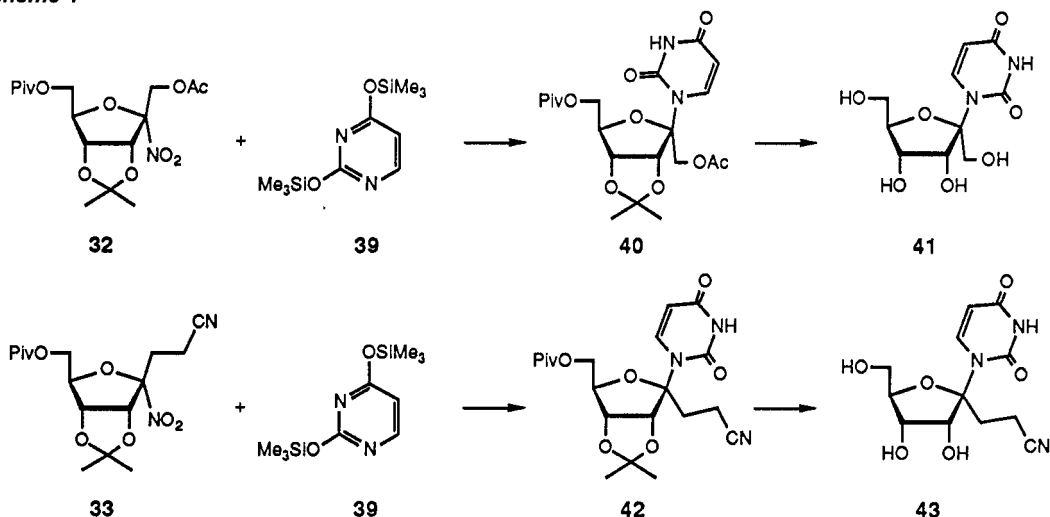
Scheme 3
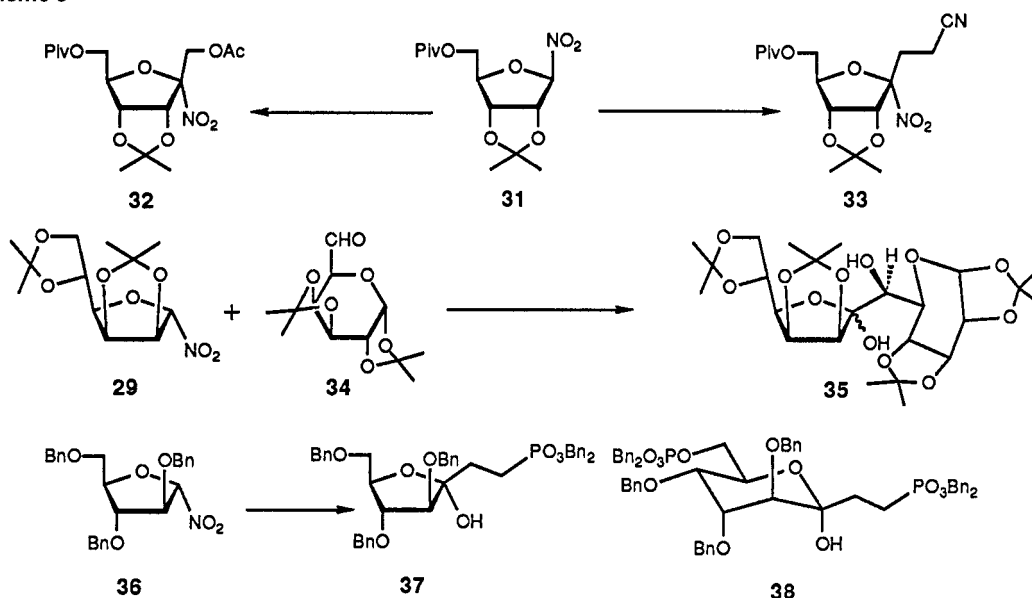
"Tertiary" nitro ethers undergo solvolysis. The dodecosulose **35** was obtained in good yields and with complete diastereoselectivity by a *Henry* reaction of **29** with **34**, followed by heating in aqueous formamide (ref. 18). The phosphonate **37**, an intermediate in the synthesis of an isosteric phosphonate analogue of fructose-1,6-bisphosphate was obtained by a *Michael* addition of the *arabino* nitro ether **36** to dibenzyl ethenephosphonate, and **38**, an intermediate for a phosphonate analogue of sedoheptulose-1,7-bisphosphate, was prepared in a similar way (ref.19).

The double role of the anomeric nitro group, to first facilitate the formation of a carbanion and then of a carboxonium ion, was applied to a synthesis of nucleoside analogues. The naturally occurring ulose-derived nucleosides decoynine and psicofuranine exhibit antitumor and antibacterial activity (ref. 20). Because of this, there is interest in methods leading to nucleosides derived from higher-carbon uloses. The nitro ether **32** (cf. *Scheme 3 and 4*) reacts with **39** in the presence of FeCl₃ to give **40** (77%), which has been deprotected to the known nucleoside **41** (ref. 21). Similarly, **39** yielded **42** (SnCl₄, 40 %) and hence **43**. The conditions required for N-glycosidation depend strongly upon the structure of the nitro ether.

Scheme 4

Michael addition to nitroglycals is an alternative to the notoriously difficult nucleophilic substitution at C(2). The N-acetyl mannosamine derivative **45** (*Scheme 5*) is formed in high yields by the reaction of the nitroglycal **44** with ammonia. The stereoelectronically controlled axial addition of ammonia is followed by an O to N migration of the acyl group. In a second step, **45** was treated with *tert*butyl bromomethacrylate and the resulting nitro ether was solvolysed at pH 6.6. The ulose **46** exists preferentially as the *keto* tautomer. It was transformed in a high-yielding four step sequence to N-acetyl neuraminic acid **47** (ref. 22).The stereoelectronic control in the β-addition is strong enough to overcome the 1,3-diaxial interaction with the C(1),O substituent of **48**. Only the N-acetyl talosamine **49** was formed (after

acetylation), while the reversible addition of azide to 48 led to the anomeric *galacto* configurated 2-azido-2-deoxy analogues.

Scheme 5
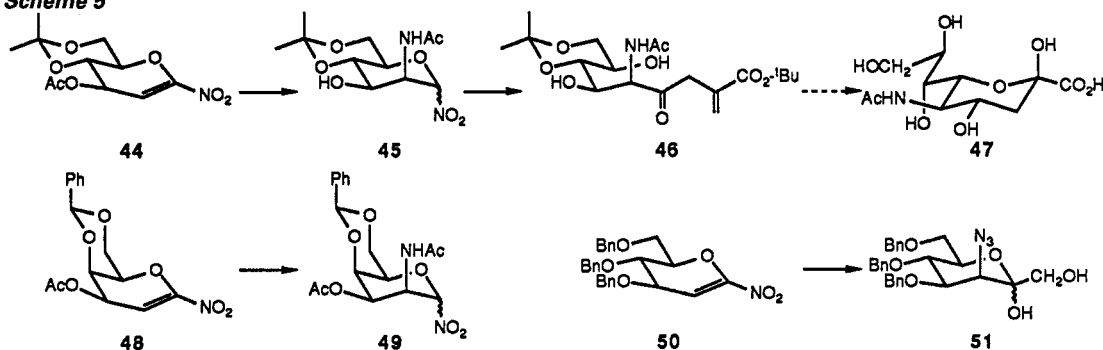
It is tempting to combine *in situ* a base catalysed β-addition with a nucleophilic reaction of the intermediate carbanion. An intermolecular version of this combination is provided by the reaction of 50 with azide in the presence of formaldehyde. The nitro group of the resulting product was replaced by a hydroxy group in contact with SiO_2, and the 3-azido heptulose 51 was isolated in high yields (ref. 22). An intramolecular version (*Scheme 6*) of the above mentioned combination is realized in the reaction of 52 with 53 (ref.23). The resulting, somewhat unstable nitro ether was reductively denitrated (ref. 24), illustrating a further useful aspect of "tertiary" nitro ethers and the generation of *glycosyl radicals*, which have been more closely examined by *Giese et al.* and by *Descotes et al.* (ref. 25).This sequence of reactions gave mainly the epimeric, *cis*-annulated pyrano[3,2-b][1]benzopyranes 54 and 55, together with small amounts of the *trans* annulated isomer of 54. The only example of an (intramolecular) acylation at C(1) is provided by the reaction of the rhamnose derived nitroglycal 56 with the sulfonyllactone 57 (ref. 26) in the presence of lithium diisopropylamide (ref. 27). *Michael* addition leads at low temperatures to epimeric, *manno* configurated adducts; at higher temperatures, C-acylation is followed by loss of phenyl sulfinate, resulting in the naphtho[2,3-b]pyrandione 58. Deprotection led to 59, the enantiomer of cryptosporin (ref. 28), thus correcting the constitution and absolute configuration which had been assigned to the natural product.

Scheme 6
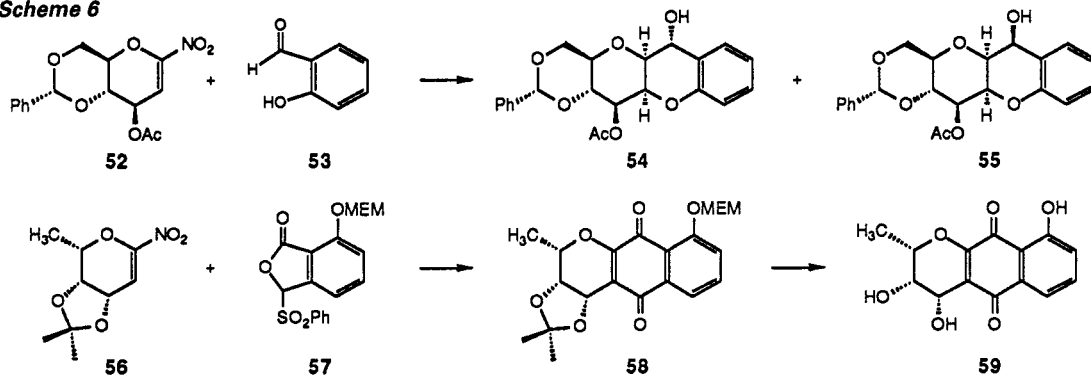
Radical intermediates are important not only in the reductive denitration of "tertiary" nitro ethers, but also in the gem. dialkylation of the anomeric center. Such a dialkylation by two identical groups has been found in the reaction of gem. bromo nitro ethers with nitromethane (ref. 16) (*Scheme 7*). *Giese et al.* (ref. 29) have treated "tertiary" nitro ethers with

Scheme 7
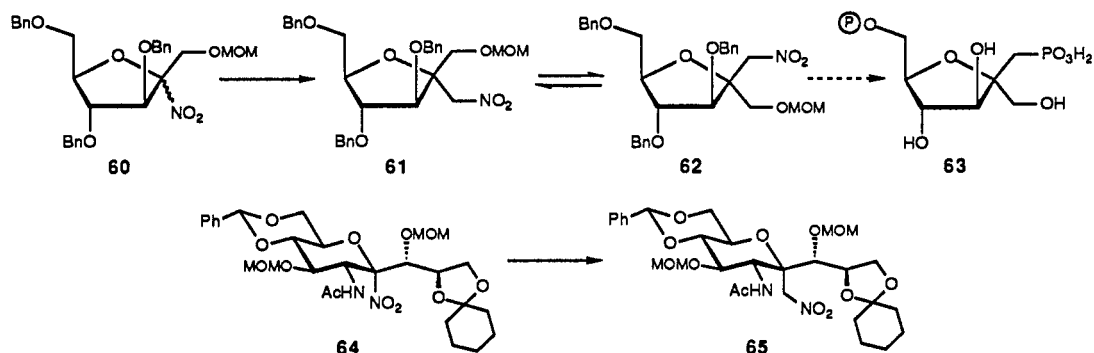
Bu₃SnH in the presence of acrylonitrile and obtained in a diastereoselective reaction and in moderate yields the product of gem. dialkylation. These authors also characterized by ESR the radical anion salt which is the intermediate formed upon attack of the tributyltin radical on the nitro group.

Radical anions are doubtlessly also generated by a one-electron transfer from nitronate anions onto nitro ethers. We found this *Kornblum* reaction (ref. 30) useful. The furanose 60 (*Scheme 7*) yields a mixture of 61 and 62 (66%). The desired diastereoisomer 62 was obtained in quite good yields by base catalyzed equilibration of 61 and 62. Ozonolysis of the nitronate salt derived from 62 led to the corresponding aldehyde on the way to the isosteric phosphonate analogue 63 of fructose-2,6-bisphosphate (ref. 31). The pyranose 64 reacted similarly, but with complete diastereoselectivity to the branched-chain nonitol 65, which has been transformed into C(6)-methyl and C(6)-hydroxymethyl substituted analogues of N-acetylneuraminic acid (ref. 32).

A shortcoming of nitro ethers, implicit in their reluctance to undergo β-elimination, is their relatively low reactivity. Thus, in a projected way to carba-disaccharides, it proved difficult to add the nitronate anion derived from 14 to sterically hindered aldehydes (ref. 33). In spite of this restriction, the concept of using nitro ethers as precursors for the generation of glycosyl carbanions has been a fruitful one. Aspects which remain to be explored include a more ample examination of the acylation at C(1), of the addition of carbon- and heteronucleophiles at C(2) and of 1,3-dipolar cycloadditions of the corresponding nitronates.

## GLYCOSYLIDENE CARBENES AND GLYCOSYLIDENE DERIVED DIAZIRINES

The functions of the anomeric nitro group to first generate glycosyl carbanions and then to serve as a leaving group in the formation of carboxonium ions may formally be combined in a derivative leading to *glycosylidene carbenes*. It was not, however, this consideration which attracted our attention to these reactive intermediates. We were interested in methods for the synthesis of glycosides which would not be based on the promoter-dependent activation of a (potential)

Scheme 8
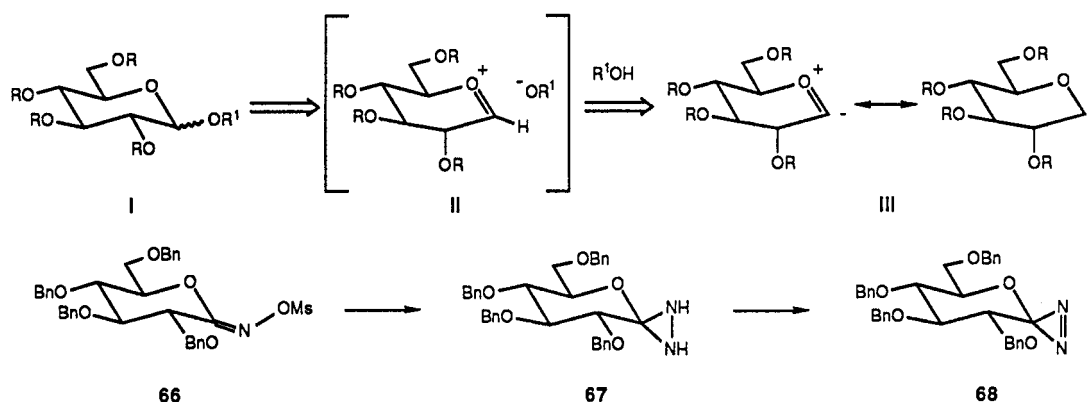
leaving group at the anomeric centre. As outlined in *Scheme 8*, a glycoside I might be formed from an ion pair II. If one imagines the formation of II by deprotonation of an alcohol, the first reactive intermediate would have to be the ylid corresponding to the carboxonium ion in II; the ylid is a resonance form of a glycosylidene carbene III. Being a member of the known class of alkoxy alkyl carbenes (see ref. 34 and lit. quoted there), III should be a nucleophilic or ambiphilic (ref. 35) singulet. It should easily (formally) insert into O,H bonds (ref. 36). Such a carbene might be generated by thermal or photochemical decomposition (ref. 37) of the 1-azi-1-deoxyglucose 68. The envisaged synthesis of glycosylidene derived diazirines by oxidation of alkoxydiaziridines proved successful both in the pyranose and furanose series; in the latter, unfortunately, the diazirines are thermally very unstable, while 68 is a crystalline and relatively stable compound (ref. 38).
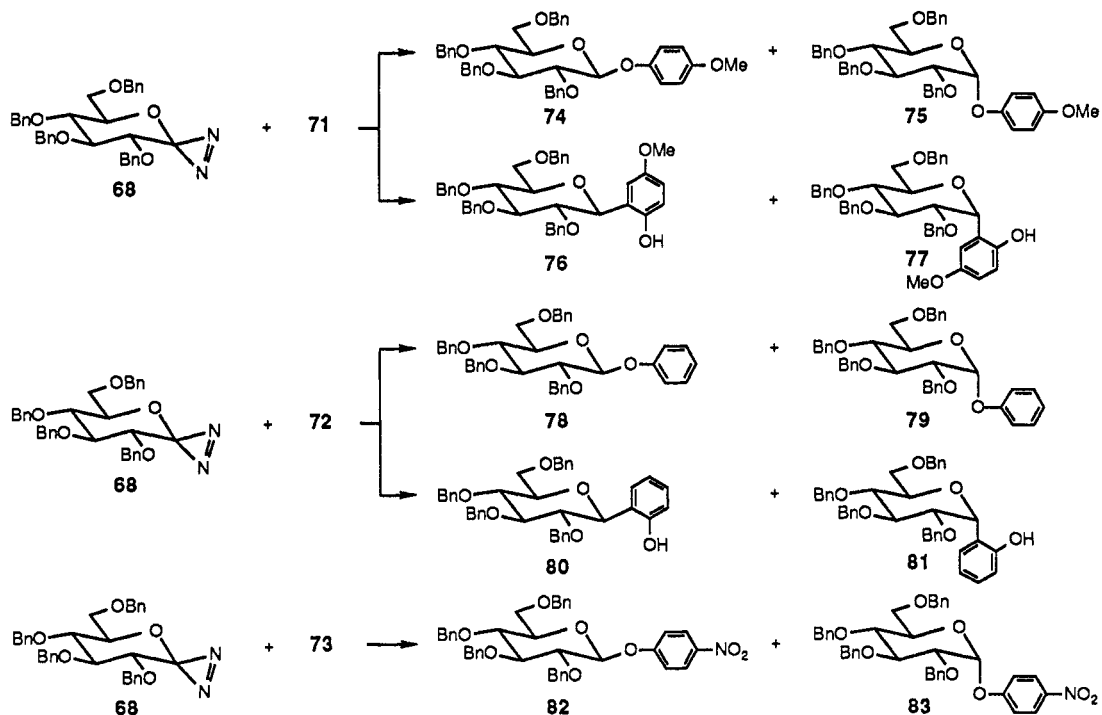
Scheme 9
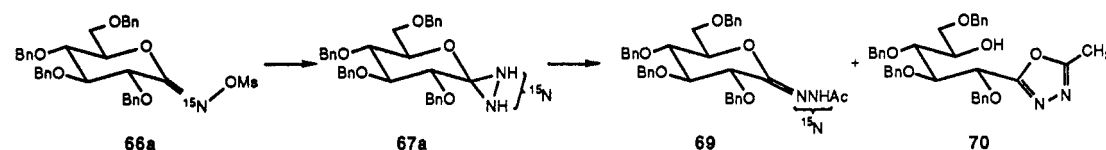
Alkoxydiaziridines, such as 67, were obtained by treating hydroximolactone-derived mesylates, such as 66, with NH₃/MeOH. Alkoxydiaziridines were not known before. As the barrier to nitrogen inversion in diaziridines is quite high (ref. 39), *cis* and *trans* isomers may exist; as a rule, the *trans* isomers are more stable (ref. 40). The crystalline hydraziglucose 67 is a mixture of the two *trans* diastereoisomers in a ratio of 95:5; similarly, the crystalline galacto- and the *manno*-analogues of 67 are 1:1 mixtures of *trans* diastereoisomers (ref. 38). Considering the novelty of alkoxydiaziridines and the interest in the axial vs. equatorial attack of nucleophiles on cyclohexanones and related compounds (ref. 41), we prepared the ¹⁵N labeled mesylate 66a and its *galacto*-analogue (*Scheme 9*). The ratio of isotopomers in 67a is 1:3; the axial attack appears to be preferred. The galacto-analogue of 66a reacts faster, leading to the isotopomeric diaziridines 84a (compare *Scheme 11*) in a ratio of 1:9. Treatment of 67a with Ac₂O led to a 1:1 mixture of the isotopomeric N-acetyl-lactone hydrazones 69. Clearly, Ac₂O does not distinguish between the two (NH) groups in 67a. The oxadiazole 70 was obtained as a byproduct. We are currently investigating the chemistry of the 1-hydraziglycoses and of glyconolactone hydrazones; oxadiazoles such as 70 may also prove interesting compounds.

Scheme 10 depicts the results of the glycosylation of p-methoxyphenol (71), phenol (72) and p-nitrophenol (73) by 68. The glycosyl donor and the acceptors were used in equimolar amounts. The following aspects of the results are noteworthy: a) The relatively electron rich phenols yielded O-aryl glycosides (74/75 from 71 and 78/79 from 72) together with C-aryl glycosides (76/77 from 71 and 80/81 from 72), while p-nitrophenol only formed O-aryl glycosides; b) the 1,2-*trans* (=β-D) O-aryl glucosides were formed in excess (74:75 = 75:25; 78:79 = 80:20; 82:83 =

60:40) and this feature is more strongly expressed with the less acidic phenols (the C-aryl glycosides were obtained in a ratio of 1:1); c) the total yields of O-glycosides are quite good and about the same (ca. 75%) for the three phenols.

Scheme 10

Scheme 11 shows the results of the glycosylation of the *galacto*-diazirine 85 with 72 and 73, and of the *manno*-diazirine 93 with 72. The diazirines 85 and 93 were not isolated, and the total yields are somewhat lower than those obtained with 68. The diastereoselectivities of the glycosylation with the *galacto*-diazirine are very similar to those obtained with the *gluco*-analogue and exclude a rationalisation of the diastereoselectivity which postulates a preassociation complex with parallel planes of the phenol and the pyranose ring, the phenol lying on top of the pyranose. The *manno*-diazirine leads mainly to the 1,2-*trans* configurated 94 (94:95 ≥ 20:1), excluding an "intrinsic" preference for the formation of equatorial glycosides. The formation of C-aryl glycosides constitutes a strong structural evidence for a protonation-deprotonation mechanism (for kinetic evidence, see ref. 36c) leading to an ion pair in which the aryloxy group
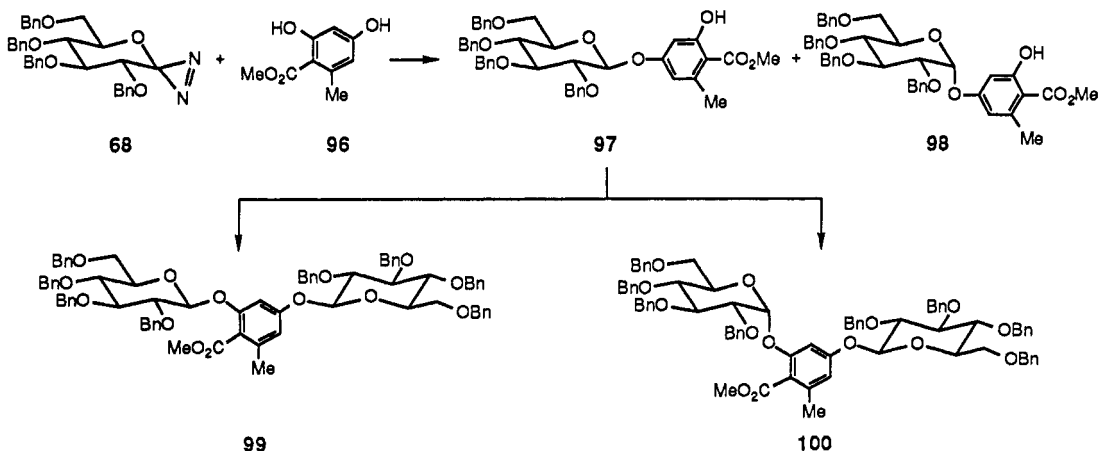
Scheme 11
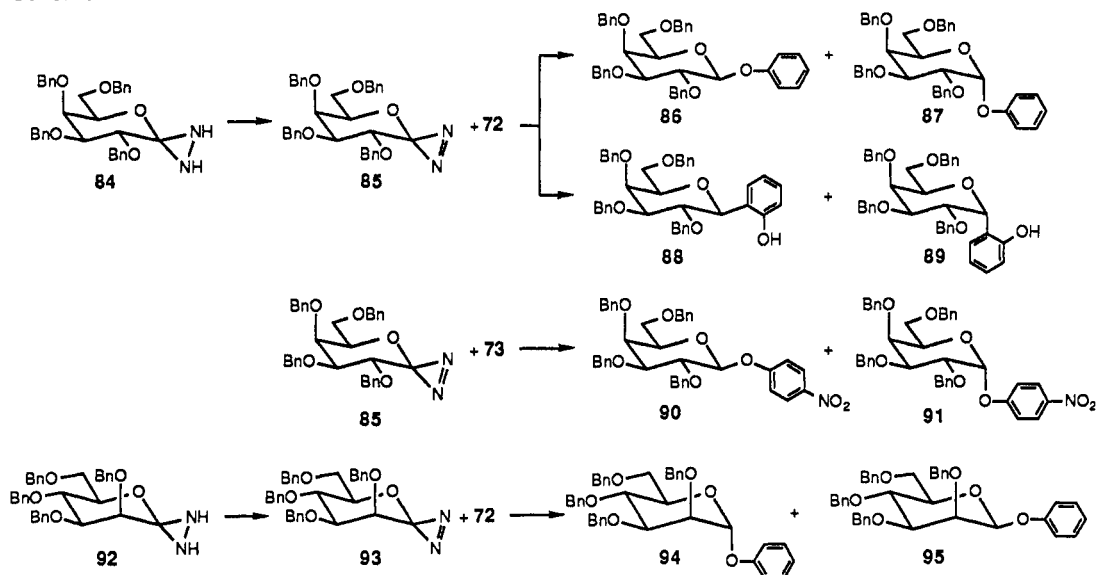
is either O- or C-alkylated. Methoxymethylcarbene displays a remarkably high selectivity in its nucleophilic reaction with alkenes (ref. 35b), and one expects that it also reacts selectively as a base. A competition experiment, in which one equivalent of the diazirine 68 was exposed to one equiv. each of 71 (pK$_{HA}$ = 10.2) and 73 (pK$_{HA}$ = 7.2) gave the

products derived from **71** and **73** in a 1:1 ratio; showing that differences in *thermodynamic* acidities in this range of pK values do not induce selectivity.
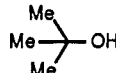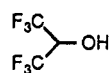
Scheme 12

To explore, if differences in *kinetic* acidity may form the basis of a regioselective glycosidation, we treated methyl or-sellinate (**96**) with one equiv. of **68** (*Scheme 12*) and obtained exclusively the anomeric monoglucosides **97** and **98**, where the non-chelated OH group had reacted. Yields were quite high (79%) and the - solvent dependent - ratio of β:α-D-anomers reached 85:15 when the reaction was performed in toluene (ref. 42). The regioselectivity was proven, *i.a.*, by acetylation of **97** and **98**. Further treatment of **97** by **68** gave the diglucosides **99** and **100** in almost equal amounts.

Scheme 13
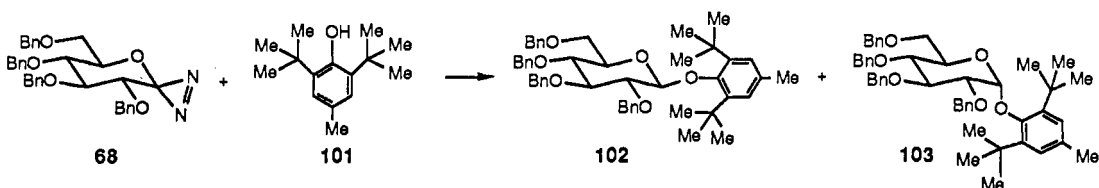
Glycosidation by carbenes implies that steric hindrance should not be an important factor. As expected, the glucosida-tion of 2,6-di-*tert*butyl-4-methylphenol (BHT, **101**) by 1 equiv. of **68** proceeded well (*Scheme 13*). The anomeric glu-cosides **101** and **102** were isolated in yields of 75-81% (**101**:**102** = 84:16 to 80:20).

Table: Glycosidation of Model Alcohols: pK$_{HA}$-Values, Yields and Diastereoselectivities

ROH	pK$_{HA}$ (ROH)	% Glycosides	α : β
MeOH	17	60	50 : 50
EtOH	18	55	50 : 50
Me$_2$CHOH	18	39	50 : 50
Me$_3$COH	19	34	50 : 50
CF$_3$CH$_2$OH	12	70	35 : 65
(CF$_3$)$_2$CHOH	9	75	20 : 80

Exploratory experiments in the glucosidation of model alcohols by 1 equiv. of **68** (*Table*) gave the desired glucosides in yields between 34 and 72%. The highest yields and the best diastereoselectivities were obtained with the most acidic alcohol, hexafluoroisopropanol, in a situation reminding one of the glycosidation of phenols. Conditions have not yet been optimised, but it appears that glycosidation proceeds better with more highly acidic (and thus less nucleophilic) al-cohols, while less acidic alcohols give rise to more byproducts such as benzyloxyglycals. In this, glycosidation by 1-aziglycoses is quite different from the *Koenigs-Knorr* type glycosidation, perhaps with the exception of special applica-

tions of the imidate method, where strongly acidic hydroxy compounds such as phosphate diesters protonate the imidoyl group (ref. 43). During the glycosidation of hexafluoroisopropanol with **68**, we observed formation of a yellow colour. The time-dependent UV-spectrum indicated the formation of a transient species with a maximum at 290 nm and a weak band in the i.r.-spectrum at 1995 cm⁻¹ (cf. ref. 35b). This may evidence the formation of a diazoether, either as intermediate or as side product. Although several cases of the rearrangement of diazirines to the more stable diazocompounds are known (ref. 44), the acid labile diazoethers have hardly been studied (ref. 45) and we have started a program to prepare such intermediates. A remarkable feature of these glycosidations is their dependence upon concentration: at a concentration of 9.1 mM in CH₂Cl₂, only the fluorinated, i.e. the acidic alcohols form glycosides, so that either a high selectivity of the carbenes or a heterolytic opening of the diazirine ring, favoured by proton transfer from ROH, (and thus a preassociation) must be assumed. *Platz et al.* (ref. 46) have determined the absolute rate constants for the reaction of the glycosylidene carbene, generated from **68** by laser flash photolysis. The kinetic data favour a mechanism involving proton transfer from the alcohol to the carbene. This carbene has a lifetime (in MeCN) of 772 ns, and is 100 times less reactive towards methanol than the parent methylmethoxy-carbene, presumably due to the benzyloxy groups which act as σ-acceptors and lower the basicity of the carbene.

Scheme 14
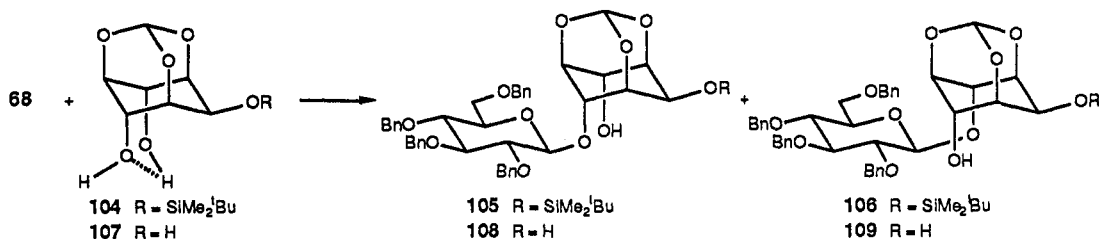
The low yields and diastereoselectivity in the glycosidation of the nonfluorinated simple alcohols is a challenge, particularly so, as 1,2:5,6-di-O-isopropylidene glucose reacts with **68** to give the glycosides in a ratio of only 2:1, albeit in a higher yield. Similarly, the glycosidation of methyl 2,3-di-O-benzyl-α-D-glucopyranoside by **68** under either thermal or photochemical (-78°) conditions is neither regio- nor diastereoselective (ref. 47). To explore the possibility of a regioselective (mono)glycosylation of diols, where the two hydroxy groups possess very different kinetic acidities, we treated **68** with the myo-inositol derivative **104** (*Scheme 14*), where one OH-group functions as H-bond donor, while the other is the H-bond acceptor and thus much more acidic. We obtained (90%) exclusively the monoglucosylated, β-D-configurated diastereoisomers **105** and **106** in about equal amounts. The triol **107** gave very similar results, leading
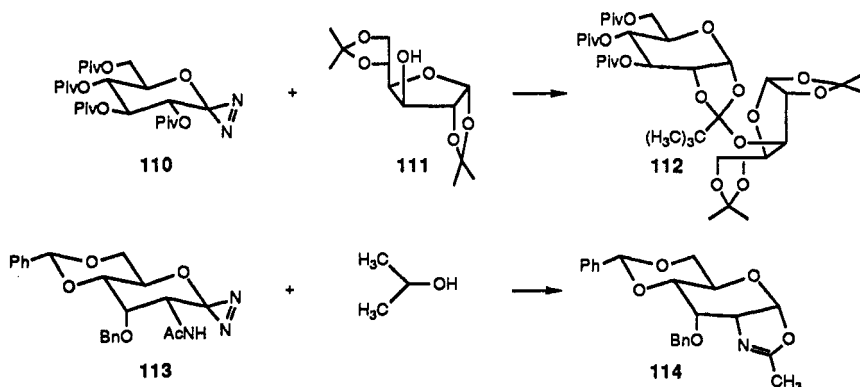
Scheme 15
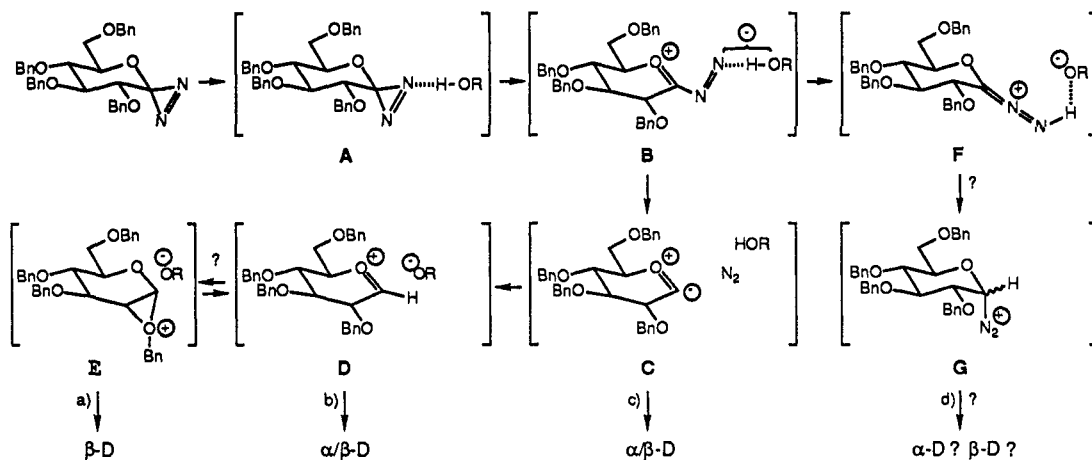
exclusively to the monoglycosylated **108** and **109** (ref. 48), and demonstrating that a regioselective monoglycosidation with a 1-azi-1-deoxyglycose is feasible, at the least in favourable cases. Presumably, this reaction also involves protonation of the carbene (and of the diazirine?). It is tempting to associate the high diastereoselectivity (no α-D-glucosides were found) - at the least in part - with a neighbouring group participation of the C(2)-benzyloxy group.

At this stage, one may advance a working hypothesis for the glycosidation of (kinetically) acidic phenols and alcohols which involves proton transfer to the azi group (→ A) (*Scheme 15*) and heterolytic opening of the diazirine ring (→ B). The ensueing zwitterion B may lose N₂ (and H⁺, or ROH resp.) to give the carbene C. Protonation of the carbene then leads to a poorly solvated and thus highly reactive carboxonium ion D where some degree of neighbouring group participation (→ E) is possible. Process a) (from E) would mainly yield 1,2-*trans* glycosides, while a mixture of anomers may result by process b) (from D). The zwitterion B, formed upon heterolysis of an N-C(1) bond may also isomerize to an N-protonated diazo compound F and hence to a diazoether, which may or may not act as a glycosylating agent (e.g. by being protonated (from the equatorial side? cf. ref. 49) at C(1) (→ G)). For less acidic alcohols, the extent to which proton transfer to the azi group and/or to the carbene takes place should be reduced. (Formation of a carbene from the aziglycose does not require protonation.) The carbene (C) may react by a more or less polarized insertion process c), which does not lead to a carboxonium ion intermediate. This may again lead to mixtures of anomers, as might process d). These hypotheses lead to a number of questions. Thus, one expects an increased stability for an O-acyl (vs. an O-alkyl) protected aziglycose if heterolysis of the N,C(1) bond and particularly if proton-transfer to the diazirine is
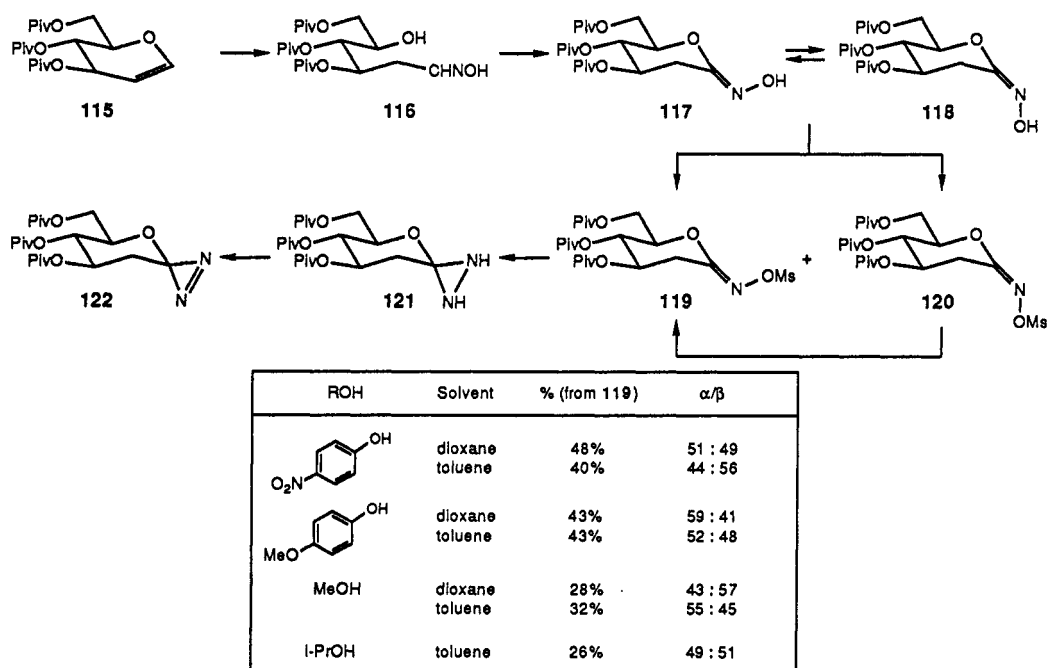
important in the (rate-determining) formation of **B** and/or **C**. If **C** is protonated, one expects a neighbouring group participation by a C(2) acyloxy group, formation of a dioxolenium ion and of orthoesters. If the C(2) benzyloxy group is relevant for the diastereoselectivity (as evidenced by the formation of 1,2-*trans* O-aryl glycosides), then 1-azi-1,2-dideoxyglycoses should show a different diastereoselectivity, and yield informations about the preference for axial vs. equatorial attack of ROH or RO⁻, respectively. Finally, diazoethers derived from **F** ought to be prepared and studied.

Scheme 16

The pivaloylated aziglucose **110** (ref. 50) indeed appears to be more stable than **68**. Exploratory experiments with **111** (*Scheme 16*) gave the orthoester **112** in moderate yields (no glycosides were observed), evidencing protonation of the carbene. Similarly, reaction of **113** with isopropanol gave the dihydrooxazole **114** as the main product (ref. 51).

Scheme 17

| ROH	Solvent	% (from 119)	α/β
O₂N—⟨⟩—OH	dioxane	48%	51 : 49
	toluene	40%	44 : 56
MeO—⟨⟩—OH	dioxane	43%	59 : 41
	toluene	43%	52 : 48
MeOH	dioxane	28% ·	43 : 57
	toluene	32%	55 : 45
I-PrOH	toluene	26%	49 : 51

The pivaloylated 1-azi-1,2-dideoxyglycose **122** was prepared as indicated in *Scheme 17* (ref. 52). An (E/Z) mixture of hydroximolactones (as observed for other 2-deoxy-hydroximolactones) was obtained form **116**. Only the (Z)-mesylate **119** reacts well to form **121**, and **120** was transformed into **121** by mild acid catalysis. The ratio, in which the anomeric O-aryl glycosides were formed are not far removed from 1:1, depend slightly upon the solvent and are not in contradiction with a neighbouring group participation of the C(2) benzyloxy group in the analogous glycosylation of **68**. Again, weakly acidic alcohols give poorer yields. As in other glycosidations with 1-aziglycoses, we observe by-products from adventitious H₂O, disaccharides, products of O-acyl and of 1,2-hydrogen-migration. As one expects a preferential axial attack of a nucleophile onto a glycosyl cation, the 1:1 ratio may indicate (partial or total) proton transfer from a randomly oriented ROH and immediate collapse of the ion pair. These questions are currently studied in more detail.

Alkoxyalkyl carbenes form cyclopropanes with electron-poor alkenes (ref. 35). Excess N-phenylmaleimide (**123**) reacted with **68** at room temperature (*Scheme 18*) yielding 80% of the *spiro*-cyclopropylpyranoses **124** and **125** (90:10) (ref. 53). Similarly, **110** gave the pivaloylated analogues of **124** and **125** (ref. 50) evidencing the formation of carbenes from **68** and from **110**. With excess acrylonitrile, **68** gave the four isomers **126-129** (70%; 51.5:31.4:8.4:5.6), again from a preferred approach from the side of O-C(5). Nucleophilic carbenes do not react diastereospecifically with

acceptor-substituted alkenes. This was also observed in the reaction of **68** with dimethyl fumarate and maleate, respectively. From the fumarate, only the *trans* cyclopropanes **130** and **131** were obtained (72%, 6:4), while the maleate yielded the *trans* and the *cis* cyclopropanes **130-133** (58%; 29:19:33:19).

Scheme 18
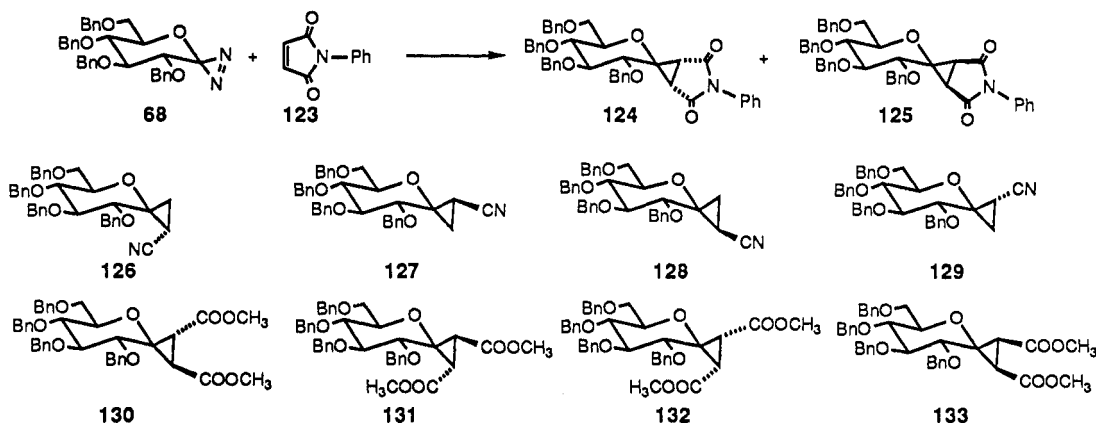
Among the unanswered questions about glycosylidene derived diazirines is the scope of the formal insertion of glycosylidene carbenes into X,H-bonds, where X symbolizes any hetero atom, particularly when (RXH) is of low acidity. In this context, we have examined the reaction of **68** with diphenylphosphine, as the insertion into the (P,H) bond should lead to glycosylphosphines and thus to enantiomerically pure and - after deprotection - to water soluble ligands for transition metals. Reaction of the diazirine **68** with Ph₂PH under thermal or under photochemical conditions afforded a mixture of the anomeric phosphines **134** and **135** (*Scheme 19*) in yields of up to 76% and α:β ratios of 55:45 (hν: 54%, 74:26). These phosphines were easily oxidized and fully characterized as their oxides **136** and **137**. The diphenylphosphine oxides were more easily available from the acetate **138**, by reaction with MeOPPh₂ in the presence of TMSOTf, according to a protocol we had developed for the synthesis of glycosylphosphonates (ref. 54).

Scheme 19
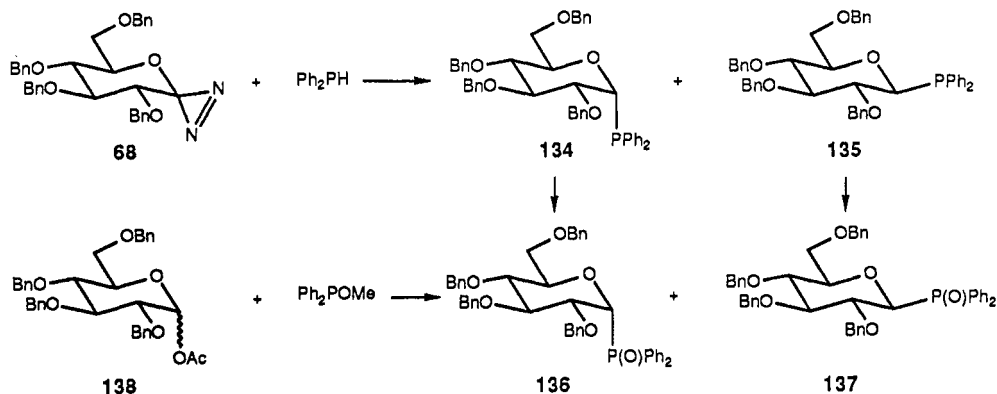
One of the problems yet to be solved is a short synthesis of the ideal precursor. *Praly et al.* (ref. 55) have very recently reported a relatively easy access to 1,1-diazido-1-deoxyglucoses which appear to form glycosylidene carbenes under photolytic conditions (ref. 56). The potential of diazirines, diazides and possibly other derivatives will certainly continue to present challenges and excitation.

Acknowledgement

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