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A new approach to the synthesis of glycosides

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Abstract – An new approach towards glycosides, which obviates the use of promoters and depends upon the acidity of the glycosyl acceptor is proposed to achieve regioselective glycosidation. Glycosylidene carbenes, generated under thermal or photolytic conditions from O-benzylated or O-acylated 1-azi-glycoses, or from glycono-1,5- (or 1,4)-lactone tosylhydrazones react with hydroxy compounds to yield glycosides. The preparation of these precursors, their structure, their thermal stability, and their products of thermolysis are discussed. A mechanism is proposed to explain and predict the reaction of 1-azi-glycoses with mono-, di-, and triols. Protonation of the carbene in the σ-plane leads to an ion-pair, which cannot immediately form glycosides. The fate of this ion pair depends upon the pK of the glycosyl acceptor, inter- and intramolecular hydrogen bonds, the direction of H-bonds, the presence of a neighbouring group at C(2), the configuration of the glycosyl acceptor, the solvent, and the temperature. Strongly acidic hydroxy compounds give glycosides in high yields and stereoselectively. Successful regio- and stereoselective glycosidation of diols and triols depends strongly upon intra- (and inter)molecular hydrogen bonds, both between the hydroxy groups of the acceptor and between functional groups of the donor and hydroxy groups of the acceptor. This is illustrated by a number of significant cases. For some of them, regioselectivity is complementary to the one observed in glycosidations of the *Koenigs-Knorr*-type, for others it is not. Reasons for this are discussed. Other cases present the preferential glycosylation of secondary hydroxy groups in the presence of a primary one, and the selective formation of α-D-glycosides of AllNAc and GlcNAc.
Intramolecular reactions of alkoxyalkyl carbenes are illustrated by a new method for the formation of benzylidene acetals under basic conditions, and by a new synthesis of homobenzofurans. New reactions, leading to the formation of C,C bonds at the anomeric centre are presented: the synthesis of spiro-oxiranes, of dialkoxy-spiro-cyclopropanes, and of the first glycosylated, enantiomerically pure derivatives of C_{60}-buckminsterfullerene.

INTRODUCTION

Most current methods for the preparation of glycosides are based on the activation – by one or the other promoter – of a leaving group at the anomeric centre (ref. 1). A wide range of (potential) leaving groups has been proposed (ref. 2). Some of them are stable in the absence of a suitable promoter and function as a temporary protecting group (ref. 1c), others are very reactive (ref. 1a). The role of participating and non-participating protecting groups in determining anomeric selectivity is well understood, and the influence of participating solvents has become clearer (ref. 3). The importance of matching the relative reactivity of glycosyl acceptor and glycosyl donor to achieve diastereoselectivity has been recognised (ref. 4). The effect of protecting groups on the ease of formation of oxycarbenium ions – largely determining the reactivity of the glycosyl donor – has been exploited under the name of "armed" and "disarmed" donors (ref. 5). These results constitute impressive advances. In spite of them, the synthesis of oligosaccharides is far from routine, and important problems remain to be solved, such as the establishment of a standardised, repetitive method for the solid phase synthesis of oligosaccharides (ref. 6) and of a (generally applicable) method for a regioselective, non-enzymatic glycosidation, obviating (largely) the need for protecting groups (ref. 7).
Conceivably, these problems will be solved by using ever more sophisticated versions of the *Koenigs-Knorr*-type glycosylation. However, the systematic analysis of this type of glycosylation is difficult, due to the large variety of leaving groups, promoters, and reaction conditions. Regioselective glycosidation requires a method which takes advantage of the – presumably subtle – differences in the reactivity of hydroxy groups. A simplification of the reaction conditions (ref. 8) is therefore important.

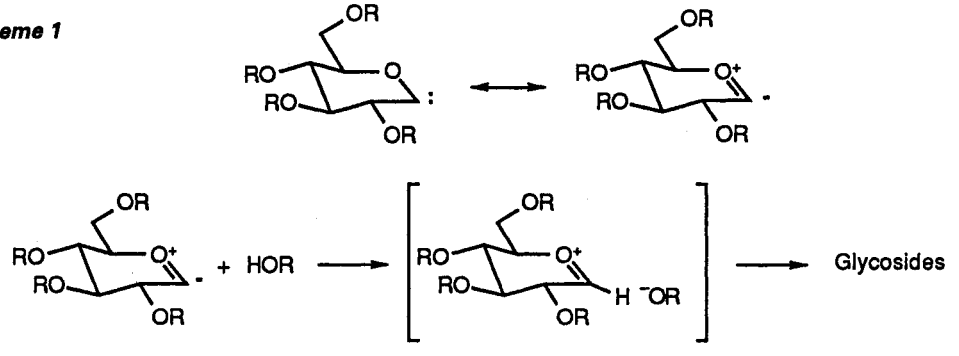
CARBENE PRECURSORS

We have proposed a glycoside synthesis *via* glycosylidene carbenes with no promoter (ref. 9, 10). According to this concept (*Scheme 1*), a cyclic, carbohydrate-derived alkoxyalkylcarbene-ylide should be protonated by a hydroxy compound (ref. 11) to form an ion-pair, realising the simultaneous activation of a glycosyl donor and of a glycosyl acceptor. The ions should then combine to a glycoside. Regioselectivity might result in so far as the rate of protonation depends upon the (kinetic) acidity of individual hydroxy groups.

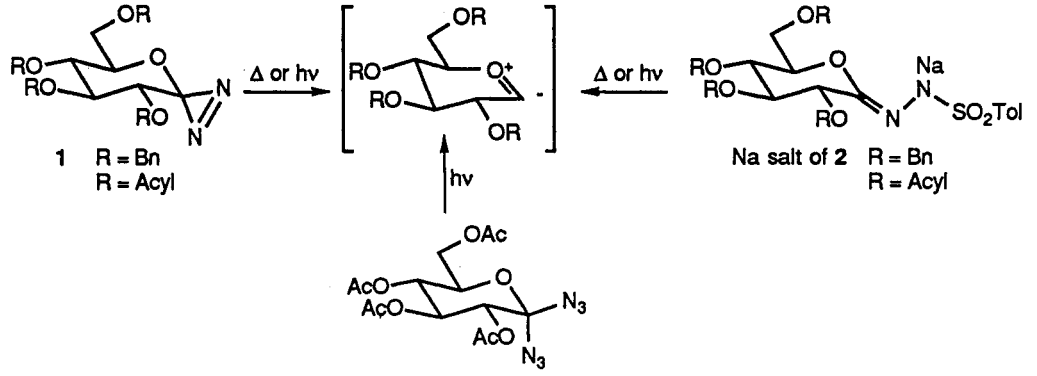
Glycosylidene carbenes may be generated by thermolysis or photolysis either of (O-alkyl or O-acyl protected) glycosylidene diazirines (ref. 9), or of the Na salts of glyconolactone tosylhydrazones (ref. 12, 13), or by photolysis of O-acyl protected 1,1-diazides (ref. 14) (*Scheme 2*).

The synthesis of glycosylidene diazirines is illustrated in *Scheme 3* which shows the preparation of the O-benzylated *gluco*-diazirine **1**. It is obtained by oxidation of the corresponding diaziridines **6**, which are formed by treating glyconhydroximo-lactone sulfonates (such as **5**) with ammonia. The sulfonate **5** is easily obtained from the oximes **3** *via* the glyconhydroximo-lactone **4**. A number of other diazirines, such as **7–11** (ref. 9, 10, 15, 16) (*see below*) have been prepared by the same method.

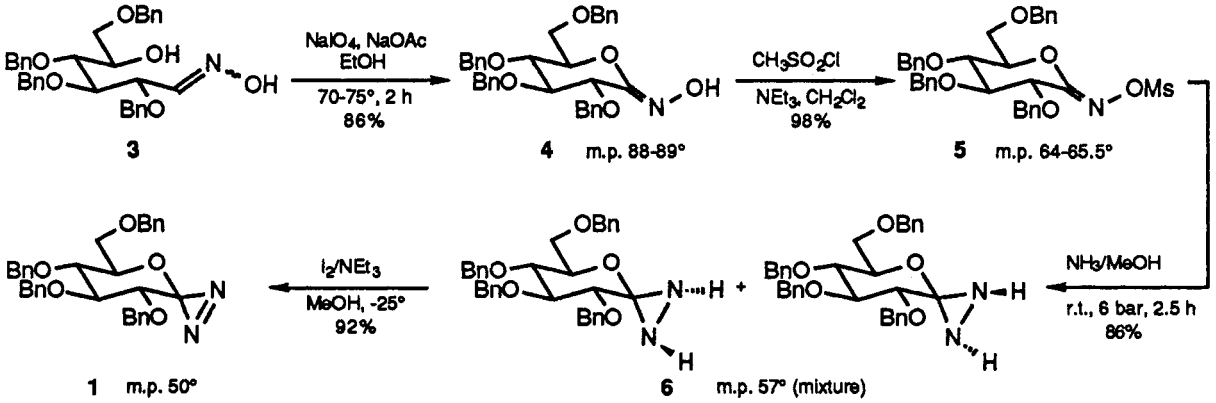
Scheme 1

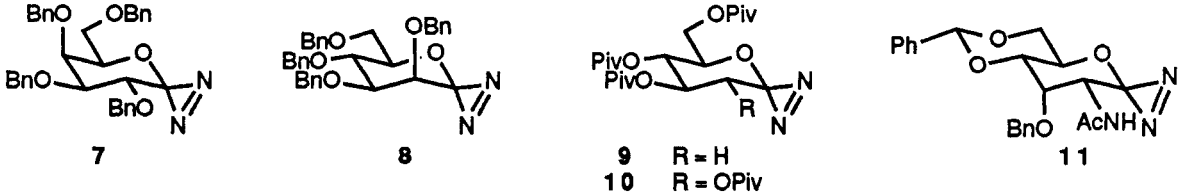


Scheme 2



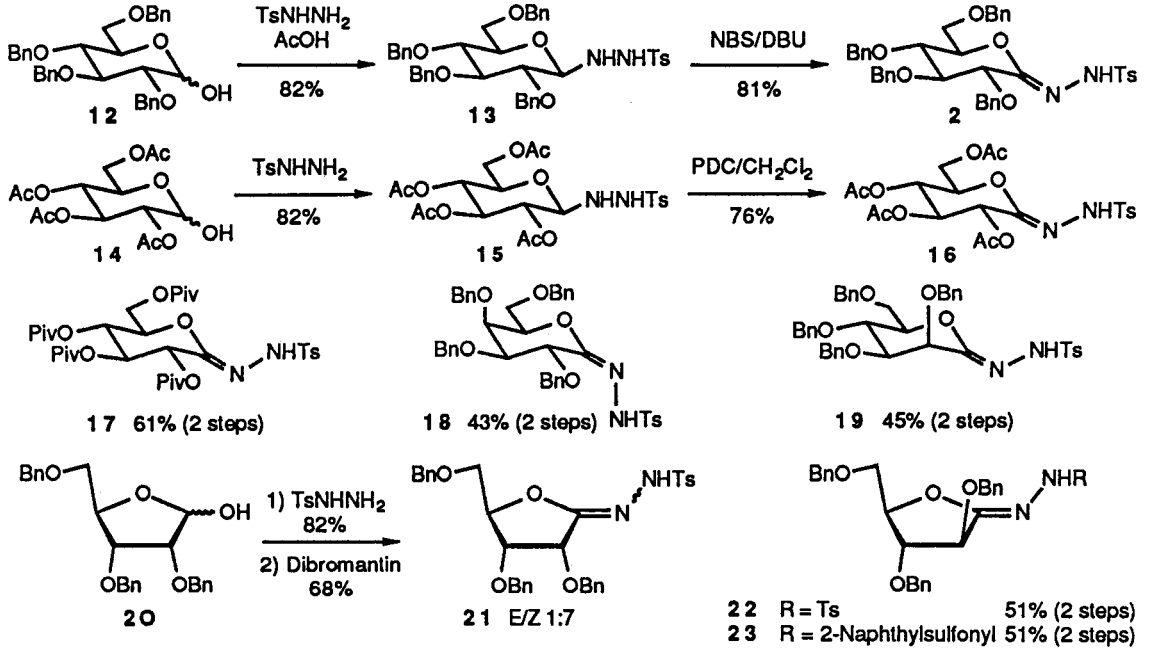
Scheme 3



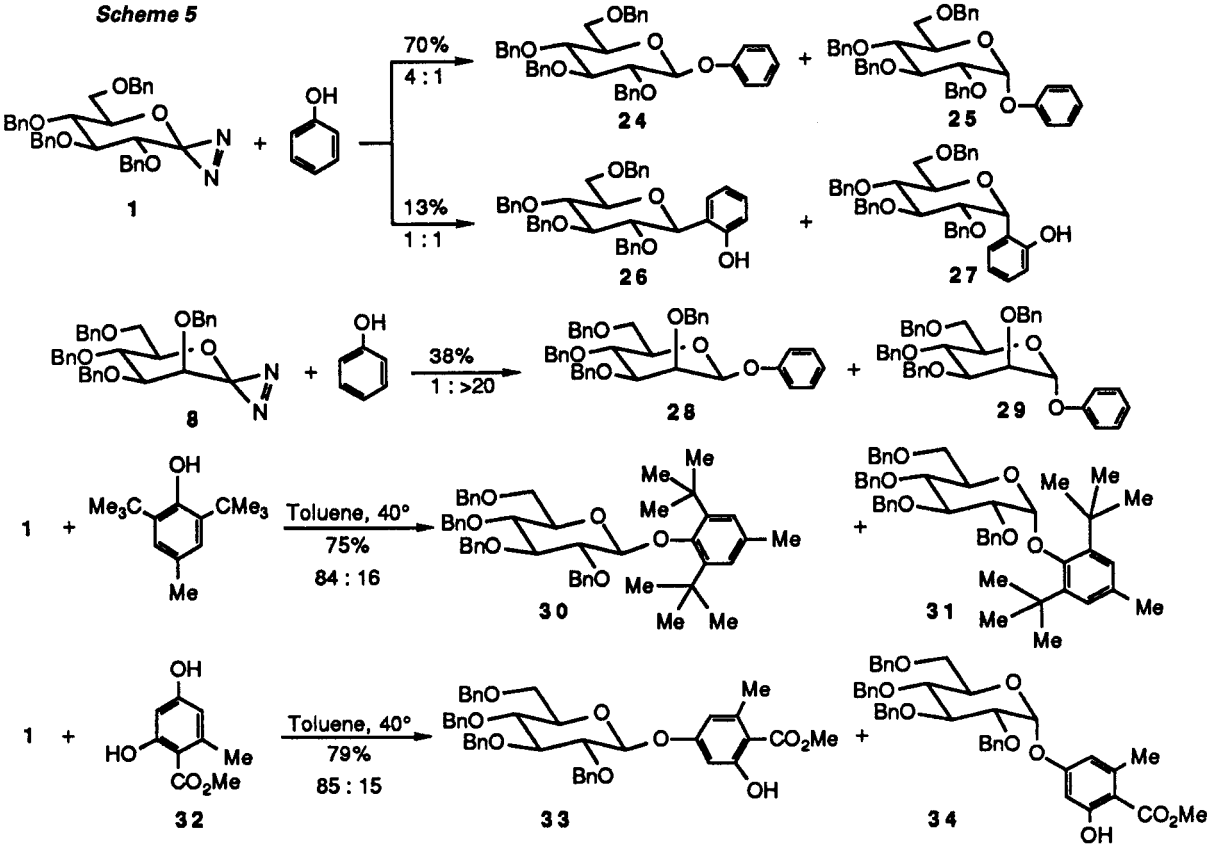


Scheme 4 shows the synthesis of some alkyl- and acyl-protected lactone tosylhydrazones of the pyranose and the furanose series. These carbene precursors are more easily accessible than the diazirines. Particularly important is the possibility to prepare furanose-derived lactone hydrazones (ref. 17), as furanose-derived diazirines decompose at very low temperatures (ref. 9). However, lactone tosylhydrazones react less cleanly then diazirines and give lower yields. Toluenesulfinate, liberated during formation of the carbenes, frequently participates in the formation of products (→ glycosylsulfones; ref. 12, 17).

Scheme 4



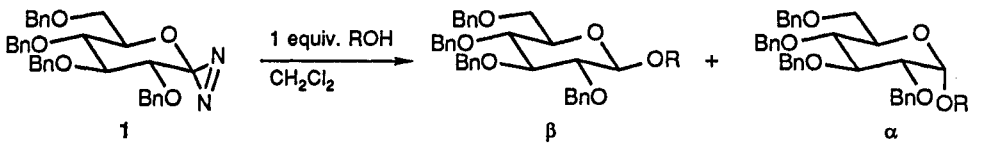
Scheme 5



GLYCOSYLATION OF PHENOLS AND OF MONOFUNCTIONAL ALCOHOLS

Scheme 5 illustrates the results of the glycosidation of phenols with diazirines. Optimised yields (for equimolar amounts of diazirine and phenol) amount to 75–80%. Main products are the 1,2-*trans* configurated O-glycosides, as demonstrated by the glycosidation of phenol by the *gluco*- and the *manno*-diazirines **1** and **8**, to yield mainly the β- and α-D-glycosides **24** and **29**, respectively. Glycosidation of nucleophilic phenols leads regioselectively to C-glycosides as byproducts. Steric hindrance of the phenol has no bearing on the yields and on the diastereoselectivity, as demonstrated by the formation of **30** and **31**. The regioselective glycosidation of methyl orsellinate (**32**) demonstrates that a hydroxy group which functions as a H-bond donor in an intramolecular H-bond is deactivated towards glycosidation; the monoglycosides **33** and **34** are obtained in good yields and again with a high degree of regioselectivity.

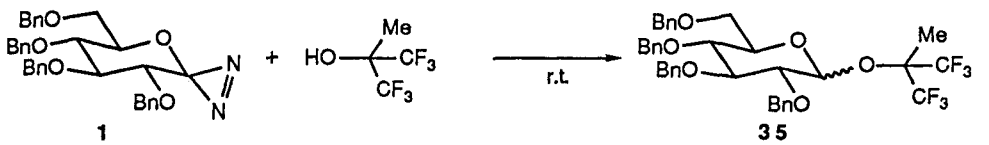
Scheme 6. Glycosidation of some monofunctional alcohols



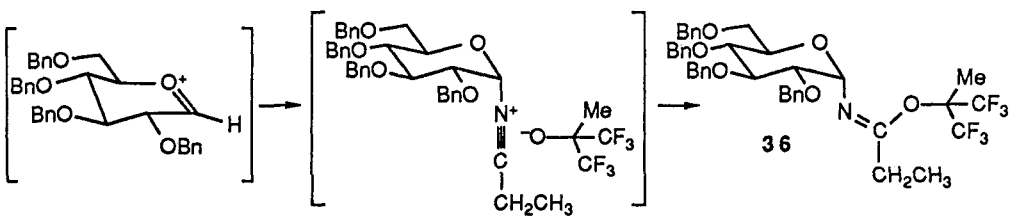
ROH	pK_{HA}	Yield [%] at r.t.	Yield [%] at –70° (hv)	β : α
CF_3CH_2OH	12.4	73	–	70 : 30
$(CF_3)_2CHOH$	9.3	77	–	78 : 22
$(CF_3)_2MeCOH$	9.6	74	–	84 : 16
MeOH	15.21	60	–	1 : 1
EtOH	15.85	55	–	1 : 1
Me_2CHOH	16.48	39	71	1 : 1
Me_3COH	16.54	34	60	1 : 1

Monofunctional alcohols form two classes with regard to glycosidation by **1** (*Scheme 6*). Strongly acidic alcohols behave similarly to phenols. With CH_2Cl_2 as the solvent, 1,2-*trans* configurated glycosides are obtained as main products and in good yields. Relatively low yields of glycosides are obtained from weakly acidic alcohols when they are used in equimolar amount, in CH_2Cl_2, and at room temperature. Yields are much better at low temperature; the carbene is then generated by photolysis. There is no stereoselectivity. Both the yields and the stereoselectivity for the glycosidation of strongly acidic alcohols depend upon the solvent. Ethers, particularly DME, are superior to CH_2Cl_2, as

Scheme 7. Influence of the solvent on the glycosidation of a hindered strongly acidic alcohol

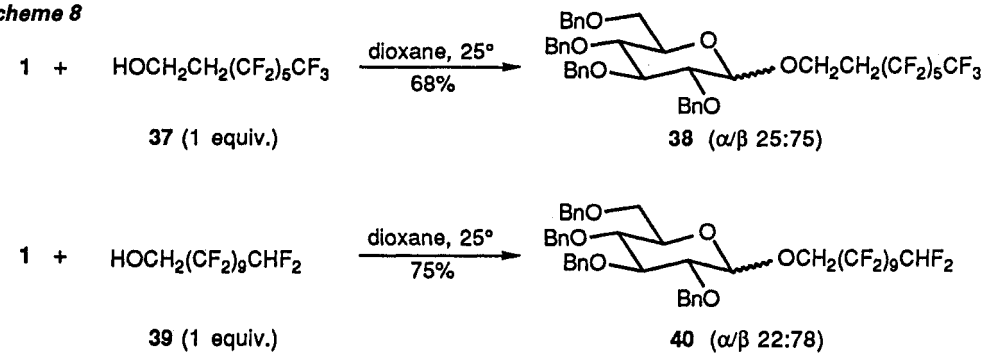


Solvent	Yield [%]	α : β
CH_2Cl_2	75	16 : 84
toluene	74	9 : 91
dioxane	76	5 : 95
THF	73	4 : 96
DME	80	2 : 98
propionitrile	54 (16% of **36**)	10 : 90
propionitrile, –60° (hv)	25 (16% of **36**)	13 : 87



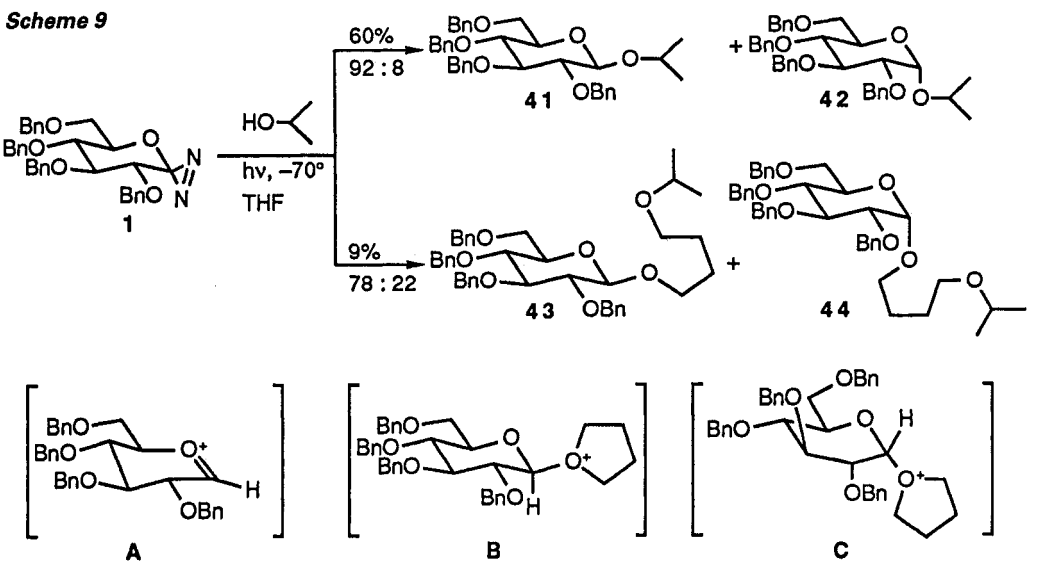
shown by the results in *Scheme 7*. These results (ref. 18) also demonstrate the absence of a significant influence of hindrance. Formation of the imidate **36** evidences solvation of an intermediate oxycarbenium ion by the nucleophilic solvent. In contrast to alcohols (ref. 3), the alcoholate attacks the nitrilium ion preferentially at the nitrilium-C, and not at the anomeric centre. Glycosylidene diazirines can be also used to prepare glycosides of long-chain, highly fluorinated alcohols (ref. 18, *Scheme 8*), which have attracted some interest as oxygen carriers (ref. 19).

Scheme 8



The outcome of the glycosidation of weakly acidic alcohols also depends upon the reaction conditions (*Scheme 9*). Thus, **1** reacts with 2-propanol in THF and at –70° to yield the anomeric glycosides **41** and **42** in a ratio of 92:8. Most significant are the glycosides **43** and **44**, isolated as byproducts of this reaction. They are products of the nucleophilic attack on the anomeric tetrahydrofuranylium ions **B** and **C** (ref. 7C, 18, 20).Together with the formation of the *Friedel-Crafts* alkylation products **26** and **27** (*Scheme 5*) in the glycosidation of phenol and the formation of the imidate **36** (*Scheme 7*), this constitutes strong evidence for the protonation of the intermediate carbene (ref. 11, 21) both by strongly and weakly acidic hydroxy compounds. We may thus advance a working hypothesis to explain the formation of 1,2-*trans* glycosides derived from strongly acidic hydroxy compounds both in weakly and in strongly coordinating solvents, the absence of stereoselectivity in the glycosidation of weakly acidic alcohols, and the formation of 1,2-*trans* (equatorial) glycosides derived from weakly acidic alcohols at low temperatures in THF as the solvent.

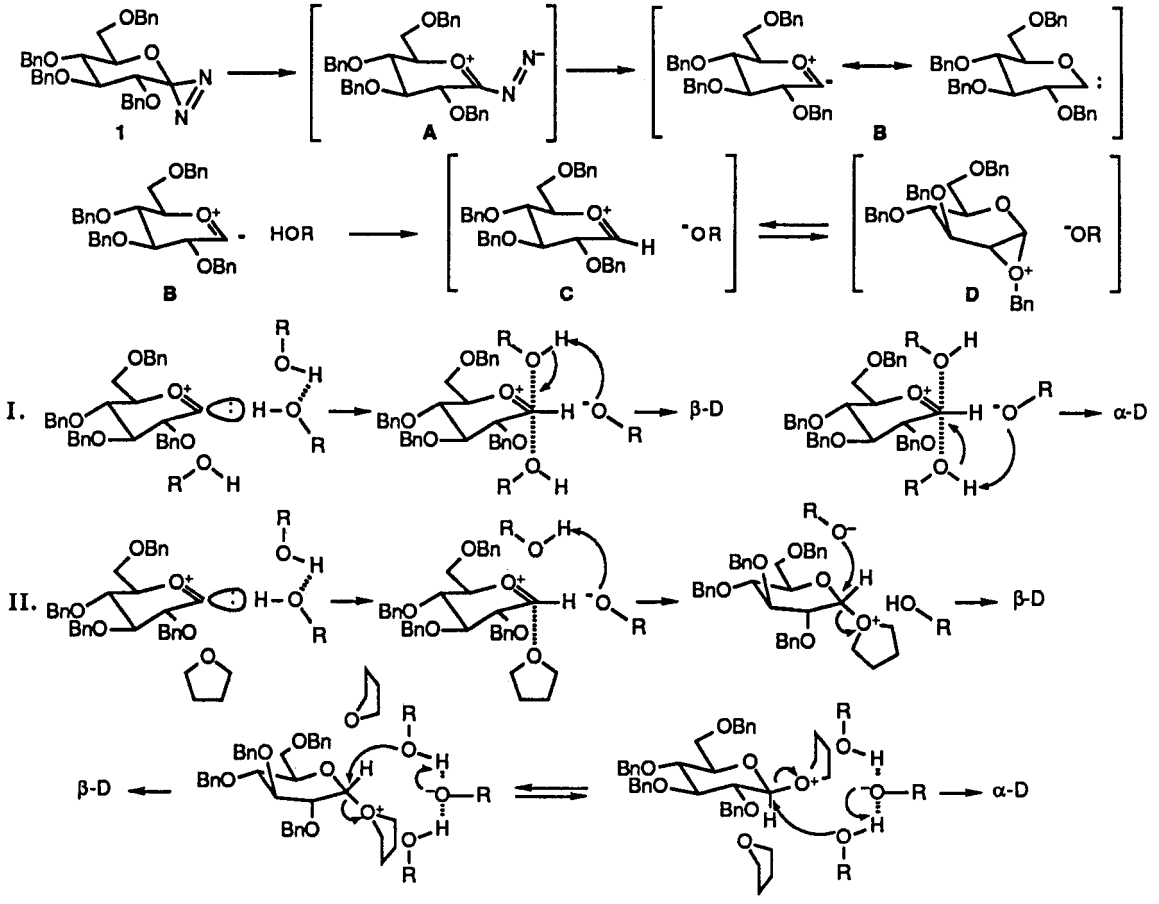
Scheme 9



WORKING HYPOTHESIS

The working hypothesis is formulated in *Scheme 10*. Three steps may be distinguished. In the first one, formation of the glycosylidene carbene is initiated by heterolysis of one of the C–N bonds of the diazirine. This leads to an intermediate zwitterion **A** with a cationic character at the anomeric centre. This zwitterion should rapidly lose nitrogen. In the second step, the resulting carbene **B** is protonated by the hydroxy compound to yield an ion pair **C**. This protonation takes place in the σ-plane of the carbene. It is important to realise that the third step, the combination of the ions to form the glycoside takes place by attack of the oxy-anion in the π-plane of the oxycarbenium ion. Unless special conditions are fulfilled (see below!), the third step is *a priori* not concerted with the second one. Solvation of the ions becomes an important issue.

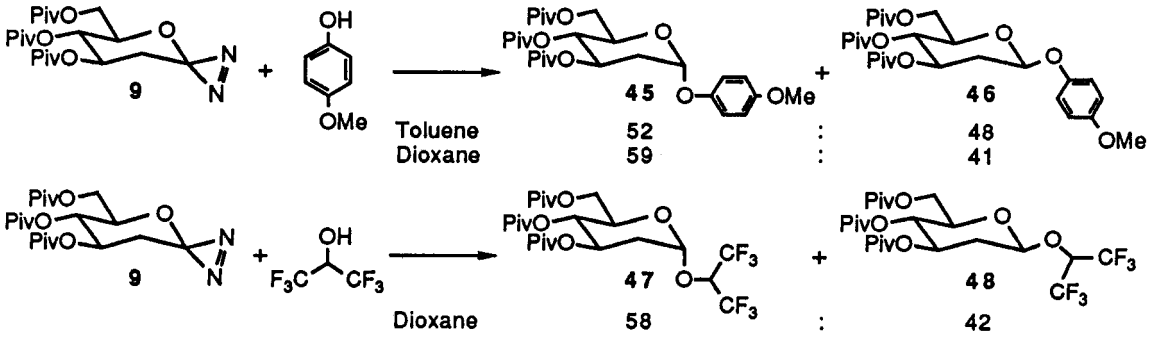
Scheme 10



Strongly acidic, and thus poorly nucleophilic alcohols will only weakly solvate the oxycarbenium ion. If they are glycosylated in a poorly coordinating solvent, the C(2)-benzyloxy group will be the best nucleophile in the neighbourhood of the cationic centre and solvate it. As a rule, this participation of the benzyloxy group is not observed for glycosylations of the *Koenigs-Knorr*-type. In *Scheme 10*, it is indicated in an extreme way (**D**). This participation directs the approach of the oxy-anion *trans* to the C(2)-benzyloxy group.

More strongly acidic alcohols lead to a faster protonation of the carbene (ref. 21). One therefore expects that oligomeric alcohol (ref. 11m, 11n) will protonate the carbene faster then monomeric alcohol. This is illustrated in the second part (I.) of *Scheme 10*. It illustrates that weakly acidic and thus relatively nucleophilic alcohols are expected to solvate the oxycarbenium ion more efficiently than the C(2)-benzyloxy group. The oxy-anion, derived from the protonating species cannot (directly) attack the oxycarbenium centre, being located in the σ-plane. However, rapid H-transfer from a hydrogen bonded neighbour (ref. 22) may generate an oxy-anion, correctly positioned for attack in the π-plane above or below of the cationic centre, to which it may already be coordinated. Either side of the cationic centre may be attacked. The newly generated oxycarbenium ion may also be solvated by the nucleophilic solvent of which the axial attack should be stereoelectronically favoured (*Scheme 10, II.*). This generates an α-D-configurated tetrahydrofuranylium ion, which, due to the reverse anomeric effect (ref. 23) may be more reactive then the equatorial anomer. At a low temperature, attack of the oxy-anion on the initially formed tetrahydrofuranylium ion leads preferentially to the

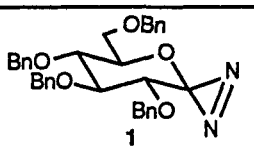
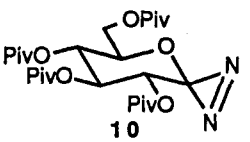
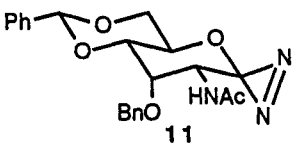
Scheme 11



equatorial glycoside; at higher temperatures, one expects equilibration of the tetrahydrofuranylium ions, with substantial loss of stereoselectivity.

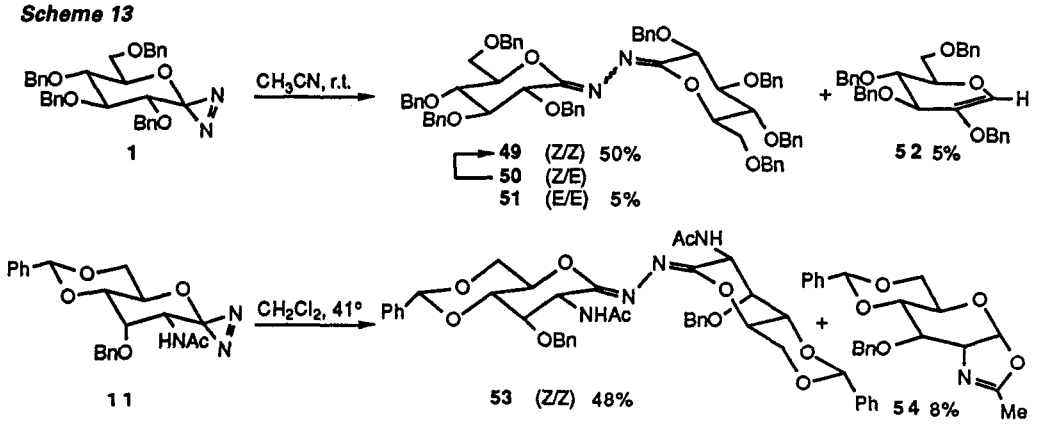
As shown in *Scheme 11*, the neighbouring group participation of the benzyloxy group is evidenced by the poor stereoselectivity in the glycosidation of 4-methoxyphenol and of hexafluoro-2-propanol with the diazirine **9**, derived from 2-deoxyglucose. At best, there is a weak preference for the axial, *1,2-cis* configurated glycosides **45** and **47** (ref. 24).

Scheme 12. Thermolysis of diazirines and activation energy at 25°

Diazirine	Solvent	E_a [kcal/mol]	τ [min]
 **1**	MeOH	23.0	33
 **10**	MeOH	25.0	202
 **11**	MeOH	28.1	4159

From a practical point of view, one should be able to predict the stability of these diazirines. The initial transformation of **1** into a zwitterion **A**, possessing a cationic character at the anomeric centre means that all the factors which *destabilise* a glycosyl cation will *stabilise* an alkoxyalkyl diazirine. We have measured the activation energy (first order kinetics) for the thermolysis (ref. 25) of the diazirines **1**, **10**, and **11** in methanol (*Scheme 12*). There is a significant difference between the activation energies of these diazirines at 25° (ref. 26), in keeping with the stronger σ-acceptor properties of the pivaloyloxy and the acetamido groups, as compared to benzyloxy groups, and with the strain imposed upon a glycosyl cation in the *trans*-trioxadecalin system (ref. 27). Ideally, one would compare the length of the two C-N bonds of each **1**, **10**, and **11** to find evidence for a preferred initial cleavage of one of these bonds. Only **11** yielded crystals suitable for X-ray analysis (ref. 28). There is a small difference for the bond lengths (< 3σ). The "pseudoaxial" bond is slightly longer, as one might expect.

Scheme 13

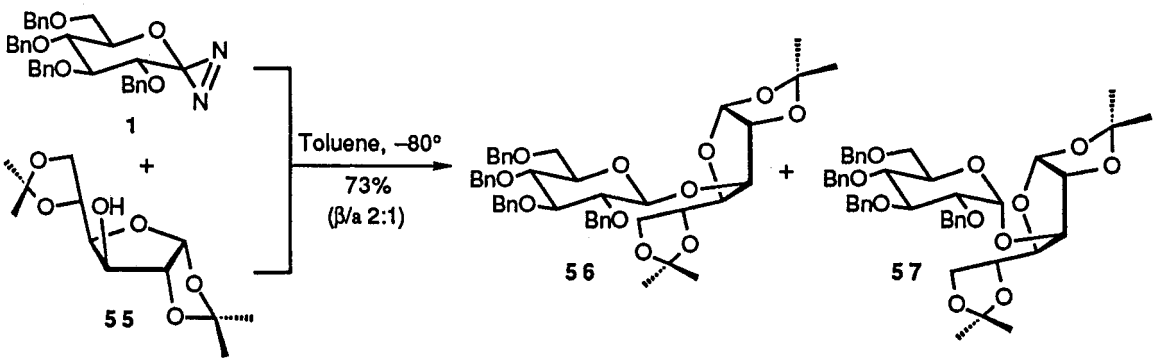


The main products of thermolysis of 1-azi-glycoses in non-hydroxylic solvents (ref. 26) are lactone azines (*Scheme 13*), derived from the interaction of carbenes with diazirines (ref. 29). At room temperature, **1** leads to a mixture of the (Z/Z), (Z/E), and (E/E) configurated isomers **49–51**. The unstable (Z/E) configurated **50** transforms into the major (Z/Z) isomer **49**. Very little of **52**, the product of H-migration, is formed. Thermolysis of **11**, necessarily at a somewhat higher temperature, leads exclusively to the (Z/Z) azine **53** and to small amounts of the oxazolidine **54**, presumably derived from the intermediate carbene by protonation and neighbouring group participation. These products of thermolysis are also observed as byproducts of reactions with weakly reactive partners.

GLYCOSYLATION OF DIOLS AND TRIOLS

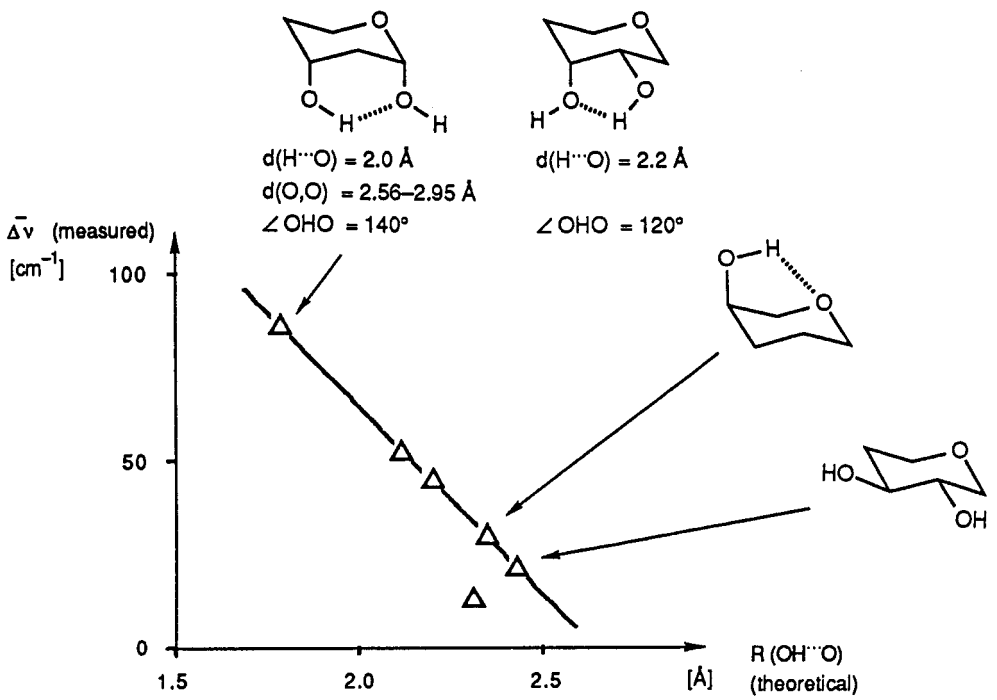
Glycosylation of monofunctional alcohols and of phenols by 1-azi-sugars shows a strong influence of the (kinetic) acidity of hydroxy compounds on yields and stereoselectivity. Regioselective glycosidation ought to succeed when there is a relatively large difference in the degree of acidity of hydroxy groups. As indicated by the regioselective glycosylation of orsellinate (*Scheme 5*), intramolecular H-bonds may lead to a differentiation of hydroxy group reactivity and to a high degree of regioselectivity. For mono- and oligosaccharides, which are less acidic than phenols, one ought to look for hydroxy groups which function as H-bond acceptors. Such hydroxy groups possess an increased kinetic acidity, which should be more important for a successful glycosidation *via* carbenes than the concomitant lowered degree of acidity for H-bond donating hydroxy groups (ref. 30). This is evidenced by the glycosylation of diisopropylideneglucose (**55**) by 1 equivalent of **1** in toluene (*Scheme 14*). Although the reaction yields 73% of the glycosides **56** and **57**, it proceeds with an unsatisfactory degree of selectivity (β-D/α-D 2:1) (ref. 18).

Scheme 14



To predict the existence of (relatively) strong H-bonds for partially protected saccharides in organic solvents, we started from the observation that intramolecular H-bonds in crystals of saccharides are much less frequent than intermolecular ones (ref. 30 p. 149 and p. 169 ff., 31). Hence, intramolecular H-bonds in crystals indicate relatively strong intramolecular H-bonds, which may persist in solution. A second parameter, directly relevant to the existence of intramolecular H-bonds in solution, is given by the shift to lower frequencies and by the broadening of O–H absorption bands in the IR spectra of dilute solutions of alcohols (ref. 30 p. 50 ff., 32).

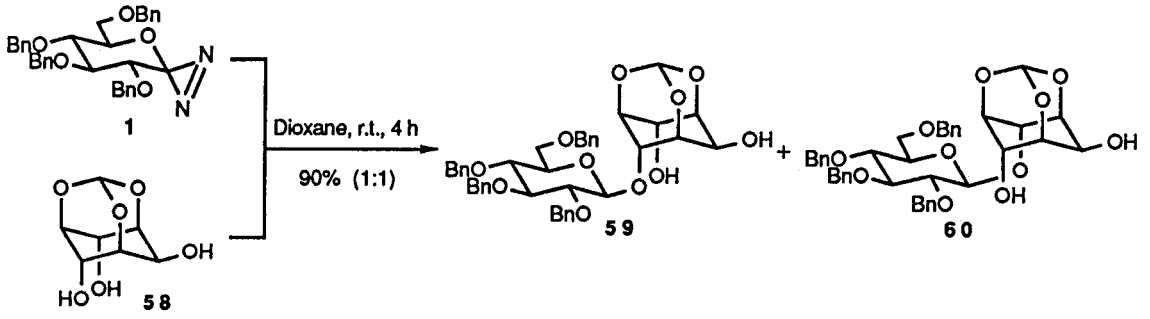
Scheme 15. Intramolecular H-bonds from X-ray analysis and IR spectroscopy



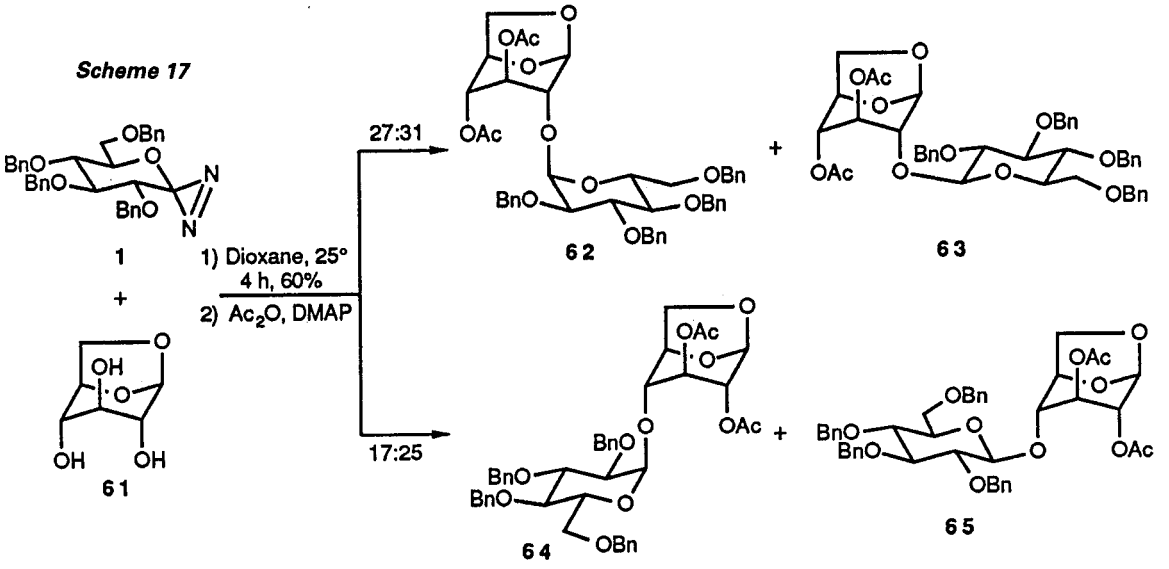
Scheme 15 (modified from ref. 32) shows a correlation of IR band shifts, (OH···O)-distances, and the relative orientation of H-bond donor and acceptor groups in pyranoses. According to this correlation, we expect the best regio-

selective glycosidations for 1,3-diaxial diols. Regioselectivity should be lower for 1,2-*cis*-diols and for diols possessing one axial hydroxy group in position 2 or 4. Regioselective glycosidation of equatorial 1,2-*trans*-diols ought to be difficult.

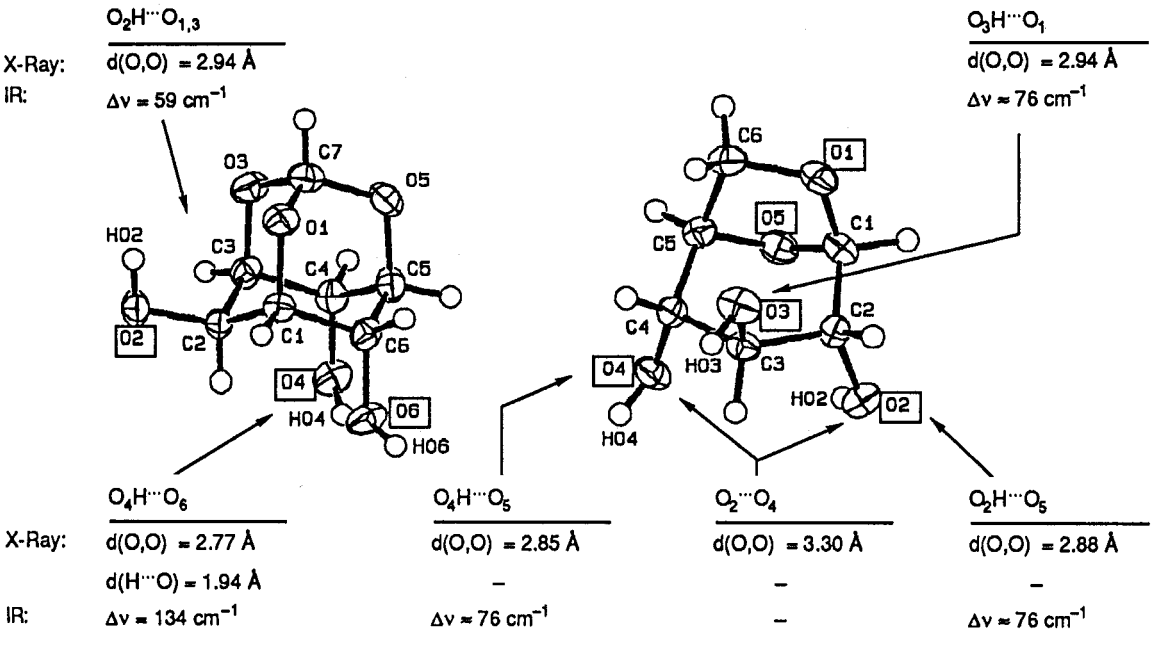
Scheme 16



Scheme 17

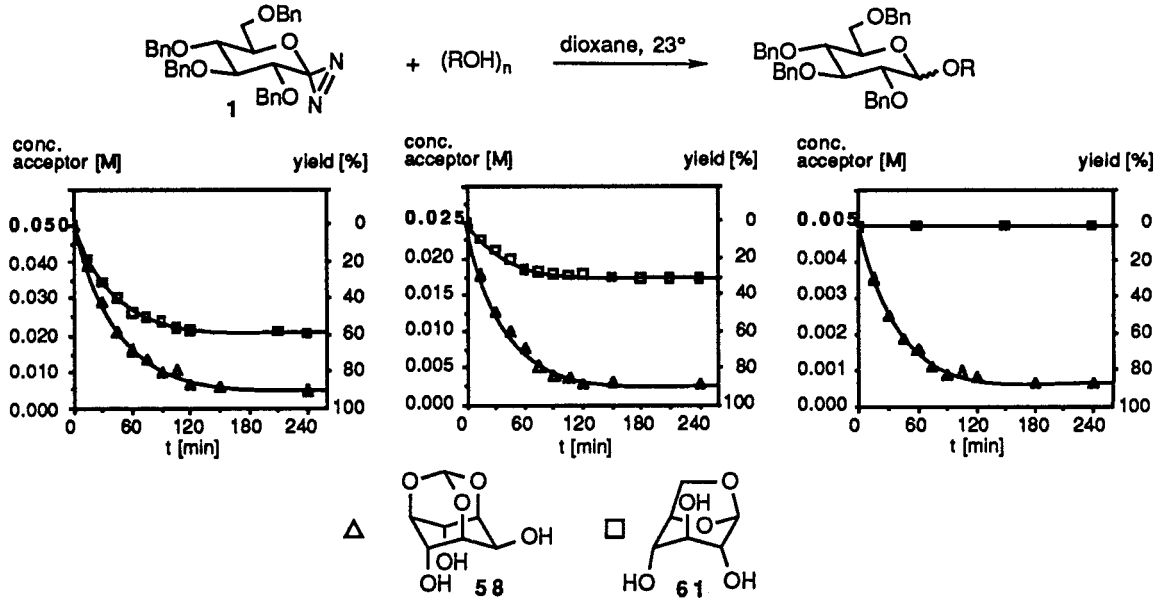


Scheme 18. X-ray structures of 58 and 61



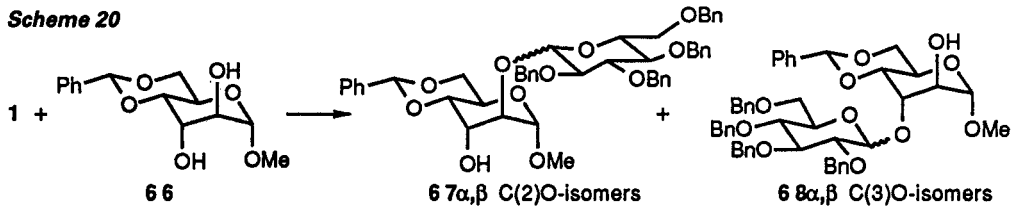
Glycosidation of the *myo*-inositol derivative **58**, possessing a 1,3-diaxial diol unit indeed yielded 90% of the two β-D-configurated *mono*glycosides **59** and **60**, derived from glycosidation of the enantiotopic axial hydroxy groups (*Scheme 16*). The equatorial hydroxy group is not glycosylated (ref. 33). Glycosylation by the 2-deoxy-1-azi-glucose **9** shows no stereoselectivity (ref. 34). These results agree with expectation. Glycosidation of 1,6-anhydro-glucose (**61**) by **1** gave markedly different results (*Scheme 17*). Yields are sensibly lower. The HO–C(3) group is practically not reactive. There is not much regiodifference for HO–C(2) (→ **62** and **63**) and HO–C(4) (→ **64** and **65**). There is a low degree of stereoselectivity. Hence, **58**, but not **61** should possess an intramolecular H-bond. Indeed, X-ray analysis of **58** (ref. 33) shows a relatively strong intramolecular H-bond (*Scheme 18*), which is also present in solution, as evidenced by a shift of 134 cm^{-1} for the IR band corresponding to the axial hydroxy groups. A smaller band shift for the equatorial hydroxy group indicates that it forms a weak H-bond, lowering its reactivity. No intramolecular H-bond is found for **61** in the solid state (ref. 35), the distance between the two *cis*-hydroxy groups being too long ("reverse reflex effect"; ref. 36). Its IR spectrum shows only one OH-band shift of 76 cm^{-1}, indicating that the three OH groups are involved in OH-bonds. While HO–C(2) and HO–C(4) compete for O(5) as H-bond acceptor, HO–C(3) may always form a H-bond with O(1), and this could explain its deactivation.

Scheme 19. Dependence of the glycosidation on the concentration of the acceptor



Does the glycosylation of **61** reflect the reactivity of the monomer, or does **61** only react because the acidity of HO–C(2) and of HO–C(4) is enhanced by intermolecular H-bonds? This question is answered by the dependence of glycoside formation upon the concentration of the triols **58** and **61** (*Scheme 19*). Increasing dilution affects the yields of glycosides derived from the triols **58** and **60** in a very different way; no influence is visible for the glycosidation of **58**, while the yields obtained from **61** are strongly affected. Lowering the concentration by one order of magnitude suppresses the formation of glycosides completely. Evidently, dimeric or oligomeric **61** reacts with the carbene.

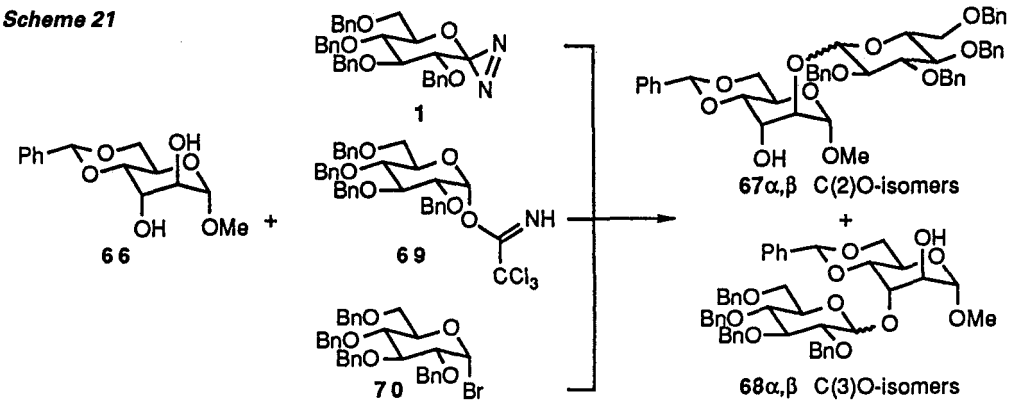
Scheme 20



Reaction conditions (1.1 eq. Diazirine)	Total yield [%]	Regioselectivity 67α,β:68α,β	Diastereoselectivity 67α:67β	68α:68β
$ClCH_2CH_2Cl$, 24°	71	93: 7	35:65	51:49
CH_2Cl_2, 24°	52	82:18	41:59	73:27
dioxane, 24°	57	87:13	18:82	18:82
THF, –80°, hv	50	71:29	5:95	17:83

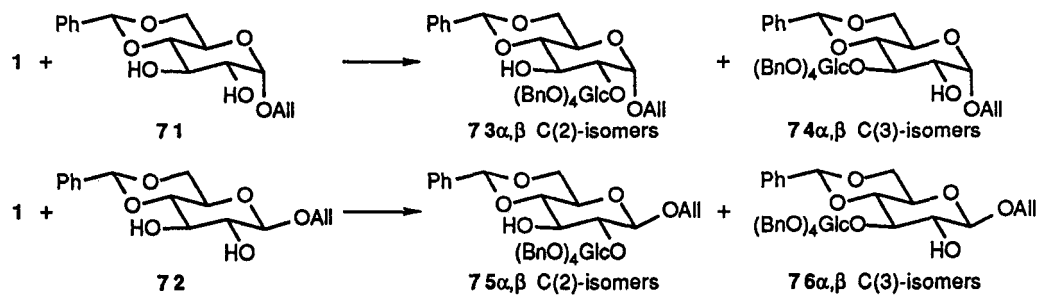
H-bond donation by an alcoholic hydroxy group lowers its kinetic acidity. Such a group should be less reactive towards a glycosylidene carbene. However, as one may consider such a hydroxy group to be partially deprotonated, it ought to be more reactive towards a glycosyl cation, i.e. in a *Koenigs-Knorr*-type glycosylation. A situation as it is realised in the *altro*-diol **66** should thus lead to a (complementary) regioselective glycosidation by either method (ref. 37). This is shown in *Scheme 20* for the reaction of **66** with **1**. Two regioisomeric pairs of anomers result. Regioselectivity is better than 9:1 and favours glycosidation at C(2), as expected. Diastereoselectivity is unsatisfactory. Yield and selectivity depend upon the reaction conditions, particularly the solvent. Regioselectivity was highest when $ClCH_2CH_2Cl$ is used, and diastereoselectivity was best in THF or dioxane. There is a consistent preference for **67β**. With the exception of CH_2Cl_2, all solvents also favour formation of **68β**. Concerning the ease of predicting H-bonds, one may note that X-ray analysis of **66** only shows intermolecular H-bonds, while IR spectra evidence a strong intramolecular H-bond. Osmometry indicates that **66** is monomeric, and dilution experiments that it reacts as the monomer!

Scheme 21



Donor	Solvent	Temp. [°C]	Promoter	Yield 67/68 [%]	Regioselectivity 67α,β:68α,β	Diastereoselectivity 67α:67β	68α:68β
1	$ClCH_2CH_2Cl$	24		71	93: 7	35:65	51:49
69	$ClCH_2CH_2Cl$	-30	1.0 eq. of $BF_3{\cdot}Et_2O$	67	9:91	46:54	52:48
70	CH_2Cl_2	24	1.0 eq. of Et_4NBr	78	12:88	21:79	only α

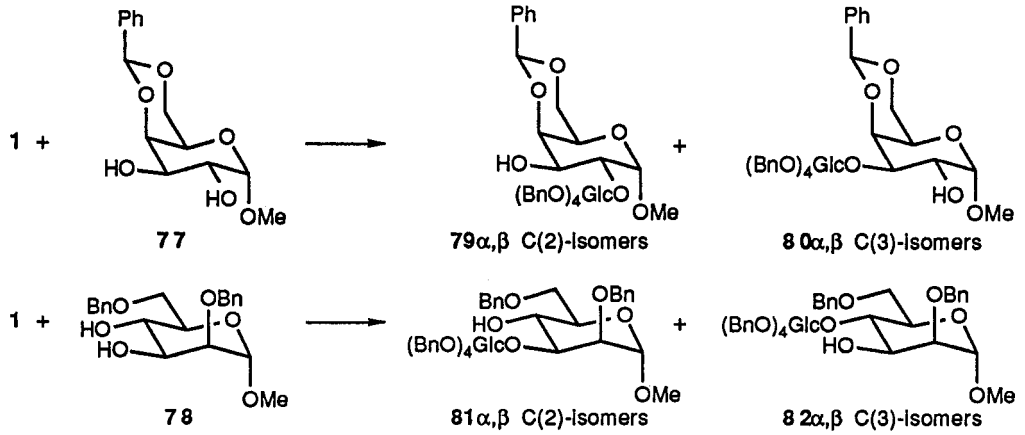
Scheme 22



Diol	Solvent	Diol : 1	Temp. [°C]	Yield [%]	Regioselectivity C(2)O : C(3)O	Diastereoselectivity α:β C(2)O	α:β C(3)O
71	Toluene	1.3 : 1.0	50	69	37 : 63	37 : 63	34 : 66
71	Dioxane	1.3 : 1.0	22	72	44 : 56	39 : 61	36 : 64
71	$ClCH_2CH_2Cl$	1.0 : 1.3	22	89	46 : 54	46 : 54	38 : 61
72	Toluene	1.3 : 1.0	70	70	47 : 53	40 : 60	44 : 56
72	Dioxane	1.3 : 1.0	22	69	46 : 54	32 : 68	38 : 62
72	$ClCH_2CH_2Cl$	1.0 : 1.3	22	94	52 : 48	53 : 47	35 : 65

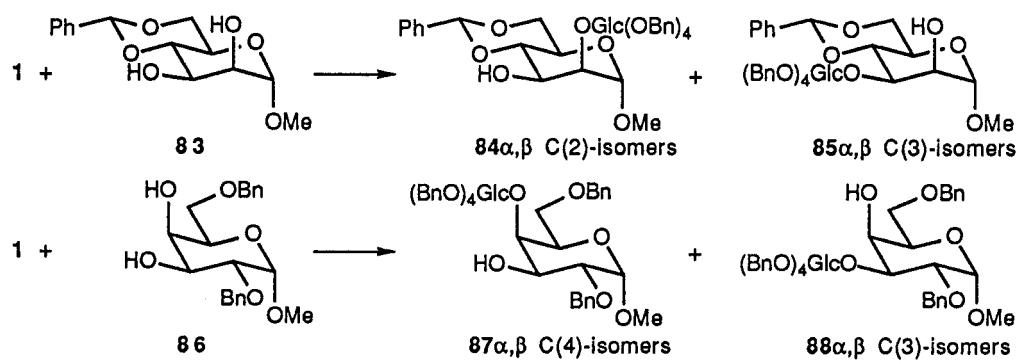
To demonstrate the complementarity between the carbene-mediated and the *Koenigs-Knorr*-type glycosylation, we exposed **66** to the conditions of the *Schmidt*- and of the *Lemieux*-glycosylation (ref. 1a and 38). Indeed, both donors, **69** and **70**, gave predominantly **68**, derived from glycosylation of HO–C(3) (*Scheme 21*). Moreover, the halide-exchange method was highly stereoselective, suggesting that it may be very well suited for the regioselective glycosylation of acceptors possessing such a H-donating hydroxy group.

Scheme 23



Diol	Solvent	Diol : 1	Temp. [°C]	Yield [%]	Regioselectivity	Diastereoselectivity	
					79α,β : 80α,β	79α:79β	80α:80β
77	Toluene	1.3 : 1.0	70	70	50 : 50	35 : 65	46 : 54
77	Dioxane	1.3 : 1.0	23	75.5	50 : 50	39 : 61	59 : 41
77	$ClCH_2CH_2Cl$	1.0 : 1.3	23	80	50 : 50	44 : 56	52 : 48
					81α,β : 82α,β	81α:81β	82α:82β
78	Toluene	1.3 : 1.0	70	75	54 : 46	64 : 36	48 : 52
78	Dioxane	1.3 : 1.0	24	71	50 : 50	59 : 41	52 : 48
78	Dioxane	1.0 : 1.3	24	80	49 : 51	61 : 39	49 : 51

Scheme 24



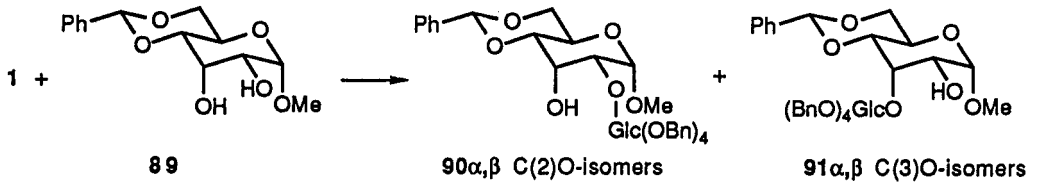
Diol	Solvent	Diol : 1	Temp. [°C]	Yield [%]	Regioselectivity	Diastereoselectivity	
					84α,β : 85α,β	84α:84β	85α:85β
83	Toluene	1.3 : 1.0	70	89	24 : 76	38 : 62	40 : 60
83	Dioxane	1.3 : 1.0	23	83	29 : 71	29 : 71	39 : 61
83	$ClCH_2CH_2Cl$	1.0 : 1.3	23	96	39 : 61	48 : 52	38 : 62
					87α,β : 88α,β	87α:87β	88α:88β
86	Toluene	1.3 : 1.0	70	68	14 : 86	47 : 53	54 : 46
86	Dioxane	1.3 : 1.0	24	67	26 : 74	39 : 61	51 : 49
86	Dioxane	1.0 : 1.3	24	74	25 : 75	39 : 61	47 : 53

To further study the effect of H-bonds upon regioselectivity, we examined the glycosidation of pyranosides possessing 1,2-*cis* axial-equatorial, and 1,2-*trans* diequatorial diol units (ref. 39). As shown in *Scheme 22*, the *trans*-diequatorial *gluco*-diols **71** and **72** are monoglycosylated in fair yields (relative to **1**). A small excess of the diazirine boosts the yield (referring to the diols) to 90%, but there is hardly any regio- and little stereoselectivity. The neighbourhood of the anomeric centre has a small influence on yield and selectivity, as may be gathered by comparing these results to those presented in *Scheme 23*. Both the 1,2-*trans* diequatorial *galacto*-diol **77** and the analogous *manno*-diol **78** react with very poor regio- and poor stereoselectivity. The situation is more favourable in 1,2-*cis* diols (*Scheme 24*). The

equatorial hydroxy group of the *manno*-diol **83** is more reactive, and yields of **85** are quite good, with a slight preference for the β-D-anomer. Similarly, the equatorial hydroxy group of the *galacto*-diol **86** is preferentially glycosylated, but again with a low degree of stereoselectivity.

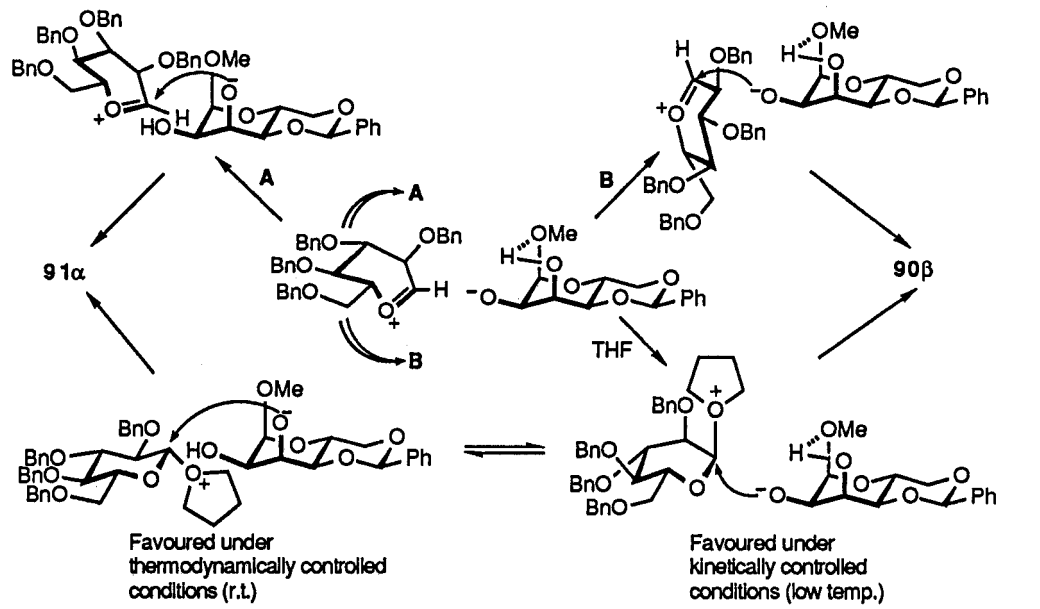
The preferential glycosylation of the equatorial hydroxy group of **86** is surprising. Similarly as for the *altro*-diol **66**, one would expect the results of the carbene-mediated and of the *Koenigs-Knorr* type glycosylation of **86** to be complementary to each other. Thus, the nucleophilicity of the axial hydroxy groups of **83** and of **86** should be enhanced, if their weak reactivity towards a carbene is due to a lowered kinetic acidity (H-bond to the ring-oxygen). It is, however, the equatorial hydroxy group of *galacto* 3,4-diols which reacts preferentially in a *Koenigs-Knorr*-glycosidation, unless highly insoluble promoters are used (ref. 7b, 7f, 7j, 7l–q, 7v, 7x, 7y).

Scheme 25



Solvent	Temp. [°C]	Yield [%]	Regioselectivity 90α,β : 91α,β	Diastereoselectivity 90α : 90β	91α : 91β
Toluene	70	79	20 : 80	32 : 68	72 : 28
Dioxane	24	81	28 : 72	39 : 61	89 : 11
THF	24	75	40 : 60	25 : 75	66 : 34
THF	–85	79	72 : 28	10 : 90	67 : 33

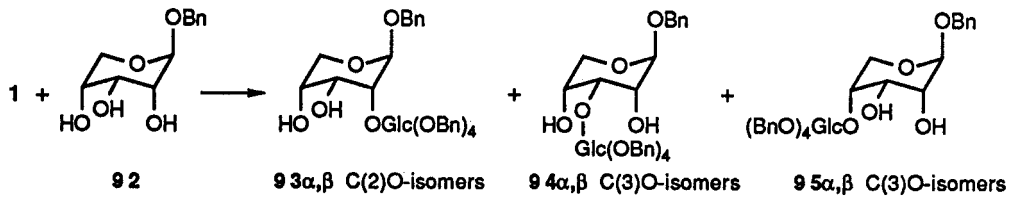
Scheme 26



The behaviour of **83** and **86** towards carbenes may find its explanation in the light of the results with the *allo*-diol **89** (*Scheme 25*). X-ray analysis, ^{1}H-NMR, and IR spectra demonstrate a H-bond between the axial HO–C(3) and the methoxy group. The kinetic acidity of HO-C(3) should thus be lowered, and one may expect glycosidation at HO–C(2). It is, however, HO–C(3) which is preferentially glycosylated, except in THF and at a low temperature. Also, one notes a different anomeric selectivity for the formation of **90** and **91**. To rationalise these results, one has to remember that protonation of the carbene by the kinetically most acidic hydroxy group takes place in the σ-plane of the carbenic centre, while the ensuing oxycarbenium ion is attacked in the π-plane. The two hydroxy groups of **89** are located in two different planes. If HO–C(2) protonates the carbene in the σ-plane, then HO–C(3) is favourably placed in the π-plane of the oxycarbenium ion. All that is required is a (facile) proton shift to $^-$O–C(3), then HO-C(3) attacks. We can explain the regio- and the stereoselectivity by assuming a specific orientation of carbene and diol, which leads to the ion pair, depicted in *Scheme 26*. If proton transfer from HO-C(3) to $^-$O–C(2) is accompanied by a relative movement of the carbocation according to **A**, one obtains **91α**. A movement according to **B** leads to attack by $^-$O–C(2), and to **90β**. The process **B** implies a (partial) dissociation of the ion pair. Hence, the preferred pathway under all conditions, except in

THF at low temperature, is formation of **91α**. For the reactions in THF, solvation of the oxycarbenium ion from the axial side is kinetically preferred, as discussed above. Substitution with inversion of the configuration at the anomeric centre requires attack by ⁻O–C(2), and leads to **90β**, the major product under these conditions. At higher temperatures, the tetrahydrofuranylium ions equilibrate, and a competing inverting substitution of the presumably more reactive β-D-anomer by ⁻O–C(3) takes place from the α-side leading to **91α** (ref. 40).

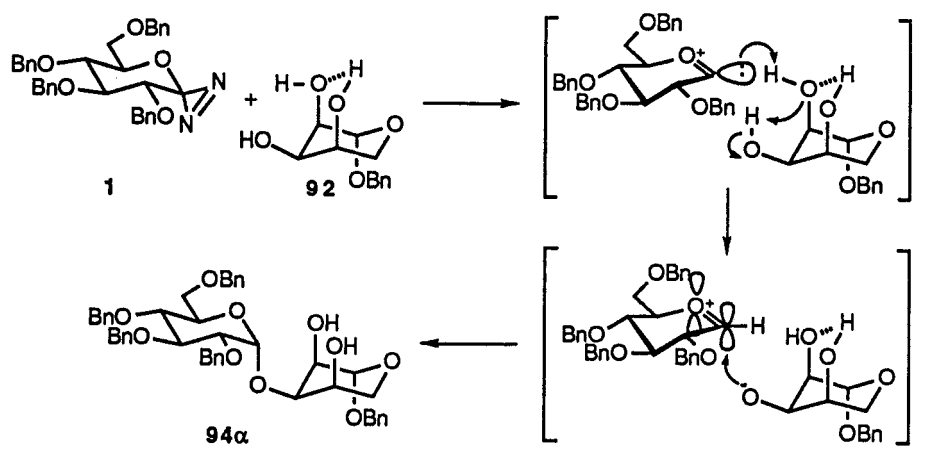
Scheme 27



92 **93α,β** C(2)O-isomers **94α,β** C(3)O-isomers **95α,β** C(3)O-isomers

Solvent	Conc.	Temp.	Total yield	Regioselectivity	Diastereoselectivity		
	[M]	[°C]	[%]	93α,β:94α,β:95α,β	93α:93β	94α:94β	95α:95β
dioxane	0.05	27	69	30 : 40 : 30	33 : 67	75 : 25	60 : 40
CH_2Cl_2	0.05	22	85	17 : 59 : 24	41 : 59	80 : 20	63 : 37
CH_2Cl_2	0.05	–78	66	14 : 57 : 29	57 : 43	75 : 25	72 : 28
CH_2Cl_2	0.005	–78	63	5 : 81 : 14	40 : 60	77 : 23	64 : 36

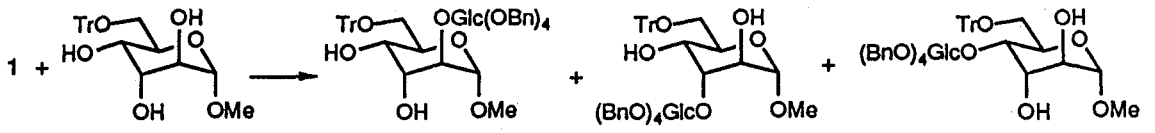
Scheme 28



Glycosidation of the *ribo*-triol **92** exemplifies a situation which is complementary to the one illustrated by the *allo*-diol **89** (*Scheme 27*). Here, protonation of the carbene by one of the axial hydroxy groups – the one acting as a H-bond acceptor in the hydrogen bonded 1,3-diaxial diol unit – should be followed by hydrogen transfer from the equatorial hydroxy group and by glycosidation at ⁻O–C(3). Indeed, the major regioisomers are **94α** and **94β**. Among the minor regioisomers, there is a slight preference for **93β**, and for **95α**. Dilution experiments suggest that the major isomer is formed from the monomeric, and the minor products from oligomeric triol. A plausible transition state is formulated in *Scheme 28* (ref. 40).

One may now attempt to predict the regioselectivity of the glycosidation of the triol **96** (*Scheme 29*). We expect a H-bond between HO–C(3) and the methoxy group and a low kinetic acidity for HO–C(3). The most acidic hydroxy group should be HO–C(2), as it is vicinal to the acetal centre, and *trans*-axial to two C–O bonds. The carbene derived from **1** should be preferentially protonated by this group. As there is no hydroxy group *cis* to ⁻O–C(2) and favourably located to attack the oxycarbenium ion in the π-plane, we have to assume dissociation of the ion pair, and attack by ⁻O–C(2). Next, we expect protonation by HO–C(4). Attack in the π-plane of the oxycarbenium ion is presumably only possible by HO–C(3) as the H-bond from HO–C(3) to the methoxy group points away from the ⁻O–C(4). Intramolecular proton transfer to ⁻O–C(4) may therefore not be rapid enough. Still, HO–C(3) should be nucleophilic enough to ensure its rapid glycosidation by the glycosyl cation. The ratio of regioisomers corresponds qualitatively to this prediction. There is little stereoselectivity in the formation of the major regioisomers **97** (dissociation of the ion-pair!), except at low temperatures in THF, where **97β** dominates, as expected (ref. 40).

Scheme 29

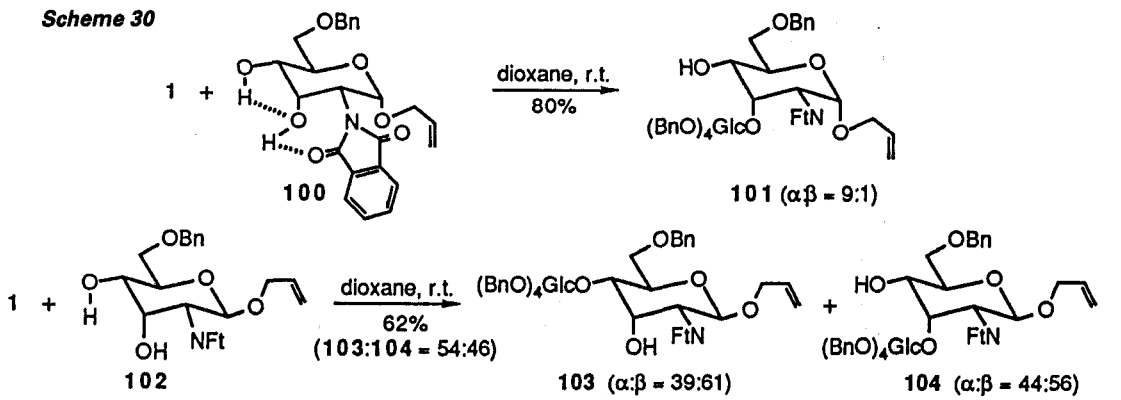


96 **97**α,β C(2)O-isomers **98**α,β C(3)O-isomers **99**α,β C(3)O-isomers

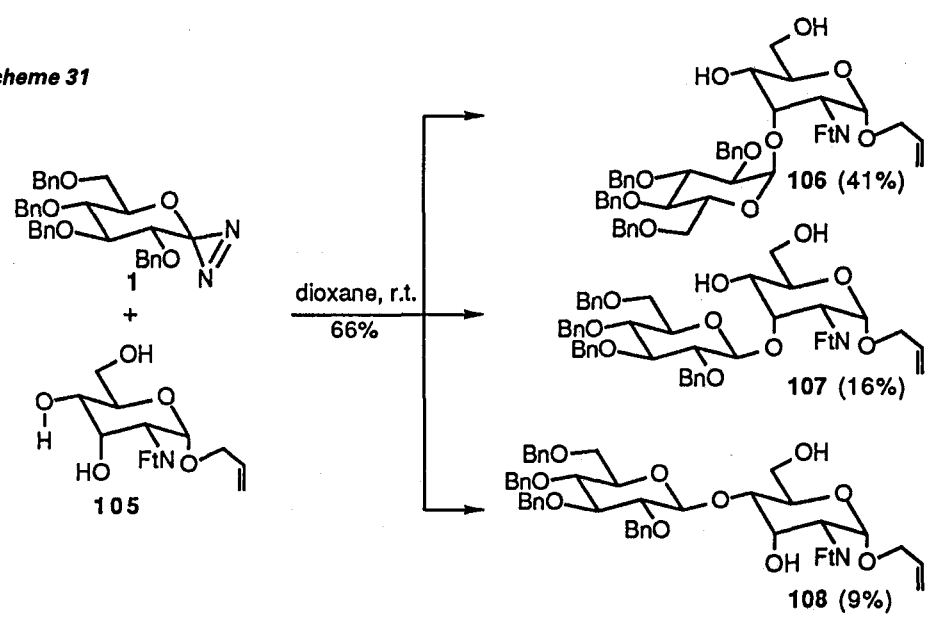
Solvent	Temp. [°C]	Total Yield [%]	Regioselectivity 97α,β:98α,β:99α,β	Diastereoselectivity 97α:97β	98α:98β	99α:99β
CH_2Cl_2	24	53	57 : 30 : 13	49 : 51	46 : 54	64 : 36
dioxane	24	49	50 : 37 : 13	62 : 38	36 : 64	54 : 46
THF	24	54	47 : 39 : 13	49 : 51	28 : 72	50 : 50
THF	–80	50	43 : 52 : 5	9 : 91	13 : 87	84 : 16

A particularly strong intramolecular H-bond (IR: $\Delta\nu = 253\ cm^{-1}$) is formed between HO–C(3) and one of the carbonyl groups of the N-phthalimido substituent in **100** (*Scheme 30*). There is also good evidence for a weaker H-bond between HO–C(4) and O–C(3). Reaction of **100** with **1** gave **101** regiospecifically and in good yields. Stereoselectivity is also high, and favours **101**α. Initial protonation by HO–C(4) is evidenced by the finding that the 4,6-O-benzylidene-analogue of **100** is not glycosylated by **1**. In **100**, as in **96**, the glycosyl cation is attacked by the neighbouring hydroxy group, as the geometry of the H-bond is unfavourable for a hydrogen transfer to the initially formed ⁻O–C(4). The conformation of the phthalimido group in the β-D anomer **102** is different from the one in **101**; yields (60%; 30% recovered **102**), regio-, and stereoselectivity of the glycosidation of **102** are much lower.

Scheme 30

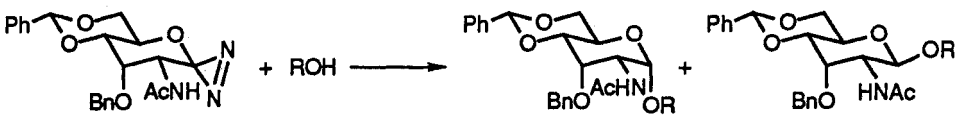


Scheme 31

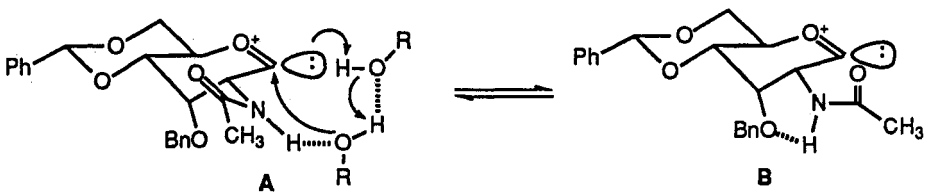


The triol **105** (*Scheme 31*) reacts again with a high degree of regioselectivity, yielding mostly **106** and its anomer **107**; no products of glycosidation of the primary hydroxy group are found. This is not trivial. The glycosyl cation, formed by deprotonation of HO–C(4) could, *a priori*, be attacked by HO–C(3) or by the primary hydroxy group. The large value of $J_{HO-C(4),H}$ in the ^{1}H-NMR spectrum of **105**, however, shows that the HO–C(4)-bond is directed below the plane of the pyranose ring. That is the direction from which the carbene approaches HO–C(4), if proton transfer to the carbene is approximately linear. Thus, the glycosyl cation will also be located below the pyranose ring plane, away from HO–C(6). One may conclude that not only the kinetic acidity of a hydroxy group and its geometric relation to neighbouring hydroxy groups, but also the population of its rotamers may be reflected in the regioselectivity of the glycosidation. Evidently, the expected higher nucleophilicity of HO–C(3) (strong H-bond!) is not to be neglected (ref. 41).

Scheme 32

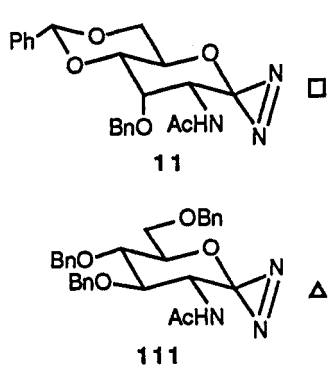


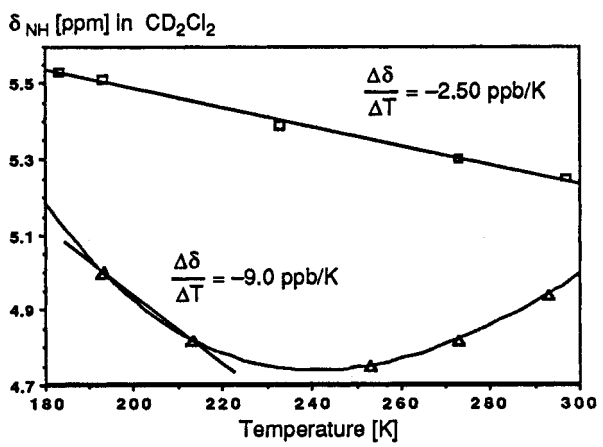
ROH	pK_{HA}	Conditions	Yield [%]	α : β
$(CF_3)_2CHOH$	9.3	CH_2Cl_2, –84° hv	109: 88	52 : 48
		CH_2Cl_2, 41°	109: 85	76 : 24
$(CH_3)_2CHOH$	17.1	CH_2Cl_2, –84° hv	110: 72	78 : 22
		CH_2Cl_2, 41°	110: 12	only α



Yet another effect of hydrogen bonding became apparent, when we examined the reaction of the AllNAc-derived diazirine **11** with alcohols (*Scheme 32*). At 41°, the strongly acidic hexafluoro-2-propanol yielded over 80% of a mixture of **109**α,β, the α-D-anomer dominating to an extent of 76:24! Stereoselectivity almost disappears at low temperature. A similar result is observed for the reaction of **11** with 2-propanol, with the difference that the stereoselectivity at low temperatures is higher for this weakly acidic alcohol. Under thermal conditions, **110**β is only formed in low yields (ref. 42).

Scheme 33

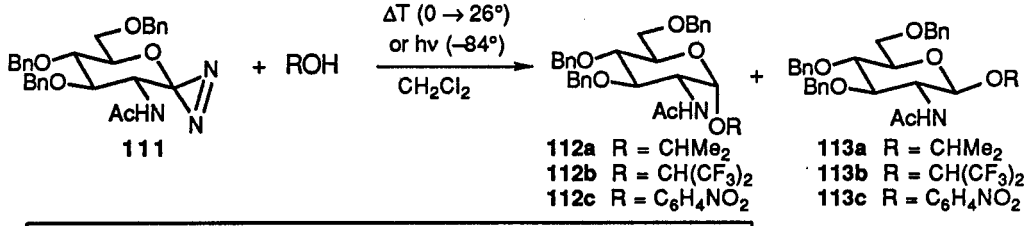




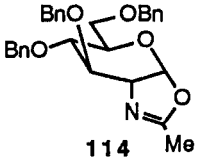
This unprecedented behaviour is explained by an intermolecular H-bond from the acetamido group to the glycosyl acceptor, as depicted in *Scheme 32* (A). This H-bond competes with an intramolecular H-bond to the benzyloxy group (B). At low temperatures, rotation around the N–C(2) bond is restricted, and the intramolecularly H-bonded species dominates. Hence, formation of the α-D-anomer is more strongly preferred at higher temperatures. The intramolecular H-bond should be much weaker – if it exists at all – for the GlcNAc-derived diazirine **111** and the carbene derived from it. This is evidenced by the temperature dependence of the chemical shift for the N–H signals of **11** and **111**

(*Scheme 33*). A linear dependence is found for **11**. At temperatures below 210 K, one finds a stronger dependence for **111**, as expected for an intermolecularly H-bonded species. At higher temperatures, the sign of the dependence is inverted: rotation of the NHAc group around the N–C(2)-bond brings the NH function into the deshielding cone of the strongly anisotropic diazirine ring (ref. 43). If this is so, then one expects a better α-selectivity for glycosidations by **112**, and this is indeed found, as shown in *Scheme 34*. The lower degree of stereoselectivity in the glycosidation of more strongly acidic alcohols reflects their lower degree of basicity, and their impaired ability to function as acceptors for the NH···OH-bond.

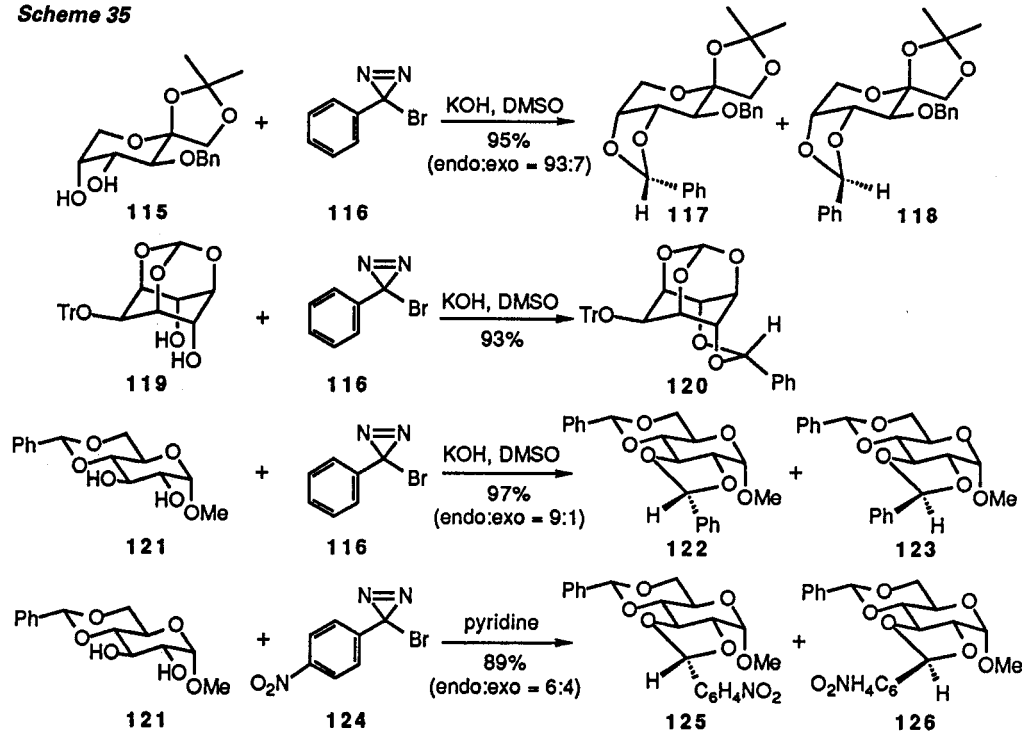
Scheme 34



ROH	Conditions	% Glycosides	α : β
H_3C, H_3C, OH	hv	70 (+ 13% **114**)	only α
F_3C, F_3C, OH	hv	72	87 : 13
	ΔT	59	71 : 29
O_2N–OH	hv	96	58 : 42



Scheme 35

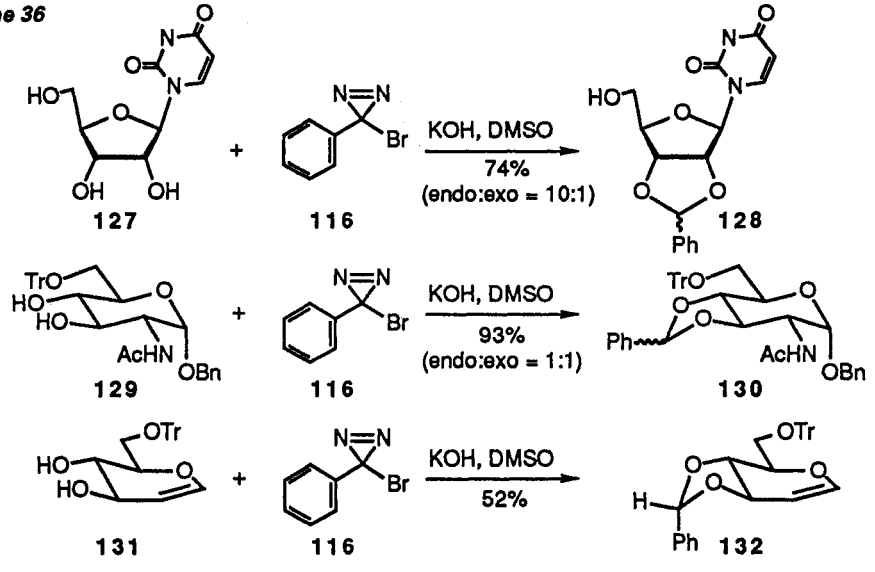


OTHER REACTIONS

The large number of transformations which are accessible *via* alkoxyalkyl carbenes, and, more specifically, *via* glycosylidene carbenes has been pointed out (ref. 10). Many have been realised outside the carbohydrate field (ref. 44), many remain to be explored. Thus, to the best of my knowledge, there is no preparatively applied intramolecular reaction of alkoxyalkyl carbenes. Such a reaction is realised in a new method for preparing benzylidene acetals (*Schemes 35 and 36*). Halodiazirines, such as **116** are prepared in about 50% yield from the commercially available benzamidines

(*Graham* reaction; ref. 44, 45). Their exchange reaction with alkoxides (*see* ref. 46 and lit. quoted there) leads to alkoxydiazirines and further to alkoxycarbenes which may insert intramolecularly into O–H bonds. Thus, the 1,2-, and 1,3-*cis* diols **115** and **119** react with excess **116** to yield the benzylidene acetals **117/118** and **120** in high yields and with a high diastereoselectivity. Similarly, the 1,2-*trans* diequatorial diol **121** reacts with **116** to afford the acetals **122/123** which have previously been obtained in low yields (ref. 47). **121** also reacted with the p-nitrophenyl diazirine **124**, obtained in about 25% from the corresponding amidinium salt (ref. 48, 49), to give the acetals **125/126**, again in high yields. Uridine (**127**) is protected as the known 2,3-O-benzylidene acetals **128** (ref. 50); the heterocycle is not attacked. The acetamido function does not interfere, as the GlcNAc-derivative **129** forms the acetals **130** in high yields. The basic reaction conditions (*compare* ref. 51) allow the protection of acid sensitive compounds, such as 6-O-trityl-glucal (**131**) (ref. 48). This method constitutes a valuable alternative to those requiring acidic conditions.

Scheme 36

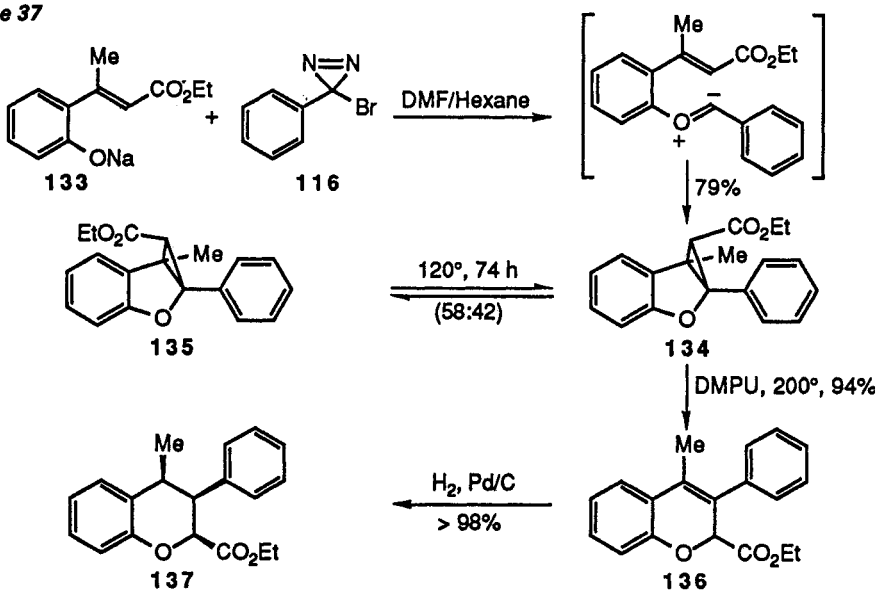


127 **116** **128**

129 **116** **130**

131 **116** **132**

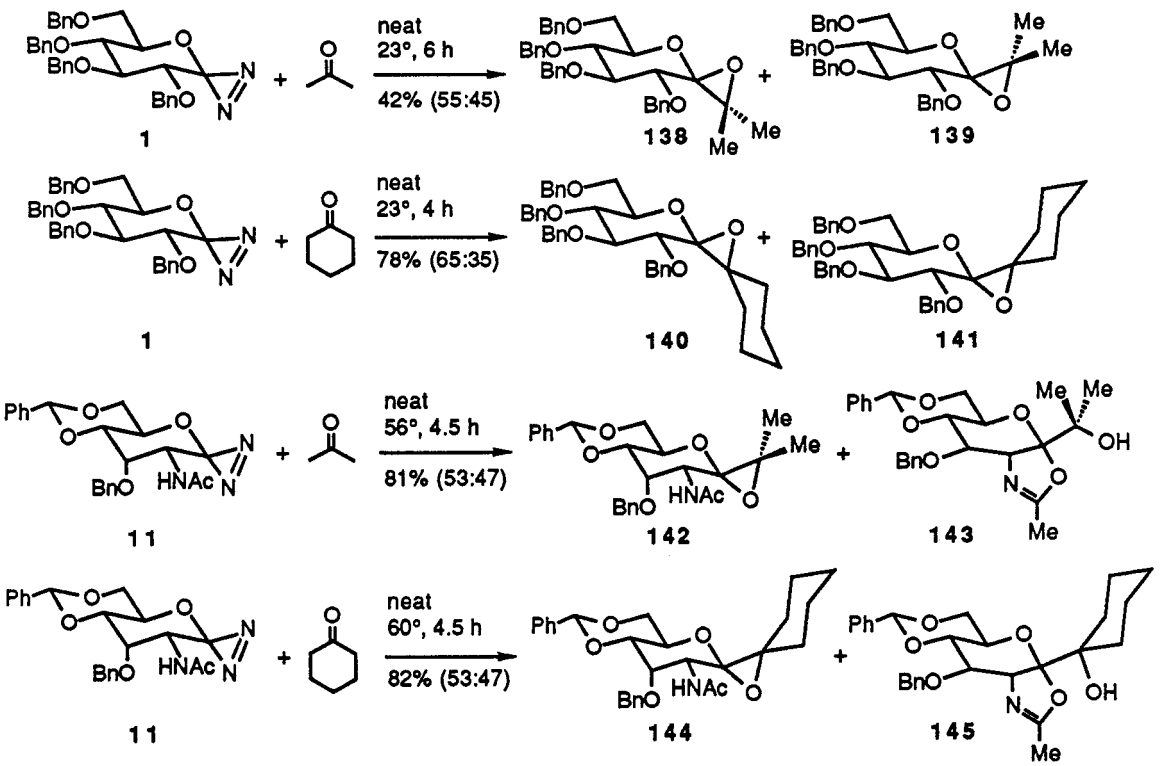
Scheme 37



133 **116** **135** **134** **137** **136**

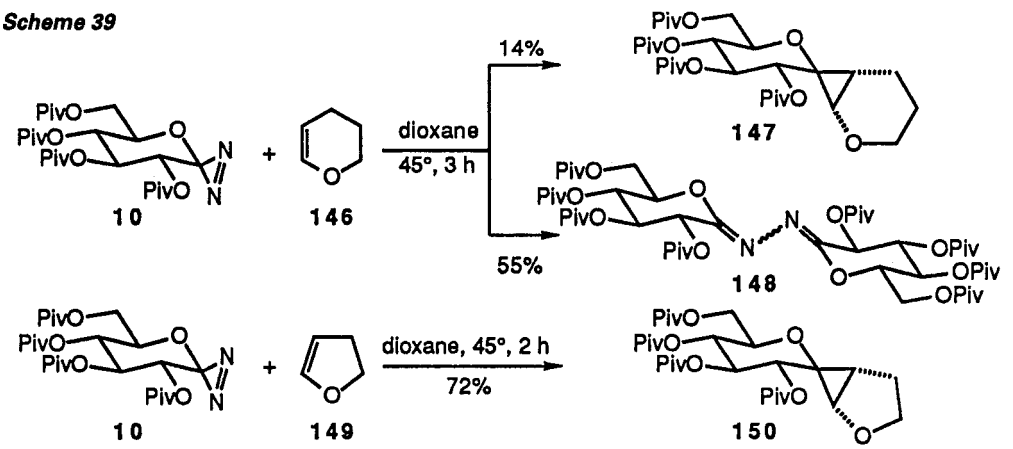
The formation of C–C-bonds by intermolecular reactions of nucleophilic carbenes with acceptor substituted alkenes is well known, also for glycosylidene carbenes (ref. 12–14, 16, 52). However, we found no case of an intramolecular version of this process. To illustrate it, we treated the o-hydroxycinnamate **133** with the halodiazirine **116** (*Scheme 37*) and obtained 79% of the homobenzofuran **134** (*compare* ref. 53). At 120°, **134** was reversibly transformed into its isomer **135** (presumably by way of a carbonyl oxide). At 200°, an electrocyclic opening of the cyclopropane ring took place and led in high yield to the benzopyran **136**, which was hydrogenated to the all-*cis* product **137** (ref. 48).

Scheme 38



The nucleophilic character of glycosylidene carbenes is also evidenced by the reaction of the diazirines **1** and **11** with acetone and cyclohexanone (*Scheme 38*). Good yields are only obtained of relatively stable oxiranes and with a large excess of ketone. Stereoselectivity is low. Although we see no evidence for an isomerisation of the diazirines to diazo compounds (ref. 54), it cannot be excluded that such a process precedes attack on the ketones (ref. 55).

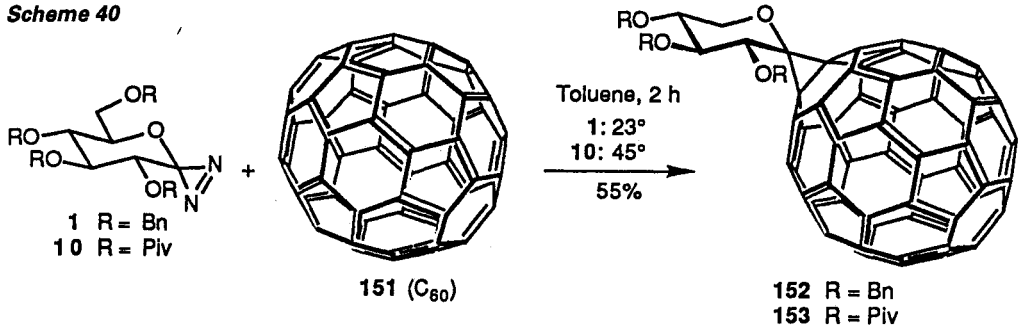
Scheme 39



The electrophilic character of glycosylidene carbenes has been evidenced by their reaction with phosphines (ref. 56). It is also evidenced by the reaction of the pivaloyl-protected diazirine **10** with excess dihydropyran **146** and dihydrofuran **149** (*Scheme 39*; ref. 57). Dihydropyran is barely reactive enough, yielding only 14% of the dialkoxycyclopropane **147** and large amounts of the lactone azine **148**, while the more reactive **149**, a model compound for furanoid glycals, afforded **150** as a single product in good yields.

Cyclopropanation by the diazirines **1** and **10** also allowed the preparation of the first enantiomerically pure, monoglycosylated C_{60}-buckminsterfullerene derivatives **152** and **153** in 55 and 54% (> 70%, based upon recovered **151**, *Scheme 40*, ref. 58). This opens the way to a number of applications, both in the area of biological chemistry and material sciences.

Scheme 40



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