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Asymmetric Synthesis of 2-Chloro- and 2-Bromo-alkanoic acids by Halogenation of α-D-Glucofuranose-Derived Silyl Ketene Acetals.[1]

P. Angibaud[a], J.L. Chaumette[a], J.R. Desmurs[b], L. Duhamel[a], G. Plé[a], J.Y. Valnot[a], P. Duhamel*[a].

a) Université de Rouen, URA CNRS 464, IRCOF, Faculté des Sciences, F-76821 Mont-Saint-Aignan Cedex, France.
b) Rhône-Poulenc Industrialisation, CRIT, 85 Avenue des Frères Perret, F-69192 Saint-Fons Cedex, France.

Abstract : *Optically active (S)-2-bromo- and 2-chloro-alkanoic acids* ***6*** *and* ***7*** *have been obtained via the diastereoselective halogenation of chiral silyl ketene acetals* ***3a-f****, and subsequent saponification of the resulting crude esters. Examples characterized by e.e. values up to 95% are reported. The diastereoface selectivity is independent of the silyl ketene acetal E/Z configuration.*

INTRODUCTION : Optically active 2-haloalkanoic acids are valuable intermediates in organic chemistry. In particular, they are precursors of enantiomerically active 2-aminoacids[2] and oxiranes[3] as well as intermediates in the synthesis of weed-killers[4] and drugs.[5] Enantiomerically pure compounds are usually obtained from the corresponding 2-aminoacids[6] or 2-hydroxyacids;[7] they have also been prepared by chemical[8] or biochemical[9] resolution of racemic 2-halocarboxylic acids. The enantioselective reduction of 2,3-unsaturated 2-haloesters with baker's yeast[10] and the diastereoselective protonation[11] and alkylation[12] of chiral 2-halo-oxazoline enolates were also proposed.

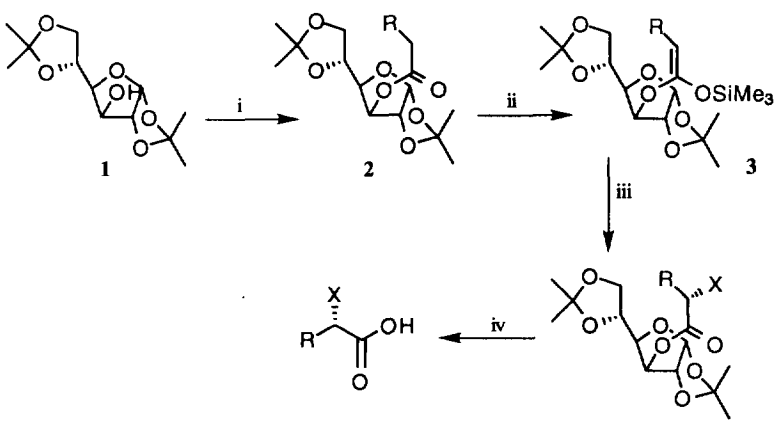
Recently, diastereoselective halogenation has received the attention of several laboratories : high diastereomeric excesses (d.e.) were reported for the halogenation of ketene acetals,[13] dioxolanones,[14] and enolates derived from imides[15] and sultams;[16] in these cases, the chiral 2-halocarboxylic acid derivatives were used directly in further chemical reactions since no removal of the chiral auxiliary nor isolation of the corresponding 2-haloacids were needed. Effective inductions were also obtained in the halogenation of chiral ketals[17] and sulfoxides.[18]

In this paper we report the halogenation of ketene acetals **3a-f** by N-chloro- and N-bromo-succinimide (NCS and NBS), leading to high diastereoselectivities (80-95% for chlorination, 70-85% for bromination) (tables 1,2)[1,19]. The chiral auxiliary, 1,2;5,6-di-O-(1-methylethylidene)-α-D-glucofuranose **1** is a commercial, cheap and non toxic substance which has been already used in some other enantio-[20] and diastereo-selective[21] reactions.

RESULTS and DISCUSSION :

Ketene acetals **3a-f** were synthesized using Corey's procedure[22] i.e. deprotonation of esters **2a-f** in the presence of trimethylchlorosilane using LDA in THF as the base at -70°C. Stereochemical ratio of ketene acetal **3a** was shown by gas chromatography (GC) and ^{1}H NMR to be 90/10, the E configuration being attributed to the major product by N.O.E.D.S. (Nuclear Overhauser Effect Difference Spectroscopy) experiments. This result is in good agreement with previous works concerning other ketene acetals derived from propionic acid.[23] The GC of **3d** also shows the presence of two stereoisomers (ratio 90/10) whereas in all other cases only one product was detected. We thus attributed the E configuration to the major isomer of all ketene acetals **3** obtained.

Halogenation of crude ketene acetals **3** with NCS or NBS proceeds rapidly in THF at -70°C leading to chloroesters **4** or bromoesters **5**. GC analysis of the crude haloesters allowed, in some cases to determine the d.e. (75-96%) (table 1). The presence of starting esters **2** was also detected in minor amounts (<10%).



2-7	a	b	c	d	e	f
R	Me	*n*-Pr	*i*-Pr	*n*-Bu	*i*-Bu	*t*-Bu

6 X=Cl **4** X=Cl

7 X=Br **5** X=Br

Scheme 1: *(i) $RCH_2COOH/DCC/DMAP$, CH_2Cl_2, 0°C ; (ii) LDA/$ClSiMe_3$, THF, -70C ; (iii) NCS (or NBS), THF, -70C ; (iv) LiOOH, THF-H_2O (3:1), 0°C (method A) ; 2.4N HCl, acetone, reflux (method B) ; LiOH, acetonitrile-hexanes (1:1:1), 0°C (method C).*

The halogenation of **3a** with NBS at -70°C was proved to be solvent dependent : lowering of the induction level was observed when going from Et_2O and THF (75%) to more polar solvents such as AcOEt (55%) and dichloromethane (25 %).

In another set of experiments ketene acetals were reacted with a variety of chlorinating (dichlorine, tertiobutylhypochlorite, hexachlorocyclohexadienone, N,N-dichlorodimethylhydantoïne) and brominating (dibromine, tetrabutylammonium tribromide, 2,4,4,6-tetrabromocyclohexadienone) agents and none of them provided higher diastereoselectivities than N-halosuccinimides. Similar observations have been reported in the literature for the halogenation of other ketene acetals,[13] although a spectacular inversion of the

diastereoselectivity was reported in the halogenation of chiral ketals with N-tetrabutylammonium tribromide instead of bromine.[17] It is also to be noted that the use of both (S) and (R) enantiomers of 4-benzyl N-chloro oxazolidinones led in THF to the same predominant diastereoisomer **4a** with 74% and 76% d.e. respectively.

In order to compare the relative velocity of the chlorination and bromination reactions, ketene acetal **3a** was submitted to a mixture of NBS and NCS (one equivalent each). The analysis of the crude product by ^1H NMR (400 MHz) and GC indicated the formation of 85% of bromoester **5a** and 15% of chloroester **4a**, a result in good agreement with the higher selectivity observed for the slower chlorination reaction.

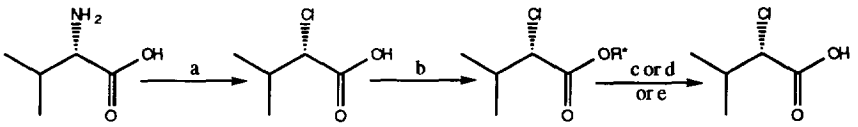
Table 1: Comparative study of methods used for the hydrolysis of haloesters **4** and **5**.

	X = Cl						X = Br					
	4		(S) **6** e.e.%[b]				**5**		(S) **7** e.e.%[b]			
R	N°	d.e.%[a]	N°	Method A	Method B	Method C	N°	d.e.%[a]	N°	Method A	Method B	Method C
Me	**4a**	90	**6a**	90	90	81	**5a**	75	**7a**	75		65
n-Pr	**4b**	89	**6b**	89			**5b**	c	**7b**	77		
i-Pr	**4c**	96	**6c**	95	95	75	**5c**	c	**7c**	84		67
n-Bu	**4d**	c	**6d**	80		78	**5d**	c	**7d**	70		
i-Bu	**4e**	91	**6e**		91	90	**5e**	c	**7e**		79	52
t-Bu	**4f**	90	**6f**	90		83	**5f**	c	**7f**	85		

(a) determinated by GC. (b) hydrolysis of 4 or 5 by LiOH/H_2O_2 (method A); HCl 2.4N (method B); LiOH (method C). The e.e. determinated by GC of the corresponding t-butylamides and confirmed by polarimetry for method C. (c) unsatisfactory separation conditions for analysis.

The high diastereoselectivity opens the road to the use of the chiral esters **4** and **5** as intermediates for further chemical reactions. However, in this work, we choose to concentrate on their transformation into 2-haloacids **6** and **7** without racemization of the newly created stereogenic center. We looked at the following experimental procedures: lithium hydroperoxide in THF-water (3:1) at 0°C (method A) which was found to give excellent results in the hydrolysis of carboxamides whereas it was reported inefficient with unactivated esters (methyl, benzyl esters);[24] 2.4N hydrochloric acid in acetone at reflux (method B); lithium hydroxide in acetonitrile-hexanes-water (1:1:1) at 0°C (method C) which was shown to be "non racemizing" in many cases.[25]

We compared the three methods and after distillation of the crude haloacids **6** or **7**, the e.e. were determined using the Watabe *et al* procedure[27] i. e. transformation into the corresponding t-butylamides and GC analysis on a Chirasil-D-Val column. As shown by results of table 1, the e.e. of the haloacids **6** and **7** obtained by methods A and B are in good accordance with the d.e. of the corresponding haloesters **4** and **5**, whereas they are generally, significantly lower when using method C, indicating a partial racemization. These results have been confirmed by hydrolysis of enantiomerically pure chloroester **4b** obtained from (S)-valine (scheme 2):



(S)-**6b** (e.e. 99%) **4b** (d.e. 98%) (S)-**6b**

	e.e.%	yield%
Method A[c]	98	75
Method B[d]	98	73
Method C[e]	80	80

Scheme 2 : *(a) $NaNO_2$, HCl ; (b) 1, DCC, DMAP, CH_2Cl_2 ; (c) LiOOH, THF-H_2O (3:1), 0°C, 0.5h ; (d) 2.4N HCl, acetone, reflux, 2h ; (e) LiOH, CH_3CN-hexanes-H_2O (1:1:1), 0°C, 11 h.*

The chiral auxiliary **1** may be recovered when using methods A and C while it is destroyed by the acidic treatment of method B. Compared to method C, method A proved to be a powerful method which readily hydrolysed crowded esters such as the t-butylacetic esters **4f** and **5f** without racemization. However we would further point out that haloesters **4** and **5** in the presence of starting esters **2** are selectively hydrolyzed under the conditions of method C; methods A and B do not exhibit such a chemioselectivity. Thus, enantiomerically enriched haloacids **6** and **7** obtained by method C show a higher chemical purity (>99%) but a lower enantiomeric excess. In all cases, haloacids of (S)-configuration are obtained. The results obtained by method A are summarized in table 2.

Table 2 : Haloacids (S)-**6** and (S)-**7** obtained from halogenation of ketene acetals **3**.

	6 (X=Cl)[a]			**7** (X=Br)[a]		
R	N°	yield %[b]	e.e. %[c]	N°	yield %[b]	e.e. %[c]
Me	**6a**	71	90	**7a**	69	75
n-Pr	**6b**	66	89	**7b**	68	77
i-Pr	**6c**	79	95	**7c**	75	84
n-Bu	**6d**	65	80	**7d**	63	70
i-Bu	**6e**[d]	75	90	**7e**[d]	75	79
t-Bu	**6f**	72	90	**7f**	71	85

*(a) obtained by hydrolysis of esters **4** or **5** with LiOH/H_2O_2 (method A) unless otherwise stated. (b) yield of distilled acids **6** or **7** versus esters **2**. (c) determinated by GC of the corresponding t-butylamides.*[27] *(d) obtained by hydrolysis of **4e** or **5e** with HCl 2.4N.*

Finally, it was shown that the diastereoface selectivity is independent of the Z or E configuration of the starting ketene acetal.[28] Using LiHMDS for the deprotonation of ester **2a** gave an equal quantity of the two isomeric ketene acetals **3a** and the results of the chlorination and bromination of the mixture are reported in table 3. As shown by these results, the E and Z isomers led to the same diastereoisomeric excesses for the chlorination (entries 1,2) while the E isomer led to a slightly higher diastereoselectivity than the Z isomer for the bromination (entries 3,4). Such examples of stereoconvergent reactions are not frequently met in the

literature.[29]

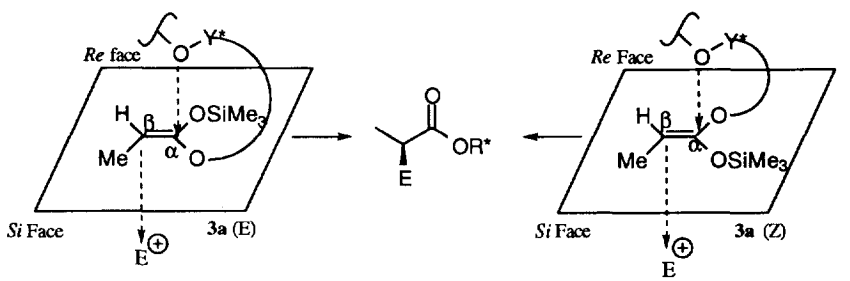
Table 3: Influence of the configuration of **3a** in the halogenation with N-halosuccinimides.

Entry	Halogenating agent	**3a** E/Z	**6-7**	e.e.% (conf)
1	NCS	90/10	**6a**	90 (S)
2	NCS	50/50	**6a**	90 (S)
3	NBS	90/10	**7a**	75 (S)
4	NBS	50/50	**7a**	65 (S)

In order to explain the introduction of the halogen atom on the *Si*-face of **3a** whatever its configuration may be, we suggest an ionic mechanism in which the diastereoface selectivity is directed by the prostereogenic β-center.[29]

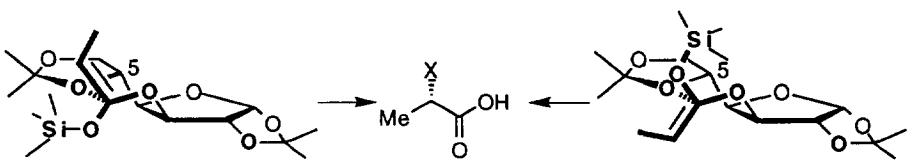
Moreover the increasing positive charge (developed on the carbon atom α as the halogenating reagent approaches the carbon atom β) could be stabilized by the interaction with the doublet of an oxygen atom of the chiral auxiliary (scheme 3).

Scheme 3 :



Only the oxygen atom of the carbon 5 of the chiral auxiliary, is able to establish this coordination.

Scheme 4 :



Models A and B, both leading to (S)-2-haloacids are the less crowded and it is to be noted that model A accounts for the weak dependence on the size of the R group for the diastereoselection observed from **3**(E).

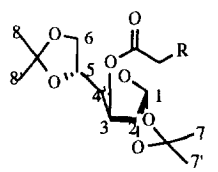
Other mechanisms competing with the ionic model proposed cannot be excluded neither can be the possibility of a radical process.

In summary, we have shown that the cheap, commercially available 1,2;5,6-di-O-(1-methylethylidene)-α-D-glucofuranose **1** was an efficient auxiliary for asymmetric halogenation of silyl ketene acetals. Further extensions are currently under investigation.

EXPERIMENTAL SECTION :

Melting points were determinated on a Kofler WME Reichert-Jung apparatus and are uncorrected. Observed rotations at the Na-D line were obtained at 20°C using a Perkin-Elmer MC 241 polarimeter and $CHCl_3$ as solvent. IR spectra were recorded on a Perkin-Elmer 16 PC FTIR spectrophotometer, in film (liquids) or diluted in $CDCl_3$ (solids). The GC analysis were realized on Hewlett-Packard HP 5890 equiped with a split/splitless injector, a flame ionization detector, and a HP 3396A integrator and fitted for routine analysis with a HP-1 column (methylsilicon, l=5m, d=0.53mm, Tinj=Tdet=200°C), for diastereomeric excess determination with a HP-1 column (methylsilicon, l=25m, d=0.25, Tinj=Tdet=200°C), and for enantiomeric excess determination of t-butylamides with a Chirasil-D-Val column (l=25m, d=0.25mm, Tinj=Tdet=200°C). ^1H NMR spectra were performed on a BRUKER AC 400, and ^{13}C NMR spectra were performed on a BRUKER AC 200 in $CDCl_3$ unless otherwise stated, chemical shifts are expressed in δ ppm. Mass spectra analysis were performed on a JEOL AX 500 apparatus at 70 eV (Electron Impact, EI), or with isobutane or ammoniac as chemical ionization gas (CI). Anhydrous THF was obtained by distillation over sodium and benzophenone. n-Butyllithium solutions were titrated according to [30]. N-Bromo and N-chloro succinimides were recrystallized from dry acetone. The absence of peroxide was proved using Quantofix® peroxide (Macherey-Nagel).

General procedure for esters **2a-f** : To alkanoic acid (60 mmol) in 50 ml of dry CH_2Cl_2, was added successively, 4-dimethylaminopyridine (5 mmol) and 1,2;5,6-di-O-(1-methylethylidene)-α-D-glucofuranose **1** (50 mmol). The solution was cooled at 0°C, before adding dicyclohexylcarbodiimide (DCC, 60 mmol) in 60 ml of dichloromethane with stirring. Stirring was maintained 1 hour at 0°C and then 2 to 5 hours at room temperature, while esterification was monitored by GC (column HP-1, l=5m, d=0,53mm). When esterification is complete, DCU was filtered, the filtrate was concentrated and the residue dissolved in 60 ml of ethyl acetate and filtered again. The organic phase was washed with 50 ml of water, followed by 3 times 50 ml of a saturated solution of $NaHCO_3$, and finally with 50 ml of brine. The organic layer was dried on $MgSO_4$, filtered, concentrated under vacuo, and the residue was chromatographied (elution : ethyl acetate/hexanes: 10/90) to afford the pure esters **2a-f**.



1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl propanoate 2a.

Yield 92%; mp 38-40°C; $[\alpha]_D^{20}$=-31.9(c=1.1); ^1H NMR δ 1.13 (t, 3H, R, 7.5Hz), 1.27, 1.28, 1.37, 1.48 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 2.34 (q, 2H, CH_2, 7.5Hz), 4.00-4.05 (m, 2H, $H_{6,6'}$), 4.18 (m, 2H, H_4, H_5), 4.45 (d, 1H, H_2, 3.7Hz), 5.23 (d, 1H, H_3, 2.0Hz), 5.84 (d, 1H, H_1, 3.7Hz); ^{13}C NMR δ 8.9, 25.1, 26.1, 26.6, 27.4, 27.7, 67.1, 72.3, 75.8, 79.7, 83.2, 104.9, 109.2, 112.1, 172.9; IR (C=O) 1740; Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.96, H, 7.65, Found : C, 56.79, H, 7.88; M.S.(EI) : 301 (M^+-15, 53), 101 (100), 43 (63).

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl pentanoate 2b.

Yield 90%; pale yellow oil; $[\alpha]_D^{20}$=-31.7 (c=1.52); ^1H NMR δ 0.87 (t, 3H, R, 7.2Hz), 1.26, 1.36, 1.47 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.31 (m, 2H, R), 1.58 (m, 2H, R), 2.31 (q, 2H, CH_2, 7.5Hz), 3.95-4.04 (m, 2H, $H_{6,6'}$), 4.16 (m, 2H, H_4, H_5), 4.43 (d, 1H, H_2, 3.7Hz), 5.22 (d, 1H, H_3, 2.0Hz), 5.83 (d, 1H, H_1, 3.7Hz); ^{13}C NMR δ 13.5, 22.0, 25.1, 26.1, 26.6, 26.6, 26.8, 33.8, 67.2, 72.3, 75.7, 79.8, 83.2, 104.9, 109.1, 112.1, 172.2; IR (C=O) 1740; Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.29, H, 8.19, Found : C, 59.28, H, 8.23; M.S.(CI) : 345 (M^++1, 100), 287 (98), 101 (5).

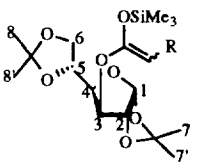
1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-3-methyl butanoate 2c.
Yield 95%; mp 28-30°C; $[\alpha]_D^{20}$=-31.9(c=1.3); ^{1}H NMR δ 0.96 (d, 6H, R, 6.3Hz), 1.29, 1.30, 1.39, 1.51 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 2.11 (m, 1H, R), 2.22 (d, 2H, CH_2, 7.3Hz), 3.96-4.08 (m, 2H, $H_{6,6'}$), 4.18 (m, 2H, H_4, H_5), 4.46 (d, 1H, H_2, 3.7Hz), 5.28 (d, 1H, H_3, 2.1Hz), 5.86 (d, 1H, H_1, 3.7Hz); ^{13}C NMR δ 22.2, 25.0, 25.7, 26.1, 26.1, 26.6, 43.2, 67.3, 72.2, 75.6, 79.8, 83.3, 104.9, 109.2, 112.1, 171.5; IR (C=O) 1740; Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.29, H, 8.19, Found: C, 59.36, H, 8.35; M.S.(EI) : 329 (M^+-15, 21), 101 (60), 85 (100).

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl hexanoate 2d.
Yield 91%; pale yellow oil; $[\alpha]_D^{20}$=-31.3(c=1.0); ^{1}H NMR δ 0.87 (t, 3H, R, 6.9Hz), 1.28, 1.28, 1.38, 1.49 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.28 (m, 4H, R), 1.62 (m, 2H, R), 2.31 (d, 2H, CH_2, 7.5Hz), 4.00-4.05 (m, 2H, $H_{6,6'}$), 4.19 (m, 2H, H_4, H_5), 4.44 (d, 1H, H_2, 3.7Hz), 5.24 (d, 1H, H_3, 1.7Hz), 5.84 (d, 1H, H_1, 3.7Hz); ^{13}C NMR δ 13.8, 22.1, 24.5, 25.1, 26.1, 26.6, 26.7, 31.0, 34.1, 67.2, 72.3, 75.7, 79.8, 83.3, 104.9, 109.2, 112.1, 172.3; IR (C=O) 1740; Anal. Calcd for $C_{18}H_{30}O_7$: C, 60.31, H, 8.44, Found: C, 60.33, H, 8.87; M.S.(CI) : 343 (M^+-15, 21), 301 (100); HR MS (CI) Calcd for $C_{18}H_{30}O_7$: 359.2068, Found: 359.2068

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-4-methyl pentanoate 2e.
Yield 92%; pale yellow oil; $[\alpha]_D^{20}$=-31.3(c=0.6); ^{1}H NMR δ 0.86 (t, 6H, R, 6.1Hz), 1.26, 1.27, 1.36, 1.48 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.48 (m, 1H, R), 1.50 (m, 2H, R), 2.31 (d, 2H, CH_2, 7.2Hz), 3.95-4.04 (m, 2H, $H_{6,6'}$), 4.17 (m, 2H, H_4, H_5), 4.43 (d, 1H, H_2, 3.7Hz), 5.22 (d, 1H, H_3, 2.0Hz), 5.83 (d, 1H, H_1, 3.7Hz); ^{13}C NMR δ 22.1, 25.1, 26.1, 26.6, 27.4, 27.4, 32.2, 33.5, 67.2, 72.3, 75.7, 79.8, 83.2, 104.9, 109.2, 112.1, 172.4; IR (C=O) 1740; Anal. Calcd for $C_{18}H_{30}O_7$: C, 60.31, H, 8.44, Found : C, 60.50, H, 8.39; M.S.(EI) : 343 (M^+-15, 30), 101 (100).

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-3,3-dimethyl butanoate 2f.
Yield 93%; mp 72-74°C; $[\alpha]_D^{20}$=-31.1(c=1.4); ^{1}H NMR δ 1.01 (s, 9H, R), 1.27, 1.28, 1.37, 1.51 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 2.21 (s, 2H, CH_2), 3.99-4.09 (m, 2H, $H_{6,6'}$), 4.20 (m, 2H, H_4, H_5), 4.46 (d, 1H, H_2, 3.7Hz), 5.24 (d, 1H, H_3, 2.6Hz), 5.85 (d, 1H, H_1, 3.7Hz); ^{13}C NMR δ 25.1, 26.1, 26.6, 26.6, 29.5, 30.8, 47.8, 67.4, 72.2, 75.7, 79.8, 83.2, 104.9, 109.2, 112.2, 170.8; IR (C=O) 1730; Anal. Calcd for $C_{18}H_{30}O_7$: C, 60.31, H, 8.44, Found : C, 60.50, H, 8.51; M.S.(EI) : 343 (M^+-15, 13), 101 (74), 43 (100).

General procedure for ketene acetals **3a-f**: To a cooled solution (-70°C) of lithium diisopropylamide (7.5 mmol), (prepared at 0°C from n-butyllithium in hexane (2.5M, 3ml, 7.5 mmol) and diisopropylamine (7.5 mmol) in 15 ml of dry THF), was added successively trimethylsilylchloride (7.5 mmol), and during 6 min, ester **2a-f** (5 mmol) in 2 ml of THF. Agitation was continued for 3 hours at this temperature and the solution was slowly warmed up to room temperature (3 hours). The solvents were removed under vacuo, and the residue was diluted with 40 ml of pentane and centrifuged. The upper solution was then collected and concentrated to afford crude **3a-f**.



1-[1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyloxy]-1-trimethylsilyloxy-prop-1-ene 3a.

^{1}H NMR δ 0.23 (s, 9H, $SiMe_3$), 1.45 (d, 3H, R, 6.6Hz), 1.30, 1.32, 1.40, 1.50 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 3.72-3.77 (2q, 1H, =CHR,(E/Z: 90/10), 6.6Hz), 4.03-4.09 (m, 2H, $H_{6,6'}$), 4.22 (dd, 1H, H_4, 3.0Hz, 7.2Hz), 4.35 (dd, 1H, H_5, 7.2Hz, 6.0 Hz), 4.53 (d, 1H, H_2, 3.7Hz), 4.61 (d, 1H, H_3, 3.0Hz), 5.86 (d, 1H, H_1, 3.7Hz); IR (C=O) 1680; M.S.(EI) for $C_{18}H_{32}SiO_7$: 388 (M^+, 1), 373 (M^+-15, 5), 101 (100), 73 (80).

The E configuration of the predominant isomer was established by N.O.E.D.S. experiments : irradiation of the trimethylsilyl group (0.23 ppm) lead to 1.75% NOE effect on the vinylic hydrogen (3.77 ppm) of the major isomer, and to 0% NOE effect on the vinylic hydrogen (3.72 ppm) of the minor isomer.

1-[1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyloxy]-1-trimethylsilyloxy-pent-1-ene 3b.

^{1}H NMR δ 0.21 (s, 9H, $SiMe_3$), 0.84 (t, 3H, R, 7.3Hz), 1.26, 1.29, 1.38, 1.46 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.26 (m, 2H, R), 1.83 (m, 2H, R), 3.74 (t, 1H, =CHR, 7.2Hz), 3.99-4.04 (m, 2H, $H_{6,6'}$), 4.19 (m, 1H, H_4), 4.29 (m, 1H, H_5), 4.52 (d, 1H, H_2, 3.7Hz), 4.57 (d, 1H, H_3, 3.0Hz), 5.83 (d, 1H, H_1, 3.7Hz); IR (C=O) 1685; M.S.(CI) for $C_{20}H_{36}SiO_7$: 417 (M^++1, 100), 401 (M^+-15, 10), 359 (28), 287 (41).

1-[1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyloxy]-1-trimethylsilyloxy-3-methyl-but-1-ene 3c.

^{1}H NMR δ 0.23 (s, 9H, $SiMe_3$), 0.90 (d, 6H, R, 6.8Hz), 1.29, 1.33, 1.42, 1.50 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 2.42 (m, 1H, R), 3.65 (d, 1H, =CHR, 9.1Hz), 4.03-4.08 (m, 2H, $H_{6,6'}$), 4.22 (dd, 1H, H_4, 3.0Hz, 6.9Hz), 4.34 (dd, 1H, H_5, 6.9Hz, 6.3Hz), 4.56 (d, 1H, H_2, 3.7Hz), 4.59 (d, 1H, H_3, 3.0Hz), 5.87 (d, 1H, H_1, 3.7Hz); IR (C=O) 1680; M.S.(EI) for $C_{20}H_{36}SiO_7$: 416 (M^+, 5), 401 (M^+-15, 19), 101 (100), 73 (86).

1-[1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyloxy]-1-trimethylsilyloxy-hex-1-ene 3d.

^{1}H NMR δ 0.21 (s, 9H, $SiMe_3$), 0.85 (m, 3H, R), 1.29, 1.33, 1.42, 1.50 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.27 (m, 4H, R), 1.87 (m, 2H, R), 3.74 (t, 1H, =CHR, 7.3Hz), 4.02-4.08 (m, 2H, $H_{6,6'}$), 4.20 (dd, 1H, H_4, 3.0Hz, 6.7Hz), 4.29 (dd, 1H, H_5, 6.7Hz, 5.6Hz), 4.52 (d, 1H, H_2, 3.7Hz), 4.57 (d, 1H, H_3, 3.0Hz), 5.84 (d, 1H, H_1, 3.7Hz); IR (C=O) 1685; M.S.(CI) for $C_{21}H_{38}SiO_7$: 431 (M^++1, 100), 415 (M^+-15, 13).

1-[1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyloxy]-1-trimethylsilyloxy-4-methyl-pent-1-ene 3e.

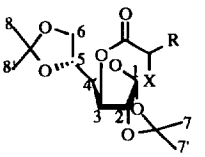
^{1}H NMR δ 0.23 (s, 9H, $SiMe_3$), 0.84 (d, 6H, R, 6.6Hz), 1.27, 1.31, 1.40, 1.48 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.48 (m, 1H, R), 1.77 (m, 2H, R), 3.76 (t, 1H, =CHR, 7.5Hz), 4.01-4.06 (m, 2H, $H_{6,6'}$), 4.21 (dd, 1H, H_4, 3.0Hz, 6.8Hz), 4.30 (dd, 1H, H_5, 6.8Hz, 5.5Hz), 4.53 (d, 1H, H_2, 3.7Hz), 4.58 (d, 1H, H_3, 3.0Hz), 5.85 (d, 1H, H_1, 3.7Hz); IR (C=O) 1685; M.S.(EI) for $C_{21}H_{38}SiO_7$: 430 (M^+, 2), 415 (M^+-15, 6), 101 (95), 73 (100).

1-[1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyloxy]-1-trimethylsilyloxy-3,3-dimethyl-but-1-ene 3f.

^{1}H NMR δ 0.22 (s, 9H, $SiMe_3$), 1.01 (s, 9H, R), 1.27, 1.31, 1.40, 1.48 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 3.73 (s, 1H, =CHR), 4.01-4.08 (m, 2H, $H_{6,6'}$), 4.18 (dd, 1H, H_4, 3.1Hz, 5.9Hz), 4.30 (dd, 1H, H_5, 5.9 & 6.0Hz),

4.54 (d, 1H, H_2, 3.7Hz), 4.69 (d, 1H, H_3, 3.1Hz), 5.83 (d, 1H, H_1, 3.7Hz); IR (C=O) 1680; M.S.(EI) for $C_{21}H_{38}SiO_7$: 415 (M^+-15, 23), 101 (100), 73 (25).

General procedure for esters **4a-f** and **5a-f**: N-halosuccinimide (7.5 mmol) was added to a cooled solution (-70°C) of **3a-f** (5 mmol) in 50 ml of dry THF. After 1 hour, 50 ml of aqueous sodium thiosulfate (0.4M), were added and the mixture was extracted with Et_2O. The organic layer was washed with sodium thiosulfate and water, dried over anhydrous magnesium sulfate, and concentrated to afford crude ester **4a-f** and **5a-f**, on which d.e. is determinated thanks to GC analysis (column HP-1, l=25m, d=0.25mm).



1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-2-chloro propanoate 4a.
^1H NMR δ 1.27, 1.28, 1.37, 1.49 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.68 (d, 3H, R, 6.9Hz), 3.97-4.10 (m, 2H, $H_{6,6'}$), 4.20 (m, 2H, H_4, H_5), 4.39 (q, 1H, CHCl, 6.9Hz), 4.47 (d, 1H, H_2, 3.7Hz), 5.30 (d, 1H, H_3, 2.4Hz), 5.87 (d, 1H, H_1, 3.7Hz); ^{13}C NMR δ 21.2, 25.1, 26.1, 26.6, 26.6, 52.1, 67.4, 72.1, 77.2, 79.9, 83.0, 105.0, 109.3, 112.4, 168.4; IR (C=O) 1745; M.S.(EI) for $C_{15}H_{23}ClO_7$: 337 (M^+-15, 12), 335 (M^+-15, 31), 101 (100).

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-2-chloro pentanoate 4b.
^1H NMR δ 0.92 (t, 3H, R, 7.4Hz), 1.27, 1.28, 1.37, 1.49 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.46 (m, 2H, R), 1.93 (m, 2H, R), 3.95-4.09 (m, 2H, $H_{6,6'}$), 4.21 (m, 2H, H_4, H_5), 4.29 (t, 1H, CHCl), 4.46 (d, 1H, H_2, 3.7Hz), 5.29 (d, 1H, H_3, 1.5Hz), 5.87 (d, 1H, H_1, 3.7Hz); ^{13}C NMR δ 13.2, 19.1, 25.0, 26.1, 26.6, 26.6, 36.6, 56.7, 67.4, 72.1, 77.0, 79.9, 82.9, 105.0, 109.3, 112.4, 168.1; IR (C=O) 1745; M.S.(CI) for $C_{17}H_{27}ClO_7$: 379 (M^++1, 100), 363 (M^+-15, 8), 321 (40), 287 (48).

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-2-chloro-3-methyl butanoate 4c.
^1H NMR δ 1.02 (d, 6H, R, 6.8Hz), 1.26, 1.28, 1.37, 1.49 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 2.25 (m, 1H, R), 3.95-4.09 (m, 2H, H_6, $H_{6'}$), 4.08 (d, 1H, CHCl, 7.2Hz), 4.20 (m, 2H, H_4, H_5), 4.44 (d, 1H, H_2, 3.7Hz), 5.30 (d, 1H, H_3, 2.3Hz), 5.87 (d, 1H, H_1, 3.7Hz); ^{13}C NMR δ 18.1, 19.4, 25.0, 26.1, 26.6, 26.6, 32.6, 64.0, 67.5, 72.0, 77.0, 79.9, 82.9, 105.0, 109.3, 112.4, 167.7; IR (C=O) 1740; M.S.(EI) for $C_{17}H_{27}ClO_7$: 365 (M^+-15, 11), 363 (M^+-15, 31), 101 (100).

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-2-chloro hexanoate 4d.
^1H NMR δ 0.88 (t, 3H, R, 7.0Hz), 1.27, 1.28, 1.37, 1.49 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.35 (m, 4H, R), 2.00 (m, 2H, R), 3.96-4.10 (m, 2H, $H_{6,6'}$), 4.18 (m, 2H, H_4, H_5), 4.26 (t, 1H, CHCl, 7.2Hz), 4.45 (d, 1H, H_2, 3.7Hz), 5.29 (d, 1H, H_3, 2.0Hz), 5.86 (d, 1H, H_1, 3.7Hz); ^{13}C NMR δ 13.7, 21.9, 25.0, 26.1, 26.6, 26.7, 27.9, 34.4, 57.0, 67.4, 72.1, 77.1, 79.9, 83.0, 105.0, 109.3, 112.4, 168.1; IR (C=O) 1750; M.S.(EI) for $C_{18}H_{29}ClO_7$: 379 (M^+-15, 10), 377 (M^+-15, 29), 101 (100).

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-2-chloro-4-methyl pentanoate 4e.
^{1}H NMR δ 0.94 (d, 6H, R, 6.8Hz), 1.30, 1.31, 1.40, 1.51 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.65 (m, 1H, R), 1.80 (m, 2H, R), 3.98-4.11 (m, 2H, $H_{6,6'}$), 4.20 (m, 2H, H_4, H_5), 4.31 (t, 1H, CHCl, 7.0Hz), 4.48 (d, 1H, H_2, 3.7Hz), 5.32 (d, 1H, H_3, 2.0Hz), 5.90 (d, 1H, H_1, 3.7Hz); IR (C=O) 1750; M.S.(CI) for $C_{18}H_{29}ClO_7$: 395 (M^++1, 23), 393 (M^++1, 23), 379 (M^+-15, 13), 377 (M^+-15, 39), 101 (44), 100 (100).

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-2-chloro-3,3-dimethyl butanoate 4f.
^{1}H NMR δ 1.08 (s, 9H, R), 1.24, 1.28, 1.36, 1.49 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 3.94-4.06 (m, 2H, $H_{6,6'}$), 4.06 (s, 1H, CHCl), 4.16 (m, 2H, H_4, H_5), 4.45 (d, 1H, H_2, 3.7Hz), 5.26 (d, 1H, H_3, 2.2Hz), 5.85 (d, 1H, H_1, 3.7Hz); ^{13}C NMR δ 25.0, 26.1, 26.3, 26.6, 26.6, 35.1, 66.8, 67.6, 72.0, 77.0, 79.9, 83.0, 105.0, 109.3, 112.4, 167.5; IR (C=O) 1740; M.S.(EI) for $C_{18}H_{29}ClO_7$: 379 (M^+-15, 10), 377 (M^+-15, 29), 101 (100).

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-2-bromo propanoate 5a.
^{1}H NMR δ 1.28, 1.28, 1.38, 1.50 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.82 (d, 3H, R, 6.9Hz), 3.97-4.15 (m, 2H, $H_{6,6'}$), 4.21 (m, 2H, H_4, H_5), 4.36 (q, 1H, CHCl, 6.9Hz), 4.48 (d, 1H, H_2, 3.6Hz), 5.29 (d, 1H, H_3, 2.8Hz), 5.88 (d, 1H, H_1, 3.6Hz); ^{13}C NMR δ 21.3, 25.1, 26.1, 26.7, 26.7, 39.4, 67.4, 72.1, 77.0, 80.0, 82.7, 105.0, 109.4, 112.4, 169.0; IR (C=O) 1745; M.S.(EI) for $C_{15}H_{23}BrO_7$: 381 (M^+-15, 22), 379 (M^+-15, 22), 101 (100).

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-2-bromo pentanoate 5b.
^{1}H NMR δ 0.91 (t, 3H, R, 7.3Hz), 1.26, 1.28, 1.36, 1.49 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.44 (m, 2H, R), 1.98 (m, 2H, R), 3.98 (m, 1H, CHCl), 4.06-4.23 (m, 2H, $H_{6,6'}$), 4.18 (m, 2H, H_4, H_5), 4.45 (d, 1H, H_2, 3.7Hz), 5.29 (d, 1H, H_3, 1.0Hz), 5.86 (d, 1H, H_1, 3.7Hz); ^{13}C NMR δ 13.2, 20.3, 25.0, 26.1, 26.6, 26.6, 36.5, 45.1, 67.4, 72.0, 76.9, 80.0, 82.8, 105.0, 109.3, 112.4, 168.3; IR (C=O) 1745; M.S.(CI) for $C_{17}H_{27}BrO_7$: 425 (M^++1, 100), 423 (M^++1, 100), 365 (34), 101 (11).

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-2-bromo-3-methyl butanoate 5c.
^{1}H NMR δ 1.02 (d, 6H, R, 6.6Hz), 1.25, 1.27, 1.36, 1.48 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 2.18 (m, 1H, R), 3.94-4.09 (m, 2H, $H_{6,6'}$), 3.98 (d, 1H, CHCl, 7.2Hz), 4.17 (m, 2H, H_4, H_5), 4.43 (d, 1H, H_2, 3.7Hz), 5.28 (d, 1H, H_3, 2.5Hz), 5.86 (d, 1H, H_1, 3.7Hz); ^{13}C NMR δ 19.7, 19.9, 25.0, 26.1, 26.6, 26.6, 32.1, 54.0, 67.5, 72.0, 76.9, 79.9, 82.8, 105.0, 109.3, 112.4, 167.8; IR (C=O) 1740; M.S.(EI) for $C_{17}H_{27}BrO_7$: 409 (M^+-15, 48), 407 (M^+-15, 47), 101 (100).

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-2-bromo hexanoate 5d.
^{1}H NMR δ 0.88 (t, 3H, R, 6.9Hz), 1.27, 1.28, 1.37, 1.49 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.35 (m, 4H, R), 2.00 (m, 2H, R), 3.98-4.07 (m, 2H, $H_{6,6'}$), 4.15 (m, 2H, H_4, H_5), 4.18 (m, 1H, CHCl), 4.45 (d, 1H, H_2, 3.4Hz), 5.29 (d, 1H, H_3, 2.0Hz), 5.86 (d, 1H, H_1, 3.4Hz); ^{13}C NMR δ 13.7, 21.9, 25.1, 25.6, 26.1, 26.6, 26.6, 34.4, 45.3, 67.4, 72.1, 76.9, 80.0, 82.8, 105.0, 109.3, 112.4, 168.1; IR (C=O) 1740; M.S.(CI) for $C_{18}H_{29}BrO_7$: 439 (M^++1, 96), 437 (M^++1, 100), 379 (34), 101 (8).

1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-2-bromo-4-methyl pentanoate 5e.
^{1}H NMR δ 0.92 (d, 6H, R, 6.8Hz), 1.29, 1.31, 1.40, 1.52 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 1.75 (m, 1H, R), 1.90 (m, 2H, R), 3.98-4.12 (m, 2H, $H_{6,6'}$), 4.20 (m, 2H, H_4, H_5), 4.27 (t, 1H, CHCl, 7.6Hz), 4.48 (d, 1H, H_2, 3.7Hz), 5.32 (d, 1H, H_3, 3.1Hz), 5.90 (d, 1H, H_1, 3.7Hz); IR (C=O) 1745; M.S.(CI) for $C_{18}H_{29}BrO_7$: 439

(M^++1, 62), 437 (M^++1, 66), 301 (99), 278 (100).

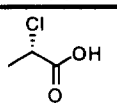
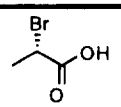
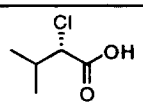
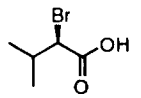
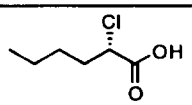
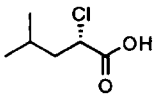
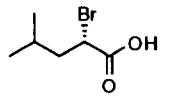
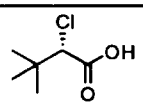
1,2;5,6-Di-O-(1-methylethylidene)-α-D-glucofuranosyl-2-bromo-3,3-dimethyl butanoate 5f. ^{1}H NMR δ 1.11 (s, 9H, R), 1.24, 1.27, 1.36, 1.48 (4s, 12H, $H_{7,7'}$, $H_{8,8'}$), 3.92-4.07 (m, 2H, $H_{6,6'}$), 4.10 (s, 1H, CHCl), 4.16 (m, 2H, H_4, H_5), 4.42 (d, 1H, H_2, 3.6Hz), 5.28 (d, 1H, H_3, 2.2Hz), 5.84 (d, 1H, H_1, 3.6Hz); ^{13}C NMR δ 25.2, 26.0, 26.7, 26.8, 26.8, 34.3, 57.8, 67.6, 72.0, 77.0, 79.9, 82.8, 105.0, 109.3, 112.3, 167.5; IR (C=O) 1755; M.S.(CI) for $C_{18}H_{29}BrO_7$: 439 (M^++1, 94), 437 (M^++1, 100), 401 (98), 381 (42).

General procedure for hydrolysis to **6a-f** and **7a-f**:

a) Method A :[31]

The crude ester **4a-d,f** or **5a-d,f** (5 mmol) was dissolved in a cooled mixture (0°C) of 75 ml of THF and 25 ml of water. Hydrogen peroxide (30%WT, 1.8 ml, 20 mmol) was first added, followed by 10 mmol of LiOH. The saponification was monitored by GC following the signal corresponding to ester **4a-d,f** or **5a-d,f**. About half an hour after, the reaction was completed, the excess of peroxide was destroyed by adding 10 % excess of a 1.5N Na_2SO_3 aqueous solution. The absence of peroxide was controlled using Quantofix peroxide, and 2-haloalkanoic acids **6a-d,f** or **7a-d,f** were isolated after acid work up and distillation. 1,2;5,6-di-O-(1-methylethylidene)-α-D-glucofuranose **1** was retrieved with 80% yield.

Optical data of enantiomerically pure 2-haloacids :

Acid	literature value	reference	Acid	literature value	reference
	$[\alpha]_D$=-14.6 (neat) $[\alpha]_D$=-15.9 (c=1, $CHCl_3$, 20°C)	27b 9b		$[\alpha]_D$=-30.9 (c=1, $CHCl_3$, 24°C)	27a
	$[\alpha]_D$=-1.47 (neat)	27b		$[\alpha]_D$=-21.1 (c=1, $CHCl_3$, 24°C)	27a
	$[\alpha]_D$=-11.7 (c=1.1, $CHCl_3$, 20°C)	9b			
	$[\alpha]_D$=-33.1 (neat)	27b		$[\alpha]_D$=-65.3 (c=2, $CHCl_3$, 24°C)	27a
	$[\alpha]_D$=+35.1 (c=1, MeOH, 20°C)	33			

b) Method B :[32]

The crude ester **4a,c,e** or **5e** (5 mmol) was dissolved in a minimum of acetone (about 5 ml); 10 ml of an aqueous solution of HCl (2.4N) were added, and the solution was heated to reflux. The hydrolysis was monitored by GC. After about one hour, acetone was removed under vacuo, and the aqueous layer was

extracted with Et_2O. The organic layers combined were washed with water, and dried over sodium sulfate. After evaporation under vacuo, the residue was distilled to afford 2-haloalkanoic acids **6a,c,e** or **7e.**

c) Method C :

The crude ester **4a,c-f** or **5a,c,e** (5 mmol) was dissolved in a cooled mixture (0°C) of 10 ml of acetonitrile, 10 ml of hexanes, 10 ml of water, and 12.5 mmol of LiOH. The saponification was monitored by GC. After 2 hours to 7 days at room temperature, depending on the alkyl chain and on the nature of the halogen, 2-haloalkanoic acids **6a,c-f** and **7a,c,e** were isolated after acid work up and distillation. 1,2;5,6-di-O-(1-methylethylidene)-α-D-glucofuranose **1** was retrieved with 70% yield.

General procedure for the derivatization of **6** and **7** into their t-butylamides : 10 mg of 2-haloacid were treated with an excess of thionyl chloride (1 ml), overnight at room temperature or 2 hours at 40°C. The excess of thionyl chloride was evaporated, and 0.5 ml of anhydrous ether were added to the residue. The solution was cooled down to 0°C before adding dropwise 1.2 ml of a 2% t-butylamine in anhydrous ether solution. The mixture was evaporated. The residue was taken by a small amount of ether, filtered, and evaporated. The crude t-butylamide free from hydrochloride salt was dissolved in dichloromethane for the GC analysis on the chirasil-D-Val column.

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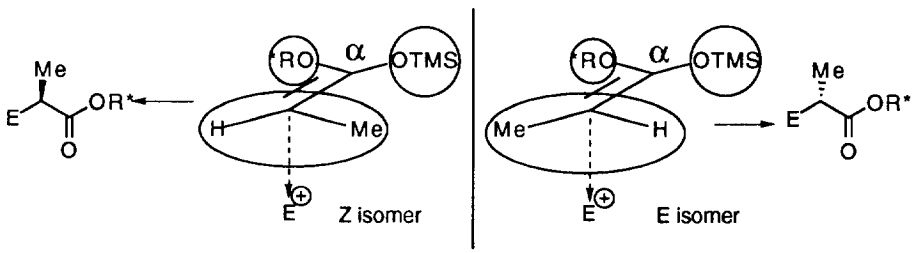
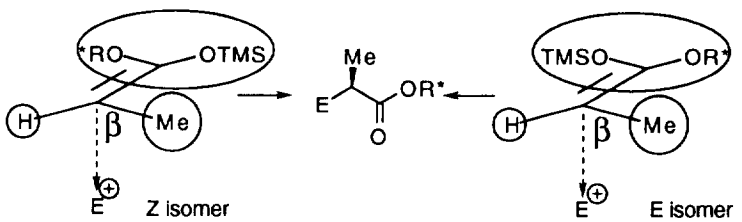
28. Equilibration of the haloesters after halogenation has been ruled out by control experiments: addition of **5a** (de=0) before or after the halogenation of **3a** by NBS at -70°C in THF led to the isolation of **5a** with the de expected owing to the added bromoester.
29. When, the reaction of two prochiral E and Z isomers leads to different predominant stereoisomers, the addition of the electrophilic reagent is directed by the interaction of the chiral moiety with the three substituents of the prostereogenic α-center, the β-carbon atom and its two substituents behaving as a whole, i.e. as one of the three substituents of the sp^2 α-carbon atom.



On the contrary the same predominant stereoisomer is obtained if the recognition involves only the β-carbon substituents, the α carbon atom and its two substituents behaving as a whole.



This interpretation[34] can be generalized to the aldolisation, for example the diastereoselective condensation of ketene acetals on benzaldehyde reported by Gennari, C.; Columbo, G.; Bertoli, G.; Schimperma, C. *J. Org. Chem.* **1987**, *52*, 2754, is directed by the β-carbon substituents of the ketene acetal.

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