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Halogenation of carbohydrates by triphenylphosphine complex reagents in highly concentrated solution under microwave activation or conventional heating

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Abstract

Halogenation of carbohydrates with triphenylphosphine and carbon tetrachloride, hexachloroethane or 1,2-dibromotetrachloroethane was shown to be very efficient in highly concentrated solutions of nonpolar solvents such as toluene or 1,2-dichloroethane, with, in some cases, addition of potassium chloride, potassium bromide, and/or pyridine. The reactions were very fast under microwave irradiation (2 to 30 min) as well as by classical heating (2 to 45 min) at 80–120 °C. Most often, the yields were better under microwave irradiation and the reaction product distribution was sometimes different from that obtained with classical methods with, in all experiments, the amount of solvent strongly reduced.

Keywords: Synthesis; Halosugars; Triphenylphosphine complex reagents; Microwave

1. Introduction

Deoxyhalosugars are useful compounds due to their industrial applications as sweeteners, male antifertility agents, as well as biochemical probes. Furthermore, they are components of clinically used antibiotics, and reveal to be valuable intermediates for the synthesis of various classes of carbohydrates, such as deoxy-, amino- and unsaturated-sugars [1,2].

Among many approaches described in the carbohydrate field for the preparation of halocompounds by substitution of a hydroxyl group, direct reaction of the hydroxyl function with various phosphorus-based halo-reagents was extensively applied since the first report of Rydon et al. [3]. More generally, triphenylphosphine and an halogen source such as tetrachloromethane, *N*-chlorosuccinimide, hexachloroethane, tetrabromomethane, *N*-bromosuccinimide, 1,2-dibromotetrachloroethane, iodoimidazole, or triiodoimidazole were used [4–12]. The reaction is generally

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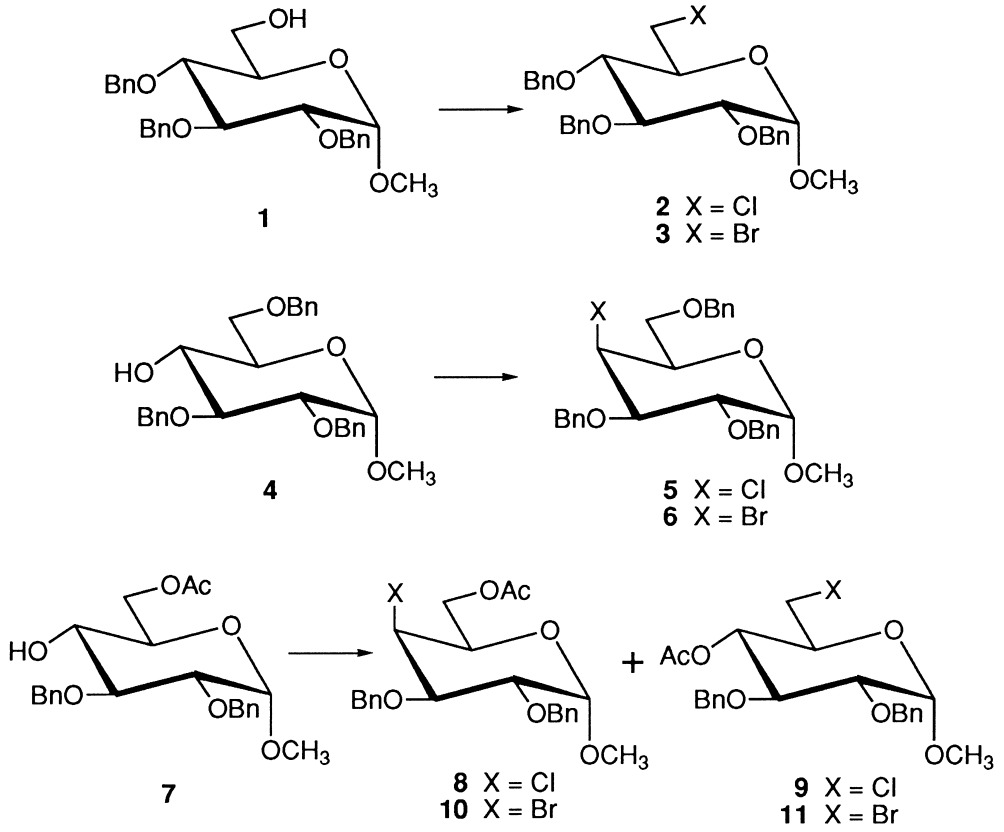
carried out on a primary alcohol function or on a secondary alcohol group diluted in various solvents. In the case of a diol, conditions for mono- or disubstitution have been established especially with iodine reagents [8].

The purpose of our research was to find a simplification of the reaction conditions, by considering different heating modes (microwave irradiation or oil-bath), the effect of solvents (presence and nature) and added salts. Microwave irradiation has been known for a few years to be an attractive alternative way when reactions required elevated temperatures. In a large number of cases, the reaction rates were greatly increased under these new conditions, particularly if the volume of the solvent was considerably reduced or completely suppressed ("dry conditions") [13–15]. We report here a study on the halogenation of carbohydrates with triphenylphosphine and chloro or bromo donors.

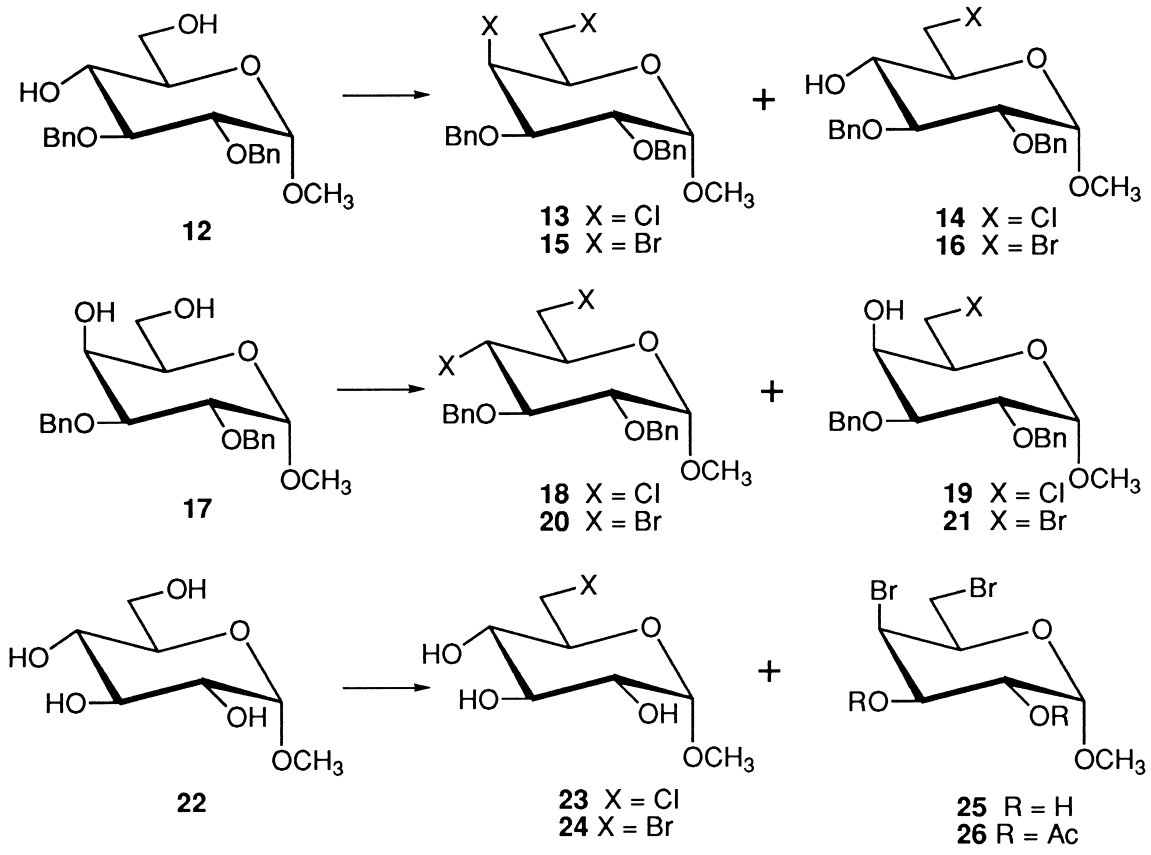
2. Results and discussion

Attempts of chlorination and bromination of the primary or secondary hydroxyl groups of the glucosides **1**, **4**, **7**, **12**, **17**, and **22** (Schemes 1 and 2) in "dry conditions" under microwave irradiation were disappointing. The temperature rise was too fast and only decomposition products were observed. Nevertheless, the reactions were considered under different conditions. It appeared that in highly concentrated reaction mixtures in toluene or 1,2-dichloroethane (1 mL for 0.5 to 3 mmol depending on the experiments, see Experimental) and sometimes with the addition of salts (potassium chloride or potassium bromide) and/or pyridine, it was possible to halogenate primary and secondary alcohol groups in good yields and within short reaction times. Tetrachloromethane, hexachloroethane and 1,2-dibromotetrachloroethane associated with triphenylphosphine were shown to be good halogen donors, while *N*-chlorosuccinimide, *N*-bromosuccinimide and tetrabromomethane were decomposed almost instantaneously under microwave irradiation.

Halogenation of monohydroxy compounds (Scheme 1, Table 1).—Reaction of the primary hydroxy group of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**1**) with triphenylphosphine (1.5 equiv) and tetrachloromethane (5 equiv) in a



Scheme 1.



Scheme 2.

minimum amount of 1,2-dichloroethane (1 mL for 2.5 mmol) under microwave irradiation was first carried out. The initial irradiation power of 150 W was chosen to promote a quick temperature increase to 100 °C, while the temperature was maintained near 100 °C by monitoring the irradiation power. After 15 min, the 6-chloro derivative **2** [16] could be isolated in 46% yield. However, with an excess of triphenylphosphine (2.5 equiv), tetrachloromethane (5 equiv) and potassium chloride (10 equiv) in the same solvent, the yield of chloride **2** was increased to 91%, within 8 min (entry 1). At the same temperature as used under microwave conditions (100 °C), conventional heating (entry 2), gave rise to a yield of only 20% within 8 min, and 69% within 30 min.

Similarly, methyl 2,3,4-tri-*O*-benzyl-6-bromo-6-deoxy-α-D-glucopyranoside (**3**) [17] was obtained by treatment of **1** with triphenylphosphine (2.5 equiv), 1,2-dibromotetrachloroethane (2.5 equiv) and potassium bromide (10 equiv) in 1,2-dichloroethane (1 mL for 1 mmol). After 7 min at 100 °C, the yields were quite similar under microwave (75%) and oil bath heating (65%) (entries 3 and 4).

Chlorination and bromination of the partially protected monosaccharides **4** and **7** were attempted under similar reaction conditions and the best results are shown in Table 1. In each case, the reaction was carried out under microwave irradiation and with classical oil bath heating for the same temperature and time. For a better evaluation of these reactions, with oil bath heating, when necessary, the reaction times were prolonged to determine the best reaction conditions.

For compound **4**, a higher yield of chloride **5** was observed with classical oil bath heating (entries 5, 6). However, for the preparation of bromide **6**, the addition of pyridine (1 mL for 1 mmol) allowed a better reaction control and a yield improvement (entries 7–10).

In the case of **7** having a readily accessible 4-hydroxyl group, chloride **8** was formed very easily following both approaches, with a low proportion of rearranged isomer **9** (entries 11, 12). On the other hand, the difference was significant for the bromination of **7** concerning total yield and relative proportions of bromide **10** and its rearranged isomer **11** (entries 13, 14). Here, the difference of

Table 1
Halogenation of monohydroxy compounds (2 mmol)

Entry	Substrate	Mode [a]	Reagents (equiv)	Conditions			Solvent (mL) [b]	Salt (equiv)	Product (yields %)
				P (W)	T (°C)	Time (min)			
1	**1**	MW	Ph_3P (2.5, CCl_4 (5)	150	100	8	B (0.8)	KCI (10)	**2** (91)
2	**1**	Δ	Ph_3P (2.5), CCl_4 (5)		100	8	B (0.8)	KCI (10)	**2** (20)
		Δ	Ph_3P (2.5), CCl_4 (5)		100	30	B (0.8)	KCI (10)	**2** (69)
3	**1**	MW	Ph_3P (2.5), $(CCl_2Br)_2$ (2.5)	150	100	7	B (2)	KBr (10)	**3** (75)
4	**1**	Δ	Ph_3P (2.5), $(CCl_2Br)_2$ (2.5)		100	7	B (2)	KBr (10)	**3** (65)
5	**4**	MW	Ph_3P (2.2), CCl_4 (5)	200	110	15	B (2)	KCl (10)	**5** (75)
6	**4**	Δ	Ph_3P (2.2), CCl_4 (5)		110	15	B (2)	KCl (10)	**5** (85)
7	**4**	MW	Ph_3P (3), $(CCl_2Br)_2$ (2)	200	70	6	B (2)	KBr (5)	**6** (40)
8	**4**	Δ	Ph_3P (3), $(CCl_2Br)_2$ (2)		70	6	B (2)	KBr (5)	**6** (16)
9	**4**	MW	Ph_3P (3), $(CCl_2Br)_2$ (2)	200	113	6	A (2), C (2)	KBr (5)	**6** (65)
10	**4**	Δ	Ph_3P (3), $(CCl_2Br)_2$ (2)		113	6	A (2), C (2)	KBr (5)	**6** (66)
11	**7**	MW	Ph_3P (2.5), CCl_4 (5)	100	100	10	B (2)	KCl (5)	**8** (91) **9** (4)
12	**7**	Δ	Ph_3P (2.5), CCl_4 (5)		100	10	B (2)	KCl (5)	**8** (70) **9** (10)
		Δ	Ph_3P (2.5), CCl_4 (5)		100	45	B (2)	KCl (5)	**8** (89) **9** (5)
13	**7**	MW	Ph_3P (2.5), $(CCl_2Br)_2$ (1.5)	200	70	6	A (2)	KBr (5)	**10** (50) **11** (13)
14	**7**	Δ	Ph_3P (2.5), $(CCl_2Br)_2$ (1.5)		70	6	A (2)	KBr (5)	**10** (12) **11** (29)

[a] MW, microwave irradiation; Δ, oil bath heating.
[b] Solvents: A, $PhCH_3$; B, $(CH_2Cl)_2$; C, C_5H_5N.

the two heating modes was especially important both with respect to reactivity (the global yield using microwave irradiation was enhanced when compared with the conventional heating under the same conditions) and selectivity. Applying microwave irradiation, the major product **10** was the expected one, whereas by classical heating the rearranged product **11** was obtained in higher yield. Such as effect on selectivity is infrequent in the literature, and only described in a very few cases [18,19]. The origin of the effect could be, under microwave irradiation, a better stabilization of the transition state leading to nucleophilic substitution (more polar and consequently more prone to interactions with the electromagnetic field) and suppressing rearrangement.

Halogenation of polyhydroxy compounds (Scheme 2, Table 2).—The dichlorination of diols **12** and **17** yielding **13** and **18**, respectively, was very easily performed and optimized in the presence of an excess of potassium chloride or potassium bromide (entries 1–3, 13, 14); with potassium bromide, surprisingly, no trace amounts of the dibromides **15** and **20** and the monobromides **16** and **21** could be detected. With oil bath heating, the reactions were much slower than under microwave activation.

For the selective preparation of the monochlorides **14** [21] and **19**, hexachloroethane appeared a more appropriate reagent. With triphenylopsphine (1.5 equiv), hexachloroethane (1–1.2 equiv), potassium chloride (20 equiv) in 1,2-dichloroethane, the yields were 92–95% after 30 min for **14** and 62–71% for **19**, nearly independent of the mode of activation (entries 4, 5, 15, 16).

Dibromination of the diols **12** and **17** was much more efficient in the presence of pyridine (entries 6–9, 17, 18). With a limited amount of reactants (entries 10–12, 19, 20), the monobromides **16** [20] and **21** [20] were the major products.

As the addition of pyridine resulted in high yields and clean reactions for the mono- and dihydroxy compounds **4**, **12** and **17**, the halogenation of methyl α-D-glucopyranoside (**22**) was attempted under similar conditions. Chlorination of **22** in the presence of pyridine, gave almost exclusively the 6-chloride **23** [7] (78% under microwave, 68% with oil bath heating within 10 min) (entries 21, 22). However, the bromination of **22** was less selective. The 4,6-dibromide **25**, isolated as diacetate **26**, was always observed besides the monobromide **24** [22] and could be the major product of the reaction when an excess of reactants was used. In the latter case, the selectivity was different under microwave irradiation, as dibromide **25** was formed in a much better yield than under conventional heating (entries 23–25).

An attempt of scaling up the chlorination of **22**, exactly under the same conditions as shown in entry 21, but on 20 g, revealed the efficiency of

Table 2
Halogenation of polyhydroxy compounds (2 mmol)

Entry	Substrate	Mode [a]	Reagents (equiv)	Conditions			Solvent (mL) [b]	Salt (equiv)	Product (yields %)
				P (W)	T (°C)	Time (min)			
1	**12**	MW	Ph_3P (2.5), CCl_4 (5)	210	110	8	A (0.7)	KCl (20)	**13** (85) **14** (9)
2	**12**	MW	Ph_3P (2.5), CCl_4 (5)	210	120	8	A (0.7)	KBr (20)	**13** (92)
3	**12**	Δ	Ph_3P (2.5), CCl_4 (5)		110	8	A (0.7)	KBr (20)	**13** (30) **14** (15)
		Δ	Ph_3P (2.5), CCl_4 (5)		110	15	A (0.7)	KBr (20)	**13** (75) **14** (6)
4	**12**	MW	Ph_3P (1.5), $(CCl_3)_2$ (1)	210	95	15	B (2.6)	KCl (20)	**14** (69)
		MW	Ph_3P (1.5), $(CCl_3)_2$ (1)	210	95	30	B (2.6)	KCl (20	**14** (95)
5	**12**	Δ	Ph_3P (1.5), $(CCl_3)_2$ (1)		95	30	B (2.6)	KCl (20)	**14** (92)
6	**12**	MW	Ph_3P (3.5), $(CCl_2Br)_2$ (3.5)	80	105	3	B (2.5)		**15** (53) **16** (10)
7	**12**	Δ	Ph_3P (2.5), $(CCl_2Br)_2$ (2.5)		100	7	B (2.5)		**15** (14) **16** (10)
		Δ	Ph_3P (2.5), $(CCl_2Br)_2$ (2.5)		100	30	B (2.5)		**15** (65) **16** (2)
8	**12**	MW	Ph_3P (2.2), $(CCl_2Br)_2$ (2.1)	210	103	7	A (3), C (1)		**15** (70) **16** (25)
9	**12**	Δ	Ph_3P (2.2), $(CCl_2Br)_2$ (2.1)		103	7	A (3), C (1)		**15** (70) **16** (18)
10	**12**	MW	Ph_3P (1.5), $(CCl_2Br)_2$ (1.5)	60,	100	3	B (2)	KBr (20)	**15** (3) **16** (38)
11	**12**	MW	Ph_3P (1.5), $(CCl_2Br)_2$ (1.45)	210	100	2.5	A (1), C (1)		**15** (9) **16** (76)
12	**12**	Δ	Ph_3P (2.5), $(CCl_2Br)_2$ (2.5)		100	2.5	A (1), C (1)		**15** (6) **16** (64)
13	**17**	MW	Ph_3P (2.5), CCl_4 (5)	210	100	8	A (1)	KBr (20)	**18** (78) **19** (9)
14	**17**	Δ	Ph_3P (2.5), CCl_4 (5)		100	8	A (1)	KBr (20)	**18** (35) **19** (24)
15	**17**	MW	Ph_3P (1.5), $(CCl_3)_2$ (1.2)	210	100	30	A (2)	KCl (10)	**18** (1.5) **19** (71)
16	**17**	Δ	Ph_3P (1.5), $(CCl_3)_2$ (1.2)		100	30	A (2)	KCl (10)	**19** (62)
17	**17**	MW	Ph_3P (2.2), $(CCl_2Br)_2$ (2.1)	210	103	7	A (3), C (1)		**20** (70) **21** (25)
18	**17**	Δ	Ph_3P (2.2), $(CCl_2Br)_2$ (2.1)		103	7	A (3), C (1)		**20** (52) **21** (15)
19	**17**	MW	Ph_3P (1.5), $(CCl_2Br)_2$ (1.45)	210	100	3	B (1), C (1)		**20** (20) **21** (72)
20	**17**	Δ	Ph_3P (1.5), $(CCl_2Br)_2$ (1.45)		100	3	B (1), C (1)		**20** (15) **21** (54)
21	**22**	MW	Ph_3P (1.5), CCl_4 (4)	210	100	10	C (0.8)	KCl (10)	**23** (78)
22	**22**	Δ	Ph_3 (1.5), CCl_4 (4)		100	10	C (0.8	KCl (10)	**23** (68)
23	**22**	MW	Ph_3P (1.2), $(CCl_2Br)_2$ (1.2)	210	100	5	A (0.4, C (1.6)	KBr (4)	**24** (25) **25** (10)
24	**22**	MW	Ph_3P (3), $(CCl_2Br)_2$ (2.5)	210	100	5	A (0.8), C (1.6)	KBr (10)	**24** (5) **25** (60)
25	**22**	Δ	Ph_3P (3), $(CCl_2Br)_2$ (2.5)		100	5	A (0.8), C (1.6)	KBr (10)	**24** (20) **25** (39)
26[c]	**22**	MW	Ph_3P (1.5), CCl_4 (4)	210	100	10	C (40)	KCl (10)	**23** (92)
27[c]	**22**	Δ	Ph_3P (1.5), CCl_4 (4)		100	10	C (40)	KCl (10)	**23** (82)

[a] MW, microwave irradiation; Δ, oil bath heating.
[b] Solvents: A, $PhCH_3$; B, $(CH_2Cl)_2$; C, C_5H_5N.
[c] Experiments on 20 g of **22**.

these new methodologies (entries 26, 27). The yields were higher than on a 1 g scale (92 and 82%) and the difference between the two heating modes remained equal, about 10%.

Conclusion.—It has been shown that under microwave irradiation as well as under conventional heating, halogenations in highly concentrated solutions are efficient and advantageous. Added salts moderate the temperature increase and raise the halogenated anion concentration. Pyridine seems to inhibit extensive decomposition and allow to raise the temperature of the reactions. Contrary to reactions in diluted solution, dihalogenation is possible in this solvent.

In some cases, a strong specific "microwave effect" was evidenced for chlorinations and brominations (Table 1, entries 1, 2; 11, 12. Table 2, entries 2, 3; 6, 7; 13, 14; 24, 25) as yields were much higher under microwave activation than on conventional heating for the same times. This strong difference was already described in several cases [15]. It could be the result of a better temperature homogeneity or modification in activation parameters (ΔG^* and ΔS^*). In the case of the bromination of **7**, under microwave and by conventional heating, a different proportion of bromide **10** and **11** was observed (Table 1, entries 13 and 14). This effect could be the result of a better stabilization of the transition state under microwave, promoting nucleophilic substitution in comparison with rearrangement.

3. Experimental

General methods.—The microwave reactor was a Synthewave 402 monomode system with focused waves; a Synthewave 1000 was used for the

experiment on 20 g scale. The temperature was always controlled during the reaction and was evaluated by an IR detector which indicated the surface temperature (the IR lecture was calibrated by tuning the emissivity factor using a thermocouple introduced inside the reaction mixture). Mechanical stirring all along the irradiation provided a good homogeneity of the materials. Automatic control of the irradiation (power and temperature) as well as data treatment were followed by a computer system. An initial power was selected, then reaction conditions were controlled using the algorithm "*tout ou peu*" which allowed a temperature control at the given value during the reaction time by varying the power between an adequate value and the lower one fixed to 5 W. Thus, the reaction was always under microwave irradiation. In order to compare microwave heating with conventional heating, the reactions were always performed under the same experimental conditions (weight of reactants, time, temperature). With an oil bath heating, the temperatures were measured inside the reaction mixture with a Quick digital thermometer and the rate of the temperature rise was similar to those measured under microwave irradiation.

Flash column chromatography was performed using 35–70 μ Silica gel (60 A C.C; S.D.S. Company). TLC was run on DC-Plastikfolien coated with Silica gel F_{254} (Schleicher and Schuell) with detection by UV light (254 nm) and heating after H_2SO_4 treatment. ^1H and ^{13}C NMR spectra (Table 3) were recorded at 250 and 62.91 MHz and at 300 and 75.49 MHz on a Bruker WP 250 and a Bruker WP 300 instrument, respectively. Chemical shifts are given in ppm downfield from internal Me_4Si. Melting points were measured on a Reichert apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. For the described compounds, $[\alpha]_D$, ^1H NMR and ^{13}C NMR values were in agreement with published ones.

General procedure for halogenation.—To a mixture of sugar substrate (2 mmol), Ph_3P, and, when necessary, KCl or KBr (see Tables 1 and 2 for mol/equiv) in an open Pyrex flask were added the solvents (0.8 to 4 mL) and the halo reagent (see Tables 1 and 2). The flask was placed in the microwave reactor and irradiated (reaction time, initial irradiation power and final temperature are indicated in Tables 1 and 2). Working up of the mixtures was carried out using one of the following procedures A or B.

For each halogenation experiment, the same conditions (weight of reactants, time, temperature) but now using a thermostat oil bath, were applied; yields are indicated in Tables 1 and 2.

Table 3
^{13}C NMR data for halogenated compounds [a]

Compound	δ (ppm) [b]						
	C-1	C-2	C-3	C-4	C-5	C-6	CH_2Ph
2	98.3	80.1	81.9	78.5	69.9	44.8	73.5, 75.3, 75.8
3	98.2	80.0	81.8	79.7	69.4	33.7	73.5, 75.4, 75.9
5	99.0	75.4[c]	76.3[c]	60.9	67.7	69.7	71.9, 73.8, 74.1
6	99.1	76.0[c]	76.3[c]	56.3	67.5	71.4	71.7, 73.9, 74.1
8	98.8	75.0	75.9	60.2	66.6	63.9	71.9, 73.9
9	98.1	79.0[c]	79.6[c]	71.6	69.5	43.9	73.6, 75.5
10	99.0	75.8	76.0	55.1	66.5	65.7	71.9, 74.2
11	98.2	79.0	79.7	72.6	69.3	31.8	73.7, 75.5
13	99.1	75.1	76.0	60.5	69.2	43.2	72.1, 74.1
14	98.3	79.9	81.2	70.8	70.4	44.7	73.3, 75.5
15	99.0	75.6	75.8	56.2	68.6	32.6	71.7, 73.9
16	98.3	79.9	81.1	72.0	70.0	33.4	73.3, 75.5
18	98.5	80.0	81.2	58.9	70.9	44.6	73.7, 76.6
19	99.6	75.5	77.4	67.6	69.9	42.8	73.1, 73.6
20	98.5	80.5	81.0	52.1	70.4	34.1	73.7, 76.5
21	98.7	75.5	77.7	68.0	69.9	30.7	73.2, 73.7
25	99.6	70.2[c]	69.4[c]	44.7	69.4[c]	32.3	
26	97.2	68.3[c]	68.4[c]	54.2	68.6[c]	32.0	

[a] For the sake of simplicity, individual chemical shifts for aromatic, benzylic, anomeric methoxy as well as acetate type carbons are not given. The experimental values were in good agreement with the expected chemical shifts.
[b] Measured in $CDCl_3$.
[c] Interchangeable assignments.

Procedure A. After cooling, the heterogeneous mixture was diluted with EtOH (1 mL), then filtered through a pad of Silica gel, eluted with 1:1 CH_2Cl_2–EtOAc (60 mL). The filtrates were concentrated, and the residues were submitted to flash chromatography on Silica gel with 1:9 to 5:5 EtOAc–heptane as eluent.

Procedure B. After cooling, the heterogeneous mixture was diluted with 1:1:1 CH_2Cl_2–EtOAc–EtOH (20 mL), then filtered through a pad of Silica gel, eluted with the same solvent. The filtrates were concentrated and the residues were suspended in water. The aqueous phase containing the monohalgenide was extracted twice with CH_2Cl_2, then concentrated, and the residue submitted to flash chromatography on Silica gel (8:2 EtOAc–heptane) to give the pure compounds.

Organic phases, containing the dihalogenide, were concentrated, and the residue was peracetylated in pyridine with an excess of Ac_2O. After 6 h at room temperature and concentration, the diacetyl-dihalogenide was isolated, after flash chromatography, by recrystallization.

Methyl 2,3,4-tri-O-*benzyl-6-chloro-6-deoxy-α*-D-*glucopyranoside* (**2**).—For experimental details, see Table 1, entries 1 and 2. $[\alpha]_D + 55°$ (*c* 0.93, CH_2Cl_2); lit. $[\alpha]_D + 56°$ [16].

Methyl 2,3,4-tri-O-*benzyl-6-bromo-6-deoxy-α*-D-*glucopyranoside* (**3**).—For experimental details, see Table 1, entries 3 and 4. $[\alpha]_D + 30°$ (*c* 1.1, $CHCl_3$); lit. $[\alpha]_D + 29.3°$ [17].

Methyl 2,3,6-tri-O-*benzyl-4-chloro-4-deoxy-α*-D-*galactopyranoside* (**5**).—For experimental details, see Table 1, entries 5 and 6. Compound **5** was isolated as syrup. $[\alpha]_D + 48°$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.45–7.25 (m, 15 H, Ph), 4.79 (2d, 2 H, CH_2Ph), 4.72 (2d, 2 H, CH_2Ph), 4.64 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.55 (d, 2 H, CH_2Ph), 4.46 (dd, 1 H, $J_{3,4}$ 4, $J_{4,5}$ 0.8 Hz, H-4), 4.10 (m, 1 H, H-5), 4.04 (dd, 1 H, $J_{2,3}$ 9 Hz, H-3), 3.89 (dd, 1 H, H-2), 3.64 (m, 2 H, H-6a,6b), 3.38 (s, 3 H, CH_3O). Anal. Calcd for $C_{28}H_{31}ClO_5$: C, 69.63; H, 6.47; Cl, 7.34. Found: C, 69.92; H, 6.25; Cl, 7.08.

Methyl 2,3,6-tri-O-*benzyl-4-bromo-4-deoxy-α*-D-*galactopyranoside* (**6**).—For experimental details, see Table 1, entries 7, 8, 9, 10. Compound **6** was isolated as a syrup. $[\alpha]_D + 116°$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.45–7.20 (m, 15 H, Ph), 4.80 (2d, 2 H, CH_2Ph), 4.72 (2d, 2 H, CH_2Ph), 4.63 (s, 1 H, H-1), 4.55 (s, 3 H, H-4 and CH_2Ph), 3.96–3.82 (m, 3 H, H-2,3,5), 3.62 (m, 2 H, H-6a,6b), 3.38 (s, 3 H, CH_3O). Anal. Calcd for $C_{28}H_{31}BrO_5$: C, 63.76; H, 6.22. Found: C, 64.01; H, 6.13.

Methyl 6-O-*acetyl-2,3-di*-O-*benzyl-4-chloro-4-deoxy-α*-D-*galactopyranoside* (**8**).—For experimental details, see Table 1, entries 11 and 12. Compound **8** was isolated as a syrup. $[\alpha]_D + 97°$ (*c* 1.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.45–7.20 (m, 10 H, Ph), 4.78 (2d, 2 H, CH_2Ph), 4.72 (2d, 2 H, CH_2Ph), 4.63 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.33 (dd, 1 H, $J_{3,4}$ 9, $J_{4,5}$ 0.8 Hz, H-4), 4.30–4.19 (m, 2 H, H-6a,6b), 4.11 (m, 1 H, H-5), 4.04 (dd, 1 H, $J_{2,3}$ 9 Hz, H-3), 3.89 (dd, 1 H, H-2), 3.36 (s, 3 H, CH_3O). Anal. Calcd for $C_{23}H_{27}ClO_6$: C, 63.52; H, 6.26. Found: C, 63.24; H, 6.29.

As minor component with a higher R_f value, 4-*O*-acetyl-2,3-di-*O*-benzyl-6-chloro-6-deoxy-α-D-glucopyranoside (**9**) was isolated by chromatography. For experimental details, see Table 1, entries 11 and 12. Compound **9** was isolated as a syrup. $[\alpha]_D + 14°$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.45–7.20 (m, 10 H, Ph), 4.88 (m, 1 H, H-4), 4.85 (2d, 2 H, CH_2Ph), 4.66 (s, 2 H, CH_2Ph), 4.61 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 3.97–3.82 (m, 2 H, H-3,5), 3.58 (dd, 1 H, $J_{2,3}$ 9 Hz, H-2), 3.52–3.45 (m, 2 H, H-6a,6b), 3.43 (s, 3 H, CH_3O). Anal. Calcd for $C_{23}H_{27}ClO_6$: C, 63.52; H, 6.26. Found: C, 63.12; H, 6.18.

Methyl 6-O-*acetyl-2,3-di*-O-*benzyl-4-bromo-4-deoxy-α*-D-*galactopyranoside* (**10**).—For experimental details, see Table 1, entries 13 and 14. Compound **10** was isolated as a syrup. $[\alpha]_D + 85°$ (*c* 1.91, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.45–7.20 (m, 10 H, Ph), 4.78 (2d, 2 H, CH_2Ph), 4.70 (2d, 2 H, CH_2Ph), 4.60 (d, 1H, $J_{1,2}$ 2 Hz, H-1), 4.40 (s, 1 H, H-4), 4.25–4.10 (m, 2 H, H-6a,6b), 3.95 (m, 1 H, H-5), 3.85 (m, 2 H, H-2,3), 3.40 (s, 3 H, CH_3O). Anal. Calcd for $C_{23}H_{27}BrO_6$: C, 57.62; H, 5.67. Found: C, 57.86; H, 5.82.

As minor component with a higher R_f value, 4-*O*-acetyl-2,3-di-*O*-benzyl-6-bromo-6-deoxy-α-D-glucopyranoside (**11**) was isolated by chromatography. For experimental details, see Table 1, entries 13 and 14. Compound **11** was isolated as a syrup. $[\alpha]_D + 16°$ (*c* 2.05, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40–7.20 (m, 10 H, Ph), 4.85 (t, 1 H, $J_{3,4}$ 9, $J_{4,5}$ 9 Hz, H-4), 4.83 (2d, 2 H, CH_2Ph), 4.63 (2d, 2 H, CH_2Ph), 4.60 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 3.93 (t, 1 H, $J_{2,3}$ 9 Hz, H-3), 3.85 (m, 1 H, H-5), 3.58 (dd, 1 H, H-2), 3.38 (dd, 1 H, $J_{5,6a}$ 2.4 $J_{6a,6b}$ 11 Hz, H-6a), 3.27 (dd, 1 H, $J_{5,6b}$ 8 Hz, H-6b), 3.40 (s, 3 H, CH_3O). Anal. Calcd for $C_{23}H_{27}BrO_6$: C, 57.62; H, 5.67. Found: C, 57.86; H, 5.78.

Methyl 2,3-di-O-*benzyl-4,6-dichloro-4,6-dideoxy-α*-D-*galactopyranoside* (**13**).—For experimental details, see Table 2, entries 1,2,3. Compound **13** was isolated as syrup. $[\alpha]_D + 63°$ (*c* 1.2, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.45–7.20 (m, 10 H, Ph), 4.76 (m, 4 H, 2 CH_2Ph), 4.60 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.45 (dd, 1 H, $J_{3,4}$ 3, $J_{4,5}$ 0.8 Hz, H-4), 4.05 (m, 2 H, H-3,5), 3.90 (dd, 1 H, $J_{2,3}$ 9.6 Hz, H-2), 3.60 (d, 2 H, $J_{5,6}$ 6 Hz, H-6a,6b), 3.40 (s, 3 H, CH_3O). Anal. Calcd for $C_{21}H_{24}Cl_2O_4$: C, 61.32; H, 5.88; Cl, 17.24; O, 15.56. Found: C, 61.51; H, 5.89; Cl, 16.98; O, 15.81.

Methyl 2,3-di-O-*benzyl-6-chloro-6-deoxy-α*-D-*glucopyranoside* (**14**).—For experimental details, see Table 2, entries 4 and 5. Compound **14** was isolated as a white solid. mp 43–45 °C; $[\alpha]_D + 89°$ (*c* 1.1, MeOH); lit. mp 50–51 °C; $[\alpha]_D + 81.5°$ [21]; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.20 (m, 10 H, Ph), 4.90 (2d, 2 H, CH_2Ph), 4.65 (m, 3 H, CH_2Ph and H-1), 3.80 (m, 3 H, H-3,5,6a), 3.70 (dd, 1 H, $J_{5,6b}$ 5.6 $J_{6a,6b}$ 11.4 Hz, H-6b), 3.55 (dd, 1 H, $J_{1,2}$ 3.6, $J_{2,3}$ 9.6 Hz, H-2), 3.46 (m, 1 H, H-4), 3.40 (s, 3 H, CH_3O).

Methyl 2,3-di-O-*benzyl-4,6-dibromo-4,6-dideoxy-α*-D-*galactopyranoside* (**15**).—For experimental details, see Table 2, entries 6, 7, 8, 9. Compound **15** was isolated as a syrup. $[\alpha]_D + 59°$ (*c* 1.13, $CHCl_3$); ^1H NMR (200 MHz, CD_3COCD_3): δ 7.30–7.10 (m, 10 H, Ph), 4.50 (m, 5 H, 2 CH_2Ph and H-1), 4.15 (d, 1 H, $J_{3,4}$ 3.6, $J_{4,5}$ 0.8 Hz, H-4), 3.95 (dd, 1 H, $J_{1,2}$ 3.6, $J_{2,3}$ 9.4 Hz, H-2), 3.75 (dd, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 3.60 (m, 1 H, H-5), 3.40 (dd, 1 H, $J_{5,6a}$ 2, $J_{6a,6b}$ 10 Hz, H-6a), 3.10 (s, 3 H, CH_3O), 3.05 (dd, 1 H, $J_{5,6b}$ 5 Hz, H-6b). Anal. Calcd for $C_{21}H_{24}Br_2O_4$: C, 50.42; H, 4.84. Found: C, 50.48; H, 4.87.

Methyl 2,3-di-O-*benzyl-6-bromo-6-deoxy-α*-D-*glucopyranoside* (**16**).—For experimental details, see Table 2, entries 10, 11, 12. Compound **16** was isolated as a syrup. $[\alpha]_D + 40°$ (*c* 1.11, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.20 (m, 10 H, Ph), 4.90 (d, 2 H, CH_2Ph), 4.65 (m, 3 H, CH_2Ph and H-1), 3.70 (m, 3 H, H-3,5,6a), 3.50 (m, 3 H, H-2,4,6b), 3.40 (s, 3 H, CH_3O). Anal. Calcd for $C_{21}H_{25}BrO_5$. 1/2 H_2O: C, 56.51; H, 5.87; Br, 17.90. Found: C, 56.55; H, 5.67; Br, 17.42.

Methyl 2,3-di-O-*benzyl-4,6-dichloro-4,6-dideoxy-α*-D-*glucopyranoside* (**18**).—For experimental details, see Table 2, entries 13 and 14. Compound **18** was isolated as syrup. $[\alpha]_D + 13.5°$ (*c* 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.20 (m, 10 H, Ph), 4.89 (2d, 2 H, CH_2Ph), 4.72 (2d, 2 H, CH_2Ph), 4.65 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 3.99 (m, 1 H, H-5), 3.93 (dd, 1 H, $J_{2,3} = J_{3,4} = 9$ Hz, H-3), 3.88–3.80 (m, 3 H, H-2,6a,6b), 3.50 (dd, 1 H, H-2), 3.42 (s, 3 H, CH_3O). Anal. Calcd for $C_{21}H_{24}Cl_2O_4$: C, 61.32; H, 5.88; Cl, 17.24. Found: C, 61.31; H, 5.98; Cl, 17.31.

Methyl 2,3-di-O-*benzyl-6-chloro-6-deoxy-α*-D-*galactopyranoside* (**19**).—For experimental details, see Table 2, entries 15 and 16. Compound **19** was isolated as a white solid. mp 94–96 °C (pentane); $[\alpha]_D + 44°$ (*c* 1.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.45–7.20 (m, 10 H, Ph), 4.72 (2d, 2 H, CH_2Ph), 4.70 (2d, 2 H, CH_2Ph), 4.64 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.05 (m, 1 H, H-4), 3.90–3.75 (m, 3 H, H-2,3,5), 3.70–3.60 (m, 2 H, H-6a,6b), 3.46 (m, 1 H, H-4), 3.39 (s, 3 H, CH_3O). Anal. Calcd for $C_{21}H_{25}ClO_5$: C, 64.20; H, 6.41; Cl, 9.03. Found: C, 64.31; H, 6.41; Cl, 9.22.

Methyl 2,3-di-O-*benzyl-4,6-dibromo-4,6-dideoxy-α*-D-*glucopyranoside* (**20**).—For experimental details, see Table 2, entries 17 and 18. Compound **20** was isolated as a syrup. $[\alpha]_D + 47°$ (*c* 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.20 (m, 10 H, Ph), 4.90 (2d, 2 H, CH_2Ph), 4.73 (2d, 2 H, CH_2Ph), 4.66 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.01 (m, 2 H, H-3,5), 3.86 (t, 1 H, $J_{3,4} = J_{4,5} = 9$ Hz, H-4), 3.81 (dd, 1 H, $J_{5,6a}$ 2.2, $J_{6a,6b}$ 11 Hz, H-6a), 3.70 (dd, 1 H, $J_{5,6b}$ 5 Hz, H-6b), 3.50 (dd, 1 H, $J_{2,3}$ 9.4 Hz, H-2), 3.42 (s, 3 H, CH_3O). Anal. Calcd for $C_{21}H_{24}Br_2O_4$: C, 50.42; H, 4.84; Br, 31.95. Found: C, 50.42; H, 4.81; Br, 32.01.

Methyl 2,3-di-O-*benzyl-6-bromo-6-deoxy-α*-D-*galactopyranoside* (**21**).—For experimental details, see Table 2, entries 19 and 20. Compound **21** was isolated as a solid. mp 105 °C (heptane); $[\alpha]_D + 40°$ (*c* 1.7, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 7.40–7.20 (m, 10 H, Ph), 4.80–4.60 (m, 4 H, 2 CH_2Ph), 4.64 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.07 (s, 1 H, H-4), 3.93–3.78 (m, 3 H, H-2,3,5), 3.58–3.47 (m, 2 H, H-6a,6b), 3.40 (s, 3 H, CH_3O). Anal. Calcd for $C_{21}H_{25}BrO_5$: C, 57.65; H, 5.76; Br, 18.27. Found: C, 57.43; H, 5.85; Br, 18.56.

Methyl 6-chloro-6-deoxy-α-D-*glucopyranoside* (**23**).—For experimental details, see Table 2, entries 21, 22, 26, 27. Compound **23** was isolated as a solid. mp 112–114 °C; $[\alpha]_D + 151°$ (*c* 1, MeOH); lit. mp 111–112 °C; $[\alpha]_D + 153°$ [7].

Methyl 6-bromo-6-deoxy-α-D-*glucopyranoside* (**24**).—For experimental details, see Table 2, entries 23, 24, 25. Compound **24** was obtained as a white solid. mp 125 °C; $[\alpha]_D + 130°$ (*c* 1.1, MeOH); lit. mp 126–127 °C; $[\alpha]_D + 132°$ [22].

A small quantity of dibromide **25** was also isolated and recrystallized from pentane. mp 130–132 °C;

$[\alpha]_D + 141°$ (*c* 1.28, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 4.83 (d, 1 H, $J_{2,3}$ 3 Hz, H-1), 4.64 (m, 1 H, H-4), 4.25 (m, 1 H, H-5), 3.82 (m, 2 H, H-2,3), 3.60–3.41 (m, 2 H, H-6a,6b), 3.50 (s, 3 H, CH_3O). Anal. Calcd for $C_7H_{12}Br_2O_4.1/2\ C_2H_5OH$: C, 28.00; H, 4.41. Found: C, 27.85; H, 3.94.

Methyl 2,3-di-O-*acetyl-4,6-dibromo-4,6-dideoxy-α*-D-*galactopyranoside* (**26**).—For experimental details, see Table 2, entry 25. The major part of dibromide **25** was in the organic phase; because of the difficulty of separation of **25** from Ph_3PO, it was isolated as the solid diacetate **26**. mp 119–120 °C (pentane). $[\alpha]_D + 168°$ (*c* 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.24 (dd, 1 H, $J_{1,2}$ 3, $J_{2,3}$ 10 Hz, H-2), 5.17 (dd, 1 H, $J_{3,4}$ 3 Hz, H-3), 5.0 (d, 1 H, H-1), 4.77 (m, 1 H, H-4), 4.10 (m, 1 H, H-5), 3.54 (dd, 1 H, $J_{5,6a}$ 7, $J_{6a,6b}$ 11 Hz, H-6a), 3.47 (s, 3 H, CH_3O), 3.41 (dd, 1 H, $J_{5,6b}$ 6 Hz, H-6b). Anal. Calcd for $C_{11}H_{16}Br_2O_6.1/2\ C_2H_5OH$: C, 33.74; H, 4.48; Br, 37.42. Found: C, 33.71; H, 4.13; Br, 37.29.

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