Regioselective Conversion of Primary Alcohols into Iodides in Unprotected Methyl Furanosides and Pyranosides

Philip R. Skaanderup, Carina Storm Poulsen, Lene Hyldtoft, Malene R. Jørgensen, Robert Madsen*

Department of Chemistry, Building 201, Technical University of Denmark, 2800 Lyngby, Denmark
Fax +4545933968; E-mail: rm@kemi.dtu.dk

Received 4 April 2002

Abstract: Two methods are described for the regioselective displacement of the primary hydroxy group in methyl glycosides with iodide. The first method is a modification of a literature procedure employing triphenylphosphine and iodine, where purification has been carried out on a reverse phase column in order to efficiently separate the desired iodoglycosides from triphenylphosphine oxide. The second method employs a new procedure using sulfonylation in pyridine with sterically hindered 2,4,6-trichloro- and 2,4,6-tribromobenzenesulfonyl chloride. The sulfonates thus formed are effective leaving groups and substitution with iodide can be carried out in a one-pot process. Protection of the iodoglycosides is also described either by benzylation with benzyl trichloroacetimidate or silylation with triethylsilyl chloride.

Key words: carbohydrates, halogenation, regioselectivity, substitution, sulfonates

Introduction

In carbohydrate chemistry regioselective substitution of a primary hydroxy group with a halide (X = I, Br, or Cl) is often carried out with triphenylphosphine in the presence of a halide source (X_2, CX_4, or NXS).[1–3] Although very good regioselectivity is usually obtained, the method suffers from one major drawback: the formation of triphenylphosphine oxide. This can be very difficult and tedious to remove. Several reports describe the regioselective iodination of unprotected methyl hexopyranosides with an iodide source and triphenylphosphine.[1a–f] The 6-iodoglycosides thus formed have been separated from triphenylphosphine oxide by acetylation[1b–e] or column chromatography on silica gel 60.[1a,f] We recently needed a number of unprotected methyl 6-deoxy-6-iodohexopyranosides and 5-deoxy-5-iodopentofuranosides for zinc-mediated fragmentations.[4] However, we were often unable to separate the iodoglycosides from triphenylphosphine oxide by silica gel chromatography. Although good separation was observed by TLC, the phosphine oxide and the iodoglycosides co-eluted completely by normal column chromatography. This prompted us to look for other methods, which either would employ a different activating agent or another chromatography technique. Herein, we report our results on the use of reverse phase column chromatography for purification of unprotected methyl ω-deoxy-ω-iodoglycosides. We also describe the development of an alternative activating agent for this reaction using sterically hindered trihalobenzenesulfonates.

Synthesis 2002, No. 12, Print: 06 09 2002.
Art Id.1437-210X,E;2002,0,12,1721,1727,ftx,en;P01402SS.pdf.

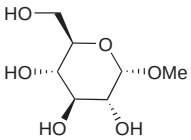
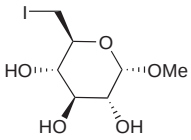
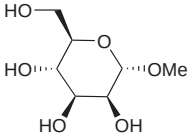
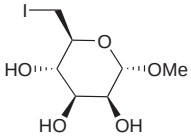
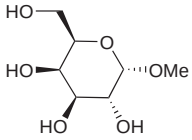
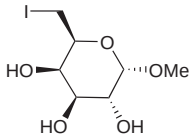
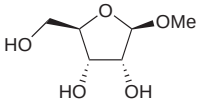
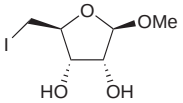
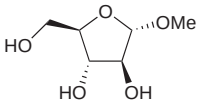
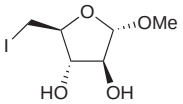
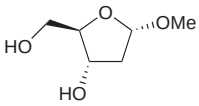
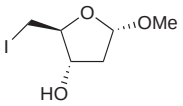
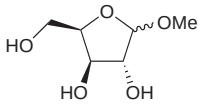
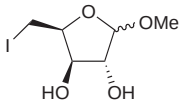
ISSN 0039-7881

Iodination with Triphenylphosphine and Iodine

The combination of triphenylphosphine, iodine, and imidazole has previously been employed as a cheap reagent system for the regioselective iodination of methyl hexopyranosides.[1c–e] The role of imidazole is to accelerate the reaction and to prevent triphenylphosphine and iodine from forming a highly insoluble salt. Normally, the iodination is carried out in toluene at reflux. However, the starting pyranosides and the products are not soluble under these conditions. Instead, we found refluxing THF to be a better solvent, which also allowed the reaction to be carried out at a lower temperature. Hereby, methyl α-D-glucopyranoside was converted cleanly into the corresponding 6-iodo compound **1** (Table 1). We were unable to separate this from triphenylphosphine oxide by column chromatography on silica gel. Various extraction procedures were also unsuccessful. Instead, chromatography on a reverse phase column with octadecyl capped silica gel 60 proved to be an efficient purification method. The imidazolium salts were first eluted from the column followed by the product **1**. This was subsequently crystallized in 77% yield from ethanol. Triphenylphosphine oxide was not eluted from the column using water–methanol (9:1). Washing with methanol regenerates the column, and we have reused the same column more than 50 times. Due to the good separation, relatively large amounts of material can be purified by this method, e.g. reactions on a 10 g scale have been purified on a column packed with 200 g of dry weight C_{18} silica gel.

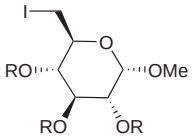
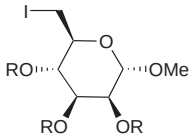
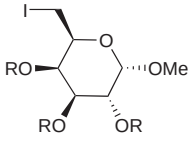
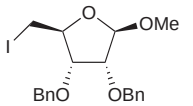
In a similar way, methyl α-D-mannopyranoside and -galactopyranoside were converted into their corresponding 6-iodoglycosides **2** and **3**. It should be noted that methyl α-D-galactopyranoside is a monohydrate and as a result 2.5 equivalents of triphenylphosphine, iodine, and imidazole were used in this experiment. The method is also applicable for regioselective iodination of pentofuranosides. Due to their better solubility in THF these pentofuranosides react within 30 minutes while the hexopyranosides require about 2 hours for the iodination to go to completion.

Table 1 Iodination with Ph_3P, I_2, and Imidazole

Substrate	Product		Appearance	Yield (%)
		**1**	crystalline (EtOH)	77
		**2**	crystalline (Et_2O)	86
		**3**	crystalline (MeOH)	51
		**4**	syrup	80
		**5**	syrup	79
		**6**	syrup	78
		**7**	syrup (α:β = 1:1)	74

In the zinc-mediated fragmentations we also needed triethylsilyl and benzyl protected methyl ω-deoxy-ω-iodoglycosides.[4] These ether protecting groups should be installed directly on the iodoglycosides. Introduction of triethylsilyl groups was straightforward using triethylsilyl chloride and imidazole in dichloromethane (Table 2). The basic conditions did not affect the primary iodide. Benzylation, on the other hand, gave rise to a complex mixture under basic conditions with sodium hydride and benzyl bromide. Instead, we found that benzylation could be carried out under acidic conditions with benzyl trichloroacetimidate and triflic acid in dioxane.[5] The reaction is fast and goes to completion within the time it takes to analyze the mixture by TLC. The pyranosides are stable to the strongly acidic medium while the furanosides are more labile and should not be exposed to these conditions for more than 10 min. This two step iodination-benzylation procedure is shorter than the literature protocol for preparation of these benzylated iodoglycosides.[6] Previous methods have typically employed a temporary protection of the primary hydroxy group followed by benzylation, removal of the temporary protecting group, and iodination of the primary position.

Table 2 Protection of Iodoglycosides

Substrate	Method[a]	Product		Yield (%)
1	A		**8** (R = TES)	94
	B		**9** (R = Bn)	80
2	A		**10** (R = TES)	98
	B		**11** (R = Bn)	96
3	A		**12** (R = TES)	94
	B		**13** (R = Bn)	73
4	B		**14**	68

[a] Method A: TESCl, imidazole, CH_2Cl_2; Method B: $BnOC(NH)CCl_3$, TfOH, dioxane.

Iodination with Trihalobenzenesulfonates and Sodium Iodide

Simultaneous with our use of reverse phase chromatography in the regioselective iodination reaction we also considered other activation techniques that would not involve triphenylphosphine. In this regard, we were particularly interested in sulfonate esters. Methane- and *p*-toluenesulfonates have been used in carbohydrate chemistry for a long time.[7] However, the substitution of these groups with nucleophiles often require rather high temperatures. The *p*-bromobenzenesulfonate is about 4 times better as a leaving group, but has only been used on a few occassions.[8] Instead, the trifluoromethanesulfonate has found widespread applications due to its superior leaving group properties.[9] However, a major drawback of all these sulfonates is the lack of regioselectivity in the sulfonylation of polyhydroxy compounds. A good regioselectivity can be obtained with 2,4,6-trimethylbenzenesulfonyl chloride, but the corresponding sulfonate ester is here a rather poor leaving group in displacement reactions.[10] Interestingly, the corresponding 2,4,6-trichloro- and 2,4,6-tribromobenzenesulfonyl chlorides **A** and **B** (Figure) are both known, but have found very little use in organic chemistry.[11] The corresponding sulfonate esters are about 30 times better leaving groups than the *p*-toluenesulfonate ester.[11] Furthermore, the steric bulk imposed by the halides in the *ortho* positions should also make **A** and **B** very regioselective reagents.

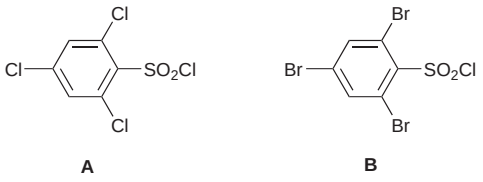
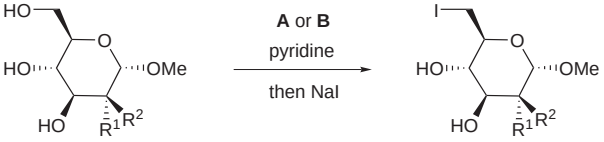


Figure The structures of 2,4,6-trichloro- and 2,4,6-tribromobenzenesulfonyl chlorides **A** and **B**

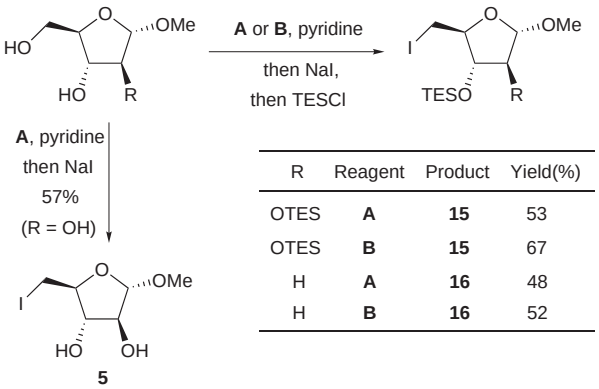
Sulfonyl chlorides **A** and **B** can both be prepared from the corresponding 1,3,5-trihalobenzene by treatment with chlorosulfonic acid.[11] Sulfonyl chloride **A** is also commercially available. When methyl α-D-glucopyranoside and α-D-mannopyranoside were treated with **A** or **B** in pyridine at –15 °C sulfonylation occurred primarily in the 6-position (Scheme 1). Although, the generated sulfonate esters were stable enough to be isolated and purified by flash chromatography, it was soon realized that the subsequent substitution reaction with iodide could in fact be carried out in the same pot. After completion of the sulfonylation reaction a small amount of DMF was added and the mixture stirred for 15 minutes. This was followed by addition of sodium iodide and stirring at 40 °C for 1.5 hours. Hereby, the corresponding 6-iodoglycosides were obtained in yields ranging from 66% to 80%. Molecular iodine was formed during the substitution if DMF was not added. The liberated iodine proved detrimental to the reaction and caused cleavage of the sulfonate ester instead of substitution. For methyl α-D-glucopyranoside a byproduct sulfonylated in the 2-position was also isolated. For methyl α-D-mannopyranoside some anhydride formation occurred during the substitution reaction. In general, tribromo reagent **B** showed a slightly better regioselectivity than trichloro reagent **A**. However, **B** is also the most expensive reagent[12] and is not commercially available. Substitution of these sulfonate esters in pyridine is sensitive to water and vigorously anhydrous conditions must be maintained to prevent hydrolysis. Sodium iodide is preferred for the substitution because it is cheap and easy to dry while lithium iodide was found to be more difficult to handle in these reactions.



R^1	R^2	Reagent	Product	Yield(%)
OH	H	**A**	**1**	66
OH	H	**B**	**1**	80
H	OH	**A**	**2**	68
H	OH	**B**	**2**	70

Scheme 1

The tandem sulfonylation-iodide substitution reaction can also be applied to methyl pentofuranosides. Reacting methyl α-D-arabinofuranoside with reagent **A** followed by addition of sodium iodide gave rise to the 5-iodofuranoside **5** in 57% yield (Scheme 2). Interestingly, the tandem reaction could be further extended by including the triethylsilylation reaction in the same pot. After treatment with the sulfonylating agent and sodium iodide, the pyridine mixture was cooled to 0 °C and triethylsilyl chloride was added. By stirring overnight, the triethylsilylated 5-iodoarabinofuranoside **15** was obtained in 53% yield. This yield could be increased to 67% by using the more regioselective reagent **B**. Similar results were obtained when the methyl furanoside of 2-deoxyribose was subjected to this cascade reaction.



R	Reagent	Product	Yield(%)
OTES	**A**	**15**	53
OTES	**B**	**15**	67
H	**A**	**16**	48
H	**B**	**16**	52

Scheme 2

The physical and spectral data of all the ω-iodoglycosides prepared are listed in Tables 3– 5.

Table 3 Physical Data for ω-Iodoglycosides

Product	R_f	Mp (°C)	$[\alpha]_D$[a]
1	0.37 ($CHCl_3$–MeOH, 8:1)	147–148[b]	+ 99.7[b]
2	0.32 ($CHCl_3$–MeOH, 8:1)	119–120[c]	+ 59.3[c]
3	0.31 ($CHCl_3$–MeOH, 8:1)	173–174[d]	+139.0
4	0.57 ($CHCl_3$–MeOH, 9:1)	70–71[e]	– 76.1[e]
5	0.46 ($CHCl_3$–MeOH, 9:1)	syrup	+ 78.6
6	0.54 (hexane–EtOAc, 1:1)	syrup	+101.4
7	0.40 ($CHCl_3$–MeOH, 9:1)	syrup	–[f]
8	0.58 (hexane–EtOAc, 20:1)	syrup	+ 65.2
9	0.60 (hexane–EtOAc, 4:1)	61–62[g]	+ 32.1[g]
10	0.57 (hexane–EtOAc, 20:1)	syrup	+ 35.9
11	0.59 (hexane–EtOAc, 4:1)	syrup	+ 28.4[h]
12	0.59 (hexane–EtOAc, 20:1)	syrup	+ 68.5
13	0.55 (hexane–EtOAc, 4:1)	syrup	+ 23.1[i]
14	0.58 (hexane–EtOAc, 4:1)	syrup	+ 16.4
15	0.72 (hexane–EtOAc, 9:1)	syrup	+ 1.4
16	0.52 (hexane–EtOAc, 9:1)	syrup	+ 95.8

[a] c = 2.0, $CHCl_3$.
[b] Lit.[1b] mp 146–147 °C, $[\alpha]_D$ +101.5 (c = 1.0, H_2O).
[c] Lit.[15] mp 120–122 °C, $[\alpha]_D^{25}$ +55.5 (c = 0.4, H_2O).
[d] Decomposition. Lit.[16] mp 162 °C (dec.).
[e] Lit.[17] mp 68–70 °C, $[\alpha]_D^{22}$ –78.3 (c = 1.05, $CHCl_3$).
[f] 1:1 Mixture of anomers.
[g] Lit.[13] mp 68–69 °C, $[\alpha]_D^{20}$ +36.0 (c = 1.05, $CHCl_3$).
[h] Lit.[6] $[\alpha]_D^{20}$ +26 (c = 1.39, $CHCl_3$).
[i] Lit.[6] $[\alpha]_D^{20}$ +23 (c = 1.10, $CHCl_3$).

Conclusion

We have shown that chromatography on a reverse phase column is an effective method for purifying unprotected methyl ω-deoxy-ω-iodo-glycosides, which have been prepared by treating methyl glycosides with triphenylphosphine, iodine, and imidazole in THF. Although, reverse phase columns are expensive they can be reused many times and due to the good separation relatively large amounts of material can be purified in each experiment. Subsequently, the iodoglycosides can be triethylsilyl or benzyl protected. This provides a short synthesis of protected iodoglycosides useful for fragmentation reactions with zinc.[4,6,13]

We have also developed an alternative iodination procedure. Methyl glycosides are regioselectively sulfonylated with trihalobenzenesulfonyl chlorides **A** or **B** in pyridine. Due to the good leaving group properties of trihalobenzenesulfonates these can undergo an S_N2 reaction with iodide directly in the pyridine solution. A subsequent triethylsilyl protection of the remaining secondary hydroxy groups can also be performed in the same pot. The regioselectivity with these trihalobenzenesulfonates is slightly lower than with triphenylphosphine and iodine particularly when trichloro reagent **A** is used. However, the sulfonylation method is sometimes more convenient especially when a subsequent protection step can be carried out in the same mixture.

TLC was performed on aluminum plates precoated with silica gel 60 F_{254} (Merck). Compounds were visualized by heating after dipping in a solution of $Ce(SO_4)_2$ (2.5 g) and $(NH_4)_6Mo_7O_{24}$ (6.25 g) in 10% aq H_2SO_4 (250 mL). Flash chromatography was performed using silica gel 60 (0.040–0.063 mm, Merck). Reverse phase flash chromatography was carried out with silica gel 60 C_{18} (0.040–0.063 mm, Macherey-Nagel). NMR spectra were recorded on a Varian Unity Inova 500 or a Varian Mercury 300 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. THF and dioxane were distilled from sodium and benzophenone while pyridine was distilled from CaH_2. Methyl furanosides of ribose, arabinose, and 2-deoxyribose were prepared anomerically pure by literature methods.[14] Microanalyses were conducted by the Department of Chemistry at the University of Copenhagen. All new compounds gave satisfactory analyses: C ±0.35; H ±0.30.

Iodination of Methyl Glycosides with Ph_3P, I_2, and Imidazole; General Procedure

A soln of the methyl glycoside (500 mg), Ph_3P (1.5 equiv), and imidazole (2.0 equiv) in anhyd THF (20 mL) was refluxed followed by the addition of a sol of I_2 (1.5 equiv) in THF (5 mL). The resulting yellow/orange solution was refluxed until TLC revealed full consumption of the starting material (0.5–2 h). A white precipitate of imidazole hydroiodide was formed. The mixture was cooled to r.t., filtered, and concentrated to give a yellow/orange syrup. This was purified by reverse phase column chromatography using H_2O–MeOH (9:1). Iodofuranosides **4**–**7** were obtained as syrups while iodopyranosides **1**–**3** were isolated as crystals and recrystallized. iodopyranoside **4** crystallized on standing (Table 1, Table 3, Table 4).

Triethylsilylation of Iodoglycosides 1–3; General Procedure

To a soln of the iodopyranoside **1**–**3** (500 mg, 1.6 mmol) and imidazole (570 mg, 8.4 mmol) in CH_2Cl_2 (15 mL) was added triethylsilyl chloride (1.2 mL, 7.1 mmol) over 2 min at r.t. Imidazole hydrochloride was observed as a white precipitate. The reaction had gone to completion after stirring for 24 h and H_2O (10 mL) was then added. The layers were separated and the organic layer dried (K_2CO_3), concentrated, and the syrupy residue purified by flash chromatography with hexane–Et_3N (20:1) (Table 2, Table 3, Table 5).

Benzylation of Iodoglycosides 1–4 with Benzyl Trichloroacetimidate; General Procedure

To an ice-cooled solution of the iodoglycoside **1**–**4** (500 mg) and benzyl trichloroacetimidate (1.3 equiv for each hydroxy group) in anhyd dioxane (10 mL) was added triflic acid (5–10 drops). Enough acid should be added to ensure that the mixture is strongly acidic. The reaction had gone to completion within 10 min at r.t. The mixture was diluted with Et_2O (20 mL) and washed with sat. aq $NaHCO_3$ (20 mL). The organic phase was dried (K_2CO_3), concentrated, and the residue purified by flash chromatography using hexane–EtOAc (5:1) (Table 2, Table 3, Table 5).

Table 4 ^{1}H and ^{13}C NMR[a] Data of Unprotected Methyl ω-Deoxy-ω-iodoglycosides, δ, *J* (Hz)

δ_H	OCH_3	H-1	H-2	H-3	H-4	H-5	H-6,6′
1	3.53	4.83	3.67	3.77	3.39	3.52	3.70, 3.47
2	3.53	4.82	4.02	3.85	3.66	3.54	3.72, 3.46
3	3.55	4.89	3.88	3.88	4.17	4.12	3.45, 3.40
J	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
1	3.8	9.8	9.4	9.4	2.1	6.4	10.7
2	1.7	3.4	9.4	9.4	2.6	6.8	11.1
3	2.0	-[b]	1.5	~0	4.5	9.0	10.5
δ_H	OCH_3	H-1	H-2	H-3	H-4	H-5	H-5′
4	3.36	4.83	4.08	4.19	4.03	3.32	3.26
5	3.38	4.94	4.15	3.91	4.08	3.39	3.33
6[c]	3.36	5.11	2.21	4.07	4.11	3.23	3.15
7α	3.47	5.03	4.15	4.27	4.38	3.31	3.22
7β	3.36	4.91	4.26	4.12	4.58	3.31	3.29
J	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$	
4	~0	5.1	5.6	6.0	7.7	9.8	
5	~0	2.1	3.4	6.8	6.0	10.2	
6[c]	4.7	6.4	2.1	4.7	6.4	10.7	
7α	4.3	3.0	4.7	8.1	6.4	9.8	
7β	~0	~0	3.8	8.1	6.8	9.4	
δ_C	OCH_3	C-1	C-2	C-3	C-4	C-5	C-6
1	56.0	100.0	71.9	73.2	74.1	70.8	7.3
2	55.7	101.8	70.5	70.8	71.3	72.2	6.9
3	56.1	100.1	68.4[d]	70.0[d]	70.8	72.0	3.1
4	55.2	108.1	75.6	75.5	82.7	7.7	
5	55.1	109.0	80.7	81.0	84.5	6.7	
6	54.9	105.6	40.8	75.6	86.0	6.4	
7α	56.0	102.2	78.2	76.5	79.2	1.7	
7β	55.1	109.1	79.4	75.9	83.5	2.0	

[a] ^{1}H NMR (500 MHz) and ^{13}C NMR (75 MHz) of compounds **1**–**3** were recorded in D_2O while compounds **4**–**7** were recorded in $CDCl_3$.
[b] Not determined due to overlapping signals.
[c] δ = 1.98 (H-2′, $J_{1,2'}$ ~0 Hz, $J_{2,2'}$ = 14.1 Hz, $J_{2',3}$ ~0 Hz).
[d] Assignments may be reversed.

Sulfonylation and Displacement of the Sulfonyl Group in Methyl Glycosides with Iodide; General Procedure (Schemes 1 and 2)
The methyl glycoside (500 mg, syrups were dried azeotropically with pyridine) was dissolved in anhyd pyridine (9 mL) and the mixture was cooled to –15 °C under argon. A solution of the sulfonyl chloride **A** or **B** (1.3 equiv) in pyridine (3 mL) was added by syringe and the mixture was stirred at –15 °C for 90 min. It was then allowed to warm to r.t. over 1 h. Anhyd DMF (0.5 mL) was added followed by stirring for an additional 15 min. Finely powdered NaI (3 equiv, dried in vacuo at 225 °C) was then added and the mixture was stirred at 40 °C for 90 min. For isolation of unprotected iodoglycosides, the pyridine mixture was diluted with EtOAc (100

Table 5 NMR[a] Data of Protected Methyl ω-Deoxy-ω-iodoglycosides

δ_H	OCH_3	H-1	H-2	H-3	H-4	H-5	H-5′	H-6	H-6′	Others
8	3.43	4.67	3.50	3.81	3.25	3.46	–	3.57	3.16	1.01–0.93, 0.75–0.51
9	3.43	4.63	3.55	4.02	3.35	3.47	–	3.47	3.29	7.35–7.26, 5.00, 4.95, 4.81, 4.80, 4.69, 4.67
10	3.48	4.58	–[b]	–[b]	–[b]	3.54	–	3.63	3.34	1.07–1.01, 0.76–0.66
11	3.38	4.76	3.80	3.90	3.78	3.52	–	3.57	3.33	7.40-7.26, 4.99, 4.76, 4.72, 4.68, 4.62 (2 H)
12	3.44	4.66	3.96	3.86	4.03	3.87	–	3.31	3.23	1.02–0.94, 0.73–0.52
13	3.42	4.65	4.02	3.93	4.03	3.85	–	3.22	3.09	7.41–7.26, 5.04, 4.89, 4.79, 4.76, 4.68, 4.63
14	3.37	4.93	3.89	3.95	4.15	3.38	3.28	–	–	7.39–7.26, 4.65, 4.60, 4.58, 4.51
15	3.40	4.69	3.94	4.04	3.86	3.47	3.24	–	–	0.98–0.96, 0.71–0.58
16	3.38	4.99	2.47	3.96	3.59	3.47	3.29	–	–	1.85 (H-2′), 0.95, 0.60
$J_{H,H}$	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	Others
8	3.4	9.0	8.5	8.5	–	–	2.1	8.5	10.2	–
9	3.8	9.5	9.0	9.4	–	–	2.6	6.4	10.7	J_{Bn} = 12.4, 11.1, 10.7
10	3.0	–[c]	–[c]	–[c]	–	–	3.4	–[c]	10.2	-
11	1.7	3.0	9.4	9.4	–	–	2.6	7.7	10.2	J_{Bn} = 12.4, 11.1
12	3.4	9.4	2.6	~0	–	–	8.1	5.6	10.2	-
13	3.8	10.2	3.0	~0	–	–	7.7	6.4	10.2	J_{Bn} = 12.0, 11.9, 11.1
14	~0	4.7	6.8	5.1	5.6	10.7	–	–	–	J_{Bn} = 12.0, 11.5
15	~0	4.0	6.8	3.9	5.6	10.8	–	–	–	-
16	6.0	8.3	6.1	3.4	4.8	10.8	–	–	–	$J_{1,2'}$ = 2.8, $J_{2,2'}$ = 13.8, $J_{2',3}$ = 5.6
δ_C	OCH_3	C-1	C-2	C-3	C-4	C-5	C-6			Others
8	54.9	99.8	74.3	74.9	76.6	71.2	8.0			7.0, 7.0, 6.7, 6.4, 5.6, 5.4, 5.1
9	55.8	98.4	80.4	81.8[d]	81.8[d]	69.6	7.9			138.8, 138.3, 138.3, 128.8, 127.9, 76.0, 75.6, 73.7
10	55.1	100.3	71.6[d]	72.6[d]	72.6[d]	69.8[d]	7.8			7.0, 6.8, 6.7, 6.3, 5.1, 5.0, 4.7, 4.5
11	55.0	99.0	74.6	79.9	78.6	71.4	7.0			138.2, 138.2, 138.1, 128.3-127.5, 75.3, 72.7, 72.0
12	55.5	100.4	69.5	72.3[d]	73.6	71.5[d]	4.4			7.0, 6.9, 6.7, 6.4, 5.2, 5.2, 4.9
13	55.5	98.7	75.8[d]	78.9	75.7[d]	71.2	3.3			138.5, 138.2, 138.1, 128.2–127.3, 74.8, 73.4 (2 C)
14	55.1	106.0	79.9	81.5	80.1	8.4	–			137.4, 137.3, 128.2–127.4, 72.3, 72.2
15	55.4	108.1	77.0	75.7	80.5	9.3	–			6.8, 6.7, 4.9
16	55.2	104.1	42.1	75.3	80.8	7.9	–			6.6, 4.7

[a] ^1H NMR (500 MHz, $CDCl_3$), ^{13}C NMR (75 MHz, $CDCl_3$).
[b] δ = 3.90–3.85 (m, 3 H).
[c] Not determined due to overlapping signals.
[d] Assignments may be reversed.

mL) and washed with 1 M aq HCl (30 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL) and the combined organic phases were dried, concentrated, and the residue purified by flash chromatography with EtOAc. Alternatively, triethylsilylation could be carried out in the same pot by the addition of triethylsilyl chloride (5 equiv) at 0 °C to the pyridine mixture. After stirring overnight at r.t. hexane (100 mL) was added and the solution washed with H_2O (3 × 25 mL). The organic phase was dried, concentrated, and the residue purified by flash chromatography (eluent: hexane–Et_3N, 99:1 → hexane–EtOAc–Et_3N, 97:2:1) (Table 3, Table 5).

Acknowledgement

We thank the Danish Natural Science Research Council for the financial support.

References

(1) (a) Leon-Ruaud, P.; Plusquellec, D. *Tetrahedron* **1991**, *47*, 5185. (b) Aspinall, G. O.; Carpenter, R. C.; Khondo, L. *Carbohydr. Res.* **1987**, *165*, 281. (c) Garegg, P. J.; Regberg, T.; Stawinski, J.; Strömberg, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, 271. (d) Garegg, P. J.; Johansson, R.; Ortega, C.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 681. (e) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866. (f) Anisuzzaman, A. K. M.; Whistler, R. L. *Carbohydr. Res.* **1978**, *61*, 511. (g) Hanessian, S.; Ponpipom, M. M.; Lavallee, P. *Carbohydr. Res.* **1972**, *24*, 45.

(2) Polymer-bound Ph_3P and other derivatives of Ph_3P have also been employed: Classon, B.; Liu, Z.; Samuelsson, B. *J. Org. Chem.* **1988**, *53*, 6126.

(3) For a general review, see: Castro, B. R. *Org. React.* **1983**, *29*, 1.

(4) (a) Poulsen, C. S.; Madsen, R. *J. Org. Chem.* **2002**, *67*, 4441. (b) Skaanderup, P. R.; Hyldtoft, L.; Madsen, R. *Monatsh. Chem.* **2002**, *133*, 467. (c) Skaanderup, P. R.; Madsen, R. *Chem. Commun.* **2001**, 1106. (d) Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444.

(5) (a) Jensen, H. S.; Limberg, G.; Pedersen, C. *Carbohydr. Res.* **1997**, *302*, 109. (b) Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.

(6) Désiré, J.; Prandi, J. *Eur. J. Org. Chem.* **2000**, 3075.

(7) (a) Ball, D. H.; Parrish, F. W. *Adv. Carbohydr. Chem.* **1968**, *23*, 269. (b) Ball, D. H.; Parrish, F. W. *Adv. Carbohydr. Chem.* **1969**, *24*, 139.

(8) Wu, M.-C.; Anderson, L.; Slife, C. W.; Jensen, L. J. *J. Org. Chem.* **1974**, *39*, 3014.

(9) Binkley, E. R.; Binkley, R. W. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, **1997**, 87.

(10) (a) Fleet, G. W. J.; Shing, T. K. M. *Tetrahedron Lett.* **1983**, *24*, 3657. (b) Ball, D. H.; Bissett, F. H.; Chalk, R. C. *Carbohydr. Res.* **1977**, *55*, 149.

(11) Guthrie, R. D.; Thang, S. *Aust. J. Chem.* **1987**, *40*, 2133.

(12) 1,3,5-Tribromobenzene is about 10 times more expensive than 1,3,5-trichlorobenzene.

(13) Kleban, M.; Kautz, U.; Greul, J.; Hilgers, P.; Kugler, R.; Dong, H.-Q.; Jäger, V. *Synthesis* **2000**, 1027.

(14) (a) El Khadem, H. S.; Audichya, T. D.; Niemeyer, D. A.; Kloss, J. *Carbohydr. Res.* **1976**, *47*, 233. (b) Ness, R. K.; Fletcher, H. G. Jr. *J. Am. Chem. Soc.* **1958**, *80*, 2007. (c) Marriott, D. P.; Bantick, J. R. *Tetrahedron Lett.* **1981**, *22*, 3657.

(15) Lehmann, J.; Benson, A. A. *J. Am. Chem. Soc.* **1964**, *86*, 4469.

(16) Lehmann, J.; Weckerle, W. *Carbohydr. Res.* **1972**, *22*, 23.

(17) Anderson, R. J.; Dixon, R. M.; Golding, B. T. *J. Organomet. Chem.* **1992**, *437*, 227.