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Novel carbohydrate transformations discovered en route to natural products

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Abstract - In the course of developing a synthetic route to the ansa chain of Streptovaricin A, it has been discovered that n-pentenyl glycosides undergo oxidative hydrolysis on treatment with halonium ion sources in aqueous solvents. Replacing water with a partially protected sugar affords di (or higher) saccharides, and the additional discovery that the protecting group at C2 can alter oxidative reaction rates by a factor of 6 has been exploited to enable a remarkable degree of finesse in the saccharide coupling protocol.

The neutral conditions of the process enable mechanistic details of glycoside hydrolysis to be determined without the use of acids. Furthermore, since the n-pentenyl residue ensures that only one of the acetal oxygens is activated, the process of bond cleavage can be examined with high specificity.

Based on the foregoing observations, a range of protecting groups incorporating the n-pentenyl acetal moiety have been developed that are all removable under neutral conditions.

INTRODUCTION

One of the enigmas of the practice of synthetic organic chemistry is that prior to embarking on a major undertaking, plans have to be laid out with meticulous attention to detail. A questionable transformation should never be incorporated in the hope that good fortune will become an ally at the appointed time. Nevertheless, there are few synthetic chemists who would cherish even the smallest hope that all steps will go as planned. Indeed, there are those who take the view that if everything did go as planned, the benefit to science would be minimal, since the exercise would have merely served to demonstrate the predictive power of the known rules under which we operate. Such people would ask, "what has this synthesis taught us that we did not know before?" In anticipation of such a question, some practitioners prefer to "develop" a new reaction and then demonstrate its validity in the context of the synthesis.

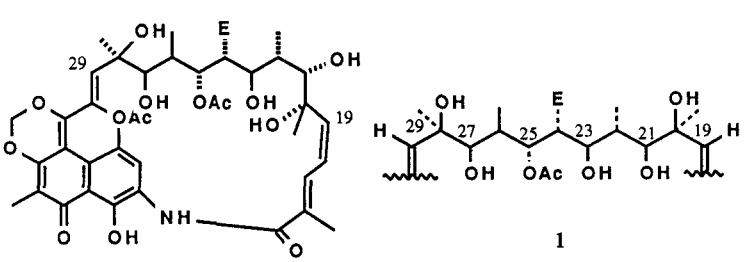
However, developing a new reaction, regardless of how clever, relies necessarily on the existing body of rules; although the new reaction may facilitate certain transformations, it may not have taught us any new science. The latter can be achieved only by sheer serendipity!

Hence, there are some practitioners who hope that a major synthetic undertaking will lead, not only to development of a new reaction, but also to the discovery of new science. It is our hope that the work described herein fulfills both of these criteria.

BACKGROUND

The research project to be discussed today originated with our desire to develop a synthetic route to the ansa chain, **1**, of streptovaricin A (Scheme I). There were several reasons why we

Scheme I



STREPTOVARICIN A
E = COOMe

1

decided to tackle this formidable target. It contains the greatest number of contiguous chiral centers (nine) of any of the ansamycins (ref. 1). Two of these, C20 and C28, are tertiary alcohols, and a second, C24, is an epimerizable center flanked by oxygens that are prone to β-elimination. These facts combine to make **1** the most complex array of contiguous chiral centers in the chemical literature.

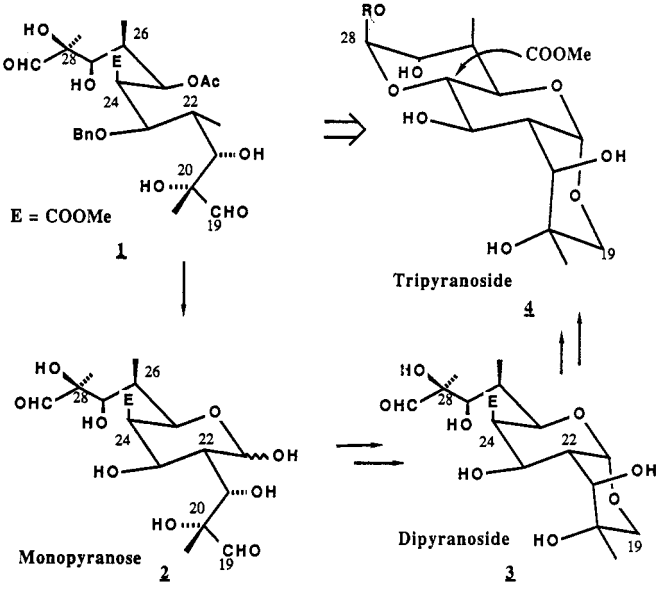
Our early interest in the use of carbohydrate derivatives for synthesizing natural products (ref. 2) was based on our observations that many reactions frequently display greater stereoselectivities with carbohydrates than with analogous carbocycles. Furthermore, the ease with which stereochemical assignments are made in carbohydrates by simple NMR techniques was seen as a distinct advantage (ref. 2).

However, further reflection showed that these assumptions were usually true only for transformations at C2, C3, and C4 of pyranosides, but not for "off-template" sites, such as C6 (ref. 3c).

In light of this limitation, we advanced the concept of pyranosidic homologation to address targets with multiple contiguous chiral centers. A detailed discussion of this concept has been presented elsewhere (ref. 3c), but is summarized in Scheme II. Thus, the C22-CH_3 of **1** is retrosynthetically oxidized to an aldehydo group which then allows formation of a monopyranose, **2**, and thence a dipyranose, **3**. Sacrifice of the C28 and C24 chiral centers permits the formation of the "upper" ring, giving the tripyranoside **4**, which can accommodate eight of the nine stereocenters of **1**.

Therefore, the tripyranoside **4** represented the first plateau, and the synthetic approach we adopted was designed to take advantage of stereocontrolling factors that are unique to carbohydrate structures.

Scheme II

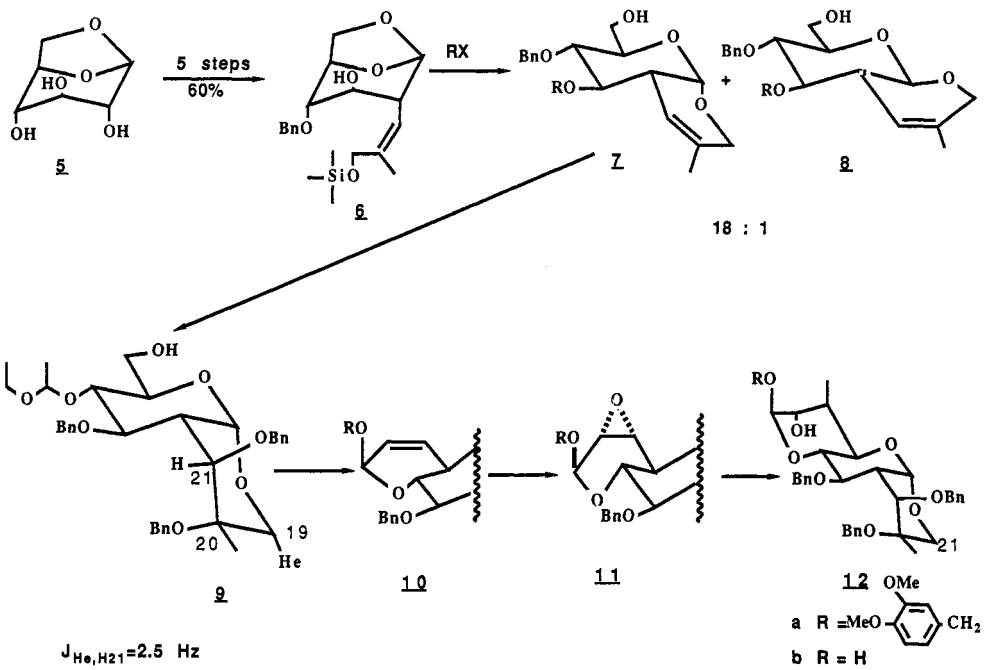


The Concept of Pyranosidic Homologation

The details for the synthesis of **4** have been published (ref. 4) and in Scheme III we show only the key features on which our strategy rests. Our starting material was levoglucosan, **5**, and a series of transformations afforded the protected allylic alcohol **6**, which underwent acid-catalyzed, intramolecular trans glycosidation to give the α and β anomers, **7** and **8**, respectively. The kinetic anomeric effect is known to favor **7**, and experimental conditions were developed that achieved an excellent 12:1 ratio of the two anomers.

Compound **7** is reminiscent of a cis-fused decalin, hence, reaction from the convex- (or β-) surface was anticipated. Indeed, stereoselective epoxidation was achieved and trans diaxial opening led to the dipyranoside **9**. The configuration at C20/C21 of **9** was evident from the W-coupling of 2.5 Hz shown in Scheme III, and the fact that the C20 and C21 hydroxyl groups could not be induced to form an isopropylidene ring.

Scheme III

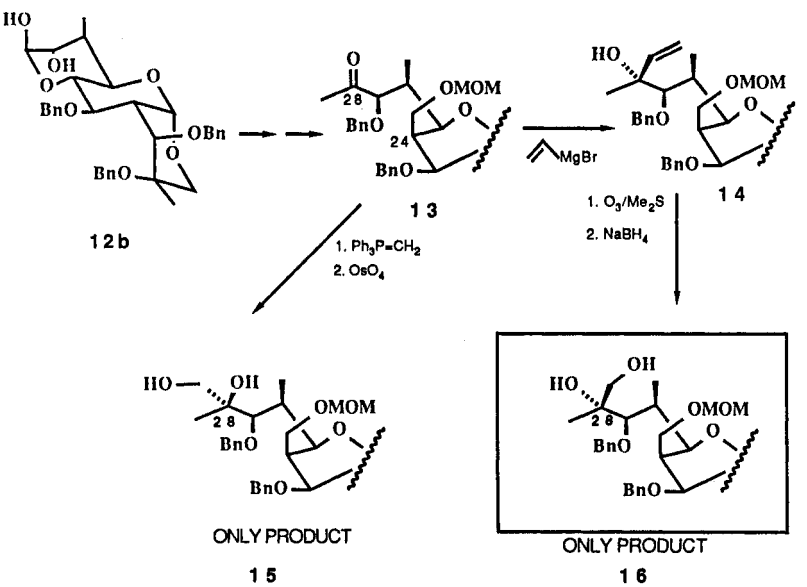


(for details see refs. 4 and 5)

With the structure of **9** secure, the "upper" ring was addressed, the kinetic anomeric effect being relied on again to ensure axial orientation of the alkoxy group in **10**. This ensured that the anti epoxide **11** was formed (ref. 5) and the trans diaxial opening of this then afforded the tripyranoside **12** (which is equivalent to **4**).

A number of key transformations were used to install the C24-CH_2OR as the synthon for the carboxyl group (ref. 6), and the the problem of the C28-tertiary alcohol was addressed. The carbonyl group of **13** was a convenient implement for this crucial stereocenter, and two strategies shown in Scheme IV were examined and found to give complementary products subsequently assigned as **15** and **16** (ref. 7). It is the latter that is required for the target **1**.

Scheme IV



(for details see refs. 6 and 7)

PROBLEM AREAS

The nine stereocenters of the target molecule **1** were now represented in **16** and we were now faced with the major task of opening the fused acetal, in order to carry out the reduction to the C22-CH_3. We had anticipated that this would be a difficult task, and our exploratory studies on the model compound **17** (Scheme V) confirmed our worst fears.

1. Thus, attempted mercaptolysis of **17** failed to yield the dithioacetal **21** (ref. 8). The principal reaction course in acidic media was ring contraction leading from **18** ---> **19** ---> **20**. Therefore, it became clear that acid catalyzed procedures could not be used for opening this type of intramolecular acetal.
Clearly, the foregoing result constituted a major problem area, since there were no known non-acidic procedures to which we could turn.

2. The second problem area emerged during other exploratory studies on the model system **22** (Scheme VI) for preparing the epimeric tertiary alcohols, **15** and **16**, shown in Scheme IV. In one experiment, the epoxide **23** was subjected to acid hydrolysis in the hope of preparing the diol **24** (ref. 9). However, the resulting product was the furanoid aldehyde **25a**. Similarly, in an attempt to prepare the bromohydrin **27**, the alkene **22** was treated with N-bromosuccinimide in aqueous acetonitrile. However, the bromomethyl tetrahydrofuran aldehyde **25b** was obtained quantitatively (ref. 10).

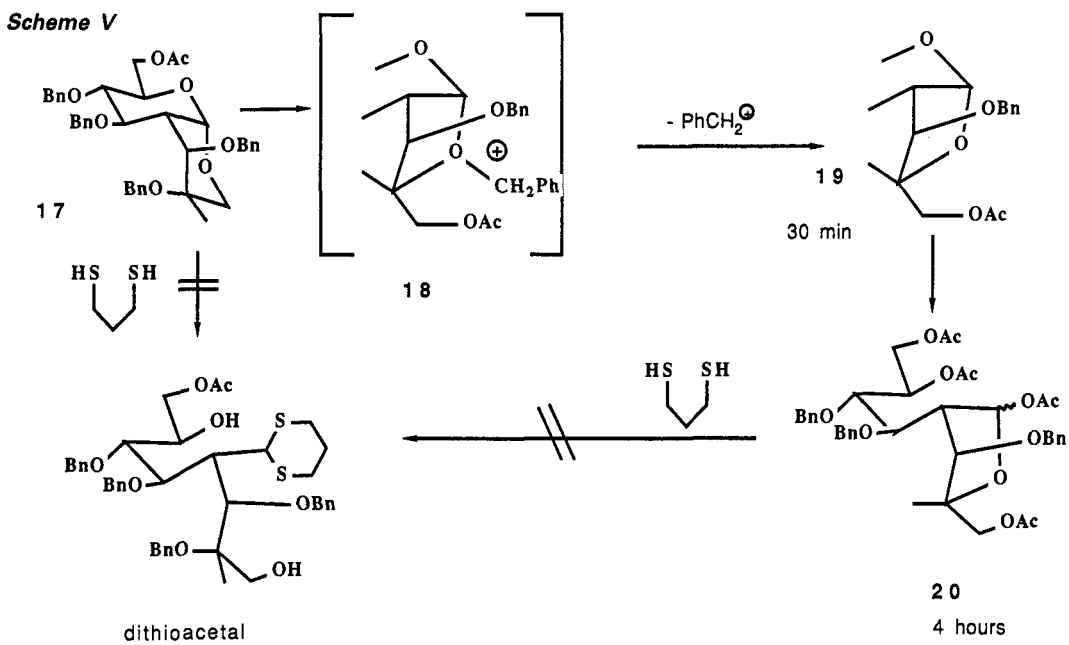
The unexpected reaction course revealed in Problem Area 2 was fortuitous because it contained the rudiments of a solution to the obstacle noted in Problem Area 1, particularly when it was subsequently discovered that reductive elimination of a suitable derivative **25b** with zinc led to the alkene **28**. **Thus, the conversion 22 ---> 25b ---> 28 constituted a tandem oxidative/reductive procedure for hydrolyzing an acetal under neutral conditions (ref. 10).** Similarly, treating **29** with NBS led to the furanoid system **30a**, and reductive elimination carried out on the corresponding glycosyl acetate **30b** afforded the olefin **31** (ref. 10).

CHEMOSPECIFIC GLYCOSIDE HYDROLYSIS

The facility of the oxidative cleavage of **22** and **29** surprised us. The process, depicted in Scheme VIIa, can be rationalized as involving intermediates **32** and **33**. At the time, we were unaware of any other instances of RO5 participation involving pyranoside ring oxygens; however, we learned subsequently of an earlier example by Pascard and co-workers (ref. 11) (Scheme VIIb) in which the diazoketone **34** afforded the oxetan-3-one **35**.

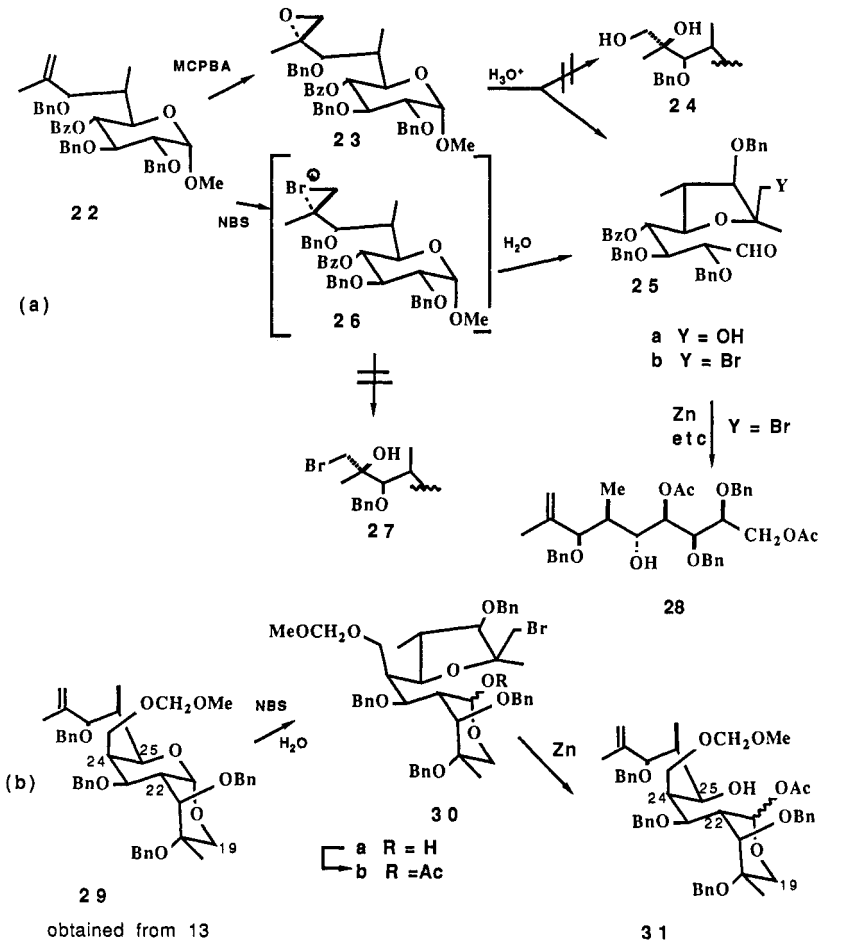
For our cases, the mechanistic details could be fleshed out, as suggested in Scheme VIIc. Thus, the basic requirement was presumed to be a 4-pentenyl acetal, **36**, and this implied that if the 4-pentenyl group was attached to the sugar glycosidically (e.g., **42**), RO5 participation should also occur, leading to the oxolanium ion **44**, and thence to hydrolysis of the glycosidic bond leading to **45a**.

Scheme V



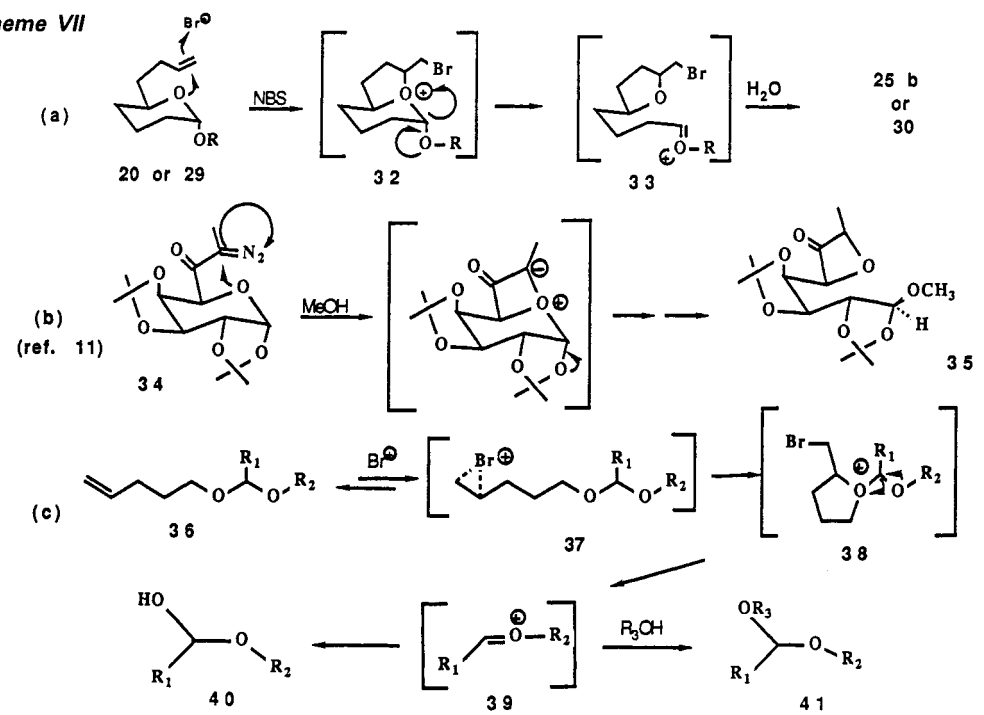
MODEL STUDIES FOR OPENING LOWER RING

Scheme VI

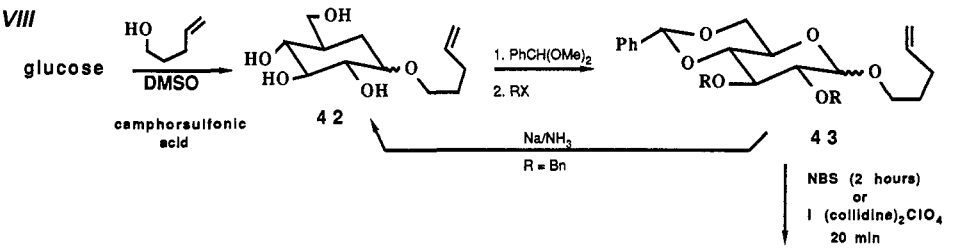


(for details see refs. 9 and 10)

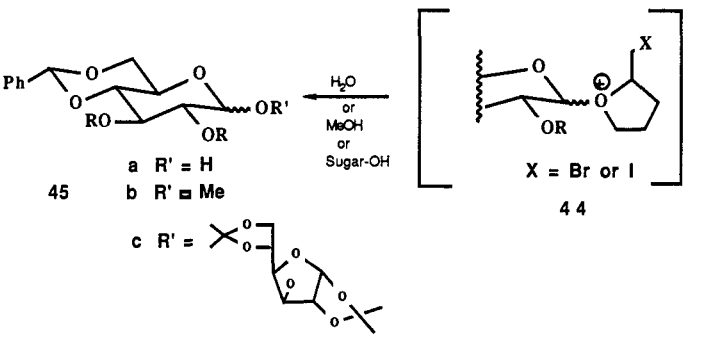
Scheme VII



Scheme VIII



Rates for reaction of 43 with NBS/H_2O/CH_3CN	
R	Time (hours)
a Ac	36
b Bn	6
c p(MeO)Bn	6
d $CH_2CH=CH_2$	9



(for details see refs. 12 and 13)

The results in Scheme VIII proved this to be the case (ref. 12). In a typical example, glucose could be glycosidated under acidic conditions with pent-4-enol alcohol to give **42**, benzylidinated, and differentially protected to give the series of derivatives **43a** ---> **d**. Treatment of these substrates with NBS under the conditions shown caused hydrolysis of the glycosidic bond with survival of a wide variety of protecting groups. The well known Hanessian-Hular reaction of the benzylidene ring (ref. 14) does not occur under these conditions, nor is the electron rich p-methoxybenzyl group affected. Even more interesting is the survival of the allyl group, as indicated with **43d**. Therefore, these results suggest that the n-pentenyl glycosidic group may be regarded as a chemospecific protecting group for the anomeric center (ref. 12). Evidently, RO5 participation leading to **44** is such an efficient process that other competing reactions are overwhelmed. The reasons for this chemoselectivity are not clear and are the subject of continuing investigations.

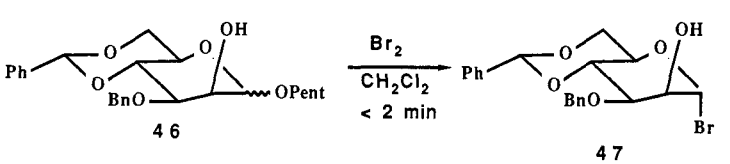
SACCHARIDE COUPLING REACTIONS

An obvious next step was to replace water with an alcohol to effect glycoside exchange. The methyl glucoside **45b** was obtained thereby, and during these studies it was shown that the reaction was faster with iodonium dicollidine perchlorate (ref. 13) than with either NBS or NIS. Using diacetone glucose as the "alcohol" led to formation of disaccharide **45c** (ref. 13).

With formation of **45c**, the use of n-pentenyl glycosides for saccharide coupling had been demonstrated (ref. 13). These results invited comparison with existing procedures. With respect to the α/β-stereoselectivities, some solvent dependency has been found which is in line with that normally observed for conventional coupling reactions (ref. 13).

In view of this, it was appropriate to ask what advantages did the n-pentenyl glycosides offer that other methods did not. At this stage, the most promising advantage appeared to be that the n-pentenyl group could be attached at the beginning of the synthetic transformation sequence, since the molecule, being a normal glycoside, would be stable to a wide array of reagents. Hydrogen is an obvious exception, but its stability to chemical reduction was demonstrated by converting **43** (R=Bn) back to **42** with sodium in liquid ammonia. Therefore, this meant that enormous flexibility was available in its use.

Scheme IX

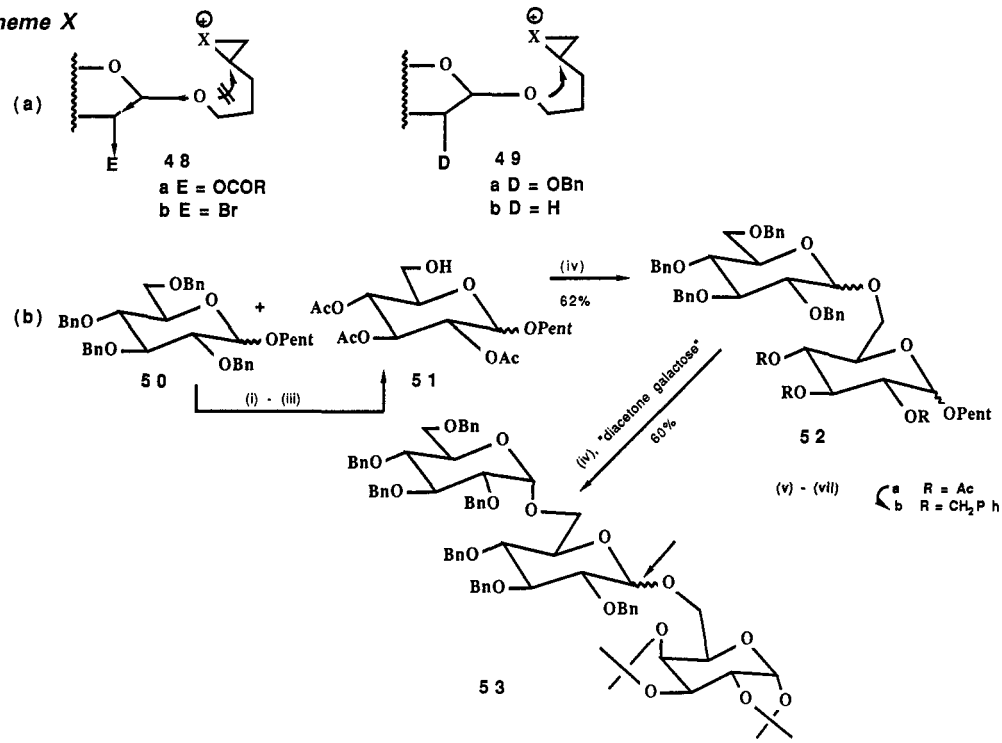


However, the most popular activated substrates for saccharide coupling continues to be glycosyl bromides, and this is understandable, since the venerable Koenigs-Knoor reaction has served for nearly 80 years, and has been honed to a remarkably high degree of finesse (ref. 15). Therefore, it is satisfying to know that treating n-pentenyl glycosides (e.g., **46**) with bromine under neutral conditions leads directly to glycosyl bromides (e.g., **47**) in less than two minutes. Thus, those who prefer to stick to "the evils they know" have the option of carrying out the normal chemical transformation sequence with an n-pentenyl glycosidic group, and then replacing it with bromine under neutral conditions just prior to the coupling event.

'ARMED' AND 'DISARMED' PENTENYL GLYCOSIDES

However, a completely novel dimension in glycoside coupling reactions with n-pentenyl glycosides emanates from the fact that, as seen in Scheme VIII, the oxidative hydrolysis proceeds more slowly when the C2 substituent is an ester (e.g., **43a**) than when it is an ether (e.g., **43b**). This observation can be rationalized, as shown in Scheme Xa. Thus, a C2 ester (e.g., **48a**) being strongly electron withdrawing, depletes the electron density on the glycosidic oxygen by rendering it less nucleophilic vis a vis the corresponding C2 ether (e.g., **49a**). Whether or not this rationalization is correct, the reactivity difference offers an opportunity to add a fascinating element of finesse to the saccharide couplings.

Scheme X



This implies that two pentenyl glycosides can be coupled without threat of self-condensation by ensuring that the alcohol donor has an ester at C2. This has been reduced to practice, as shown in Scheme Xb. No self-condensation of **51** was observed, and the resulting disaccharide **52a** is also "disarmed" by the C2 ester so that it will not react further with **51** to give a trisaccharide. However, at the appointed time, the system can be "armed" by replacing the C2 ester with an ether, as in **52b**. Thus, condensation is possible at the next stage, leading to the trisaccharide **53** (ref. 16).

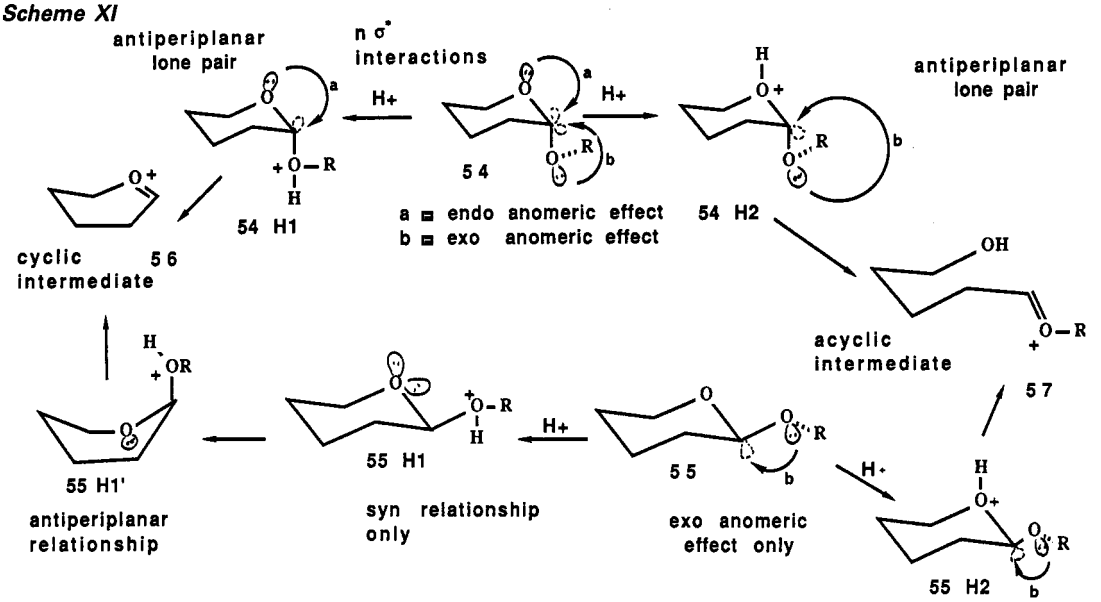
Therefore, the ether/ester pair emerges as an armed/disarmed couple, and in view of the proposed electronic requirements in Scheme Xa, similar armed/disarmed couples can be readily conceived. Hydrogen/halogen is such a pair, and it has also been successfully explored (ref. 16).

MECHANIC ASPECTS OF GLYCOSIDE HYDROLYSIS

Background

The ability to "arm" and "disarm" the glycosidic center by use of the C2 substituent is a new development in the synthetic chemistry of the anomeric center. An equally novel opportunity is presented to examine mechanistic details of anomeric transformations because, assuming the correctness of the mechanistic details in Scheme VIII, it is now possible to specifically activate one of the two oxygens at the anomeric center. **Thus, it becomes possible to explore mechanistic aspects of glycoside hydrolysis without using acids, and with certainty as to the site of activation.**

Scheme XI



It is now firmly established that the stable ground state conformations of α- and β glycosides can be represented as shown in **54** and **55**, respectively, in which there are delocalizations of the electron lone pairs into the nσ* orbitals which give rise to exo- and endo-anomeric effects (ref. 17). These orbital perturbations reinforce (ref. 18) (rather than replace) the dipole interactions postulated in earlier rationalizations of the anomeric effect (ref. 19).

While there seems to be general agreement on the ground state stabilizations, there is less agreement in "explaining" the reactivity differences between the anomers. Rationalization of the glycoside hydrolysis has been at the heart of theories on stereoelectronic control in organic reactions, as championed most vigorously by Deslongchamps (ref. 20). The essence of the theory is that the protonated α glycoside **54** is ideally set for elimination to give the cyclic oxocarbonium ion **56** because the lone pair is antiperiplanar to the departing group. For the β glycoside, the ideal antiperiplanar arrangement can be achieved only by adopting a boat conformation, such as **55H1'** (ref. 21).

However, many β glycosides hydrolyze faster than α (ref. 22), which seems inconsistent with such energy-demanding conformational changes. To accommodate this apparent discrepancy, Deslongchamps has suggested that the reactive conformation of the β anomer (e.g., **55H1'**), is of higher ground state energy than that of the α anomer (e.g., **54H1**), (ref. 21). Nevertheless, the "antiperiplanar lone pair hypothesis" in glycoside hydrolysis has met with strong objections, notably by Sinnott (ref. 23), based on a wide range of kinetic isotope studies.

In spite of these differences, there appears to be general agreement that the cyclic oxocarbonium ion **56** is the intermediate in glycoside hydrolysis (ref. 24). However, the dormant controversy (ref. 25) advocating the acyclic intermediate (e.g., **57**) has recently been reawakened as a result of experimental studies by Guindon (ref. 26) and Franck (ref. 27), and computer modelling studies by Karplus (ref. 28). By the use of computer simulations, Karplus has suggested that lysozyme action on β glycosides leads to an acyclic oxocarbonium ion in which the antiperiplanar lone pair on the glycosidic oxygen is involved in breaking the bond to O5, as illustrated in **55H2**. This explanation is in keeping with the Deslongchamps antiperiplanar lone pair postulate, except that the roles of the oxygens are opposite to those advocated in **54H1** and **55H1'** and, by corrolary, that the exo anomeric effect is involved.

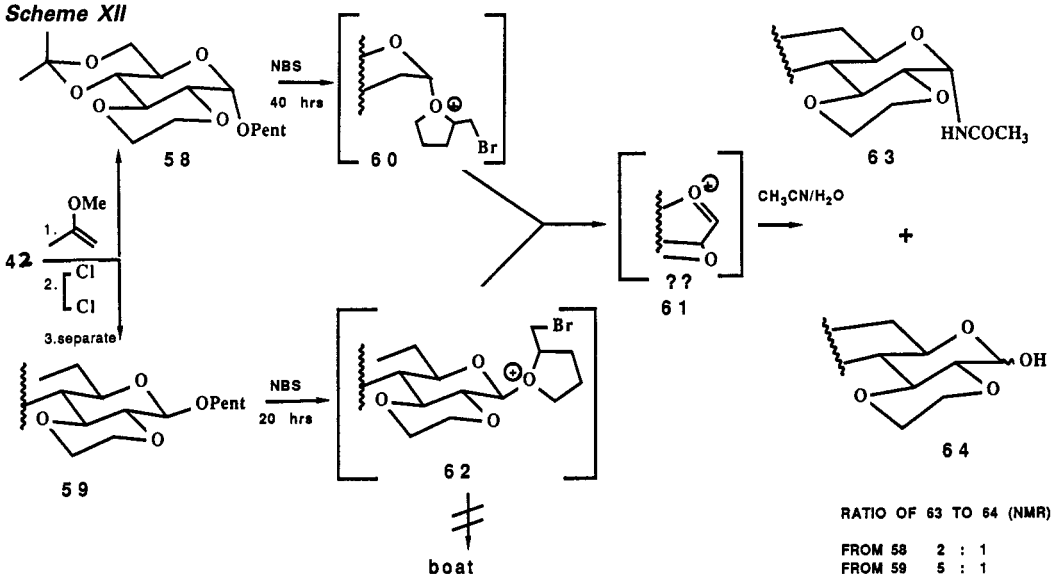
Therefore, it is appropriate to ask whether α glycosides might not hydrolyze through the cyclic oxocarbonium ion **56**, while β glycosides go through the acyclic counterpart **57**. In this connection, the recent work of Praly and Lemieux (ref. 29) is highly pertinent, since it shows that in α glycoside ground states, the exo and endo anomeric effects oppose each other, while in β glycosides, the exo anomeric effect is unopposed and hence much stronger.

The foregoing discussions suffer because they cannot be tested experimentally. Thus, in acid catalyzed processes, proton transfer between the two oxygens of the acetal would be so rapid that protonation could not be the rate determining step. **An obvious advantage of the n-pentenyl glycosides is that is it possible to activate a specific oxygen under neutral conditions.**

HYDROLYSIS OF CONFORMATIONALLY LOCKED SUBSTRATES

We decided to examine the brominolysis for the conformationally restrained anomers **58** and **59**. These substrates were readily prepared via selective acetonation, as described by Gelas and Horton (ref. 30), followed by reaction with dichloroethane under phase transfer conditions patterned after the work of Cesare and Gross (ref. 31). The solvolysis results for these materials are summarized in Scheme XII and present food for thought on several levels. Firstly, note that the products from both anomers are the α acetamide, **63**, and the aldose **64**. secondly, as indicated, the product ratios are different for each anomer. Experiments designed to account for these observations are currently underway and will be disclosed in due course.

Scheme XII



However, irrespective of the product ratios, the relative reactivities of **58** and **59** are an intriguing result. In **60**, the oxolanium ion and the lone pair are in perfect antiperiplanar alignment and hence should be ideally disposed for stereoelectronic elimination to give the oxocarbonium ion **61**. On the other hand, the trans-fused rings in **62** make it prohibitive for the molecule to adopt a boat conformation (comparable to **55**), although a half-chair conformation is allowed. In any event, **59** has been hydrolyzed at a comparable rate to **58**, even though the latter has the antiperiplanar lone pair arrangement.

AB INITIO CALCULATIONS

These results have prompted us to carry out ab initio studies on the protonation and fragmentation of the simplest acetal, dimethoxymethane. As has been clearly established (ref. 32), the ground state conformations of the starting material are, in order of increasing energy, gauche-gauche (GG), gauche-anti (GA), and anti-anti (AA, Scheme XIIIa). A proton was then placed 1.0 angstrom from the oxygen of interest, and the geometries were optimized for bond breaking and reorganization (Scheme XIIIb) using Gaussian 82/86 at the 3-21G level (ref. 33). **(Notably, the protonated oxygen is nearly planar sp^2 (i.e., after protonation, one lone pair is brought into the plane, while the other becomes a p-type orbital).**
The relative protonation energies from the calculations are shown in Table I. It is assumed that these are of the same order as the activation energies required to achieve the transition states. The GG conformer has C2 symmetry, so protonation on either oxygen gives the same state, GGH. The optimized structure is one in which (a) substantial $C{=}O^+$ character has developed, with the CO bond shortened to 1.34 angstroms, (b) bond lengthening to the departing oxygen is substantial at 1.57 angstroms, and (c) both of these structural features are approaching orthogonality.

GG

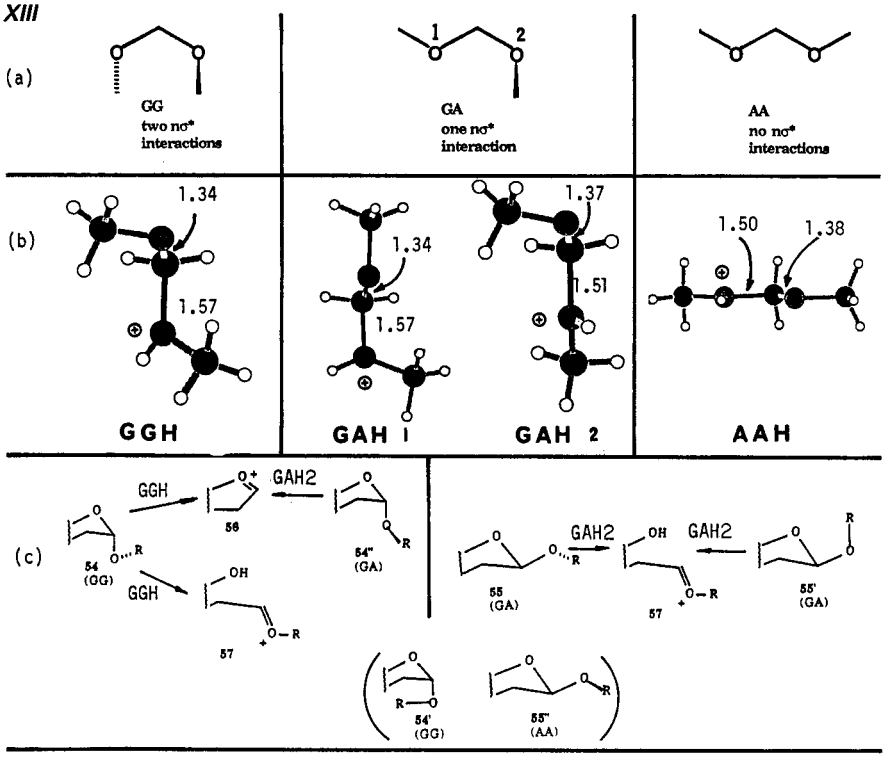
AA

The AA conformer also has C2 symmetry, so protonation on either oxygen leads to the same analysis. However, in AAH (a) bond shortening is only to 1.3806 angstrom, (b) bond lengthening at 1.5041 is very little, and (c) orthogonality is poorly achieved in comparison with GGH.

GA

The GA conformer is interesting because protonation of the two oxygens, numbered arbitrarily

Scheme XIII



(a) rotamers of dimethoxymethane.

(b) protonated conformers of dimethoxymethane after geometry optimization.

(c) endo vs. exo cyclic protonation of α and β glycosides, as predicted in part (b).

Table I Relative Protonation Energies for Dimethoxymethane Conformers (kcal/mole)[a]

GGH	1.8
GAH2	1.7
GAH1	0.0

[a] These values were obtained by setting up isodesmic reactions for each conjugate acid (ref. 34).

as 01 and 02, leads to different results. The lower-energy result, GAH1, is given by localizing the proton on the oxygen that is not engaged in an nσ* interaction. **Bond lengthening, bond shortening, and orthogonality are seen to be as highly developed in GAH1 and in GGH.** Both of these are seen to be isoenergetic and isostructural, and are both on the reaction coordinate to the cyclic oxocarbonium ion.

On the other hand, protonation of the oxygen involved in nσ* delocalization leads to GAH2 in which bond shortening, bond lengthening, and orthogonality are nearly as poor as in AAH.

Therefore, the conclusion from this analysis is that GA would be best hydrolyzed by protonation of the oxygen not involved in nσ* delocalization. This conclusion is in keeping with Deslongchamps' crucial postulate (ref. 35).

We can now extrapolate the conclusions in Scheme XIIIb to the typical α and β glycosides (e.g., **54** and **55**), which gives a more detailed picture in Scheme XIIIc than was presented in Scheme XI. The preferred conformer **54** is GG (Scheme XIIIc); hence, protonation of either oxygen is equally favored.[a] Accordingly, formation of cyclic and acyclic oxonium ions **56** and **57** should also be equally favored. Conformer **54'**, which is usually considered to be sterically prohibited, is also GG, and would therefore lead to the same intermediates.

Note a: This conclusion ignores the many differences between the pyranosides **54** and **55** in Scheme XIIIc, and dimethoxymethanes in Scheme XIIIa.

Conformer **54"**, which is of intermediate ground state stability, has a GA arrangement, and protonation on the exo cyclic oxygen is preferred since this corresponds to GAH1, the least energetic pathway. Hence, formation of the cyclic oxocarbonium ion **56** is favored.

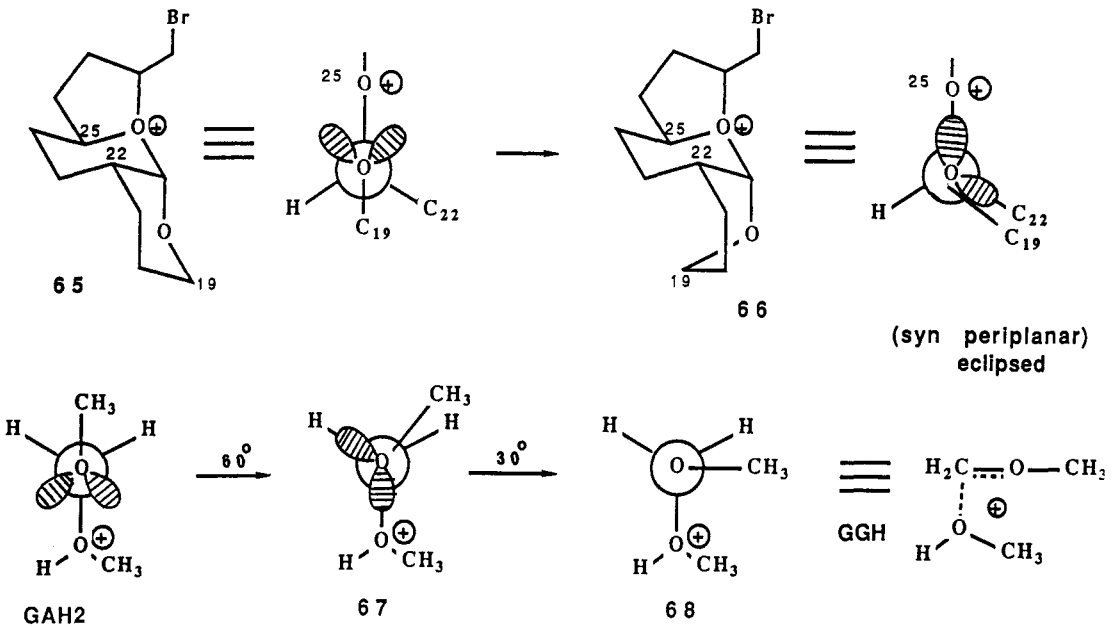
The β glycoside has two GA arrangements, **55** and **55'**, the former being the more sterically favored. Protonation of the ring oxygen of both conformers correspond to GAH1 and hence is favored so that formation of the acyclic oxocarbonium ion **57** is expected. The third conformation, **55"**, has an AA arrangement and is so unfavorable that its hydrolysis can be ignored.

From the foregoing analysis we conclude that the α glycosides 54 may hydrolyze through either the cyclic oxocarbonium ion, 56, or the acyclic counterpart, 57, while β glycosides 55 prefer to hydrolyze through the acyclic oxocarbonium ion 57. Furthermore, since the α glycoside suffers from the conflict noted above by Praly and Lemieux (ref. 29), it seems reasonable that β glycosides should hydrolyze faster, which is in keeping with experimental observations.

However, the result in Scheme XII with regard to the conformationally locked α- and β n-pentenyl glycosides raises a further complicating issue. The β glycoside **59** did hydrolyze at a faster rate. **However, it should be noted that the activated oxygen is exo cyclic; hence, formation of an acyclic oxocarbonium ion (corresponding to 57), does not apply here.** Thus, the molecule is forced to react either from the GAH2 arrangement or through the eclipsed (syn periplanar) half-chair conformer.

Is syn elimination so prohibitive? Apparently not, because a similar situation was encountered with the molecule that led to these studies. Thus, structure **65** represents the intermediate from **29** (Scheme VIa) with all the substituents removed, for the sake of clarity. This corresponds to GAH2, the lone pairs being gauche (syn clinal) to the oxonium ion. Conversion to the boat **66** gives an eclipsed (syn periplanar) arrangement. Further distortion to obtain a lone pair in antiperiplanar relationship to the oxonium ion induces extreme strain.

Scheme XIV



The problem described in the last two paragraphs prompted us to explore the energy surface that connects the unfavorable GAH2 and the (supposedly) favorable antiperiplanar rotamer proposed by Deslongchamps, with the reactivity model, GGH. **The plot in Figure 1 shows that after a 60° rotation to the eclipsed (syn periplanar) conformer 67, the system plunges down towards GGH.** In other words, syn elimination from **67** is a highly favored process and would be expected to shunt the torsional pathway into the reaction coordinate before conformations corresponding to **69** (Figure 1) would be achieved. This conclusion is in line with the Principle of Least Nuclear Motion favored by Sinnott (ref. 23).

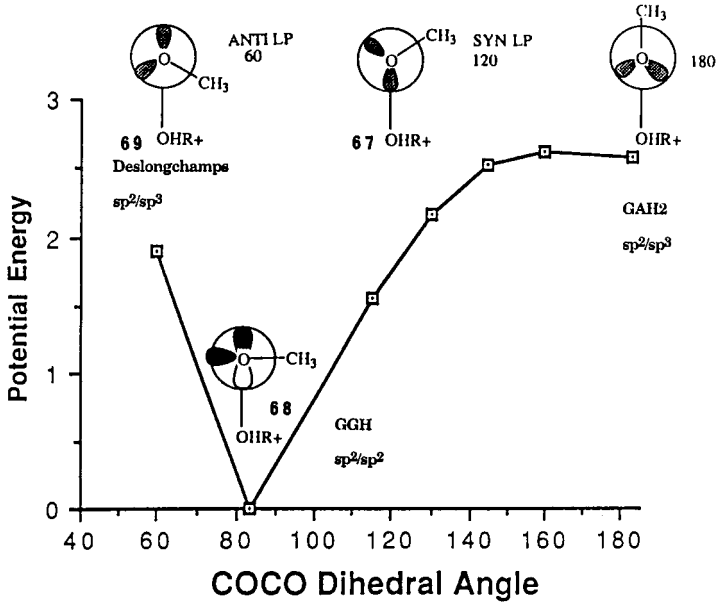
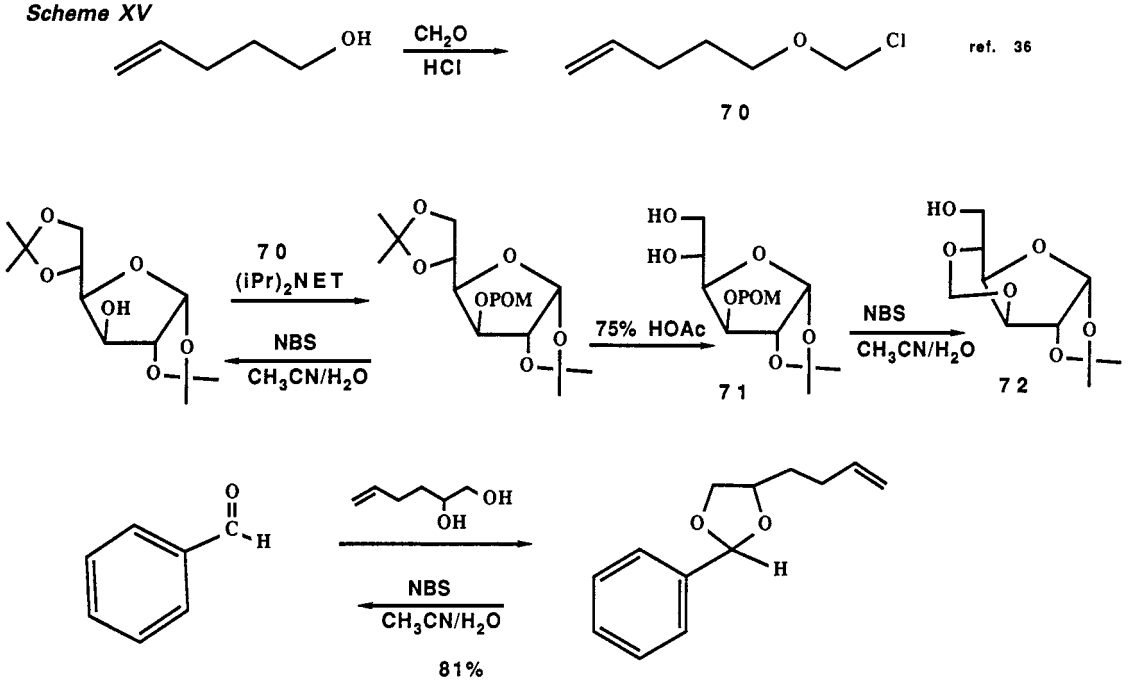


Figure 1

EFFECT OF PROTONATION ON THE DESLONGCHAMPS PATHWAY

Scheme XV



n-PENTENYL ACETAL PROTECTIVE GROUPS

Finally, the n-pentenyl acetal residue offers novel opportunities to develop a new series of protecting groups that can be removed under neutral conditions. 4-Pentenyloxymethyl chloride (POMCl, **70**), is a known compound (ref. 33). The protection/deprotection of "diacetone glucose" (Scheme XV) illustrates its utility, and the relative acid stability of the protecting group is evident from its survival in **71**. Notably, a suitably placed internal alcohol can capture the intermediate, as is obvious from the formation of **72**.

The protection of carbonyl compounds was probed by the use of benzaldehyde. Thus, the successful deprotection, without any evidence for oxidation of the liberated benzaldehyde, is a strong statement for the mildness of the oxidative deprotection conditions.

CONCLUSIONS

(Caveat: The theoretical calculations described in the manuscript are based on gas-phase phenomena and these may not be directly transferable to reactions taking place in solution.)

1. In keeping with previously established data, the order of stability of dimethoxymethane conformers is GG, GA, and AA (Scheme XIIIa).

Thus, for pyranosides in the $^4C_1$ conformation, α glycosides (which are normally GG) are more stable than β (which are normally GA).

2. *Relatively speaking*, the protonation GA+proton ---> GAH2 leads to a more stable state than GG+proton ---> GGH.

For pyranosides, this means that protonation of the ring oxygen of β D anomers (which is GAH2, Scheme XIII) is the most energetically favorable option--better than protonation of (a) the glycosidic oxygen of the β anomers, (b) the ring oxygen of α anomers, or (c) the glycosidic oxygen of α anomers.

3. In addition to the energy considerations above, geometry-optimization of the various protonated conformers indicates that in GAH2 (and GGH), bond reorganization is very far advanced. This means that these conjugate acids, GAH2 and GGH, are very close to the transition states, so the protonation energies are virtually the same as the activation energies.

For pyranosides, this means that protonation of the ring oxygen of β glycosides (GAH2) leads almost immediately to the formation of the acyclic oxocarbonium ion (Scheme XIIIc).

For α glycosides, protonation of the ring and glycosidic oxygens leading to acyclic and cyclic oxocarbonium ions, respectively, are either GGH or GAH2.

4. In the case of GAH2 and GGH, discussed in 3, an antiperiplanar lone pair of electrons is presented to the leaving group in each case. For the β D anomers, protonation of the glycosidic oxygen leads to GAH1 in which the lone pairs are gauche to the leaving group. In order to change this unfavorable situation and achieve the (presumed!) ideal antiperiplanar arrangement, the molecule must go from a chair to a boat, which is equivalent to rotating Newman projections of GAH1 through 120°. However, after a 60° rotation an eclipsed (syn periplanar) projection exists that has been found to be on the energy pathway to the geometry-optimzed GAH2 (equivalent to GGH).

Therefore, for β pyranosides, the formation of cyclic oxocarbonium ions occurs readily by protonation of the glycosidic oxygen, followed by a 60° rotation to the eclipsed syn periplanar alignment.

SUMMARY

The serendipitous observations in Scheme VI have given rise to novel approaches to saccharide coupling, new opportunities for mechanistic probes, and new procedures for oxygen protection. It is our hope that we have thereby returned something to the rich storehouse of carbohydrate chemistry from which we have drawn so liberally in the past.

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