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Evidence for Cyclic Bromonium Ion Transfer in Electrophilic Bromination of Alkenes: Reaction of ω-Alkenyl Glycosides with Aqueous N-Bromosuccinimide

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Abstract: Evidence is provided to support the theory that intermolecular Br^+ transfer from a cyclic bromonium ion to an alkene occurs readily and can indeed overwhelm alternative reaction pathways. In the course of a study to determine which ω-alkenyl glycosides could serve as glycosyl donors, it was found that upon treatment with N-bromosuccinimide (NBS) in aqueous acetonitrile, under conditions in which an n-pentenyl glycoside underwent oxidative hydrolysis to the corresponding hemi-acetal, allyl, butenyl, and hexenyl analogs gave bromohydrin addition products. It was further found that when pentenyl and hexenyl analogs were made to compete for an insufficient amount of NBS, the former reacted while the latter was apparently recovered unchanged. However, both reacted independently at similar rates. In addition, the phenomenon was found to be concentration dependent. These results are consistent with the intermolecular, non-degenerate transfer of Br^+ from cyclic bromonium ion to alkene.

INTRODUCTION

That olefins decolorize bromine is a qualitative test that is taught in introductory organic chemistry,[1] and as befits this history, bromination of alkenes may be considered as the prototypical electrophilic addition reaction. Investigations into the mechanism of the reaction have been unceasing,[2] but a notable point of inflection occurred with the isolation, in Wynberg's laboratory,[3] of the first stable cyclic bromonium ion from the reaction of adamantylideneadamantane **1** with molecular bromine (Scheme 1a). The product was subsequently characterized by x-ray analysis by Brown and coworkers as the salt **2**.[4]

This landmark development enabled novel application of strategies for acquiring mechanistic details of this classic reaction, and as part of their elegant studies on this topic, [5] Brown and coworkers established the degenerate translocation of Br^+ indicated in Scheme 1b.[6] That this interchange could indeed also occur in non-degenerate systems was also shown in Brown's laboratory, for example by translocation to cyclohexene (Scheme 1c).[6] Very recently, the use of compound **2** for halocyclization reactions (Scheme 1d) has been demonstrated by Neverov and Brown.[7]

The translocations in Scheme 1 could conceivably be related, fortuitously, to the stability and/or sterically hindered nature of ion **2**. We therefore present evidence in this manuscript, based on "normal" alkenes, to support Brown's postulate that ".... intermolcular Br^+ transfer from ion to olefin must be considered as competitive with various product-forming steps during the electrophilic bromination of olefins."[6]

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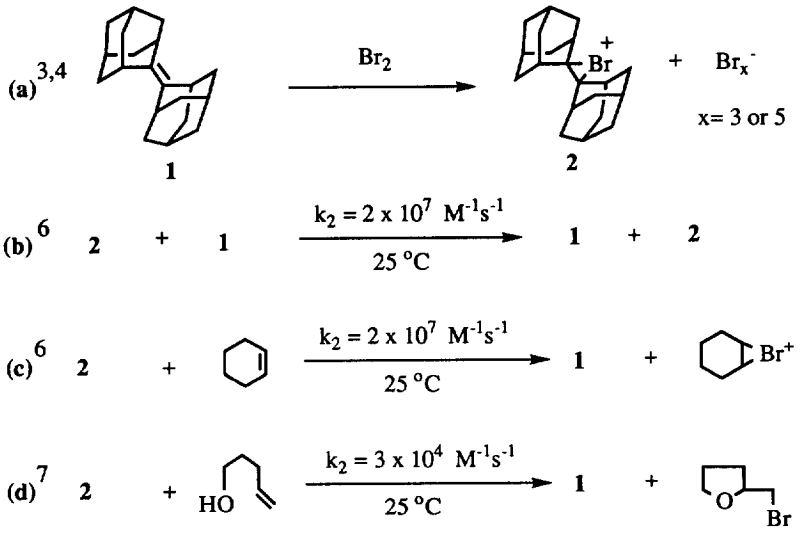
Scheme 1



BACKGROUND

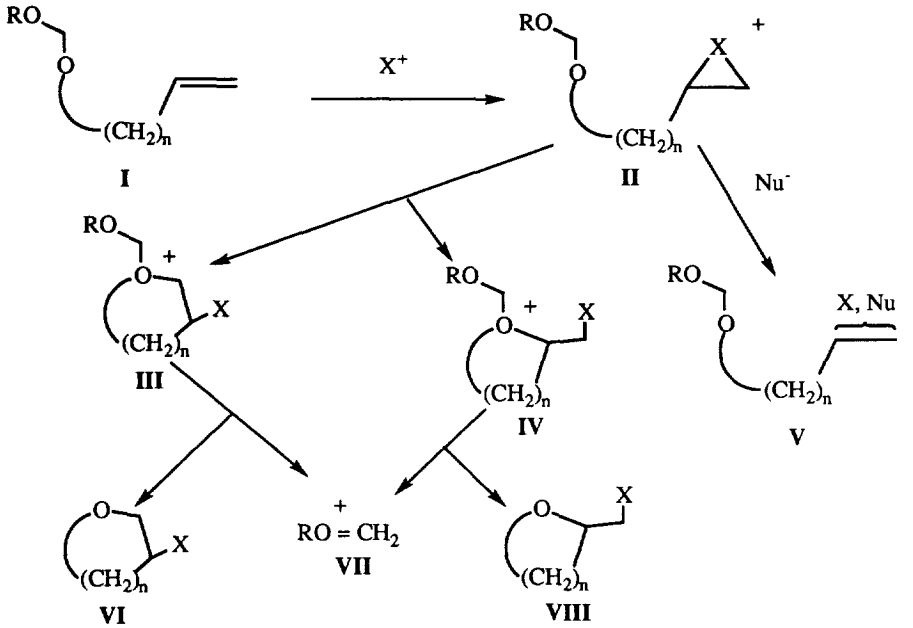
The serendipitous circumstances that led to the development of n-pentenyl glycosides (NPGs) as glycosyl donors has been described in detail elsewhere.[8] The key observation that prompted interest was rationalized by the sequence of events **II**--->**IV**--->**VII** depicted in Scheme 2, the first step of which is seen to be an example of "RO5 participation",[9] the participating oxygen in this case being part of an acetal function.

Could other alkenyl glycosides also serve the dual roles of protection and latent activation? In the context of the cascade of ions in Scheme 2, the answer to this question would depend on the ease with which the cyclic halonium intermediate, **II**, underwent scission by the acetal oxygen. Some insight could be gained from the trends that had been recognized by Winstein, Allred, Heck and Glick,[10] for anchimeric assistance by neighboring methoxy group in solvolytic nucleophilic substitutions.[11] These workers determined that the ring size of the resulting cyclic oxonium ion was the determining factor, the trend being $3,4 << 5 > 6 > 7$.[12]

However the ring size of the derived oxonium ion depends, in turn, on the site of the displacement in precursor **II**, since either **III** or **IV** could result. For this issue, Baldwin's rules[13] for ring forming reactions provided some help. Thus the rules for opening three-membered rings to form cyclic structures, "seem to lie between those for tetrahedral and trigonal systems".[13] On this basis, oxonium ions of ring sizes three (**IV** n=1) and four (i.e. **IV** n=2) which result from 3 and 4 *exo*-tet processes, are unambiguously favored over their 3 and 4 *endo*-tet alternatives, **III** n=0 and **III** n=1 respectively. On the other hand a pyranylium ion (**III**, n=3 or **IV** n= 4) could be obtained by either 6 *endo*-trig or 6 *exo*-tet processes, respectively, since both are favored.

Yet another complicating feature arose from the possibility of non-regioselective ring cleavage of **II** by an external nucleophile leading to regioisomers **V**. Indeed the facile formation of such addition products is the basis of a protocol by which NPG donor activity can be switched on or off upon demand.[14]

Scheme 2



It was instructive to determine how other ω–alkenyl glycosides would fare. Allyl glycosides, introduced by Gigg thirty years ago[15], are used frequently for protection of the anomeric center since cleavage can be effected readily under mild conditions.[16] Could allyl glycosides also serve as anomeric activators, thereby fulfilling the same dual roles of protection and /or activation as NPGs? This possibility relies on the interplay of kinetic and thermodynamic factors related to the formation and stability of the three-membered ion (**IV**, n=1) and four-membered alternatives (**IV**, n=2). Alternative **III** n=1 may be ignored, since this would result from a highly unfavorable 4 *endo*-trig ring forming processes.[12]

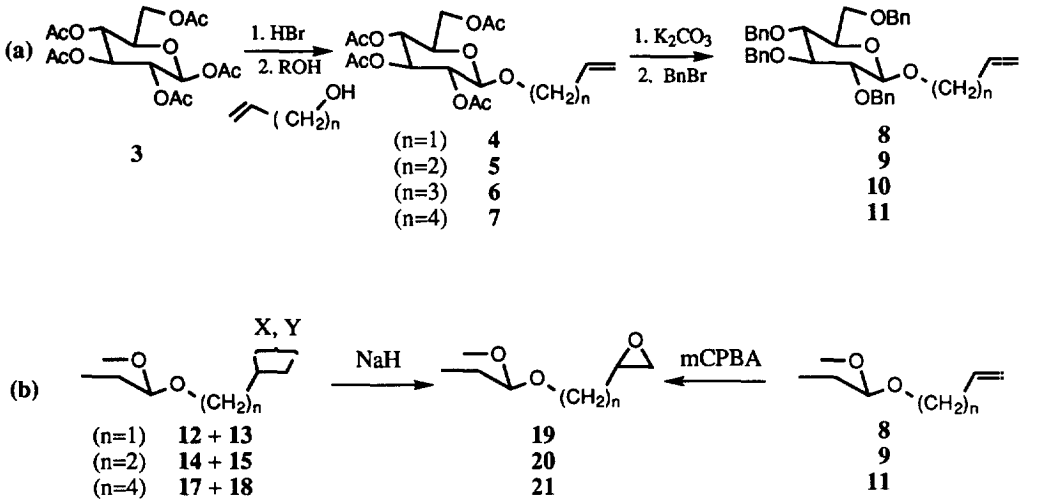
It was therefore decided to study the ω– alkenyl analogs allyl, butenyl, pentenyl, hexenyl, i.e., **I**, n=1, 2, 3, 4 respectively, and in this manuscript we describe the results of our investigations.

SUBSTRATES AND PRODUCTS

Wilson and Fraser-Reid recently reported that there could be large variations, relative and absolute, in the rates of oxidative hydrolysis of α/β anomeric pairs of n-pentenyl glycosides.[17] In order to avoid complications arising from such differences it was therefore decided to use only the β anomers **8**--->**11**. Their preparation from β-D glucose pentaacetate **3** was carried out as shown in Scheme 3a following the procedure reported by Stick and Rodriguez for compound **10**.[18]

As indicated in Scheme 2, upon treatment with aqueous N-bromosuccinimide,[19] each substrate could conceivably react to give either hydrolysis or addition products . However, previous work in our laboratory

Scheme 3



had shown that a 75mM solution of NBS in 1 % aqueous in acetonitrile would give exclusive hydrolysis of most NPGs.[20] A stock solution of this composition was therefore prepared from freshly distilled acetonitrile and freshly recrystallized N-bromosuccinimide. Portions of this solution were added to each of four flasks containing weighed amounts of each substrate **8**--->**11**. The resulting solution was stirred at room temperature and monitored by TLC for disappearance of starting material at which time the reaction mixture was poured into sodium thiosulfate solution, and worked up in the usual way.[8]

The products of the reactions are shown in Table 1. In the case substrates **8**, **9** and **11**, the absence of the hydrolysis product, 2, 3, 4, 6-tetra-O-benzyl-D-glucopyranose **16**,[21] was evident from TLC, but was nevertheless confirmed by HPLC. In each case the product was comprised of two components which upon treatment with sodium hydride in tetrahydrofuran, afforded a single substance **19**, **20**, and **21** respectively (Scheme 3b). That these were the corresponding epoxides was ensured by preparing the same materials in reactions of the pertinent alkene, **8**, **9** or **11**, with *meta*chloroperbenzoic acid.

The regiochemistry of the members of each bromohydrin pair, was determined by testing qualitatively for a primary alcohol by reaction with trityl chloride in pyridine at room temperature.[22] In each case these isomers, i.e. the anti-Markovnikov products **13**, **15**, and **18**, were the minor components, and were more polar on TLC.

DISCUSSION

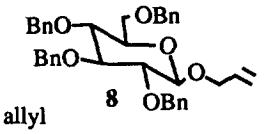
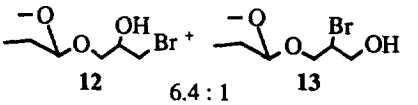
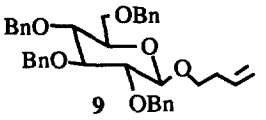
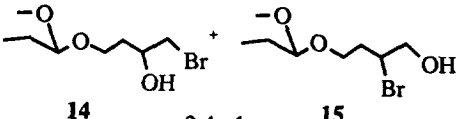
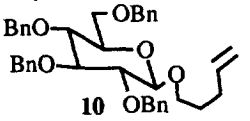
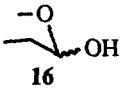
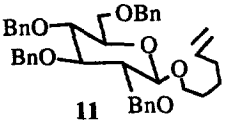
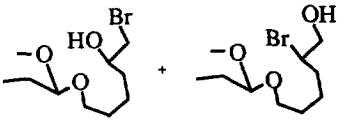
Two Seminal Results

Our attention was focused on two pieces of data in Table 1:

(a) the exclusiveness of reaction, hydrolysis to the aldose *versus* addition to give bromohydrins;

(b) the times required for disappearance of starting materials.

Table 1. Reaction of ω-Alkenyl Glycosides with Aqueous N-Bromosuccinimide.[a]

Substrate	Products[b]	Reaction Times[c]	k_{rel}[d]
 allyl	 6.4 : 1	10 h 25 min	4.4
 butenyl	 2.4 : 1	6 h 45 min	2.9
 pentenyl		2 h 20 min	1
 hexenyl	 2.8 : 1	5 h 9 min	2.3

[a] For reaction conditions see **Experimental.**

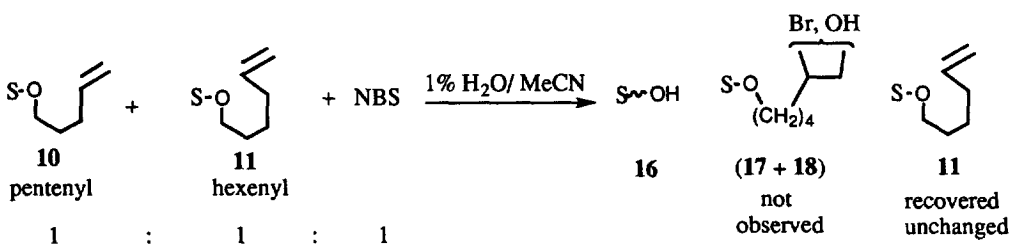
[b] For proof of structures see **Substrates and Products.**

[c] As determined by TLC -- see **Experimental** .

[d] Based on data in "Reaction Times" column.

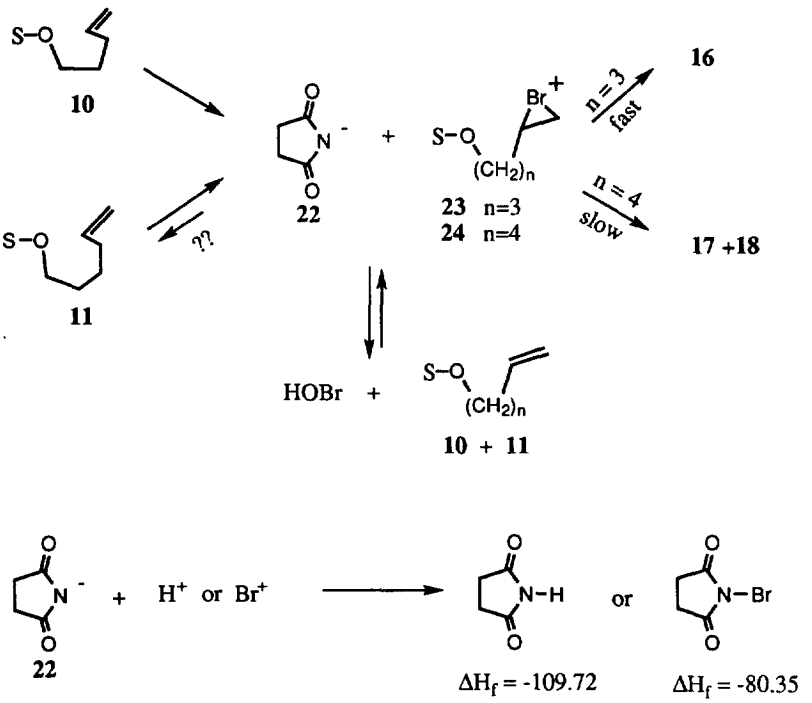
The comparatively slower reaction of allyl glycoside **8** could be attributed to a decrease in electron density of the double bond arising from inductive withdrawal by the glycosidic oxygen.[23] This effect should taper off in **9** (as indeed appears to be the case judging from its improved reactivity *vis-a-vis* **8**), and be completely absent in **11**. Thus the slightly faster reaction of **10** over **11** could be a manifestation of the well established trend concerning the relative rates of formation of 5 *versus* 6 membered rings,[12] leading to the furanylium and pyranylium ions **IV,** n=3 and 4 respectively.

Scheme 4



It was therefore decided to allow **10** and **11** to compete for one equivalent of NBS. Expectations were that at the end of the reaction, there would be a mixture of **16**, (**17**+ **18**) and unreacted starting materials **10** and **11**. *Aldose **16** was indeed obtained; but the hexenyl glycoside **11** was recovered in nearly quantitative yield, while there was no evidence of unreacted **10** nor of bromohydrin products **17** + **18** (Scheme 4).*

Scheme 5



One possible rationalization, as suggested in Scheme 5, is based on the premise that the reaction of alkenes with NBS is reversible, a circumstance which would more greatly affect the slower reacting intermediate **24** than the faster reacting counterpart **23**. However the heats of formation[24] of succinimide and N-bromosuccinimide are -109.72 and -80.35 kcal/mol respectively (Scheme 5), and the pka of succinimide is 9.62[25], all of which imply that ion **22** would pick H^+ more readily that it would remove Br^+ from a cyclic bromonium ion. We could therefore rule out a steady state situation in which a reversible reaction with NBS ensured a persistent concentration of intermediate **23**.

Since water is present in the reaction medium, could reversible formation of HOBr lead to a steady state supply of **23**? Evidence against this possibility comes from two sources. First, ion **2** crystallizes with a molecule of H_2O in the cell.[26] Second, in connection with the study summarized in Scheme 1d, Brown and co-workers found that addition of pentanol accelerated the reaction.[7] Both of these observations are inconsistent with ready formation of HOBr.

Rate Studies:

Rationalization of these results required better reactivity data than the TLC times reported in Table 1. Pseudo-first order rate constants were therefore determined by using the glycosides **10** and **11** in tenfold excess over NBS. The reaction could therefore be followed by iodometric titration of the unreacted NBS (see Experimental). The pseudo-first order rate constants (k') were calculated from the slopes of $\ln \{[NBS]_0/[NBS]_{t=x}\}$ versus time by the method of least squares using equations (1) -> (4) shown below.

Rate Law Calculations:

$$-\frac{d[NBS]}{dt} = k\,[NBS]\,[Sugar] \qquad (1)$$

Since [Sugar] >> [NBS]:

$$-\frac{d[NBS]}{dt} = k'[NBS] \qquad (2)$$

$$-\frac{d[NBS]}{[NBS]} = k'\,dt \qquad (3)$$

$$\ln \frac{[NBS]_0}{[NBS]_{t=x}} = k't \qquad (4)$$

For **10** $k_1 = 2.39 \times 10^{-4}\ s^{-1}$

11 $k_1 = 6.3 \times 10^{-5}\ s^{-1}$

From these values, the reactivity ratio for **10** and **11** is 3.8:1. This slight difference in reactivity could hardly, by itself, account for the exclusive reaction of **10**, and total recovery of **11** reported in Scheme 4.

Calculation of the Ratio (9:8) Predicted by Pseudo-First Order Rate Constants:

A system of equations was derived in order to calculate the ratio of unreacted **11**: **10** in the competition reactions, as predicted by the pseudo-first order rate constants (*vide infra*). The rate equations for the reactions of **10** and **11** are:

Pentenyl Glycoside (**10**): $-\frac{d[P]}{dt} = k_p'\,[P]\,[NBS]$ [P] = Pentenyl Glycoside (**10**)

Hexenyl Glycoside (**11**): $-\frac{d[H]}{dt} = k_h'\,[H]\,[NBS]$ [H] = Hexenyl Glycoside (**11**)

Since both sugars are in the same reaction medium, the NBS terms cancel out and rearrangement gives:

$$\frac{d[P]}{[P]} = \frac{k_p'}{k_h'}\,\frac{d[H]}{[H]}$$

Integration of the above equation from time zero (t_O) to time final (t_F) gives equation (5):

$$\int \frac{d[P]}{[P]} = \frac{k_p'}{k_h'} \int \frac{d[H]}{[H]}$$

$$\ln \frac{[P]_F}{[P]_O} = \frac{k_p'}{k_h'} \ln \frac{[H]_F}{[H]_O} \qquad (5)$$

Independent experiments showed that all of the NBS ($\pm$ 2%) was consumed during the reaction. Hence:

$$([P]_O - [P]_F) + ([H]_O - [H]_F) = [NBS]_O \qquad (6)$$

The ratio of unreacted hexenyl to pentenyl glycoside is represented by x in equation 7. Substitution of a value for x into equation 6 gives equation 8 and thence equation 9. From these equations, the amounts of unreacted hexenyl and pentenyl glycosides can be calculated for each value of x. When the latter values are substituted back into equation 5, the relative ratio k_p'/k_h' can be determined. However, since k_p'/k_h' is known to be 3.8:1 in this case, one arrives by selecting x in an iterative procedure at a final value as predicted by the pseudo-first order rate constants ($k_p'/k_h' = 3.8$) for the ratio of **11**: **10** equal to 2.6 (x = 2.6).

$$x = \frac{[H]_F}{[P]_F} \qquad (7)$$

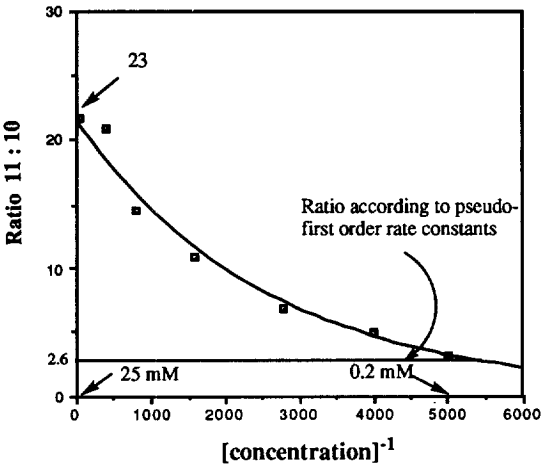
$$([P]_O - [P]_F) + ([H]_O - x[P]_F) = [NBS]_O \qquad (8)$$

$$[P]_F = \frac{-[NBS]_O + [P]_O + [H]_O}{x + 1} \qquad (9)$$

The Critical Concentration Dependence

In connection with Scheme 5, reversibility was ruled out as a means of obtaining a steady state concentration of **23** (*vide supra*). In the case of the translocation reactions reported by Brown and coworkers (Scheme 1 b,c,d), the calculated second order rate constants imply that the reactions are virtually diffusion controlled. If this is also applied to the competition in Scheme 4, the process should be concentration dependent. Testing this possibility required more refined monitoring of the reaction than was possible by TLC. Indeed although TLC had indicated the **absence** of **10** at the end of the competition experiment (Scheme 4), **HPLC monitors showed that *10* was indeed present, and that the ratio of *11* to *10* at the end of the reaction was 23:1.** This ratio should decrease for a concentration-dependent, diffusion-controlled process and this was indeed found, as seen from Figure 1. Thus the ratio of unreacted **11** to **10** fell from 23:1 to 3.1:1 experimentally, well within experimental error of the 2.6:1 ratio predicted from the pseudo-first order rate constants.

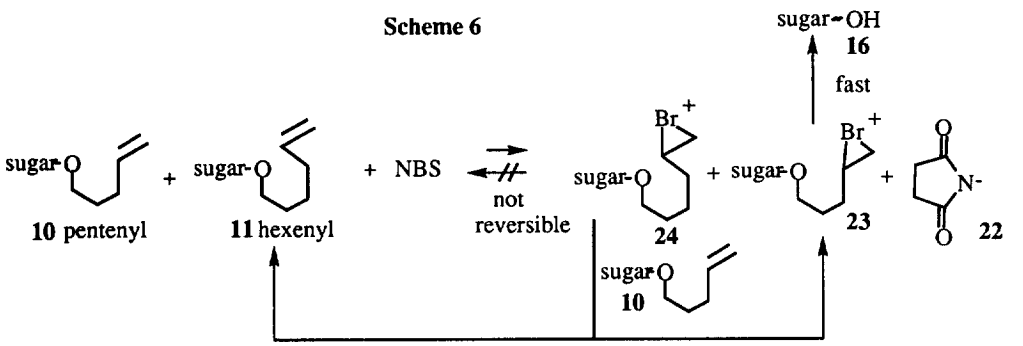
Figure 1. Competition Experiment -- Hexenyl vs. Pentenyl with Varying Concentrations



CONCLUSION

The simple premise is that if substrates **10** and **11** were reacting independently in the competition experiment (Scheme 4) one would expect to see some evidence of products from less reactive **11**. Therefore it must be concluded that the presence of **10** affects the reaction of **11**. In Scheme 6, we depict a cogent rationalization for the results of the competition experiment , wherein alkene **10** apparently reacts but alkene **11** does not. We suggest that, actually both **10** and **11** react to give the corresponding cyclic bromonium ions **23** and **24**, respectively, the former progressing rapidly to the hydrolysis product **16**.

Scheme 6



Based on Brown's precedents[6], it is proposed that a diffusion controlled process takes place, resulting in the formation of the more reactive species (**23**) at the expense of the less (**24**), as depicted in Scheme 6. Such a process would be concentration dependent and strong support has come from the study depicted in Figure 1, which shows that as the reaction medium for the competition experiments is made more dilute, the

reaction of the two alkenes is more and more in keeping with their pseudo-first order rate constants and, by corollary, less and less affected by diffusion controlled transfer of Br^+.

In reaching this conclusion, it was argued above that debromination of **24** by a reaction which regenerates NBS was implausible in view of the heats of formation of the participants and well as the pka of succinimide (*vide supra*). *However, even if 23 and 25 were being formed reversibly, the conclusion based as it is on Figure 1, would still stand.*

It can therefore be concluded that for ordinary, unhindered, electronically similar and (nearly) equally reactive alkenes, Brown's postulate that ".... intermolecular Br^+ transfer from ion to olefin must be considered as competitive with various product-forming steps during the electrophilic bromination of olefins"[6] can be extended to all olefins, not just adamantylideneadamantane, **1**.

EXPERIMENTAL

General. All ^1H and ^{13}C NMR spectra were recorded on either a Varian XL-300 or GE QE-300 spectrometer using $CDCl_3$. Abbreviations for NMR data are as follows: s= singlet, d= doublet, m= multiplet, dd= doublet of doublets, t= triplet. Coupling constants are reported in Hertz and chemical shifts are in ppm on the delta scale. ^1H (300 MHz) and ^{13}C (75 MHz) chemical shifts are reported relative to $CHCl_3$ as an internal standard. HPLC analysis was carried out on a Rainin Dynamax HPLC system interfaced with a Macintosh computer, a UV detector (265 nm), and either a Dynamax 60-A semi-prep column or a Dynamax 60 analytical column. Mass spectra were recorded on a JEOL JMS-SX102A mass spectrometer operating at a 3 or 10K resolution. Fast atom bombardment (FAB) mass spectra were conducted using a dithiothreitol/dithioerythritol matrix with xenon as the fast atom. Optical rotations were determined at the sodium D line with a Perkin-Elmer 241 polarimeter. Melting points were determined in capillary tubes and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc. of Norcross, GA. TLC plates were Kieselgel 60 F_{254} (Merck Art. 5554). Carbohydrate compounds were visualized on the TLC plate by charring with "Hannesian dip" (2.5 g cerium sulfate hydrate, 6.25g ammonium molybdate tetrahydrate, 225 mL H_2O, and 25 mL concentrated H_2SO_4). Dichloromethane was distilled from P_2O_5. Acetonitirile was distilled from CaH_2. Tetrahydrofuran and diethylether were distilled from sodium benzophenone ketyl. Dimethylformamide was dried over CaH_2. N-Bromosuccinimide was recrystallized from H_2O.

Methods

General Procedure for Kinetics Studies with Alkenyl Glycosides:

N-Bromosuccinimide (NBS) induced reactions of the ω–alkenyl glycosides (**8, 9, 10, 11**) were carried out by accurately weighing 25-50 mg of the glycosides into four separate flasks wrapped in aluminum foil. An accurately weighed amount of NBS (recrystallized from H_2O, dried over P_2O_5 under vacuum) was added to a standard solution of 1% H_2O/MeCN to make a solution that contained 3 mmol NBS in 40 ml solution (75 mM). An appropriate amount of this solution was pipetted into the reaction flasks to make 25 mM solutions with respect to each sugar, and the mixtures were stirred at room temperature. The reaction times were measured by looking for the disappearance of the respective starting materials as judged by TLC (80:20 light

petroleum: EtOAc) . These times were then used to determine the relative reaction times shown in Table 1. The reactions were quenched by adding 10% $Na_2S_2O_3$, diluted with CH_2Cl_2, and extracted with brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Each reaction was analyzed by HPLC using a solvent gradient of 93:7 hexanes:EtOAc -> 20:80 hexanes:EtOAc over 50 minutes. The presence or absence of hydrolysis product was confirmed by co-injection of the crude reaction mixtures with the authentic hemi-acetal, **16**.

General Procedure for Competition Experiments:

Compounds **10** (50.0 mg, 0.0821 mmol) and **11** (51.2, 0.0821 mmol) were added to a flask covered with aluminum foil. The initial **11** : **10** ratio, determined by dissolving the starting materials in $CHCl_3$ and injecting an aliquot onto the HPLC (column= Dynamax 60-A, silica, analytical column; UV detector= 265 nm; flow rate = 1.0 mL/min; 93:7 hexanes:EtOAc -> 20:80 hexanes: EtOAc over 50 min.), was 0.971:1.000 based on the integrated areas as measured by the chromatograph. The $CHCl_3$ was then evaporated, and the residue was dried under vacuum. Pre-prepared 1% H_2O/MeCN was then added to provide a 40 mM solution containing 1 equiv. of NBS . Aliquots (0.5 mL) of this reaction solution were then diluted to various concentrations (25 mM, 2.5 mM, 1.25 mM, 0.625 mM, 0.357 mM, 0.250mM, 0.200 mM) in separate flasks covered with foil, and the mixtures were stirred at room temperature until complete disappearance of NBS as determined by treatment of aliquots with 10% KI solution and starch indicator solution. The reactions were then quenched with 10% $Na_2S_2O_3$ solution, diluted with CH_2Cl_2, and extracted with brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated. Each reaction product was analyzed by HPLC to determine the final **11**:**10** ratios, using the same conditions as described above.

General Procedure for Obtaining Pseudo-First Order Rate Constants:

The reactions of **10** and **11** were conducted in separate flasks wrapped in aluminum foil under pseudo-first order conditions { [sugar] >> [NBS]}. Compounds **10** and **11** (1.606 mmol) were combined separately with NBS (0.1606 mmol) in 1%H_2O/MeCN solution to give final concentrations: [**10** or **11**] = 80.3 mM and [NBS] = 8.03 mM. A blank solution of the NBS in 1% H_2O/MeCN was used to determine $[NBS]_0$ and the reaction was followed by iodometric titration of the unreacted NBS contained within aliquots, using a standardized solution of Na_2SO_3. Typically, aliquots (1 mL) were taken at various times and diluted with 50 mL H_2O. Titration of the solution with $Na_2S_2O_3$ solution (0.01 N) was carried out until the solution became pale yellow, and then starch indicator solution (1 mL) was added. The titration was continued until the endpoint was reached.

Materials

General Procedure for Preparing Precursors 4, 5, 6, 7.

Glucose pentaacetate (**3**) (25.52g, 65.27 mmol) was dissolved in CH_2Cl_2 (125 mL) under argon. A 30% solution of HBr in AcOH (50 mL)was added to the flask, and the reaction was stirred under darkness at room temperature overnight. The reaction solution was diluted with CH_2Cl_2 (200 mL) and poured over ice. The organic layer was then extracted with cold H_2O (2 X 100 mL), cold saturated $NaHCO_3$ (2 X 150 mL) and brine (2 X 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to give tetra-*O*-acetyl-

α-D-glucopyranoside bromide in quantitative yield. A portion of this material (15.0 g, 36.5 mmol) and the alkenyl alcohol (103.6 mmol; 3 eq) were dissolved in CH_2Cl_2 (80 mL) under argon and stirred with freshly activated, powdered 4 Å molecular sieves (19 g) for 30 min. Silver carbonate (11.1 g, 40.3 mmol, 1.1 eq) was then added and the reaction mixture was stirred for 60 h at room temperature under darkness. The reaction mixture was then diluted with CH_2Cl_2 (500 mL) filtered through a wet Celite pad, and washed consecutively with saturated $NaHCO_3$ (200 mL) and brine (200 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated, and flash chromatographed (85:15 --> 60:40 light petroleum- EtOAc) to give the peracetylated alkenyl glycoside as a white solid.

2-Propenyl 2,3,4,6-Tetra-*O*-acetyl-β–D-glucopyranoside (4)

60% yield; R_f = 0.43 (60:40 light petroleum-EtOAc), $[\alpha]_D$= -23.38 ° (c=1.66, $CHCl_3$) mp = 87.5 - 88 °C (light petroleum, diethyl ether) .^{1}H NMR ($CDCl_3$): δ = 1.99 (s, 3 H, 3-OAc), 2.02 (s, 3 H, 4-OAc), 2.05 (s, 3 H, 2- OAc), 2.09 (s, 3 H, 6-OAc), 3.69 (m, 1 H, H-5), 4.09 (dd, 1 H, $OC\underline{H}_2CH{=}CH_2$), 4.13 (dd, 1 H, $J_{5,6'}$ = 2.5 Hz, H-6'), 4.24 (dd, 1 H,$J_{5,6}$ = 4.6 Hz, $J_{6,6'}$= 12.3 Hz, H-6), 4.35 (dd, 1 H, $OC\underline{H}_2CH{=}CH_2$), 4.55 (d, 1 H, H-1, $J_{1,2}$= 7.9 Hz), 5.01 (m, 2 H, $OCH_2CH{=}C\underline{H}_2$), 5.10 (m, 1 H, H-2), 5.19-5.31 (m, 2H , H-4, H-3), 5.82 (m, 1 H, $OCH_2C\underline{H}{=}CH_2$). ^{13}C NMR ($CDCl_3$): δ = 170.7 , 170.3 , 169.4 , 164.3 (C=O), 133.3 ($OCH_2\underline{C}H{=}CH_2$), 117.7 ($OCH_2CH{=}\underline{C}H_2$), 99.5 (C-1).

Anal. : Calcd. for $C_{17}H_{24}O_{10}$: C, 52.58; H, 6.23; Found: C, 52.70; H, 6.27.

3-Butenyl 2,3,4,6-Tetra-*O*-acetyl-β–D-glucopyranoside (5)

65% yield R_f = 0.45 (60:40 light petroleum: EtOAc), $[\alpha]_D$= -19.4° (c= 1.08, $CHCl_3$) , mp= 77-78°C. (light petroleum / diethyl ether). ^{1}H NMR ($CDCl_3$): δ = 1.99 (s, 3 H, 3-OAc), 2.02 (s, 3 H, 4-OAc), 2.05 (s, 3 H, 2- OAc), 2.09 (s, 3 H, 6-OAc), 3.52 (m, 1 H, $OC\underline{H}_2CH_2CH{=}CH_2$), 3.69 (m, 1 H, H-5), 3.93 (m, 1 H, $OC\underline{H}_2CH_2CH{=}CH_2$), 4.14 (dd, 1 H,$J_{5,6'}$ = 2.0 Hz, H-6'), 4.27 (dd, 1 H, $J_{5,6}$ = 4.6 Hz, $J_{6,6'}$= 12.4 Hz, H-6), 4.50(d, 1 H, H-1, J = 8.1 Hz), 4.97 (m, 2 H, $OCH_2CH_2CH{=}C\underline{H}_2$), 5.03 (m, 1 H, H-2), 5.07 (t, 1 H, H-4), 5.20 (t, 1 H,$J_{2,3}$ = $J_{3,4}$= 9.5 Hz, H-3), 5.78 (m, 1 H, $OCH_2CH_2C\underline{H}{=}CH_2$). ^{13}C NMR ($CDCl_3$): δ = 170.7, 170.3, 169.4, 169.3 (C=O), 134.4 ($OCH_2CH_2\underline{C}H{=}CH_2$), 116.8 ($OCH_2CH_2CH{=}\underline{C}H_2$), 100.8 (C-1).

Anal.: Calcd. for $C_{18}H_{26}O_{10}$: C, 53.92; H, 6.51; Found: C, 53.80; H, 6.55.

4-Pentenyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (6)

76% yield; R_f = 0.48 (60:40 light petroleum: EtOAc), $[\alpha]_D$= -19.5° (c= 1.06, $CHCl_3$) , mp= 47-48°C (light petroleum: diethyl ether) . ^{1}H NMR ($CDCl_3$): δ = 1.69-1.61 (m, 2 H, $OCH_2C\underline{H}_2CH_2CH{=}CH_2$), 1.99 (s, 3 H, 3-OAc), 2.02 (s, 3 H, 4-OAc), 2.05 (s, 3 H, 2- OAc), 2.09 (s, 3 H, 6-OAc), 3.46 (m, 1 H, $OC\underline{H}_2CH_2CH_2CH{=}CH_2$), 3.67 (m, 1 H, H-5), 3.85 (m, 1 H, $OC\underline{H}_2CH_2CH_2CH{=}CH_2$), 4.13 (dd, 1 H, $J_{5,6'}$ = 2.4 Hz, H-6'), 4.24 (dd, 1 H, $J_{5,6}$ = 4.7 Hz, $J_{6,6'}$= 12.2 Hz, H-6), 4.48(d, 1 H, H-1, $J_{1,2}$= 7.9 Hz), 4.94 (m, 2 H, $OCH_2CH_2CH_2CH{=}C\underline{H}_2$), 5.01 (m, 1 H, H-2), 5.05 (t, 1 H, H-4), 5.18 (t, 1 H, $J_{2,3}$ = $J_{3,4}$= 9.6 Hz, H-3), 5.78 (m, 1 H, $OCH_2CH_2CH_2C\underline{H}{=}CH_2$). ^{13}C NMR ($CDCl_3$): δ = 170.7, 170.3, 169.4, 169.3 (C=O), 137.8 ($OCH_2CH_2CH_2\underline{C}H{=}CH_2$), 115.1 ($OCH_2CH_2CH{=}\underline{C}H_2$), 100.8 (C-1).

Anal.: Calcd. for $C_{19}H_{28}O_{10}$: C, 54.80, H, 6.78; Found: C, 54.80; H, 6.80.

5-Hexenyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (7)

55% yield; R_f = 0.50 (60:40 light petroleum: EtOAc), $[\alpha]_D$= -17.4° (c= 1.06, $CHCl_3$), mp= 40-41°C (light petroleum: diethyl ether) ^1H NMR ($CDCl_3$): δ = 1.42 (m, 2 H, $OCH_2CH_2C\underline{H}_2CH_2CH=CH_2$), 1.70 (m, 2 H, $OCH_2C\underline{H}_2CH_2CH_2CH=CH_2$), 1.99 (s, 3 H, 3-OAc), 2.02 (s, 3 H, 4-OAc), 2.05 (s, 3 H, 2- OAc), 2.09 (s, 3 H, 6-OAc), 3.47 (m, 1 H, $OC\underline{H}_2CH_2CH_2CH_2CH=CH_2$), 3.69 (m, 1 H, H-5), 3.89 (m, 1 H, $OC\underline{H}_2CH_2CH_2CH_2CH=CH_2$), 4.15 (dd, 1 H, $J_{5,6'}$ = 2.4 Hz, H-6'), 4.28 (dd, 1 H, $J_{5,6}$ = 4.7 Hz, $J_{6,6'}$= 12.4Hz, H-6), 4.49 (d, 1 H, H-1, J = 8.0 Hz), 4.94 (m, 2 H, $OCH_2CH_2CH_2CH_2CH=C\underline{H}_2$), 5.01 (m, 1 H, H-2), 5.08 (t, 1 H, H-4), 5.19 (t, 1 H, $J_{2,3} = J_{3,4}$= 9.6 Hz,H-3), 5.79 (m, 1 H, $OCH_2CH_2CH_2C\underline{H}=CH_2$). ^{13}C NMR ($CDCl_3$): δ = 170.7, 170.3, 169.4, 169.3 (C=O), 138.5 ($OCH_2CH_2CH_2CH_2\underline{C}H=CH_2$), 114.7 ($OCH_2CH_2CH_2CH=\underline{C}H_2$), 100.8 (C-1).

Anal.: Calcd. for $C_{20}H_{30}O_{10}$: c, 55.81, H, 7.02; Found: C, 55.96; H, 7.06.

General Procedure for Preparing Alkenyl Glycosides 8, 9, 10, 11.

To a solution of alkenyl glycoside (15 mmol) in anhydrous methanol (75 mL) was added a catalytic amount of anhydrous K_2CO_3 (ca. 200 mg) and the suspension was stirred at room temperature under argon for 4.5 h. The mixture was filtered through a Celite pad and concentrated to give the tetrol as a puffy yellow foam. To a stirred solution of the tetrol in dimethylformamide at 0 °C under argon was added NaH (60% dispersion, 5 eq). Benzyl bromide (6 eq) was added dropwise at 0 °C and the mixture was then stirred at room temperature for 8 h. The reaction was quenched with methanol, diluted with diethyl ether (200 mL), and washed consecutively with cold H_2O (1 X 150 mL), saturated $NaHCO_3$ (2 X 100 mL), and brine (2 X 100 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and the residue flash chromatographed (95:5 –> 90:10 light petroleum: EtOAc) to yield the alkenyl glycosides as white solids.

2-Propenyl 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranoside (8)

79% yield; R_f = 0.60 (80:20 light petroleum: EtOAc), $[\alpha]_D$ = + 7.60 (c= 1.07, $CHCl_3$), m.p. = 91.0 - 91.8 °C (ethanol). ^1H NMR ($CDCl_3$): δ = 3.45-3.69 (m, 6 H), 4.15 (m, 1 H, $OC\underline{H}_2CH=CH_2$), 4.45 (d, 1 H, $PhC\underline{H}_2$), 4.5-5.65 (m, 5 H), 4.70 - 4.85 (m, 3H, $PhC\underline{H}_2$), 4.95 (t, 1 H), 5.21 (dd, 1 H, $OCH_2CH=C\underline{H}_2$), 5.35 (dd, 1 H, $OCH_2CH=C\underline{H}_2$), 5.97 (m, 1 H, $OCH_2C\underline{H}=CH_2$), 7.35 (m, 20 H, aromatic). ^{13}C = 138.6-134.0 (aromatic C-1, $OCH_2\underline{C}H=CH_2$), 128.0-127.6 (aromatic), 117.3 ($OCH_2CH=\underline{C}H_2$), 102.8 (C-1).

Anal.: Calcd. for $C_{37}H_{40}O_6$: C, 76.52, H, 6.94; Found: C, 76.25, H, 7.02.

3-Butenyl 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranoside (9)

84 % yield; R_f = 0.62 (80:20 light petroleum: EtOAc), $[\alpha]_D$ = + 6.07 ° (c=1.10, $CHCl_3$), m.p. = 63.1-64 °C (ethanol). ^1H NMR ($CDCl_3$): δ = 2.45 (m, 2 H, $OCH_2C\underline{H}_2CH=CH_2$), 3.43 (m, 1H), 3.53 - 3.79 (m, 5 H), 4.94 (m, 2H), 5.05 -5.16 (m, 2H), 5.87 (m, 1 H, $OCH_2CH_2\underline{C}H=CH_2$), 7.32 (m, 20 H, aromatic). ^{13}C NMR ($CDCl_3$): δ = 138.7-135.1 (aromatic C-1, $OCH_2CH_2\underline{C}H=CH_2$), 128.4 - 127.7 (aromatic), 116.7 ($OCH_2CH_2CH=\underline{C}H_2$), 103.7 (C-1).

Anal.: Calcd. for $C_{38}H_{42}O_6$: C, 76.74, H, 7.12; Found: C, 76.51, H, 7.19.

4-Pentenyl 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranoside (10)

68 % yield; R_f = 0.69 (80:20 light petroleum: EtOAc), $[\alpha]_D$ = + 5.48 °(c=1.06, $CHCl_3$), m.p. = 70-71 °C (ethanol). ^1H NMR ($CDCl_3$): δ = 1.72 (m, 2 H, $OCH_2C\underline{H}_2CH_2CH{=}CH_2$) 2.11 (m, 2 H, $OCH_2CH_2C\underline{H}_2CH{=}CH_2$), 3.38 (m, 1 H), 3.45 - 3.69 (m, 5 H), 3.91 (m, 1 H, $OC\underline{H}_2CH_2CH_2CH{=}CH_2$), 4.32 (d, 1 H, $PhC\underline{H}_2$), 4.50 - 4.61 (m, 4 H), 4.78 (m, 3 H), 4.98 (m, 4 H, $=CH_2$), 5.82 (m, 1 H, $OCH_2CH_2CH_2C\underline{H}{=}CH_2$), 7.35 (m, 20 H, aromatic). ^{13}C NMR ($CDCl_3$): δ = 138.7-138.1 (aromatic C-1, $OCH_2CH_2CH_2\underline{C}H{=}CH_2$), 128.4 - 127.6 (aromatic), 115.0 ($OCH_2CH_2CH_2CH{=}\underline{C}H_2$), 103.8 (C-1).

Anal.: Calcd. for $C_{39}H_{44}O_6$: C, 76.95, H, 7.28; Found: C, 76.74, H, 7.33.

5-Hexenyl 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranoside (11)

81 % yield; R_f = 0.72 (80:20 light petroleum: EtOAc), $[\alpha]_D$ = + 4.83 ° (c=1.00, $CHCl_3$), m.p. = 47.5-47.8 °C (ethanol). ^1H NMR ($CDCl_3$): δ = 1.51 (m, 2 H, $OCH_2CH_2C\underline{H}_2CH_2CH{=}CH_2$),1.68 (m, 2 H, $OCH_2C\underline{H}_2CH_2CH_2CH{=}CH_2$) 2.11 (m, 2 H, $OCH_2CH_2CH_2C\underline{H}_2CH{=}CH_2$), 3.41 - 3.79 (m, 6H), 3.97 (m, 1 H, $OC\underline{H}_2CH_2CH_2CH_2CH{=}CH_2$), 4.4 (d, 1H), 4.5 - 4.65 (m, 3H), 4.70 -4.85 (3H, $PhC\underline{H}_2$), 4.90-5.05 (m, 4 H), 5.79 (m, 1H, $OCH_2CH_2CH_2CH_2C\underline{H}{=}CH_2$), 7.3 (m, 20 H, aromatic). ^{13}C NMR ($CDCl_3$): δ = 138.7-138.1 (aromatic C-1, $OCH_2CH_2CH_2CH_2\underline{C}H{=}CH_2$), 128.4 - 127.62 (aromatic), 114.7 ($OCH_2CH_2CH_2CH{=}\underline{C}H_2$), 103.7 (C-1).

Anal.: Calcd. for $C_{40}H_{46}O_6$: C, 77.14; H, 7.44; Found: C, 77.10; H, 7.46.

General Procedure for Epoxidation of 6, 7, 8, 9.

(a) From Regioisomeric Bromohydrins (10-13, 15-16):

Alkenyl glycosides (**8,9, 11**) (0.5 mmol) were stirred with NBS (3eq) in a 1% H_2O/MeCN solution (25 mM) overnight. The reaction was quenched with 10% Na_2SO_3 solution, diluted with CH_2Cl_2, extracted with brine, and dried over Na_2SO_4. After concentration , the yellow-brown oil was treated with NaH (60% disp., 4 eq) in THF (8 mL) for 12 h at room temperature before being quenched with methanol, diluted with diethyl ether (75 mL), and washed with saturated $NaHCO_3$ (25 mL)and brine (25 mL). The organic layer was dried over $MgSO_4$, concentrated, and flash chromatographed (85:15 –> 75:25 light petroleum: EtOAc) to give the epoxides in good yields. Yields were 63% from the allyl, 78% from butenyl, 79% from hexenyl substrates. Both bromohydrins (Markovnikov; anti-Makovnikov) reacted to give the epoxide product. These epoxides matched the authentic epoxides derived from MCPBA epoxidation of the alkenyl glycosides.

(b) By MCPBA:

To a stirred solution of alkenyl glycoside **6, 7, or 9** (0.2 mmol) in CH_2Cl_2 (5 mL) at 0 °C under argon was added MCPBA (70 mg, 1.5 eq). After 8 h at room temperature, the mixture was heated at 45 °C for an additional 7 h. The reaction was diluted with EtOAc (20 mL) and washed with saturated $NaHSO_3$ (13 mL), saturated $NaHCO_3$ (15 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, concentrated, and flash chromatographed (85:15 –> 75:25 light petroleum: EtOAc) to give the epoxides as white solids. Yields: from allyl 59%, butenyl 87%, hexenyl 86%.

2,3 Epoxypropyl Tetra-*O*-benzyl-β-D-glucopyranoside (19)

R_f = 0.37 (80:20 light petroleum: EtOAc), m.p. = 84-85 °C (ethanol). ^1H NMR ($CDCl_3$): δ = 2.61 - 2.82 (m, 2 H, CH_2 epoxide), 3.25 (m, 1 H, CH epoxide), 3.45-3.95 (m, 6H), 4.15 (m, 1 H), 4.41- 4.63 (m, 4 H), 4.70-4.86 (m, 4 H), 4.95 (m, 2 H), 7.35 (m, 20 H), aromatic).

Anal: Calcd. for $C_{37}H_{40}O_7$: C, 74.48; H, 6.76. Found: C, 74.23; H, 6.80.

3,4 Epoxybutyl Tetra-*O*-benzyl-β-D-glucopyranoside (20)

R_f = 0.40 (85:15 light petroleum: EtOAc), mp= 65-66°C (ethanol). ^1H NMR ($CDCl_3$): δ = 1.85 (m, 2 H, OCH_2 epoxide), 2.51 (m, 1 H, $OCH_2C\underline{H}_2CHOCH_2$), 2.75 (M, 1 H, $OCH_2C\underline{H}_2CHOCH_2$), 3.05 (m, 1 H, OCH epoxide), 3.43 (m, 1 H), 3.53 - 3.79 (m, 5 H), 4.05 (m, 1 H, $OC\underline{H}_2CH_2CH{=}CH_2$), 4.40 (d, 1 H, $PhC\underline{H}_2$), 4.50 - 4.61 (m, 3 H), 4.65- 4.85 (m, 4 H), 4.95 (m, 2 H), 5.05 - 5.16 (m, 2 H), 7.32 (m, 20 H, aromatic). ^{13}C NMR ($CDCl_3$): 138.6-138.1 (C-1 aromatic), 128.4-127.7 (aromatic), 103.8, 103.5 (C-1), 50.0 ($\underline{C}H$ epoxide),47.3, 47.0 ($\underline{C}H_2$ epoxide).

Anal: Calcd. for $C_{38}H_{42}O_7$: C, 74.73; H, 6.93; Found: C, 74.55; H, 6.95.

3,4 Epoxyhexyl Tetra-*O*-benzyl-β-D-glucopyranoside (21)

R_f = 0.49 (85:15 light petroleum: EtOAc), mp= 37-38°C (ethanol). ^1H NMR ($CDCl_3$): δ = 1.51-1.80 (m, 6 H), 2.45 (m, 1 H, OCH_2 epoxide), 2.71 (m, 1 H, OCH_2 epoxide), 2.89 (m, 1 H, OCH epoxide), 3.41-3.79 (m, 6H), 3.97 (m, 1 H, $OC\underline{H}_2CH_2CH_2CH_2CHOCH_2$), 4.40 (d, 1 H, $PhC\underline{H}_2$), 4.50 - 4.65 (m, 3 H), 4.78 (m, 3 H), 4.98 (m, 4 H), 7.35 (m, 20 H, aromatic). ^{13}C NMR ($CDCl_3$): 138.6-138.1 (C-1 aromatic), 128.4-127.7 (aromatic), 100.6, 99.5 (C-1), 61.4, 61.4 ($\underline{C}H$ epoxide), 49.7 ($\underline{C}H_2$ epoxide). HRMS Found $(M-H)^+$ = 637.3187; Calculated for $C_{40}H_{45}O_7$ = 637.3165.

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