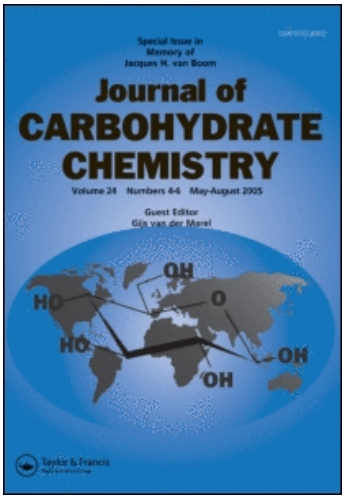
This article was downloaded by:
On: *23 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Improvements in the Regioselectivity of Alkylation Reactions of Stannylene Acetals

Huiping Qin[a]; T. Bruce Grindley[a]
[a] Department of Chemistry, Dalhousie University, Canada

To cite this Article Qin, Huiping and Grindley, T. Bruce(1996) 'Improvements in the Regioselectivity of Alkylation Reactions of Stannylene Acetals', Journal of Carbohydrate Chemistry, 15: 1, 95 — 108
To link to this Article: DOI: 10.1080/07328309608005428
URL: http://dx.doi.org/10.1080/07328309608005428

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

J. CARBOHYDRATE CHEMISTRY, 15(1), 95-108 (1996)

IMPROVEMENTS IN THE REGIOSELECTIVITY OF ALKYLATION REACTIONS OF STANNYLENE ACETALS

Huiping Qin and T. Bruce Grindley

Department of Chemistry, Dalhousie University,
Halifax, N.S., Canada B3H 4J3

Received April 24, 1995 - Final Form October 18, 1995

Downloaded At: 08:47 23 January 2011

ABSTRACT

The regioselectivity of benzylation of stannylene acetals of *trans*-diols on pyranose rings is improved by performing the reaction in benzyl bromide, for instance, for methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside, the ratio of 2-*O*-benzyl ether to 3-*O*-benzyl ether changed from 70:20 in DMF to 74:8 in benzyl bromide, then improved further to 84:2 if the dihexylstannylene acetal was used. Standard conditions for methylation of stannylene acetals are methyl iodide in DMF. Non-polar conditions give much improved regioselectivity; the *O*-2 to *O*-3 product ratio for the above dibutylstannylene acetal changed from 57:30 in DMF to 84:13 with methyl iodide in 1,1,2,2-tetrachloroethane or 90:8 with methyl triflate in chloroform. Examples of benzylation and methylation reactions on different dialkylstannylene acetals on three different *trans*-diols are included.

INTRODUCTION

Regioselective alkylations of carbohydrates are of interest to obtain synthetic intermediates and also to prepare the many naturally occurring compounds that contain *O*-methyl and other *O*-alkyl groups. Several methods are available for the regioselective introduction of alkyl groups: reductive cleavage of benzylidene groups,[1,2] activation of

Copyright © 1996 by Marcel Dekker, Inc.

hydroxyl groups through the formation of tributylstannyl ethers,[3,4,5] phase transfer catalysis,[6] selective activation through copper chelates,[7] activation via electrochemical reduction,[8] and the selective activation of diols with dialkylstannylene acetals.[3,4] A number of different synthetic procedures have been used in the last technique. This report describes an evaluation of the regioselectivity obtained with existing procedures and our approaches to obtaining improved regioselectivity.

Dibutylstannylene acetals often undergo acylation and oxidation reactions with excellent regioselectivity.[3,4,9] However, alkylation reactions on the same substrate often occur with considerably less regioselectivity. For instance, benzoylation of the dibutylstannylene acetal of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) in benzene gave only the 2-*O*-benzoyl derivative in 93% yield;[10] benzylation with benzyl bromide in DMF gave the 2-*O*-benzyl and 3-*O*-benzyl derivatives in 70 and 20% yields, respectively,[11] while methylation with methyl iodide in DMF was even less selective, yielding 57% of the 2-*O*-methyl derivative and 30% of the 3-*O*-methyl derivative.[10] Benzoylation of benzyl 4,6-*O*-benzylidene-2,3-dibutylstannylene-β-D-galactopyranoside in benzene gave the 3-*O*-benzoate in 95% yield;[10] benzylation in benzene containing tetrabutylammonium bromide at reflux gave a mixture of the 3- and 2- *O*-benzyl ethers in 55 and 10% yields, respectively.[12]

We have recently developed a kinetic analysis of those reactions of stannylene acetals that are conducted in the absence of added nucleophiles.[13,14] Dialkylstannylene acetals exist in solutions of non-polar solvents as mixtures of dimers and higher oligomers, in which one dimer is often predominant.[9,13,15] When equilibration of the two most populated dimers (dimer 1 and dimer 2) is fast relative to the rate of reaction, it was shown that:

$$\text{regioselectivity} = 2 \times (\text{rate constant from dimer 1} / \text{rate constant from dimer 2}) \times ([\text{dimer 1}] / [\text{dimer 2}])$$

It was thought that the regioselectivity of alkylation reactions could be improved by employing reaction conditions under which dimers are the most important species present in solution, that is, in non-polar solvents without added nucleophiles. We now report the results of an investigation of the effects of these reaction conditions and also the effects of using different alkyl groups on tin on the regioselectivity obtained in alkylation reactions of dialkylstannylene acetals derived from three hexopyranosides containing *trans*-1,2-diol units.

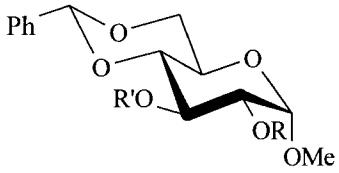
Downloaded At: 08:47 23 January 2011

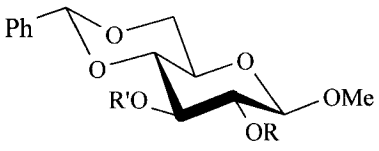
RESULTS AND DISCUSSION

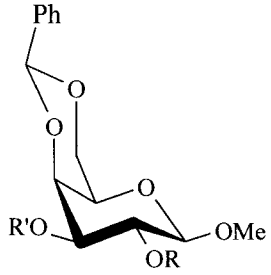
Benzylation and methylation reactions have been performed under a variety of conditions on stannylene acetals derived from *trans*-1,2-diols on pyranose rings in methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**), methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**2**), and methyl 4,6-*O*-benzylidene-β-D-galactopyranoside (**3**). The table summarizes results obtained for these compounds, including literature results, and also literature results for related compounds.

As mentioned in the introduction, reaction of the dibutylstannylene acetal of **1** with benzyl bromide in DMF gave a 2-*O*-benzyl / 3-*O*-benzyl mixture in the ratio of 70 to 20;[11] a recent repetition under similar conditions gave 46 to 19.[16] Boons et al. surprisingly reported that reaction in toluene or benzene in the presence of tetrabutylammonium iodide only gave the 2-*O*-benzyl derivative of **1** in 83% yield,[17,18] but selectivity more consistent with other literature results was obtained when this reaction was repeated under identical conditions, 41 to 15 in favor of *O*-2 substitution.[16] Better selectivities for benzylation of dialkylstannylene acetals of **1** were obtained here by performing the reactions in benzyl bromide particularly when dialkyltin derivatives having larger alkyl groups on tin were employed. Dialkyltin oxides, other than butyl or *t*-butyl are not available commercially but

Downloaded At: 08:47 23 January 2011







1	R = R' = H	**2**	R = R' = H	**3**	R = R' = H
4	R = Bn, R' = H	**6**	R = Bn, R' = H	**8**	R = Bn, R' = H
5	R = H, R' = Bn	**7**	R = H, R' = Bn	**9**	R = H, R' = Bn
10	R = Me, R' = H	**12**	R = Me, R' = H	**14**	R = Me, R' = H
11	R = H, R' = Me	**13**	R = H, R' = Me	**15**	R = H, R' = Me

Downloaded At: 08:47 23 January 2011

can be prepared easily from the alkyl halide.[19] The best regioselectivity was obtained using the dihexylstannylene acetal in benzyl bromide, which gave a selectivity of 82:2.

Reaction of the dibutylstannylene acetal of **1** with various benzyl halides in the presence of added nucleophiles gave poorer selectivity. It was recently reported that the conditions that give excellent regioselectivity for benzylation of *cis*-diols, namely, benzyl bromide in DMF containing cesium fluoride,[3,20,21] gave reversed but relatively poor regioselectivity with the dibutylstannylene acetal of **1** giving isolated yields for the 2-*O*-benzyl and 3-*O*-benzyl ethers of 25 and 52%, respectively.[16] Approximately the same result was obtained here: 36% *O*-2 substitution and 64% *O*-3 substitution based on integration of signals in the crude reaction mixture. These same authors[16] also reported that allylation and *p*-methoxybenzylation of the dibutylstannylene acetal of **1** in the presence of cesium fluoride in DMF gave reasonable preference for the 3-*O*-substituted products. With tetraalkylammonium halides as added nucleophiles, modest preferences were obtained for reaction at *O*-2 using benzyl bromide in DMF or acetonitrile,[16] allyl bromide in DMF,[16] *p*-methoxybenzyl chloride[16] or 2-nitrobenzyl bromide in acetonitrile (See Table 2).[22] Phase transfer catalysed benzylation[6] and allylation[23] of **1** gave similar preferences, 54 and 52.5% of the *O*-2 product and 20 and 20% of the *O*-3 products, respectively.

On the basis of the above results, it might be expected that the bromide ions released during the reaction under the current conditions would influence the regioselectivity of the reaction. Since the concentration of these ions should increase as the reaction proceeds, the regioselectivity obtained, for instance, for **1**, should also decrease as the reaction proceeds. TLC evidence suggested that no such effect was obtained either for the benzylation reactions discussed above or for the methylation reactions discussed below. The halide ion effect was probably insignificant here because, for the most part, the halide ions produced in the reaction become covalently bonded to the tin atoms from the reacted stannylene acetals to form dibutylhalotin ethers.[24,25]

The conditions developed here gave better yields for benzylation of compound **3** than previously reported[12] but the regioselectivity was not improved. Benzylation of the dibutylstannylene acetal of thiophenyl glycoside analog of **3** in acetonitrile using tetrabutylammonium bromide as an added nucleophile gave the 3-*O*-benzyl ether in 70% yield.[26]

Table. Regioselectivity obtained in alkylation reactions of some *trans*-diols

Compound	alkyl group in stannylene	solvent[a]	Conditions temp (°C)	time (h)	reagent	added nucleophile[b]	% yield[c] *O*-2	*O*-3	Ref
1	bu	DMF, BnBr	100	2	BnBr	none	70	20	11
	bu	DMF, BnBr	100	3	BnBr	none	46	19	16
	bu	CH_3CN	80	24	2-NO_2BnBr	none	24	12	22
	bu	CH_3CN	80	16	4-MeOBnCl	TBAI	48	18	16
	bu	BnBr	85	30	BnBr	none	74	8	
	bu	DMF, BnBr	50	48	BnBr	TBAI	41	15	16
	bu	DMF	25	3	BnBr	CsF	36	64[d]	
	bu	DMF	25	16	BnBr	CsF	25	52	16
	bu	DMF	25	16	4-MeOBnCl	CsF	17	25	16
	hex	BnBr	85	96	BnBr	none	82	2	
	bu	DMF	45	20	MeI	none	57	30	10
	bu	TCE	130	22	MeI	none	84	13	
	neohex	TCE	130	22	MeI	none	89	10	
	bu	DCE	25	10	MeOTf	none	64	14	
	bu	$CHCl_3$	25	1	MeOTf	none	90	8	
2	bu	benzene	80	18	BnBr	TBAB	29	61	27
	bu	BnBr	85	34	BnBr	none	46	48	
	bu	DMF	45	10	MeI	none	22	66	27
	bu	TCE	130	22	MeI	none	52	46	
	neohex	TCE	130	22	MeI	none	62	36	
	isobu	TCE	130	22	MeI	none	46	53	
	bu	$CHCl_3$	25	1	MeOTf	none	34	64	
	bu	benzene	80	18	AllBr	TBAB	33	60	27
3	bu	benzene	80	e	BnBr	TBAB	10	55	12
	bu	BnBr	85	45	BnBr	none	15	72	
	hex	BnBr	85	24	BnBr	none	20	73	
	hexamethylene	BnBr	85	29	BnBr	none	16	61	
	bu[f]	TCE	130	27	MeI	none	5	77	
	bu	DCE	25	1	MeOTf	none	6	77	
	bu	$CHCl_3$	25	1	MeOTf	none	7	72	

a. TCE is 1,1,2,2-tetrachloroethane, DCE is 1,2-dichloroethane. b. TBAB is tetrabutylammonium bromide, TBAI is tetrabutylammonium iodide. c. Isolated yields unless noted otherwise. d. Yields based on ^{1}H nmr integrals of crude product. e. Not reported. f. 16% yield of 2,3-di-*O*-methyl derivative also.

Downloaded At: 08:47 23 January 2011

For compound **2**, the regioselectivity under these conditions was altered to favor reaction at *O*-2 more but good regioselectivity was not achieved. *O*-2 is thought[9] to be dicoordinate in the most populated dimer of the dibutylstannylene acetal of compound **2** and hence should be favored for reaction more under the conditions used here. Analogs of **2** with thioethyl and thiophenyl glycosides rather than methyl on benzylation in DMF using CsF as an added nucleophile gave some selectivity for reaction at *O*-3 (65% and 66%, respectively).[28] A slightly better regioselectivity for *O*-3 of the thiophenyl glycoside (72%) was reported for *p*-methoxybenzylation in toluene with tetrabutylammonium bromide as an added nucleophile[29] but a lower yield (48%) was obtained in acetonitrile.[30] Similar regioselectivity (70%) for benzylation at *O*-3 of **2** can be obtained by reaction of benzyl bromide and tetrabutylammonium iodide with the copper chelate in THF.[31]

Downloaded At: 08:47 23 January 2011

The conditions most commonly used for methylation and those previously used for compounds **1** and **2** are methyl iodide in DMF at 45 °C. Regioselectivity under these conditions was much worse than that achieved in benzylation for compound **1**[11] and slightly more in favor of *O*-3 for compound **2**.[27] In ^{119}Sn NMR spectra of stannylene acetals recorded in DMF, all signals are very broad. This observation indicates that an exhange process is occurring in solution, most likely between the species that are predominant in non-coordinating solvents, the dimers, with a species having a considerably different chemical shift, most likely the coordinated monomer.[32]

Two sets of conditions have been developed here that give better regioselectivity than that previously reported. Reaction with the dibutylstannylene acetal of **1** in 1,1,2,2-tetrachloroethane (TCE) with methyl iodide at 130 °C gave an *O*-2/*O*-3 product ratio of 84 to 13, much better than ratio of 57 to 30 obtained previously.[10] Further improvement to 89 to 10 was achieved if the dihexylstannylene acetal was employed. Application of these conditions to compound **2** reversed the direction of the regioselectivity obtained under normal conditions[27] of *O*-2 to *O*-3 of 22 to 66. Yield ratios for reaction at *O*-2 to *O*-3 of 52 to 46 were obtained using the dibutylstannylene acetal and 62 to 36 using the dineohexylstannylene acetal. Methylation had not been performed previously on the dibutylstannylene acetal of compound **3**. In TCE, excellent regioselectivity for reaction at *O*-3 over *O*-2 of 77 to 5 was obtained.

It was hoped that better regioselectivity could be obtained using a more active methylating reagent at lower reaction temperatures. Methyl triflate reacts with stannylene

acetals in chloroform at room temperature more rapidly than does methyl iodide in TCE at 130 °C. The regioselectivity obtained is of the same order as in TCE but varies from compound to compound. For instance, that obtained for the dibutylstannylene acetal of **1** was better, 90 to 8 versus 84 to 13 in TCE. However, nearly identical regioselectivity was obtained for the dibutylstannylene acetal of **3** and that for the dibutylstannylene acetal of **2** was similar to the result in DMF.

CONCLUSIONS

Better regioselectivity is obtained in the alkylation reactions of dialkylstannylene acetals of *trans*-diols if the reactions are run in non-polar solvents in the absence of added nucleophiles than if they are run in polar solvents or in the presence of added nucleophiles. This improvement in regioselectivity occurs because the stannylene acetals exist mainly as dimers in non-polar solvents but to a significant extent as coordinated monomers in polar solvents[31] or in the presence of added nucleophiles.[33] The improvement was not as striking for alkylation reactions as it was for *p*-toluenesulfonation reactions because the activation energies for alkylation reactions are larger. Regioselectivity is controlled by a competition between the ratio of the rate constants for reaction from the two possible dimers and the position of the equilibrium between the dimers.[13,14] With larger activition energies, the position of the equililibrium becomes less important than the ratio of the rate constants.

Good selectivity for benzylation of dialkylstannylene acetals of *trans*-diols is obtained by performing the reaction in benzyl bromide. Much better regioselectivity for methylation of these compounds is obtained by using methyl iodide in 1,1,2,2-tetrachloroethane or methyl triflate in chloroform than the commonly used conditions of methyl iodide in DMF. Employment of larger alkyl groups in the dialkylstannylene acetals also results in increased regioselectivity for these substrates but use of the hexamethylenestannylene acetal does not.

EXPERIMENTAL

General Methods. Melting points were determined with a Fisher-Johns melting point apparatus and were uncorrected. Specific rotations were measured on a Perkin-Elmer model 141 polarimeter. TLC was performed on 0.20 mm thick Merck silica gel 60F-254 aluminum sheets cut to be approximately 7 cm long. Components were located by spraying with 2%

Downloaded At: 08:47 23 January 2011

ceric sulfate in 1M sulfuric acid and heating on a hot plate until coloration occurred. Flash column chromatography was performed on silica gel 60 PF-254 for preparative chromatography. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-250 NMR spectrometer. Solutions for NMR spectra were prepared in chloroform-*d* unless otherwise stated. Chemical shifts are reported in ppm downfield from internal TMS for ^{1}H and ^{13}C NMR spectra; for some spectra, the central peak of chloroform-*d*, at δ 77.0 was used as a secondary reference for ^{13}C NMR assignments. Most ^{1}H and ^{13}C NMR assignments were confirmed by 2D COSY and HETCOR experiments.

General Method for Benzylation: Benzylation of Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside (1) Via its 2,3-*O*-Dibutylstannylene Acetal. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**, 0.280 g, 1 mmol) and dibutyltin oxide (0.249 g, 1.0 equiv) were refluxed in toluene (40 mL) for 12 h in an apparatus for the azeotropic removal of water. The solvent was evaporated, and then benzyl bromide (10 mL) was added. The mixture was stirred at 80-90 °C until TLC indicated that the starting material had disappeared (30 h). The reaction mixture was cooled, diluted with chloroform (20 mL), and the solution was washed with water (50 mL). The organic layer was dried with magnesium sulphate, then concentrated. The remaining liquid residue was fractionated by flash chromatography using a solvent gradient changing from toluene to ethyl acetate to give methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**4**, 0.275 g, 74%), which crystallized from ethyl acetate as fine colorless needles: mp 131-132 °C; $[\alpha]_D^{25}$ +33.7° (*c* 8.0, chloroform); lit.[6] 131-132 °C, $[\alpha]_D^{25}$ +35°; and methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**5**, 0.029 g, 8%), which was a solid residue, mp 180-181 °C, $[\alpha]_D^{25}$ +80° (*c* 0.12, chloroform); lit.[6] 187-188 °C, $[\alpha]_D$ +78°.

Benzylation of Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside (1) Via its Dihexylstannylene Acetal. Compound **1** (0.284 g, 1 mmol) was reacted with dihexyltin oxide (0.306 g, 1.0 equiv) in toluene (25 mL), then with excess benzyl bromide (6 mL) for 96 h as in the general procedure. Flash column chromatography with gradient elution from toluene : ethyl acetate (15:1) to ethyl acetate yielded methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**4**, 0.308 g, 82%) and methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**5**, 6 mg, 2%).

Benzylation of Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside (1) Via its Dibutylstannylene Acetal in the Presence of CsF in DMF. Compound **1** (0.278 g, 1

Downloaded At: 08:47 23 January 2011

mmol) and dibutyltin oxide (0.303 g, 1.2 equiv) were refluxed in toluene (20 mL) for 12 h in an apparatus for the azeotropic removal of water. The solvent was evaporated and cesium fluoride (0.394 g, 1.2 equiv) was added. The reaction flask was kept under vacuum for 2 h. DMF (5 mL) and excess benzyl bromide (0.5 mL) were added and the reaction mixture was stirred for 19 h when TLC showed that all starting material had been consumed. The reaction mixture was concentrated, the residue was taken up in ethyl acetate, and the resulting solution was dried over sodium sulfate. The solution was concentrated to a solid residue: yield 0.331 g, 90%; ^{1}H NMR δ 5.56 , 5.50 (2s, ratio of integrals 1.67 to 1.0, CHPhs), 4.95, 4.68 (2d, ratio of integrals 1.88 to 1.0, H-1s), average ratio of 1 : 1.8 for 2-*O* and 3-*O* substitution.

Benzylation of Methyl 4,6-*O*-Benzylidene-β-D-glucopyranoside (2) Via its Dibutylstannylene Acetal. Compound **2** (0.283 g, 1 mmol) was reacted with dibutyltin oxide (0.249 g, 1 equiv) in toluene (28 mL), then with excess benzyl bromide (6 mL) for 34 h as in the general procedure. Flash chromatography with gradient elution from toluene: ethyl acetate (15:1) to ethyl acetate yielded methyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**6**): yield 0.170 g, 46%; mp 125-126 °C; $[\alpha]_D^{25}$ -24.0° (*c* 1.82, chloroform); lit.[34] 124-125 °C; $[\alpha]_D^{25}$ -26.0°; and methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**7**): yield 0.180 g, 48%; mp 177-178 °C, $[\alpha]_D^{25}$ -40.0° (*c* 0.14, chloroform); lit.[35] mp 180°, $[\alpha]_D^{25}$ -45.5°.

Benzylation of Methyl 4,6-*O*-Benzylidene-β-D-glucopyranoside (2) Via its Diisobutylstannylene Acetal and Dineohexylstannylene Acetal. Reaction of compound **2** (1 mmol) with diisobutyltin oxide or dineohexyltin oxide (1 equiv) in toluene (28 mL), then with excess benzyl bromide (6 mL) for 42 h was performed as in the general procedure. When TLC indicated that two products were obtained in approximately equal amounts, further investigation was not performed.

Benzylation of Methyl 4,6-*O*-Benzylidene-β-D-galactopyranoside (3) Via its Dibutylstannylene Acetal. Reaction of compound **3** (0.281 g, 1 mmol) with dibutyltin oxide (0.251 g, 1 equiv) in toluene (30 mL), then with excess benzyl bromide (6 mL) for 45 h was performed as in the general procedure. A flash column with an eluent of hexane : ethyl acetate (2:1) yielded methyl 2-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (**8**); yield 0.055 g, 15%; solid residue, mp 108-110 °C; $[\alpha]_D^{24}$ +21.0° (*c* 1.15, chloroform); lit.[36] mp

Downloaded At: 08:47 23 January 2011

108-111°C; $[\alpha]_D^{25}$ +22°; and methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (**9**); yield 0.268 g, 72%; needles; mp 199-200 °C, $[\alpha]_D^{25}$ +56.2° (*c* 0.48, chloroform); lit.[35] 200-201 °C, $[\alpha]_D^{25}$ +56°.

Benzylation of Methyl 4,6-*O*-Benzylidene-β-D-galactopyranoside (3) Via its Dihexylstannylene Acetal. Reaction of compound **3** (0.280 g, 1 mmol) with dihexyltin oxide (0.311g, 1.0 equiv) in toluene (30 mL), then with excess benzyl bromide (6 mL) for 24 h was performed as in the general procedure. Compound **8** (0.060 g, 20%) and compound **9** (0.224 g, 73%) were obtained along with trace amount of starting material.

Benzylation of Methyl 4,6-*O*-Benzylidene-β-D-galactopyranoside (3) Via its Hexamethylenestannylene Acetal. Reaction of compound **3** (0.280 g, 1 mmol) with hexamethylenetin oxide (0.222g, 1.0 equiv) in toluene (40 mL), then with excess benzyl bromide (6 mL) for 29 h was performed as in the general procedure. Compound **8** (0.056 g, 16%) and compound **9** (0.212 g, 61%) were obtained with starting material (0.016g, 4%).

General Method for Methylation of Methyl 4,6-*O*-Benzylidene-D-hexopyranosides with Methyl Iodide. Methylation of Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside (1) Via its Dibutylstannylene Acetal. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) (0.283 g, 1 mmol) and dibutyltin oxide (0.249 g, 1 eq.) were refluxed in toluene (30 mL) for 12 h in an apparatus for the azeotropic removal of water. The solvent was evaporated, then 1,1,2,2-tetrachloroethane (30 mL) and methyl iodide (3 mL) were added subsequently under nitrogen. The mixture was stirred at 130 °C until TLC indicated that the starting material had disappeared (22 h). The reaction mixture was cooled, diluted with chloroform (20 mL) and the solution was washed with water (50 mL). The organic layer was dried with magnesium sulphate, then concentrated. The remaining liquid residue was fractionated by flash chromatography using a solvent gradient changing from hexane to hexane : ethyl acetate (2:1) to give methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside (**11**): yield 0.039 g, 13%; mp 153-154°C; $[\alpha]_D^{25}$ +112.1° (*c* 0.25, chloroform); lit.[33] 153-4 °C; $[\alpha]_D^{25}$ +114.4°; and methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-glucopyranoside (**10**) (0.249 g, 84%), crystallized from ethyl acetate as fine needles: mp 170-171 °C; $[\alpha]_D^{25}$ +91.1° (*c* 0.73, chloroform); lit.[33] mp 166 °C; $[\alpha]_D^{25}$ +96.4°.

Methylation of 1 Via Dineohexylstannylene Acetal. Reaction of compound **1** (0.284 g, 1 mmol) with dineohexyltin oxide (0.305 g, 1 equiv) in toluene (30 mL), then with

Downloaded At: 08:47 23 January 2011

excess methyl iodide (3 mL) in 1,1,2,2-tetrachloroethane (30 mL) for 22 h as in the general procedure yielded compound **11** (0.030 g) and compound **10** (0.264 g) in 10% and 89% yields, respectively.

Methylation of Methyl 4,6-*O*-Benzylidene-β-D-glucopyranoside (2) Via its Dibutylstannylene Acetal. Reaction of compound **2** (0.284 g, 1 mmol) with dibutyltin oxide (0.249 g, 1 equiv) in toluene (28 mL), then with excess methyl iodide (3 mL) in 1,1,2,2-tetrachloroethane (30 mL) for 22 h as in the general procedure yielded methyl 4,6-*O*-benzylidene-2-*O*-methyl-β-D-glucopyranoside (**12**) (0.155 g, 52%), mp 176-177 °C, $[\alpha]_D^{25}$ -65.4° (*c* 1.65, chloroform); lit.[33] 175-176 °C; $[\alpha]_D^{25}$ -67.3°; and methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside (**13**) (0.138 g, 46%), mp 174-175 °C, $[\alpha]_D^{25}$ -50.8° (*c* 0.54, chloroform); lit.[33] 172-3 °C, $[\alpha]_D^{25}$ -40.0°.

Methylation of 2 Via its Dineohexylstannylene Acetal. Reaction of compound **2** (0.283 g, 1 mmol) with dineohexyltin oxide (0.305 g, 1 equiv) in toluene (28 mL), then with excess methyl iodide (3 mL) in 1,1,2,2-tetrachloroethane (30 mL) for 22 h as in the general procedure yielded compound **12** (0.183 g, 62%), and compound **13** (0.108 g, 36%).

Methylation of 2 Via its Diisobutylstannylene Acetal. Reaction of compound **2** (0.284 g, 1 mmol) with diisobutyltin oxide (0.249 g, 1 equiv) in toluene (28 mL), then with excess methyl iodide (3 mL) in 1,1,2,2-tetrachloroethane (25 mL) for 22 h as in the general procedure yielded compound **12** (0.139 g, 46%), and compound **13** (0.157 g, 53%).

Methylation of Methyl 4,6-*O*-Benzylidene-β-D-galactopyranoside (3) Via its Dibutylstannylene Acetal. Reaction of compound **3** (0.368 g, 1.3 mmol) with dibutyltin oxide (0.251 g, 1 equiv) in toluene (25 mL), then with excess methyl iodide (3 mL) in 1,1,2,2-tetrachloroethane (20 mL) was performed for 27 h as in the general procedure. Flash chromatography of the product mixture with chloroform : ethyl acetate (from 3:1 to 1:2) as eluent yielded methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-β-D-galactopyranoside (**16**) (0.066 g, 16%): mp 148-149 °C; $[\alpha]_D^{25}$ +15.8° (*c* 0.94, chloroform); lit.[37] 148 °C; $[\alpha]_D^{25}$ +18.2°; methyl 4,6-*O*-benzylidene-2-*O*-methyl-β-D-galactopyranoside (**14**) (0.019 g, 5%): mp 167-169 °C; $[\alpha]_D^{25}$ -25° (*c* 0.32, chloroform); lit.[38] 169-171 °C; $[\alpha]_D^{25}$ -29°; and methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-galactopyranoside (**15**) (0.296 g, 77%), mp 211-2 °C, $[\alpha]_D^{25}$ +31.7° (*c* 0.24, chloroform); lit.[37] 216-7 °C, $[\alpha]_D^{25}$ +25°.

General Method for Methylation of Methyl 4,6-*O*-Benzylidene-D-hexopyranosides with Methyl Triflate. Methylation of Methyl 4,6-*O*-Benzylidene-α-D-

Downloaded At: 08:47 23 January 2011

glucopyranoside (1) Via its Dibutylstannylene Acetal in 1,2-Dichloroethane. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) (0.274 g, 1 mmol) and dibutyltin oxide (0.330 g, 1.2 equiv) were refluxed in toluene (25 mL) for 12 h in an apparatus for the azeotropic removal of water. The solvent was evaporated, then 1,2-dichloroethane (10 mL) and methyl triflate (0.8 mL) were added subsequently under nitrogen. The mixture was stirred at room temperature for 10 h. The reaction mixture was diluted with chloroform (20 mL) and the solution was washed with water (40 mL). The organic layer was dried with magnesium sulphate, then concentrated. The remaining liquid residue was fractionated by flash chromatography with a solvent system of 2:1 of hexane to ethyl acetate to give compound **11** (0.040 g, 14%), compound **10** (0.177 g, 64%), and starting material (0.011 g, 4%).

Methylation of Methyl 4,6-*O*-Benzylidene-α-D-glucopyranoside (1) Via its Dibutylstannylene Acetal in Chloroform. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) (0.281 g, 1 mmol) and dibutyltin oxide (0.302 g, 1.2 equiv) were refluxed in toluene (40 mL) for 8 h in an apparatus for the azeotropic removal of water. The solvent was evaporated, then anhydrous chloroform (10 mL) and methyl triflate (0.6 mL) were added subsequently under nitrogen. The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with chloroform (20 mL) and the solution was washed with aqueous sodium bicarbonate solution (40 mL). The organic layer was dried with magnesium sulphate, then concentrated. The remaining liquid residue was fractionated by flash chromatography as in the general procedure to give compound **11** (0.024 g, 8%), and compound **10** (0.266 g, 90%).

Methylation of Methyl 4,6-*O*-Benzylidene-β-D-glucopyranoside (2) Via Dibutylstannylene Acetal in Chloroform. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**2**) (0.278 g, 1 mmol) and dibutyltin oxide (0.306 g, 1.2 equiv) were refluxed in toluene (30 mL) for 12 h in an apparatus for the azeotropic removal of water. Methylation with methyl triflate (0.6 mL) in 5 mL chloroform was complete within 1 h. Flash chromatography gave compound **12** (0.099 g, 34%), and compound **13** (0.187 g, 64%).

Methylation of Methyl 4,6-*O*-Benzylidene-β-D-galactopyranoside (3) Via its Dibutylstannylene Acetal in 1,2-Dichloroethane. Reaction of compound **3** (0.278 g, 1 mmol) with dibutyltin oxide (0.306 g, 1.2 equiv) in toluene (25 mL), then with excess methyl triflate (0.8 mL) in 1,2-dichloroethane (10 mL) was performed for 1 h as in the general

Downloaded At: 08:47 23 January 2011

procedure. Flash chromatography of the product mixture with chloroform : ethyl acetate (2:1) as eluent yielded compound **14** (0.018 g, 6%) and compound **15** (0.225 g, 77%).

Methylation of Methyl 4,6-*O*-Benzylidene-β-D-galactopyranoside (3) Via its Dibutylstannylene Acetal in Chloroform. Reaction of compound **3** (0.275 g, 1 mmol) with dibutyltin oxide (0.296 g, 1.2 equiv) in toluene (20 mL), then with excess methyl triflate (0.6 mL) in 1,2-dichloroethane (5 mL) was performed for 1 h as in the general procedure. Flash chromatography of the product mixture as before yielded compound **14** (0.022 g, 7%) and compound **15** (0.208 g, 72%).

ACKNOWLEDGEMENT

This work was supported by the Natural Sciences and Engineering Council of Canada. We are grateful to ARMRC for NMR time.

Downloaded At: 08:47 23 January 2011

REFERENCES

1. P. J. Garegg, H. Hultberg and S. Wallin, *Carbohydr. Res.*, **108**, 97 (1982).
2. J. Gelas, *Adv. Carbohydr. Chem. Biochem.*, **39**, 71 (1981).
3. T. B. Grindley in *Synthetic Oligosaccharides: Indispensable Probes for the Life Sciences*; Kovác, P. Ed.; ACS: Washington, 1994; Chap. 4, pp 51-76.
4. S. David and S. Hanessian, *Tetrahedron*, **41**, 643 (1985); M. Pereyre, J. P. Quintard and A. Rahm, *Tin in Organic Synthesis*, Butterworths: London, 1987, Chap. 11.
5. T. Ogawa and M. Matsui, *Carbohydr. Res.*, **62**, C1 (1978); T. Ogawa, Y. Takahashi and M. Matsui, *Carbohydr. Res.*, **102**, 207 (1982).
6. P. J. Garegg, T. Iversen and S. Oscarson, *Carbohydr. Res.*, **50**, C12 (1976); **50**, C5 (1976).
7. R. Eby, K. T. Webster and C. Schuerch, *Carbohydr. Res.*, **129**, 111 (1984).
8. C. H. Hamann, S. Fischer, H. Polligkeit and P. Wolf, *J. Carbohydr. Chem.*, **12**, 173 (1993).
9. T. B. Grindley and R. Thangarasa, *Can. J. Chem.* **68**, 1007 (1990).
10. S. David and A. Thiéffry, *J. Chem. Soc., Perkin Trans. I*, 1568 (1979).
11. T. Ogawa and T. Kaburgi, *Carbohydr. Res.*, **103**, 53 (1982).
12. S. David, A. Thiéffry and A. Veyrières, *J. Chem. Soc., Perkin Trans. I*, 1796 (1981).
13. X. Kong and T. B. Grindley, *Can. J. Chem.*, **72**, 2396 (1994).
14. X. Kong and T. B. Grindley, *Can. J. Chem.*, **72**, 2405 (1994).
15. T. B. Grindley and R. Thangarasa, *J. Am. Chem. Soc.*, **112**, 1364 (1990).
16. D. J. Jenkins and B. V. L. Potter, *Carbohydr. Res.*, **265**, 145 (1994).
17. G.-J. Boons, G. H. Castle, J. A. Clase, P. Grice, S.V. Ley and C. Pinel, *Synlett*, 1993, 913.
18. G.-J. Boons, G. H. Castle, J. A. Clase, P. Grice, S.V. Ley and C. Pinel, *Synlett*, 1994, 764.
19. X. Kong, T. B. Grindley, P. K. Bakshi and T. S. Cameron, *Organometallics*, **12**, 4881, (1993).

20. S. J. Danishefsky and R. Hungate, *J. Am. Chem. Soc.*, **108**, 2486 (1986).
21. N. Nagashima and M. Ohno, *Chem. Pharm. Bull. Jap.*, **39**, 1972 (1991).
22. J. E. T. Corrie, *J. Chem. Soc., Perkin Trans. I*, 2161 (1993)
23. S. Basu and J. N. Pal, *Carbohydr. Res.*, **208**, 241 (1990)
24. H. Qin and T. B. Grindley, *J. Carbohydr. Chem.*, **13,** 475 (1994).
25. S. Roelens, *J. Chem. Soc., Perkin Trans. II*, 1617 (1988).
26. A. Fernandez-Mayoralas, A. Marra, M. Trumtel, A. Veyrières and P. Sinaÿ, *Carbohydr. Res*, **188**, 81 (1989).
27. K. Takeo and K. Shibata, *Carbohydr. Res.*, **133**, 147 (1984).
28. H. M. Zuurmond, P. A. M. van der Klein, G. A. van der Marel and J. H. van Boom, *Tetrahedron*, **49**, 6501 (1993).
29. R. Verduyn, M. Douwes, P. A. M. van der Klein, E. M. Mösinger, G. A. van der Marel and J. H. van Boom, *Tetrahedron*, **49**, 7301 (1993).
30. V. Pedretti, A. Veyrières and P. Sinaÿ, *Tetrahedron*, **46**, 77 (1990).
31. B. Classon, P. J. Garegg, S. Oscarson and A.-K. Tidén, *Carbohydr. Res.*, **216**, 187 (1991).
32. S. David, A. Thiéffry, and A. Forchioni, *Tetrahedron Lett.*, **22**, 2647 (1981).
33. R. Thangarasa, PhD Thesis, Dalhousie University, 1990.
34. Y. Kondo, *Agr. Biol. Chem.*, **39**, 1879 (1975).
35. P. A. Finan and C. D. Warren, *J. Chem. Soc.*, 3089 (1962).
36. J. Kihlberg, T. Frejd, K. Jansson and G. Magnusson, *Carbohydr. Res.*, **152**, 113 (1986).
37. W. Szeja, *Pol. J. Chem.*, **55**, 1503 (1981).
38. J. Kihlberg, T. Freid, K. Jansson, S. Kitzing and G. Magnusson, *Carbohydr. Res.*, **185**, 171 (1989).

Downloaded At: 08:47 23 January 2011