Carbohydrate Research, 220 (1991) 101–115
Elsevier Science Publishers B.V., Amsterdam

A one-step *C*-linked disaccharide synthesis from carbohydrate allylsilanes and tri-*O*-acetyl-D-glucal

Anna de Raadt and Arnold E. Stütz
Institut für Organische Chemie der Technischen Universität Graz, Stremayrgasse 16, A-8010 Graz (Austria)

(Received March 18th, 1991; accepted April 25th, 1991)

ABSTRACT

The reaction of protected glucuronic esters **2** and **7**, as well as D-glucuronolactone derivative **11**, with (trimethylsilyl)methylmagnesium chloride in ether led to the corresponding stable bis-silyl adducts **3**, **8**, and **12**, respectively. In Peterson-type reactions catalysed with mild acid, these compounds yielded carbohydrate allylsilanes **4**, **9**, and **13**, respectively. Synthons **4** and **9** were coupled with tri-*O*-acetyl-D-glucal in a boron trifluoride-catalysed "carbon-Ferrier rearrangement" reaction to give *C*-linked disaccharides *i.e.*, so-called "*C*-disaccharides" **16** and **17**, respectively, in fair yields. Structural assignments of the anomeric configuration at the *C*-glycosylic carbon in the 2,3-unsaturated ring of these coupling products with the aid of n.m.r. spectroscopic methods unambiguously showed that α-D-*C*-linked disaccharides had been formed.

INTRODUCTION

C-linked disaccharides (*i.e.*, so-called "*C*-disaccharides") have attracted considerable interest in the past years, not only because of their potential as glycosidase inhibitors and non-nutrative sweeteners, but also because these compounds are challenging synthetic targets. Investigations of their conformational behaviour have also been conducted. In these compounds two monosaccharide units are linked by a carbon bridge (ideally a methylene moiety) instead of the usual anomeric oxygen. The first synthetic approach was presented by Rouzaud and Sinaÿ who synthesised a protected "methyl *C*-gentiobioside" from tetra-*O*-benzyl-D-gluconolactone and a dibromomethylene derivative of α-D-*gluco*-dialdose[1]. A free-radical *C*-linked disaccharide synthesis was reported by Giese and coworkers[2], who obtained *C*-2-connected *C*-linked disaccharides employing a carbohydrate-derived α-methylene lactone. More recently, extensive synthetic work and studies of the conformational behaviour of various *C*-linked disaccharides were carried out by Kishi and coworkers, who synthesised, amongst other epimers, "*C*-maltosides" *via* the Wittig reaction of a C-4-branched phosphorane to the free aldehyde of an otherwise protected D-arabinose[3]. Further work yielded the carbon analogues of isomaltose and gentiobiose, as well as the 1,3-linked *C*-glycosylic analogues of D-galactopyranosyl-α-D-galacto- and -α-D-glucopyranoside. The conformations of these *C*-linked disaccharides were compared to those of their natural counterparts[4–7]. A synthesis of "*C*-sucrose" was also reported by the same group[8]. Nicotra and coworkers published the preparation of the structurally very similar 1-(α-D-glucopyranosyl)-1-deoxy-D-fructose[9]. Both groups used allylsilane meth-

0008-6215/91/$ 03.50

odology to obtain simple *C*-glucopyranosyl compounds, which were subsequently chain-extended and suitably functionalized. Dawson and coworkers recently synthesised *C*-linked disaccharides by a 1,3-dipolar cycloaddition of an *O*-acetylated xylose nitrile oxide to ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside, followed by the reductive hydrolytic cleavage of the resulting 2-isoxazolines[10]. A comparatively simple Lewis acid-catalyzed dimerisation of 1-deoxy-3,4,6-tri-*O*-benzyl-D-fructofuranose was reported to afford an anomeric mixture of furanoid *C*-linked disaccharides[11]. Schmidt and Preuss linked 1-*C*-lithiated glycals to 4-*C*-formyl-D-glucose and -D-galactose derivatives to obtain the corresponding β(1→4) linked *C*-linked disaccharides containing oxygenated carbon bridges[12]. A similar approach *via* lithiated 1-sulfones had been reported by Beau and Sinaÿ[13].

A β(1→4)-*C*-linked disaccharide congener was synthesised by Armstrong and Daly, who connected two suitably modified glucose derivatives by an acetylenic bridge[14]. Other *C*-linked disaccharide analogues, most of them lacking the one-carbon bridge, were obtained by an acid-catalyzed dimerisation of tri-*O*-acetyl-D-glucal (3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol), pioneered by Ferrier[15] in 1969, by Diels–Alder approaches[16], from 1-*C*-nitrosugars[17], as well as by the reaction of tri-*O*-acetyl-D-glucal with a carbohydrate-derived silyl enol ether[18].

In the context of attempts to find an easy access to *C*-linked disaccharides which are useful for further synthetic transformations into novel *C*-linked oligosaccharides, we have become interested in allylsilane methodology due to both its preparative simplicity as well as the readily available information on the stereochemical outcome of such carbon–carbon bond formations. Allylsilanes are well established chemical tools in organic synthesis[19] and have become widely used reagents for the synthesis of *C*-glycosyl compounds. The simplest member of this class of reagents, allyltrimethylsilane, has been coupled to a number of glycosyl donors such as glycosyl halides[20,21] and *C*-glycosyl esters[22,23] to give saturated allyl *C*-glycosyl compounds, the α-configuration preponderating in the D-*gluco* series. More elaborate products have been obtained exploiting allylsilanes substituted in the α-(OAc, COOEt), β-(Me,Br) and γ-(Me, allyl) positions[21,23,24]. Allylsilanes also react with glycals, for example tri-*O*-acetyl-D-glucal, in the presence of Lewis acids to give 2,3-unsaturated *C*-glycosyl compounds, in the so called "carbon-Ferrier rearrangement"[25]. α-Configured products are obtained from glycals of the *arabino*-series. Compared to the extensive use of allylsilanes with saturated glycosyl donors, however, relatively few allylsilane derivatives have been used in this reaction, such as allyl trimethylsilane[26] as well as (*E*)- and (*Z*)-crotylsilanes[25].

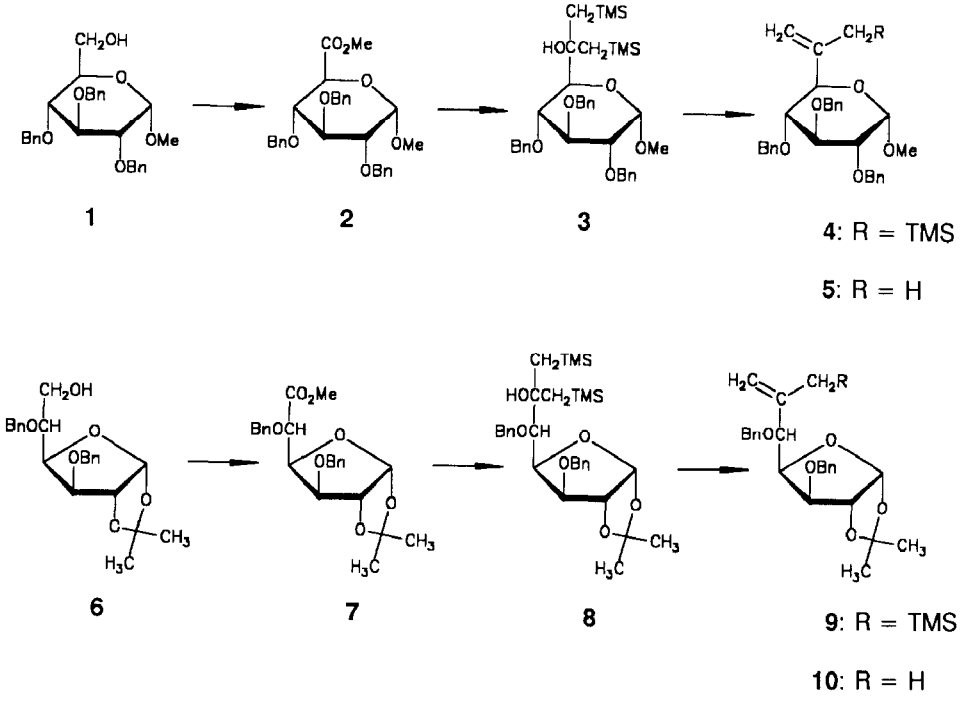
The synthetic methods for the preparation of allylsilanes have been recently reviewed[27]. In view of their preparative potential, we have tried to extend the scope of this approach to highly functionalized compounds derived from carbohydrate esters and lactones. The *C*-linked disaccharides so obtained should bear an *exo*-double bond in β-position to the *C*-glycosylic carbon atom. Such *exo*-double bonds are the structural features of a large variety of natural products such as mycalamide A[28], halichochondrin B[29], and palytoxin[30], just to mention a few, and have also been exploited as precursors to spiro-oxiranes *e.g.*, in a synthesis of oleandromycin derivatives[31] and of "*C*-sucrose"[8].

Hydroxylation of such an *exo*-double bond recently gave access to branched-chain higher-carbon sugars[32]. This methodology would, therefore, clearly allow easy access to intermediates with such structural moieties.

The Grignard reaction of esters or lactones with two molar equivalents of (trimethylsilyl)methylmagnesium halide proceeds *via* α-silyl-ketones and is known to give chain-extended branched bis-silyl compounds which upon treatment with base or acid in a Peterson-type reaction yield substituted allylsilanes[33]. (A cerium-mediated variation of the Grignard reaction has been reported to give improved yields[34], and related Reformatsky-type reactions of silylmethylketones and acylsilanes have been investigated in this department[35].)

RESULTS AND DISCUSSION

Following this general approach we reacted methyl (methyl 2,3,4-tri-*O*-benzyl-α-D-gluco-pyranosid)uronate (**2**, Scheme 1), easily accessible from methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[36] (**1**) by oxidation with pyridinium dichromate in *N,N*-dimethylformamide, followed by treatment of the resulting glucuronic acid with an excess etheral diazomethane, with ten equivalents of (trimethylsilyl)methylmagnesium chloride (freshly prepared from chlorotrimethylsilylmethane) in ether at 0°. The uronic ester was rapidly converted into a single, less polar compound, which, after extraction



Bn, benzyl; TMS, trimethylsilyl

SCHEME 1

TABLE I

^{1}H-N.m.r. data for compounds (in $CDCl_3$)

Compound	*Chemical Shifts* (δ)								
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-7*	*H-7'*	exo-CH_2	*Others*
2	4.64	3.62	4.04	3.73	4.24	—	—	—	3.43 (OMe); 3.73 (CO_2Me); 4.60–5.03, 7.25–7.37 (CH_2Ph).
3	4.55	3.51	4.00	3.57	3.65	1.24/0.95	1.17/0.91	—	3.49 (OMe); 4.61–5.02, 7.24–7.43 (CH_2Ph); 0.13, 0.09 ($SiMe_3$); 3.39 (6-OH).
4	4.57	3.51	3.96	3.40	3.99	1.61		5.06,4.85	3.37 (OMe), 4.58–4.96; 7.25–7.36 (CH_2Ph), 0.04 ($SiMe_3$).
5	4.58	3.49	3.96	3.40	4.03	1.72		5.12,5.01	3.40 (OMe); 4.53–4.95, 7.08–7.32 (CH_2Ph).
7	5.87	4.53	4.06	4.38	4.30	—	—	—	3.68 (CO_2Me); 1.38, 1.30 (2-Pr), 4.60–5.03, 7.26–7.39 (CH_2Ph).
8	5.90	4.64	4.08	4.27	3.87	1.06–1.27		—	2.99 (6-OH); 1.30, 1.47 (2-Pr); 4.37–4.68, 7.16–7.28 (CH_2Ph); 0.09, 0.06 ($SiMe_3$).
9	5.96	4.60	4.15	4.16–4.21		1.70		5.18,5.04	1.51, 1.33 (2-Pr); 4.24–4.65, 7.27–7.34 (CH_2Ph); 0.12 ($SiMe_3$).
10	5.92	4.60	4.14	4.27	4.22	1.84		5.16	1.48, 1.32 (2-Pr); 4.20–4.67; 7.26–7.33 (CH_2Ph).
12	5.88	4.48	4.10	4.18	4.41	1.11–1.32		—	4.62 (3-OH); 2.06 (6-OH); 1.40, 1.24 (2-Pr), 0.03, 0.02 ($SiMe_3$); 0.86, 0.14, 0.10 (*tert*-BuSiMe_2).
13	5.97	4.46	4.17	4.23	4.56	1.71	1.33	5.24,4.88	5.08 (3-OH); 1.50, 1.31 (2-Pr); 0.06 ($SiMe_3$); 0.91, 0.14, 0.09 (*tert*-BuSiMe_2).
14	5.96	4.48	4.02	4.25	4.67	1.81		5.15,5.01	4.97 (3-OH); 1.47, 1.31 (2-Pr); 0.89, 0.12, 0.07 (*tert*-BuSiMe_2).

Compound	*Coupling constants (Hz)*[a]				
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{7,7'}$
2	3.6	9.7	9.2	9.9	—
3	3.9	9.6	8.7	9.8	14.9
4	3.6	9.7	9.7	9.7	—
5	3.5	9.7	9.5	9.7	—
7	3.7	—	3.0	9.3	—
8	3.7	—	2.8	9.4	n.r.
9	3.7	—	2.5	n.r.	—
10	3.6	—	2.6	9.4	—
12	3.7	—	2.9	n.r.	14.5
13	3.7	—	2.9	n.r.	14.5
14	3.7	—	n.r.	n.r.	—

[a] In compounds 7–14 $J_{2,3} < 0.5$ Hz; n.r., not resolved. CH_2Ph, benzyl; $SiMe_3$, trimethylsilyl; *tert*$BuSiMe_2$, *tert*-butyldimethylsilyl. For convenience H-7 and H-7′ refer to the protons of the terminal methyl or (trimethylsilyl)methyl group. The olefinic protons are listed under *exo*-CH_2.

TABLE II

^{13}C-N.m.r. chemical shifts for compounds (in $CDCl_3$)

Compound	*Chemical shifts* (δ)								
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	exo-CH_2	*Others*
2	98.9	79.6[a]	81.5	79.7[a]	70.3[b]	170.1	—	—	55.7 (OMe); 52.5 (CO_2*Me*); 75.9, 75.2, 73.7[b] (CH_2Ph).
3	98.9	80.4	84.1	81.5	72.1	77.3	30.1	—	56.6 (OMe); 75.3, 74.9, 74.5 (CH_2Ph); 2.0 (TMS).
4	98.3	80.4	82.1	81.8	73.5[a]	144.8	23.3	112.3	55.6 (OMe); 76.0, 75.1, 74.6[a] (CH_2Ph); −0.8 (TMS).
5	98.4	80.3	82.2	80.7	73.6	142.2	18.2	116.3	55.4 (OMe); 76.1, 74.9, 74.7 (CH_2Ph).
7	105.4		81.5, 81.0, 80.9		75.9	171.7	—	—	52.2 (CO_2*Me*); 112.4, 26.9, 26.4 (2-Pr); 72.8, 72.2 (CH_2Ph).
8	105.4		83.1, 81.6, 80.9, 80.7, 78.8[a]				29.2/ 29.1	—	112.2, 27.1, 26.7 (2-Pr); 75.0[a], 71.3 (CH_2Ph); 1.3 (TMS).
9	105.5		82.4, 82.2, 81.2, 80.6			144.6	20.8	113.6	111.7, 27.0, 26.5 (2-Pr); 70.5, 72.5 (CH_2Ph); −0.4 (TMS).
10	105.3		82.5, 82.0, 80.1, 79.9			142.2	17.0	117.0	111.9, 27.2, 26.7 (2-Pr); 72.6, 70.1 (CH_2Ph).
12	103.4		85.7, 81.6, 77.3, 76.9, 76.5, 76.4				30.2/ 29.0		111.1, 27.7, 26.7 (2-Pr), 26.0, 18.2 (*tert*Bu); 0.65 (TMS); −4.1, −5.1 (SiMe_2)
13	105.2		85.5, 78.6, 76.9, 75.9			144.3	23.3	110.3	111.5, 27.0, 26.2 (2-Pr); 25.9, 18.4 (*tert*Bu); −1.2 (TMS), −5.0 (SiMe_2).
14	104.9		85.7, 79.7, 77.0, 76.1			143.4	17.0	113.7	111.6, 27.0, 26.3 (2-Pr); 25.9, 19.2 (*tert*Bu); −4.9, −5.1 (SiMe_2).

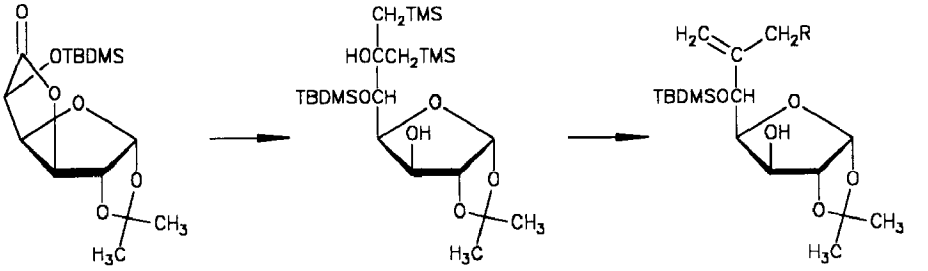
[a,b] Assignments in the same entry can be interchanged. TMS, trimethylsilyl; *tert*Bu and $SiMe_2$, *tert*-butyldimethylsilyl. For convenience C-7 in this table always refers to the terminal CH_2SiMe_3 or CH_3 carbon.

and chromatographic purification, turned out to be the desired 6-bis-*C*-[(trimethylsilyl) methyl]glucose derivative **3**. The typical yields in these experiments ranged from 55 to 65%.

The relatively large excess of the Grignard reagent proved necessary to avoid the formation of by-products, such as methyl 2,3-di-*O*-benzyl-6-bis-*C*-[(trimethylsilyl)methyl]-α-L-*threo*-hex-4-enopyranoside {$[\alpha]_D$ +103°; ^{13}C-n.m.r.: C-1, 100 p.p.m.; C-4, 93.8 p.p.m.; C-5, 158.0 p.p.m.; presumably formed by β-elimination of the 4-*O*-benzyl group prior to the attack of the Grignard reagent}, which arose upon otherwise extended reaction times.

Subtle treatment with *p*-toluenesulfonic acid monohydrate in dichloromethane converted compound **3** into two products, the main product being methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-6-*C*-methylene-7-*C*-trimethylsilyl-α-D-*gluco*-hepto-1,5-pyranoside (**4**). The minor, more polar component, was identified as the product of protodesilylation of allylsilane **4**, namely methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-6-*C*-methyl-α-D-*gluco*-hept-6-eno-1,5-pyranoside (**5**). The amount of the latter compound increased with prolonged reaction times.

In a second set of experiments we employed methyl (3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuran)uronate (**7**), obtained in two steps from 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**) (ref. 37), as the starting material. Repeating the above procedure smoothly led to the desired, less polar, 6-bis-(trimethylsilyl)methyl adduct **8** in 57% isolated yield. It seems noteworthy that in the ^{13}C-n.m.r. spectrum of this compound (Table II) the signals of the two silyl-substituted methylene carbons have different chemical shifts (29.1 and 29.2 p.p.m., respectively). Its reaction with *p*-toluenesulfonic acid in dichloromethane readily gave the corresponding allylsilane **9**. Again, as the only by-product, desilylated 3,5-di-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-6-*C*-methyl-α-D-*gluco*-hept-6-eno-1,4-furanose (**10**) was observed.



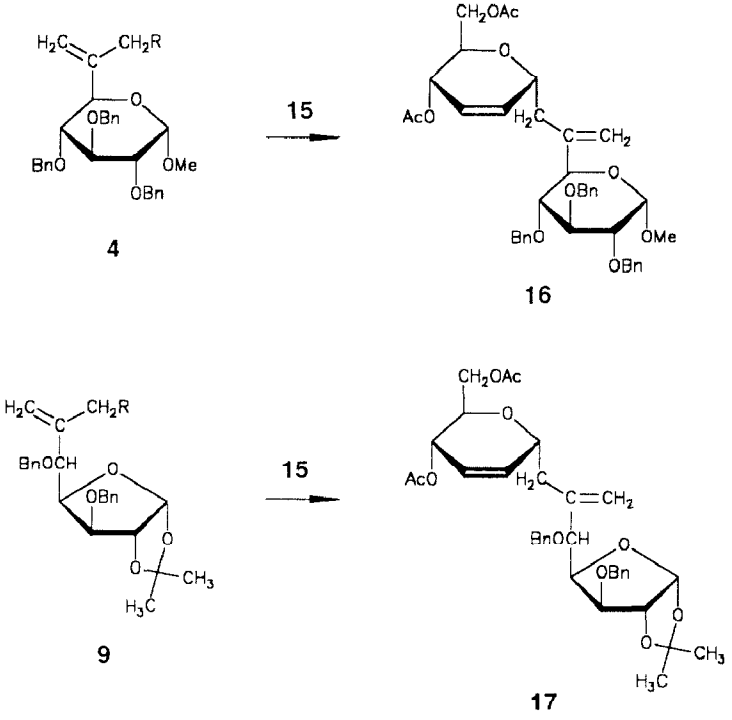
11 **12** **13**: R = TMS **14**: R = H

TBDMS, *tert*-butyldimethylsilyl; TMS, trimethylsilyl

SCHEME 2

We also chose 5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone (**11**) (ref. 38) as a precursor for this allylsilane synthesis. This compound gave the corresponding branched disilane **12** having a free hydroxy group at C-3 in 62% yield (Scheme 2). Usual treatment with small amounts of *p*-toluenesulfonic acid in dichloromethane at ambient temperature led to the corresponding allyl silane **13** together with small amounts of the desilylated compound **14**, thus demonstrating that this sequence also is compatible with silyl protecting groups. In the ^{1}H-n.m.r. spectra of compounds **13** and **14** protons H-3, H-4, and H-5 are displayed as poorly resolved narrow signals (Table I). After conventional acetylation of O-3, the expected chemical shifts and coupling patterns were found (3-*O*-acetyl-**13**: $J_{3,4}$ 2.7, $J_{4,5}$ 9.2 Hz; 3-*O*-acetyl-**14**: $J_{3,4}$ 2.7, $J_{4,5}$ 8.0 Hz).

To investigate the synthetic utility of the prepared carbohydrate allylsilanes in carbon–carbon bond formations useful for *C*-linked disaccharide syntheses, we first investigated the reaction of the pyranoid *O*-benzyl-protected allylsilane **4** with tri-*O*-acetyl-D-glucal (**15**) in the presence of Lewis acid.



4 16 9 17

Ac, acetyl; Bn, benzyl; TMS, trimethylsilyl

SCHEME 3

To a fivefold excess of glucal **15** in dichloromethane, allylsilane **4** (Scheme 3) and a catalytic amount of boron trifluoride etherate were added at 0°, and the mixture was kept at ambient temperature until allylsilane **4** had been quantitatively converted into a single u.v.-active, more polar product. This compound behaved chromatographically

TABLE III

^{1}H-N.m.r. data for *C*-linked disaccharides (in $CDCl_3$)

Compound	*Chemical shifts* (δ)[a]														
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-7*	*H-7a*	*H-1'*	*H-2'*	*H-3'*	*H-4'*	*H-5'*	*H-6'*	*H-6a'*	*Others*
16	4.61	3.53	4.00	3.40	4.13	2.45	2.30	4.45	5.91	5.77	5.13	3.93	4.25	4.13	5.35,5.26 (*exo*-methylene); 3.38 (OMe).
17	5.89	4.58	4.14	4.20	n.r.	2.62	2.37	n.r.	5.97	5.77	5.17	3.98	n.r.	n.r.	5.36,5.31 (*exo*-methylene); 1.46, 1.30 (2-Pr).

Compound	*Coupling constants (Hz)*															
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{7,7a}$	$J_{7,1'}$	$J_{7a,1'}$	$J_{1',2'}$	$J_{1',3'}$	$J_{2',3'}$	$J_{2',4'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'}$	$J_{5',6a'}$	$J_{6',6a'}$
16	3.6	9.7	n.r.	10	15.2	8.4	3.9	1.8	2.3	10.4	1.8	2.3	6.4	6.4	3.4	12
17	3.6	—	2.7	n.r.	15.2	8.3	5.5	1.8	2.3	10.5	1.9	2.0	6.4	6.4	3.7	n.r.

[a] n.r., not sufficiently resolved. The protons of the protecting groups are displayed in the expected regions.

TABLE IV

^{13}C-N.m.r. chemical shifts for *C*-linked disaccharides (in $CDCl_3$)

Compound	*Chemical shifts* (δ)														
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	*C-1'*	*C-2'*	*C-3'*	*C-4'*	*C-5'*	*C-6'*	exo-CH_2	*Others*
16	98.4	80.3	82.2	81.4	73.6	142.6	36.0	71.1	133.5[a]	123.9[a]	65.4	69.9	63.2	117.3	55.6 (OMe)
17	105.4	82.3	82.1	81.0	80.4	142.7	35.1	71.3	133.7[a]	123.9[a]	65.6	69.6	63.4	118.3	111.9, 27.1, 26.5 (2-Pr).

[a] Assignments in the same line can be interchanged. Appropriate resonances were observed for the protecting groups.

very similarly to artifacts arising from the reaction of excess glycal with the catalyst. Therefore, careful chromatographic separation was required which, in small-scale experiments, could be conveniently achieved by preparative thin-layer chromatography (see Experimental). The pure syrupy material was thus obtained in 35–45% isolated yield and exhibited an optical rotation of $+50°$. The n.m.r. spectra exhibited all the structural features expected for the desired coupling product **16**. In the ^{13}C-n.m.r. spectrum of *C*-linked disaccharide **16** (Table IV) the C-2′ and C-3′-signals of the 2,3-unsaturated *C*-glycosyl compound appear at 133.5 and 123.9 p.p.m., respectively ($CDCl_3$ as solvent), and the carbons involved in the *exo*-double bond exhibit resonances at 142.6 (C-6) and 117.3 p.p.m. The signal of the carbon of the methylene bridge between the two units appears at 36.0 p.p.m.

The anomeric configuration of *C*-linked disaccharide **16** was tentatively assigned according to the positions of the *C*-glycosylic carbon C-1′ (71.1 p.p.m.) and C-5′ (69.9 p.p.m.). For similar 2,3-unsaturated *C*-glycopyranosyl compounds, it has been shown[18,39] that the *C*-glycosylic carbon signals for α-anomers (70–72 p.p.m.) are exhibited about 2 p.p.m. upfield to those of the corresponding β-anomers. More distinctly, the C-5′ signals of the α-anomers were observed around 72 p.p.m., while those of the β-anomers were displayed 5 p.p.m. more downfield. Based on these guidelines the α-configuration was assigned to the unsaturated ring of *C*-linked disaccharide **16**. In the ^{1}H-n.m.r. spectrum the protons of the bridging methylene unit are displayed at 2.30 and 2.45 p.p.m. as two doublets of doublets with a *gem* coupling of 15.2 Hz and coupling constants of 3.9 and 8.4 Hz, respectively, arising from their interaction with H-1′, the proton attached to the *C*-glycosylic centre C-1′ (Table III). The signal of the latter appears as a multiplet centred at 4.45 p.p.m. H-4′ is displayed as a narrow multiplet at 5.13 p.p.m., while the H-5′-signal is located at 3.93 p.p.m. The protons of the *exo*-double bond are displayed as two singlets at 5.26 and 5.35 p.p.m., respectively. The coupling constant $J_{4,5}$ 6.4 Hz clearly indicates the conformational mobility of the unsaturated ring, again pointing to the fact that the *C*-glycosylic centre is α-configured. In general, β-anomers have been found to be conformationally more rigid displaying coupling constants $J_{4,5}$ of approximately 9 Hz[18,39]. N.O.e.-experiments supported the assignment of the configuration of the unsaturated ring in compound **16** to the α-series as no enhancement of the signal of H-1′ was observed upon irradiation of H-5′ and *vice versa*. No evidence was found for the formation of the respective β-anomer.

Extending this methodology to furanoid allylsilane **9**, employing essentially the same simple procedure as for the synthesis of compound **16**, gave *C*-linked disaccharide **17** as the only u.v.-active product in 30–40% isolated yield, albeit after relatively tedious chromatographic separation from D-glucal artifacts. (It seems noteworthy that the precursor to allylsilane **9**, bis-silyl alcohol **8**, can be used directly for this coupling reaction.)

Compound **17** had an optical rotation of $+16°$ and could be easily identified from its n.m.r. spectrum. The relevant structural features exhibited in pyranoid *C*-linked disaccharide **16** were also observed in coupling product **17**. The signals of the carbons involved in the endocyclic double bond, C-2′ and C-3′, appear at 133.7 and 123.9 p.p.m.,

respectively, while the carbon atoms of the exocyclic double bond display resonances at 142.7 and 118.3 p.p.m. The resonance of the bridging methylene moiety is found at 35.1 p.p.m. The resonances of C-1′ and C-5′ are located at 71.3 and 69.6 p.p.m., respectively. Accordingly the anomeric configuration of the unsaturated ring in compound **17** was assigned to be α. The ^{1}H-n.m.r. spectrum of *C*-linked disaccharide **17** also clearly displayed the expected features, H-4′ and H-5′ being displayed as narrow multiplets at 5.18 and 3.98 p.p.m., respectively, the shape and coupling pattern of which demonstrating that again the α-*C*-glycosyl derivative had been formed. It should be mentioned that, as with the di-*O*-benzyl precursors in the furanose series, the ^{1}H-n.m.r. spectrum of compound **17** is poorly resolved due to superposition of the methylene protons of the protecting groups with those of the ring protons.

In an analogous manner we also attempted to couple *O*-silyl protected furanoid allylsilane **13** with glycal **15**. In this case, however, the isolation of the presumably formed coupling product was not only made more difficult by the lack of u.v. activity but also by the partial removal of the silyl protecting group under the acidic reaction conditions. Optimised reaction conditions, as well as a better means of product detection and isolation, are currently under investigation.

These results clearly establish the practical use of carbohydrate-derived allylsilanes for the synthesis of *C*-linked disaccharides. Altering the structural features of the glucal moiety and/or the allylsilane employed should give easy access to a variety of interesting structures. The *exo*-double bond is a very useful structural feature, as has been recently demonstrated in a synthesis of "*C*-sucrose"[8]. Preliminary results suggest that the reported allylsilanes can also be coupled to saturated glycosyl donors. Details in this respect will be presented in due course.

EXPERIMENTAL

General methods. — Melting points were recorded on a Tottoli apparatus and are uncorrected. Optical rotations were measured at 20° from 0.5–5% solutions on a JASCO Digital Polarimeter with a path length of 10 cm. ^{1}H-N.m.r. spectra (at 300 MHz) and ^{13}C-n.m.r. spectra (at 75.47 MHz) were recorded on a BRUKER MSL 300 spectrometer. Signals in the ^{13}C-n.m.r. spectra, when necessary, were assigned by ^{1}H–^{13}C heteronuclear shift-correlation experiments. In the cases indicated, the assignments of proton signals were confirmed by spin-decoupling experiments. T.l.c. was performed on precoated aluminium sheets (E. Merck 5554) using 1:1, 3:2, and 3:1 (v/v) petroleum ether–ethyl acetate mixtures as eluents. T.l.c. plates were developed by spraying with a solution of vanillin (5% w/v) in conc. sulfuric acid and warming. For column chromatography Silica Gel 60 (E. Merck) was used. Preparative t.l.c. was performed on precoated glass plates (E. Merck 5715, 5744 and, when necessary, 5642). Dry solvents were used for all reactions.

General procedure for the preparation of methyl uronates. — To a solution of the respective primary alcohol (5 mmol) in *N,N*-dimethylformamide (40 mL) pyridinium dichromate (7.5 g, 20 mmol) was added, and the mixture was stirred at ambient

temperature for 16 h. The resulting dark slurry was partitioned between ether and 5% aq. HCl and the aq. phase was washed twice with ether. The combined organic layers were dried over sodium sulfate. After the removal of the drying agent by filtration, freshly prepared etheral diazomethane solution was added to the filtrate until t.l.c. indicated the quantitative conversion of the uronic acid to a less polar product. A few drops of glacial acetic acid were added to destroy excess diazomethane, the solution was concentrated under reduced pressure, and the resulting material was chromatographed [3:1 (v/v) petroleum ether–ethyl acetate] to obtain the respective pure methyl uronate.

General procedure for Grignard reactions. — To magnesium turnings (0.5 g, 20 mmol) in dry ether (15 mL) a crystal of iodine and (chloromethyl)trimethylsilane (1.5 mL, 10.8 mmol) were added, and the vigorously stirred mixture was warmed with a blow-dryer until the characteristic brown iodine colour disappeared. After the strongly exothermic reaction had ceased, the dark mixture was cooled in an ice-bath, and an etheral solution of the respective uronic ester or lactone (1 mmol in 5 mL) was added dropwise by syringe. After 1 h at 0° the mixture was allowed to reach ambient temperature, and stirring was continued until the starting material could not be detected by t.l.c. [3:2 (v/v) petroleum ether–ethyl acetate]. Dichloromethane (50 mL) was added, and the solution was consecutively washed with 5% aq. HCl and 5% aq. sodium hydrogencarbonate, dried (sodium sulfate), and concentrated under reduced pressure. Chromatography [5:1 (v/v) petroleum ether–ethyl acetate] gave the respective pure bis-silyl adduct as a colourless syrup.

General procedure for the allylsilane preparation. — To a 5% solution of the respective bis-silyl sugar (0.5 mmol) in dichloromethane, *p*-toluenesulfonic acid monohydrate (5–10mol%) was added, and the clear solution was stirred until t.l.c. indicated that all starting material had reacted to give two slightly more polar products. (In case of the conversion of compound **8** into allylsilane **9** h.p.t.l.c. plates (E. Merck 5642) had to be used.) The solution was washed with 5% aq. sodium hydrogencarbonate, dried (sodium sulfate), and concentrated under reduced pressure. The resulting oily residue was chromatographically separated [6:1 (v/v) petroleum ether–ethyl acetate] to give the respective allylsilane as the main product and small amounts of the respective more polar product of proto-desilylation.

General procedure for the coupling reactions. — To a solution of tri-*O*-acetyl-D-glucal (**15**, 160 mg, 0.6 mmol) and the respective allylsilane (0.1 to 0.15 mmol) in dry dichloromethane (3 mL), a catalytic amount of boron trifluoride etherate was added. The mixture was stirred at ambient temperature under an atmosphere of dry nitrogen until no remaining allylsilane could be detected by t.l.c. [3:2 (v/v) petroleum ether–ethyl acetate] and a single, more polar, u.v.-active product had been formed. The reaction mixture was diluted with dichloromethane (50 mL), washed with 5% aq. sodium hydrogencarbonate solution, dried (sodium sulfate), and concentrated under reduced pressure. The remaining syrupy residue was repeatedly chromatographed [3:1 (v/v) petroleum ether–ethyl acetate] to isolate the respective pure *C*-linked disaccharide.

Methyl (methyl 2,3,4-tri-O-*benzyl*-α-D-*glucopyranosid)uronate* (**2**). — Uronic ester **2** was prepared from primary alcohol **1** (ref. 36) (2.3 g, 5 mmol) following the

respective general procedure and was isolated in 78% yield (1.9 g) as a colourless syrup: $[\alpha]_D$ +48.0° (dichloromethane). For ^{1}H-n.m.r. data, see Table I; for ^{13}C-n.m.r. data, see Table II.

Anal. Calc. for $C_{29}H_{32}O_7$: C, 70.71; H, 6.55. Found: C, 70.58; H, 6.70.

*Methyl 2,3,4-tri-*O*-benzyl-6-bis-*C*-[(trimethylsilyl)methyl]-α-*D*-glucopyranoside* (**3**). — Reaction of methyluronate **2** with (trimethylsilyl)methylmagnesium chloride according to the general procedure for Grignard reactions led to the syrupy bis-silyl adduct **3** (380 mg, 60%): $[\alpha]_D$ +31.4° (chloroform). For ^{1}H-n.m.r. data, see Table I, for ^{13}C-n.m.r. data, see Table II.

Anal. Calc. for $C_{36}H_{52}O_6Si_2$: C, 67.88; H, 8.23. Found: C, 67.25; H, 8.35.

*Methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-6-*C*-methylene-7-*C*-trimethylsilyl-α-*D*-gluco-hepto-1,5-pyranoside* (**4**) and *2,3,4-tri-*O*-benzyl-6,7-dideoxy-6-*C*-methyl-α-*D*-gluco-hept-6-eno-1,5-pyranoside* (**5**). — Applying the general procedure for the allylsilane preparation to compound **3** (640 mg, 1.0 mmol) gave allylsilane **4** (450 mg, 82%) as a colourless syrup: $[\alpha]_D$ −18.5° (chloroform). For ^{1}H-n.m.r. data, see Table I; for ^{13}C-n.m.r. data, see Table II.

Anal. Calc. for $C_{33}H_{42}O_5Si$: C, 72.49; H, 7.74. Found: C, 72.88; H, 7.85.

As the only side-product, syrupy methyl 2,3,4-tri-*O*-benzyl-6,7-dideoxy-6-*C*-methyl-α-*D*-*gluco*-hept-6-eno-1,5-pyranoside (**5**) was isolated (62 mg, 13%): $[\alpha]_D$ +13.1° (dichloromethane). For ^{1}H-n.m.r. data, see Table I; for ^{13}C-n.m.r. data, see Table II.

Anal. Calc. for $C_{30}H_{34}O_5$: C, 75.92; H, 7.22. Found: C, 75.71; H, 7.28.

*Methyl (3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-*D*-glucofuran)uronate* (**7**). — Application of the general procedure for the preparation of methyl uronates to primary alcohol **6** (ref. 37) (2.0 g, 5 mmol) gave crystalline methyl ester **7** (1.78 g, 83%): m.p. 69–70.5°, $[\alpha]_D$ −41.8° (dichloromethane). For ^{1}H-n.m.r. data, see Table I; for ^{13}C-n.m.r. data, see Table II.

Anal. Calc. for $C_{24}H_{28}O_7$: C, 67.28; H, 6.59. Found: C, 67.15; H, 6.51.

*3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-6-bis-*C*-[(trimethylsilyl)methyl]-α-*D*-glucofuranose* (**8**). — Following the general procedure for the Grignard reactions, methyl ester **7** (430 mg, 1.0 mmol) gave bis-silyl adduct **8** (330 mg, 57%) as a colourless syrup: $[\alpha]_D$ −48.4° (dichloromethane). For ^{1}H-n.m.r. data, see Table I; for ^{13}C-n.m.r. data, see Table II.

Anal. Calc. for $C_{31}H_{48}O_6Si_2$: C, 64.99; H, 8.45. Found: C, 65.06; H, 8.53.

*3,5-Di-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-6-*C*-methylene-7-*C*-trimethylsilyl-α-*D*-*gluco*-hepto-1,4-furanose* (**9**) *and 3,5-di-*O*-benzyl-6,7-dideoxy-1,2-*O*-isopropylidene-6-*C*-methyl-α-*D*-*gluco*-hept-6-eno-1,4-furanose* (**10**). — Compound **8** (290 mg, 0.51 mmol) was subjected to the general procedure for the allylsilane preparation to give allylsilane **9** (208 mg, 85%) as a colourless oil: $[\alpha]_D$ −32.7° (dichloromethane). For ^{1}H-n.m.r. data, see Table I; for ^{13}C-n.m.r. data, see Table II.

Anal. Calc. for $C_{28}H_{38}O_5Si$: C, 69.67; H, 7.94. Found: C, 69.75; H, 8.04.

The more polar side-product **10** (23 mg, 11%) was also a syrup: $[\alpha]_D$ −42.2° (dichloromethane). For ^{1}H-n.m.r. data, see Table I; for ^{13}C-n.m.r. data, see Table II.

Anal. Calc. for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37. Found: C, 73.22; H, 7.37.

5-O-tert-Butyldimethylsilyl-1,2-O-isopropylidene-6-bis-C-[(trimethylsilyl)methyl]-α-D-gluco-1,4-furanose (**12**). — 5-*O*-*tert*-Butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone[38] (**11**, 330 mg, 1.0 mmol) was reacted following the general procedure for the Grignard reaction and gave bis-silyl adduct **12** (300 mg, 62%) as a colourless syrup: $[\alpha]_D$ −13.5° (dichloromethane). For ^{1}H-n.m.r. data, see Table I; for ^{13}C-n.m.r. data, see Table II.

Anal. Calc. for $C_{23}H_{50}O_6Si_2$: C, 57.69; H, 10.53. Found: C, 57.53; H, 10.88.

5-O-tert-Butyldimethylsilyl-6,7-dideoxy-1,2-O-isopropylidene-6-C-methylene-7-C-trimethylsilyl-α-D-gluco-hepto-1,4-furanose (**13**) and *5-O-tert-butyldimethylsilyl-6,7-dideoxy-1,2-O-isopropylidene-6-C-methyl-α-D-gluco-hept-6-eno-1,4-furanose* (**14**). — According to the general procedure for the allylsilane preparation, bis-silyl compound **12** (250 mg, 0.52 mmol) was converted into syrupy allylsilane **13** (162 mg, 80%): $[\alpha]_D$ +8.9° (dichloromethane). For ^{1}H-n.m.r. data, see Table I; for ^{13}C-n.m.r. data, see Table II.

Anal. Calc. for $C_{20}H_{40}O_5Si$: C, 61.81; H, 10.37. Found: C, 61.59; H, 10.40.

The more polar by-product **14** (18 mg, 11%) was also a syrup: $[\alpha]_D$ −22.0° (dichloromethane). For ^{1}H-n.m.r. data, see Table I; for ^{13}C-n.m.r. data, see Table II.

Anal. Calc. for $C_{17}H_{32}O_5$: C, 64.53; H, 10.19. Found: C, 64.50; H, 10.29.

Methyl 11,13-di-O-acetyl-8,12-anhydro-2,3,4-tri-O-benzyl-6,7-dideoxy-6-C-methylene-D-ribo-α-D-gluco-trideca-9-eno-1,5-pyranoside (**16**). — Allylsilane **4** (82 mg, 0.15 mmol) was reacted with tri-*O*-acetyl-D-glucal (**15**) according to the general coupling procedure to give the *C*-linked disaccharide **16** (46 mg, 45%) as a colourless syrup: $[\alpha]_D$ +50.0° (dichloromethane). For ^{1}H-n.m.r. data, see Table III; for ^{13}C-n.m.r. data, see Table IV.

Anal. Calc. for $C_{40}H_{46}O_{10}$: C, 69.95; H, 6.75. Found: C, 70.01; H, 6.88.

11,13-Di-O-acetyl-8,12-anhydro-3,5-di-O-benzyl-6,7-dideoxy-1,2-O-isopropylidene-6-C-methylene-D-ribo-α-D-gluco-trideca-9-eno-1,4-furanose (**17**). — Following the respective general procedure, tri-*O*-acetyl-D-glucal (**15**) and allylsilane **9** (60 mg, 0.124 mmol) were coupled to give the *C*-linked disaccharide **17** (29 mg, 37%), which was isolated as a clear oil: $[\alpha]_D$ +16.0° (dichloromethane). For ^{1}H-n.m.r. data, see Table III; for ^{13}C-n.m.r. data, see Table IV.

Anal. Calc. for $C_{35}H_{42}O_{10}$: C, 67.51; H, 6.80. Found: C, 67.39; H, 6.81.

ACKNOWLEDGMENTS

We thank Dr. A. Fürstner for helpful discussions, Ing. C. Illaszewicz for the n.O.e. experiments and recording some of the n.m.r. spectra, as well as Dipl.-Ing. H. Baumgartner for performing the 2D-n.m.r. experiments.

REFERENCES

1 D. Rouzaud and P. Sinaÿ, *J. Chem. Soc., Chem. Commun.*, (1983) 1353–1354.
2 B. Giese and T. Witzel, *Angew. Chem. Int. Ed. Engl.*, 25 (1986) 450–451; B. Giese, M. Hoch, C. Lamberth and R. R. Schmidt, *Tetrahedron Lett.*, 29 (1988) 1375–1378.

3 S. A. Babirad, Y. Wang, and Y. Kishi, *J. Org. Chem.*, 52 (1987) 1370–1372.
4 P. G. Goekjian, T.-C. Wu, H.-Y. Kang, and Y. Kishi, *J. Org. Chem.*, 52 (1987) 4823–4825.
5 S. A. Babirad, Y. Wang, P. G. Goekjian, and Y. Kishi, *J. Org. Chem.*, 52 (1987) 4825–4827.
6 Y. Wang, P. G. Goekjian, D. M. Ryckman, and Y. Kishi, *J. Org. Chem.*, 53 (1988) 4151–4153.
7 W. H. Miller, D. M. Ryckman, P. G. Goekjian, Y. Wang, and Y. Kishi, *J. Org. Chem.*, 53 (1988) 5582–5584.
8 U. C. Dyer and Y. Kishi, *J. Org. Chem.*, 53 (1988) 3384–3386.
9 M. Carcano, F. Nicotra, L. Panza, and G. Russo, *J. Chem. Soc., Chem. Commun.*, (1989) 642–643.
10 I. M. Dawson, T. Johnson, R. M. Paton, and R. A. C. Rennie, *J. Chem. Soc., Chem. Commun.*, (1988) 1339–1340.
11 A. Boschetti, F. Nicotra, L. Panza, G. Russo, and L. Zucchelli, *J. Chem. Soc., Chem. Commun.*, (1989) 1085–1086.
12 R. R. Schmidt and R. Preuss, *Tetrahedron Lett.*, 30 (1989) 3409–3412.
13 J.-M. Beau and P. Sinaÿ, *Tetrahedron Lett.*, 26 (1985) 6189–6192 and 6193–6196.
14 S. M. Daly and R. W. Armstrong, *Tetrahedron Lett.*, 30 (1989) 5713–5716.
15 R. J. Ferrier and N. Prasad, *J. Chem. Soc., C*, (1969) 581–586.
16 S. J. Danishefsky, C. J. Maring, M. R. Barbachyn, and B. E. Segmuller, *J. Org. Chem.*, 49 (1984) 4564–4565; J. Jurczak, T. Bauer, and S. Jarosz, *Tetrahedron Lett.*, 25 (1984) 4809–4812; S. Danishefsky, W. H. Pearson, D. F. Harvey, C. J. Maring, and J. P. Springer, *J. Am. Chem. Soc.*, 107 (1985) 1256–1268.
17 B. Aebischer, R. Meuwly, and A. Vasella, *Helv. Chim. Acta*, 65 (1984) 2236–2241.
18 R. D. Dawe and B. Fraser-Reid, *J. Org. Chem.*, 49 (1984) 522–528.
19 T. H. Chan and I. Fleming, *Synthesis*, (1979) 761–786; Z. N. Parnes, and G. I. Bolestova, *Synthesis*, (1984) 991–1008.
20 K. C. Nicolaou, R. E. Dolle, A. Chucholowski, and J. L. Randall, *J. Chem. Soc., Chem. Commun.*, (1984) 1153–1154; Y. Araki, N. Kobayashi, K. Watanabe, and Y. Ishido, *J. Carbohydr. Chem.*, 4 (1985) 565–585.
21 A. Hosomi, Y. Sakata, and H. Sakurai, *Carbohydr. Res.*, 171 (1987) 223–232.
22 M. D. Lewis, J. K. Cha, and Y. Kishi, *J. Am. Chem. Soc.*, 104 (1982) 4976–4978; A. Giannis and K. Sandhoff, *Tetrahedron Lett.*, 26 (1985) 1479–1482; P. Allevi, M. Anastasia, P. Ciuffreda, A. Fiecchi, and A. Scala, *J. Chem. Soc., Chem. Commun.*, (1987) 1245–1246.
23 D. Horton and T. Miyake, *Carbohydr. Res.*, 184 (1988) 221–229.
24 J. S. Panek and M. A. Sparks, *J. Org. Chem.*, 54 (1989) 2034–2038.
25 S. J. Danishefsky, S. DeNinno, and P. Lartey, *J. Am. Chem. Soc.*, 109 (1987) 2082–2089.
26 S. J. Danishefsky and J. F. Kerwin, Jr., *J. Org. Chem.*, 47 (1982) 3803–3805.
27 T. K. Sakar, *Synthesis*, (1990) 969–983 and 1101–1111.
28 N. B. Perry, J. W. Blunt, and M. H. G. Munro, *J. Am. Chem. Soc.*, 110 (1988) 4850–4851.
29 A. J. Cooper and R. G. Salomon, *Tetrahedron Lett.*, 31 (1990) 3813–3816.
30 J. K. Cha, W. J. Christ, J. M. Finan, H. Fujioka, Y. Kishi, L. L. Klein, S. S. Ko, J. Leder, W. W. McWorther, K.-P. Pfaff, M. Yonaga, D. Uemura, and Y. Hirata, *J. Am. Chem. Soc.*, 104 (1982), 7369–7371.
31 K. Tatsuta, H. Gunji, S. Tajima, T. Ishiyama, S. Imai, S. Okuyama, and S. Fukatsu, *J. Antibiot.*, 43 (1990) 909–911.
32 S. Jeganathan and P. Vogel, *Tetrahedron Lett.*, 31 (1990) 1717–1720.
33 A. D. Petrov, V. A. Ponomarenko, and A. D. Snegova, *Doklady Akad. Nauk S.S.S.R.*, 112 (1957) 79; I. Fleming and A. Pearce, *J. Chem. Soc., Perkin Trans. 1*, (1981) 251–255.
34 M. B. Anderson and P. L. Fuchs, *Synth. Commun.*, 17 (1987) 621–635; B. A. Narayanan and W. H. Bunnelle, *Tetrahedron Lett.*, 28 (1987) 6261–6264; T. V. Lee, J. R. Porter, and F. S. Roden, *Tetrahedron Lett.*, 29 (1988) 5009–5012; T. V. Lee, J. A. Channon, C. Cregg, J. R. Porter, F. S. Roden, and H. Yeoh, *Tetrahedron*, 45 (1989) 5877–5886.
35 A. Fürstner, G. Kollegger, and H. Weidmann, unpublished results.
36 A. Liptak, I. Jodal, and P. Nanasi, *Carbohydr. Res.*, 44 (1975) 1–11.
37 K. Dax, W. Wolflehner, and H. Weidmann, *Carbohydr. Res.*, 65 (1978) 132–138.
38 H. P. Wessel, *J. Carbohydr. Chem.*, 8 (1989) 443–455.
39 M. Brakta, P. Lhoste, and D. Sinou, *J. Org. Chem.*, 54 (1989) 1890–1896, and references therein.