Pergamon

Tetrahedron, Vol. 53, No. 9, pp. 3417-3424, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00064-1

Stereoelectronic Control in Two-Step Additions to Tri-*O*-Benzyl-D-Glucal Initiated by Electrophilic Halogens‡

Giuseppe Bellucci, Cinzia Chiappe,* Felicia D'Andrea, Giacomo Lo Moro

Dipartimento di Chimica Bioorganica, via Bonanno 33, 56126 Pisa, Italy

Abstract: The product distribution obtained in electrophilic reactions of Br_2, N-bromosuccinimmide (NBS), tetrabutylammonium tribromide, tetrabutylammonium bromochloride, NBS-Et_3N•3HF, ICl-NaN_3 and MCPBA-KF with tri-O-benzyl-D-glucal in aprotic and protic solvents have been determined by NMR. The results have been rationalized on the basis of the stereoelectronic α-anomeric effect able to stabilize the transition state related to the electrophilic or nucleophilic step.

The anomeric effect,[1] is the tendency of an electronegative group X at C(1) in tetrahydropyranyl derivatives with to assume the axial conformation, in contrast with the usual equatorial preference. The discussion about the origin of the anomeric effect is nearly as old as the term itself, and although the initial explanation[2] assumed that electrostatic repulsive forces between the dipole due to the ring oxygen lone pairs and the exocyclic C-X at C(1) was responsable for the axial preference of electronegative anomeric substituents, a more recent rationalization, based on experimental data and theoretical calculations, proposes that the anomeric effect is due to a stabilizing interaction arising from orbital overlap between an oxygen lone pair (n) and the C-X antibonding (σ^*) orbital.[3] Probably both these interactions are operative, but the molecular-orbital interpretation is currently favored.[4] The anomeric effect as usually understood is a thermodynamic effect, concerned with the ground state properties of molecules, but the most recent developments in this area involve stereoelectronic effects on reactivity. Since transition states may be more sensitive to these effects than ground states of molecules, they may in principle be magnified when they operate on rates of reaction. A stabilizing interaction, involving hyperconjugative σ assistance between the σ^* orbital of the incipient bond with neighbouring occupied orbitals was postulated as an overriding stereoelectronic factor in π-facial diastereoselection occurring in nucleophilic and electrophilic additions by Cieplack,[5] and it has been recently shown[6] to play an important role even in the two-step additions initiated by electrophilic halogens to methylenecyclohexanes.

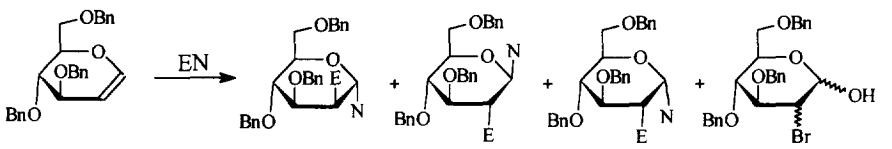
Since this interaction has been considered[5] an attempt to generalize the concept of kinetic anomeric effect, during an investigation aimed at the stereoselective synthesis of the allyl glycosides of tri-*O*-benzyl-D-glucal to use as substrates for a study on the diastereoselective functionalization of allyl alcohols bonded to a chiral auxiliary, we decided to examine the stereo- and regio-chemistry of additions initiated by electrophilic halogen to this olefin, to be compared with that of the peroxyacid-KF epoxidation. This brought us to reconsider the debated problem of the anomeric effect in electrophilic additions to this class of compounds, that had not been previously examined taking into account the mechanism of the two-step additions of the mentioned type.

‡Dedicated to the memory of Professor Giuseppe Bellucci (d. March 3, 1996).

Results and Discussion

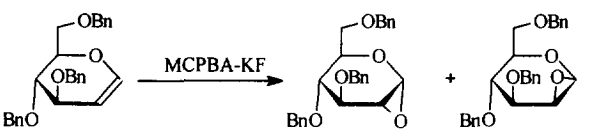
The investigated reactions are sketched in Scheme I and the products are reported in Table 1. The reactions were chosen in order to lead to products whose regio and stereochemistry was known or could be determined by ^{1}H and/or ^{13}C NMR analysis on the basis of the chemical shift of the C(1) and C(2) carbons and of the H(1) and H(2) protons as well as on the basis of the vicinal coupling constants for the H(1) and H(2) protons.

SCHEME 1



1 **2** **3** **4** **5**

a: E = N = Br, **b**: E = Br, N = CH_3O, **c**: E = I, N = N_3, **d**: E = Br, N = F, **e**: E = Br, N = Cl



1 **6** **7**

90% 10%

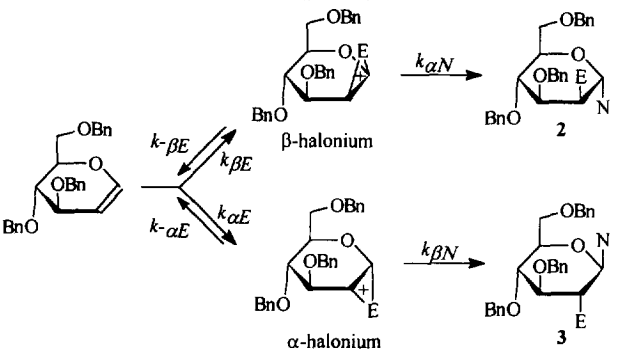
The product distributions of all investigated additions were accurately measured by NMR analysis of the reaction mixtures on the basis of the H(1) and /or C(1) signals, which were different for each set of epimers.

The peroxyacid epoxidation, carried out in this case under anhydrous conditions in the presence of KF,[7] is a typical one-step, irreversible electrophilic addition and can be taken as a model for the electrophilic step of two-step additions initiated by electrophilic halogens, leading to halonium ion intermediates. The preference for the α attack in the epoxidation of glycals, bearing no stereocontrolling OH groups,[8] can be related to a stereoelectronic effect. Indeed, whereas steric hindrance due to the protons at the C(3) and C(6) positions favours the equatorial attack, orbital overlap between the endocyclic oxygen lone pair and the developing antibonding σ* orbital stabilizes the transition state related to the α approach. In unhindered glucals of type **1** the stereoelectronic effect overcomes the steric one, causing the observed preference for α face and leading to the epoxide **6** as the main product.

This model can likewise explain the stereochemistry of the two-step electrophilic halogen additions to the double bond, for which three different pathways can be considered. *a*) The electrophilic halogen binds to both the olefinic carbons in the transition state to give a bridged halonium ion intermediate and the process is irreversible (Scheme 2, $k_{-\alpha E}=k_{-\beta E}=0$). In this case the formation of the intermediate can be stereoelectronically assisted giving the α–halonium ion and the subsequent fast nucleophilic attack on this intermediate occurs with inversion at the anomeric carbon, leading regiospecifically to β-gluco derivatives (**3**) as the main products. The stereochemical result can be therefore considered as evidence for the product

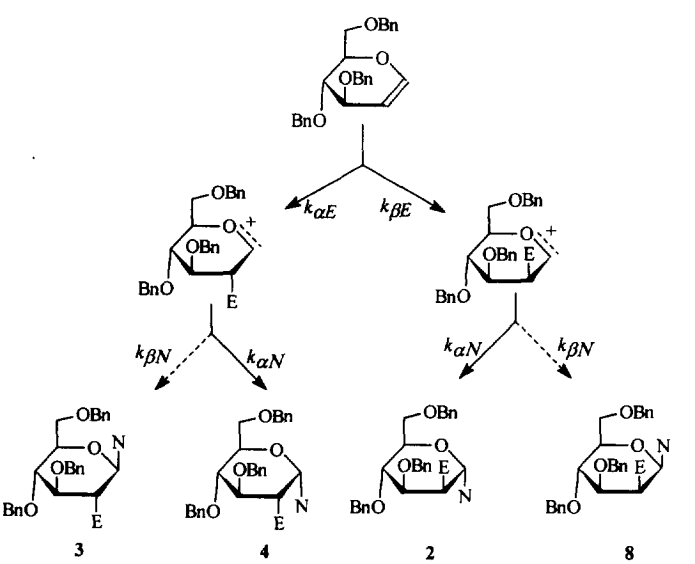
determining formation of bridged intermediates. *b*) The electrophilic step involves the reversible formation of halonium ions (Scheme 2, $k_{-\alpha E}=k_{-\beta E}\neq 0$). In this case the overall regio- and stereochemistry of the addition will be determined by the relative rate of interconversion of the intermediates with respect to their trapping by nucleophile. Indeed, if the rate of interconversion of the α and β halonium intermediates is comparable with those of their nucleophilic opening, the stereochemistry will be determined partially in both the electrophilic and the nucleophilic step. A balance of opposite effects in the two steps (i.e. stereoelectronic stabilization of axial approach of the electrophile against stabilization of the axial approach of the nucleophile at the anomeric carbon of the halonium intermediate) may be responsible for a loss of stereoselectivity. On the other hand, if the rate of interconversion is faster than the nucleophilic trapping of the intermediate the preferential formation of compounds of type **2** should be observed.

SCHEME 2



c) The electrophilic step involves the irreversible formation open halocarbonium ions. In this situation their capture by nucleophiles, rather than their formation, could preferentially occur with stereoelectronic assistance by α attack, leading to products of type **2** and **4** having the nucleophile in the α position (Scheme 3).

SCHEME 3



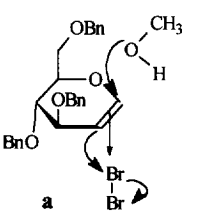
Pathway *b* and the related rationalization can explain the product distribution arising from the reaction of **1** with ICl/NaN_3 in acetonitrile (run 1), where reversibly formed iodonium ion intermediates are surely involved,[9,10] and their capture by the nucleophile determines the stereoselective formation of compound **2c**.

Table 1. Products Ratios Obtained in Electrophilic Additions to Glucal 1.

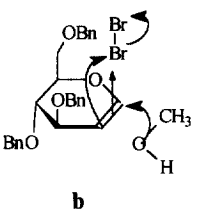
Run	Reagent	Products					
	1	**2**		**3**		**4**	
		N, E	%	N, E	%	N, E	%
1	ICl/NaN_3/ CH_3CN	N_3, I	87	N_3, I	13		
2	Br_2/ DCE	Br, Br	40			Br, Br	60
3	Br_2/ MeOH	MeO, Br	55	MeO, Br	45		
4	NBS/ MeOH	MeO, Br	55	MeO, Br	45		
5	Bu_4NBr_3/ DCE	Br, Br	87	Br, Br	traces	Br, Br	13
6	Bu_4Br_2Cl/ DCE	Cl, Br	53	Cl, Br	31	Cl, Br	16
7	NBS-Et_3N•3HF/DCM	F, Br	72	F, Br	28		

In the Br_2 addition in an aprotic solvent (run 2) instead open bromocarbonium ions are probably involved, whose formation occurs through a transition state having low, if any, bonding between the bromine atom and the anomeric carbon. No anomeric effect can therefore been involved in the electrophilic step and both gluco and manno cyclic oxacarbenium ions are formed ($k_{\alpha E} \cong k_{\beta E}$). The subsequent trapping by the nucleophile, Br_3^- in the aprotic DCE, occurs therefore with anomeric assistance giving compounds **4** and **2** as the sole dibromides.

It is noteworthy that when the reaction is carried out in methanol, using either Br_2 or N-bromosuccinimide (NBS) as brominating agents (runs 3 and 4), only the trans addition products **2b** and **3b**, arising from solvent incorporation are formed. In particular, in this solvent, the β-glucoderivative **3b** rather than the α anomer **4b** is formed, pointing to a negligible anomeric effect in the nucleophilic step.[11] Since in the Br_2 addition the nature of the intermediate is considered to be independent of the solvent,[12] this behaviour can be explained considering that in methanol nucleophilic assistance by the solvent can occur in the electrophilic step. A process of this type, represented as shown in **a** and **b**, in which the solvent is positioned in an appropriate configuration for anti attack, the transition state is early and the life time of the intermediate is very short, if any, could indeed accout for the observed anti stereoselectivity of the reaction. Furthemore, since a mechanism of this type reduces the importance of the α anomeric effect on the nucleophilic attack enhancing that on the electrophilic one it can also explain the observed formation of compounds **2b** and **3b** in practically equal amounts.



a



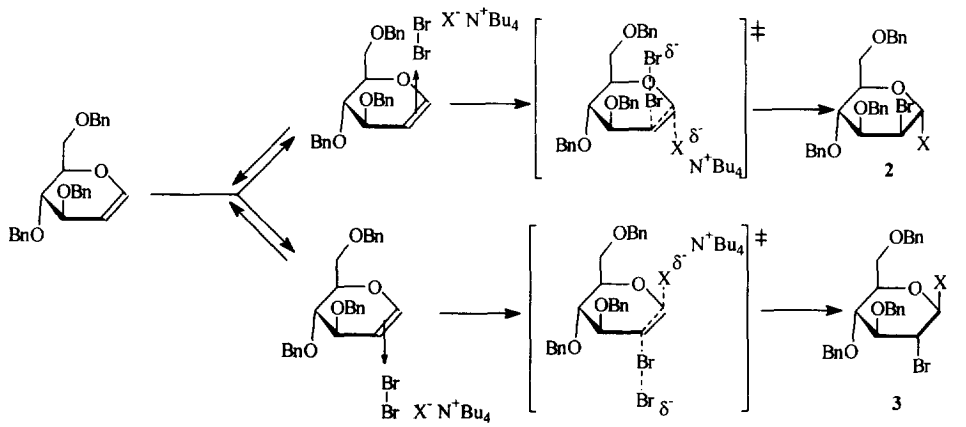
b

It is noteworthy that the bromination of **1** in acetonitrile (containing 1% H_2O) occurs without solvent incorporation. Dibromides **2a** (43%) and **4a** (17%) and the pyranose **5** (40%), due to the trapping of the

oxocarbenium ion intermediate by water, or only **5** are indeed formed, respectively, by reaction with Br_2 and NBS. This behaviour is in contrast with the product distribution obtained[13] in bromination of cyclohexene in the same solvent which gives, beside the corresponding dibromide, large amounts of *trans*-2-bromocyclohexaneacetammide, arising from the reaction with water of the first formed bromoacetonitrilium ion. A strong structure dependence in the formation of N-acetyl-α-D-glucopyranosylamines was also observed in the oxidative hydrolysis of pent-4-enyl glycosides carried out with NBS in acetonitrile and a possible effect of the sugar structure on the reactivity of the oxocarbenium ion, which can affect the tendency of this intermediate to trap acetonitrile, has been tentatively proposed.[14] In the Br_2 addition is, however, known that the chemoselectivity, expressed as the percentage of the solvent incorporating products, can be influenced by several factors such as the polar and steric effects of the substituents, the nature of the counteranion of the intermediate, and the life-time of the ion pairs.[15] Furthermore, when dissymmetrical ions are involved,[16] the chemoselectivity has been correlated with the charge distribution on the carbocationic site. An increase in the hardness of this centre would favour its attack by the nucleophile which is relatively harder. In our case on going from cyclohexene, whose bromination occurs through a bridged bromonium ion intermediate, to the glucal **1**, involving an open bromocarbonium ion intermediate, the hardness of the carbon certainly increases and this, considering the relative softness of the solvent, could favour the attack of the counteranion, the Br_3^- or Br^- anion.

The use of Bu_4NBr_3 as brominating reagent was examined in order to obtain information about the stereochemistry of additions in which product formation is completely controlled during the nucleophilic step. It has been shown,[17] indeed, that at variance with the Br_2 and NBS reactions, the Br_3^- reaction does not involve the formation of bromonium-bromocarbonium ions intermediate, but occurs through a rate and product determining nucleophilic attack of Br^- on equilibrating olefin-Br_2 charge transfer complexes formed at the two faces of the double bond. In the corresponding transition state the formation of the bond of the nucleophile to the anomeric carbon is concerted with the bonding of bromine to the C(2) carbon (Scheme 4).

SCHEME 4



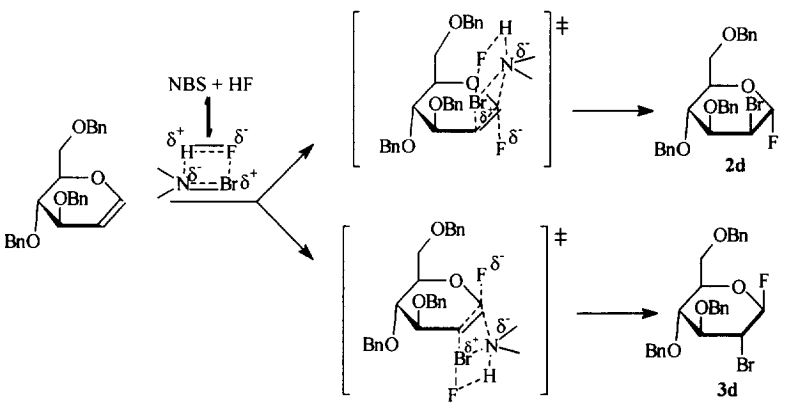
The formation of the anomeric bond from the α side (run 5) can therefore again be favoured by the stereoelectronic effect, which leads to the selective formation (*ca.* 87) of the trans product **2a**. The syn addition

adduct **4a**, corresponding to a *ca.* 10% of the total products, can arise from an *in situ* anomerization of the corresponding trans product **3a**, catalyzed by the Br^-, or by the competition of the free Br_2 addition. The possibility of competition between the formation of a bromocarbonium bromide ion pair and the nucleophilic attack by Br^- on the olefin-Br_2 charge transfer complex, has been recently demonstrated to occur during the bromination of highly reactive olefins with Br_3^-.[18] However, independently of the way of formation, the presence of **4a** in the reaction mixture does not affect the stereochemical picture of the reaction, the selectivity being given by the percentage of the manno compound **2a**.

Even if the reaction of Bu_4NBr_2Cl probably occurs with a mechanism similar to that of Bu_4NBr_3, the lower selectivity (run 6) towards the product arising from the anomerically assisted nucleophilic α attack at the C(1) carbon, **2e**, can be attributed to the higher nucleophilicy of the Cl^- anion with respect to the Br^- one in the aprotic DCE,[19] which could affect the position of the related transition state. An earlier transition state could indeed markedly decrease the α anomeric effect on the attack of nucleophile, as shown also by the Br_2 addition in methanol, making the alternative β attack on the charge transfer complex competitive. Related to the formation of the syn adduct **4e**, the same explanation may be valid for the formation of **4c**.

Finally, the anti stereoselectivity observed in the reaction of NBS-Et_3N•3HF (run 7), at variance with the reaction carried out with NBS in methanol, strongly supports the mechanism proposed[20] for the bromofluorination of olefins with NBS in the presence of HF-pyridine, which does not lead to a fully developed cation, but rather the Br^+ addition is concerted with the asynchronous attack of fluoride. For this reaction the formation of a polarized NBS-HF complex, which reacts with the olefin through a transition state of the type reported in Scheme 5 to give the anti addition products, has been indeed proposed.

SCHEME 5



The stereoelectronic control on these transition states, favouring the formation of the anomeric C-F bond, could explain the observed selectivity favouring **2d**.

In conclusion, all examined additions initiated by electrophilic halogens appear, in agreement with the results obtained with the methylenecyclohexanes,[6] consistent with the model based on the stereoelectronic control of the reaction, no matter if the stereochemical outcome is determined during the electrophilic or the nucleophilic step.

Experimental

^1H NMR spectra were registered in $CDCl_3$ with a Bruker AM 360 instrument containing TMS as the internal reference. All solvents were reagent grade and were used without further purification. Commercial tri-*O*-benzyl-D-glucal (97%), N-bromosuccinimide (99%), tetrabutylammonium tribromide (98%), tetrabutylammonium chloride (dry, 99%), bromine (1 ml sealed ampules), and iodine monochloride (A.C.S reagent) were used as supplied. The epoxidation of **1** with *m*-chloroperoxybenzoic acid-KF was carried out as previously reported.[7]

Additions of ICl and NaN_3. Iodine monochloride (0.55 mmol) was added at 0 °C to 1.5 mmol of NaN_3 dissolved in 2.5 ml of CH_3CN. After 10 min olefin **1** (0.5 mmol), dissolved in 2.5 ml of the same solvent and precooled at 0 °C was added. The mixture was stirred at 0 °C for 15 min, then diluted with a 10% aqueous $NaHSO_3$, extracted with dichloromethane, dried and evaporated. The crude residues were analyzed by ^1H and ^{13}C NMR. The product ratio is reported in Table 1. Selected NMR data. **2c**, ^1H NMR ($CDCl_3$, δ ppm): 5.75 (d, J = 1.4 Hz, 1H, H-1), ^{13}C NMR ($CDCl_3$, δ ppm): 91.5 (C-1), 31.9 (C-2). **3c**, ^1H NMR ($CDCl_3$, δ ppm): 4.87 (d, J = 9.9 Hz, 1H, H-1), ^{13}C NMR ($CDCl_3$, δ ppm): 91.2 (C-1), 31.3 (C-2).[21]

Reactions with N-bromosuccinimide. A methanol or acetonitrile solution of N-bromosuccinimmide (10 ml, 10^{-2} M) was rapidly mixed with 10 ml of a 10^{-2} M solutions of olefin **1** in the same solvent. The reaction mixture was stirred at room temperature for 2-3 h, then diluted with a 10% aqueous $NaHSO_3$, extracted with dichloromethane, dried and evaporated. The crude residue was analysed by ^1H and ^{13}C NMR. The product ratios are reported in Table 1.

Additions of N-bromosuccinimide-Et_3N•3HF. N-Bromosuccinimide (2 mmol) and Et_3N•3HF (3.6 mmol) was added to 2 mmol of olefin **1** dissolved in 2 ml of dichloromethane. The mixture was stirred at room temperature for 8 h, then washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. The crude residues were analyzed by ^1H and ^{13}C NMR. The product ratio is reported in Table 1. Selected NMR data. **2d**, ^1H NMR ($CDCl_3$, δ ppm): 5.82 (dd, J = 51 and 1.4 Hz, 1H, H-1), ^{13}C NMR ($CDCl_3$, δ ppm): 107.4 (d, J = 223 Hz, C-1), 48.9 (d, J = 35 Hz, C-2). **3d**, ^1H NMR ($CDCl_3$, δ ppm): 5.27 (dd, J = 51 and 7.5 Hz, 1H, H-1), ^{13}C NMR ($CDCl_3$, δ ppm): 108.3 (d, J = 220 Hz, C-1), 51.3 (d, J = 30 Hz, C-2).

Additions of Bromine and Bu_4NBr_3.

a) In 1,2.Dichloroethane. 1,2-Dichloroethane solutions of Br_2 or Bu_4NBr_3 (5 ml, 10^{-2} M) were rapidly mixed with 5 ml of 10^{-2} M solutions of olefin **1** in the same solvent. When the color had completely disappeared, the reaction mixtures were evaporated (after washing with water for the Bu_4NBr_3 reactions), and the residues were analyzed by ^1H and ^{13}C NMR. The product ratios are shown in Table 1. Selected NMR data. **2a**, ^1H NMR ($CDCl_3$, δ ppm): 6.72 (d, J = 1.4 Hz, 1H, H-1), ^{13}C NMR ($CDCl_3$, δ ppm): 87.9 (C-1), 54.11 (C-2). **4a**, ^1H NMR ($CDCl_3$, δ ppm): 6.52 (d, J = 2.0 Hz, 1H, H-1), ^{13}C NMR ($CDCl_3$, δ ppm): 91.7 (C-1), 51.80 (C-2).[22]

b) In protic solvent. The same procedure used for the reactions of Br_2 in 1,2-dichloroethane was applied to the brominations in methanol and acetonitrile. At the end of the reactions the mixtures were diluted with water and the products were extracted with dichloromethane and analyzed by ^1H and ^{13}C NMR. The product ratios are reported in Table 1. Selected NMR data. **2b**, ^1H NMR ($CDCl_3$, δ ppm): 3.35 (s, CH_3O). ^{13}C NMR ($CDCl_3$, δ ppm): 100.9 (C-1), 55.00 (C-2), 51.15 (CH_3O). **3b**, ^1H NMR ($CDCl_3$, δ ppm): 3.55 (s, CH_3O). ^{13}C NMR ($CDCl_3$, δ ppm): 103.5 (C-1), 57.00 (C-2), 52.95 (CH_3O).

Additions of Bu_4NBr_2Cl. Dry tetrabutylammonium chloride (10 mmol) was added to 50 ml of a 10^{-2} M solution of Br_2 in 1,2-dichloroethane. The solution immediately turned to yellow, while the Br_2 absorption band centered at 410 nm disappeared and a new intense UV band appeared, whose λ_{max} = 242 nm was determined under more diluted conditions. This solution was rapidly mixed with 50 ml of a 10^{-2} M solution of the appropriate olefin **1** in the same solvent. The mixtures were stored in the dark at room temperature for *ca.* 1 h, then repeatedly washed with water, dried and evaporated. The residue was analyzed by ^1H and ^{13}C NMR. Selected NMR data. **2e**, ^1H NMR ($CDCl_3$, δ ppm): 6.35 (d, J = 1.2 Hz, 1H, H-1), ^{13}C NMR ($CDCl_3$, δ ppm): 92.4 (C-1), 53.60 (C-2). **3e**, ^1H NMR ($CDCl_3$, δ ppm): 5.30 (d, J = 9.3 Hz, 1H, H-1), ^{13}C NMR ($CDCl_3$, δ ppm): 90.7 (C-1), 55.80 (C-2). **4e**, ^1H NMR ($CDCl_3$, δ ppm): 6.15 (d, J = 3.3 Hz, 1H, H-1), ^{13}C NMR ($CDCl_3$, δ ppm): 94.36 (C-1), 51.5 (C-2).

Acknowledgement. This work was supported in part by grants from Consiglio Nazionale delle Ricerche (CNR, Roma) and Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST, Roma).

REFERENCES

1. Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Spinger: New York, 1983. Juaristi, E.; Cuevas, G. *Tetrahedron*, **1992**, *48*, 5019.
2. Edward, J. T. *Chem Ind.* **1955**, 1102.
3. Romers, C.; Altona, C.; Buys, H.R.; Havinga, E. In *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L. Ed.; Wiley-Intersciences: New York, 1969.
4. Paulsen, H.; Györgydeák, Z.; Friedmann, M *Chem. Ber* **1974**, *107*, 1590.
5. Cieplack, A. S.; tail, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.
6. Bellucci, G.; Chiappe, C.; Lo Moro, G. *J. Org. Chem.* **1995**, *60*, 6214.
7. Bellucci, G.; Catelani, G.; Chiappe, C.; D'Andrea, F. *Tetrahedron Lett.* **1994**, *35*, 8433.
8. Berti, G. In *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L. Ed.; Wiley-Intersciences: New York, 1973, 95-187.
9. Bowers, A, Denot, E. Becerra, R. *J. Am. Chem. Soc.* **1960**, 82, 4007.
10. Freppel, C.; Richer, J.-C *Tetrahedron Lett.* **1972**, *23*, 2321.
11. The absence of **4b** excludes even the possibility of in situ anomerization of the products, showing that the product distribution obtained in the Br_2 and NBS additions is under kinetic control.
12. Ruasse, F.-M. *Adv. Phys. Org. Chem.* **1993**, *28*, 207.
13. Bellucci, G.; Bianchini, R.; Chiappe, C. *J. Org. Chem.* **1991**, *56*, 3067.
14. Ratcliffe, A. J.; Fraser-Reid, B *J. Chem. Soc. Perkin Trans. I* **1989**, 1805.
15. Chrétien, J. R.; Coudert, J.-D., Ruasse, M.-F. *J. Org. Chem.* **1993**, *58*, 1917.
16. Duboins, J.-E.; Chrétien, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 3506.
17. Bellucci, G.; Bianchini, R.; Ambrosetti, R.; Ingrosso, G. *J. Org. Chem.* **1985**, *50*, 3313.
18. Bellucci, G.; Chiappe, C.; Lo Moro, G. *J. Org. Chem.* submitted.
19. Winstein, Savedoff, Smith, Stevens, *Tetrahedron Lett.* **1960**, *9*, 24.
20. Zupan, M. Pollak; A. *J. Chem. Soc. Perkin I*,
21. Lafont, D.; Descotes, G. *Carbohydrate Res.* **1987**, *166*, 195.
22. Teichmann, M.; Descotes, G.; Lafont, D *Synthesis*, **1993**, 889.

(*Received in UK* 31 *December* 1996; *accepted* 16 *January* 1997)