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A Stereocontrolled Radical Access to *C*-Allyl β-D-Glycopyranosides from Glycopyranosylidene Dihalides found *En Route* to *C*-Glycodienes

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Abstract: Application of the Keck reaction to peracetylated glycopyranosylidene dihalides under mild conditions led efficiently to chloro *C*-allyl glycosides which were converted to either the corresponding *C*-allyl β-D-glycosides or *C*-D-glycodienes on treatment with, respectively, tri-*n*-butyltin hydride and DBU.

C-Glycosides constitute a wide class of well-studied glycomimetics.[1,2] The biological properties of naturally-occurring *C*-glycosides and the hope that synthetic ones could find applications in various fields due to the stability of the *C*-glycosidic bond towards hydrolysis, stimulate this interest.[1,2] Among this class, *C*-allyl glycosides constitute a group of synthetically useful compounds. In particular, they lead to *C*-epoxypropyl glycosides recognized as active site-directed irreversible inhibitors of sugar processing enzymes.[3] They also allow a wide range of synthetic transformations based on the smooth cleavage of the C=C unsaturated bond to produce reactive aldehyde groups suitable for further modifications.[4] In addition, the access and synthetic potential of *C*-vinyl[5] and *C*-alkynyl[6,7] glycosides has been developed recently. Access to *C*-allyl glycosides rests on three main routes: *i*) treatment of benzylated glycono-δ-lactones with allylmagnesium bromide followed by stereoselective reduction of the hemiketal produced with triethylsilane and boron trifluoride etherate as the catalyst,[8] *ii*) treatment of protected glycosyl fluorides, 1-*O*-acetyl glycopyranoses and other sugar derivatives with allyltrimethylsilane in the presence of a Lewis acid,[1,2,8,9] *iii*) the Keck reaction[10,11] based on either tri-*n*-butylallyltin[1,2] or allylic sulfides and sulfones.[12] Variable yields and moderate stereoselectivities, usually in favour of α-anomers except for the Kishi method[8] are the main limitations of these routes. The nucleophilic displacement of sugar halides by allylmagnesium bromide which has been reported[5] is not a widely used method, probably due to its low selectivity.[13] We disclose in this note a ready access to new *C*-glycopyranosylidene dienes and a stereocontrolled route to *C*-allyl β-D-glycopyranosides from accessible peracetylated glycopyranosylidene dihalides.[14]

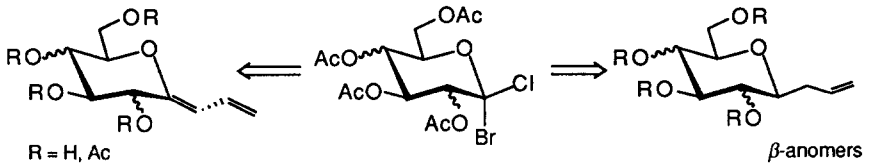
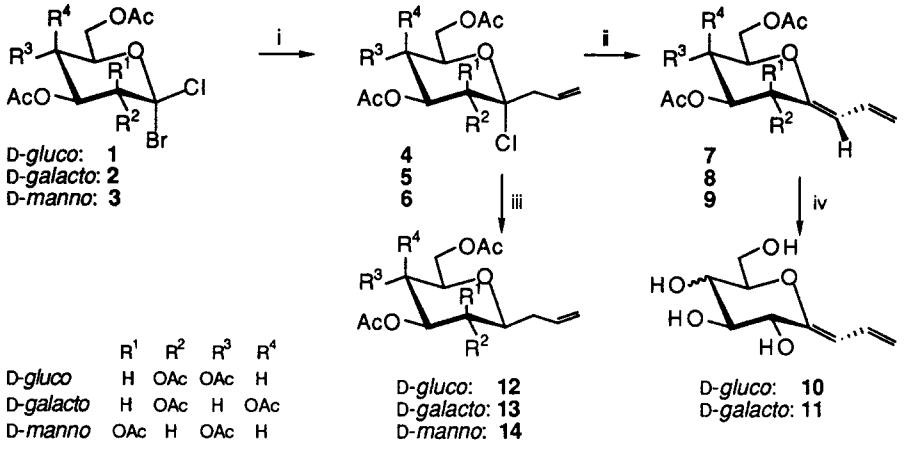


Figure 1

We applied the Keck reaction to the 2,3,4,6-tetra-*O*-acetyl-1-bromo-β-D-glycopyranosyl chlorides **1**, **2**, and **3**.[14] Although the Keck radical allylation of protected sugar halides is generally carried out in refluxing aromatic solvents[10] (tri-*n*-butylallyltin, AIBN), we found advantageous to resort to photolytic conditions (UV light irradiation) compatible with lower temperatures (~30°C). Under our conditions (see typical procedure), complete transformation of the starting sugar halides was more selective and occurred faster (~30 min) with unfiltered light rather than with pyrex-filtered light (~24 h). After purification by column chromatography, the reaction products **4**, **5** and **6** could be obtained in 86, 51 and 34 % yield respectively. Compounds **4**, **5** and **6** were pure diastereoisomers with a (*R*) configuration at the anomeric centre (chlorine atom on the α-face) as deduced from ^{1}H NMR data.[15] This structural feature was interpreted, as in a related case,[16] on the basis of the anomeric effect. The α-orientation of the chlorine atom in **4**, **5** and **6** was deduced on the basis of the chemical shifts measured for the H-3 and H-5 protons which are close to values reported for acetylated glycopyranosylidene dichlorides.[14,15] On treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile, hydrogen chloride elimination occurred in **4**, **5** and **6** to afford **7**, **8** and **9** in good yield (50 - 63 % isolated). The (*Z*) configuration of the exocyclic double bond was deduced from the chemical shift of the vinylic proton next to the ring (see scheme 1) in **7** (5.55 ppm), **8** (5.51 ppm) and **9** (5.73 ppm). On comparison with data reported earlier by us[16] and others[17] for analogous structures, this proton should appear downfield (~6.2 ppm) for the (*E*) isomers. This feature was also convincingly supported by the n.O.e. effect observed on selective irradiation of the vinylic proton in **9**. This resulted in a 10 % enhancement of the H-2 proton signal (**9**: R^2 = H) in difference spectra (and *vice versa*). *C*-Glycodienes **7** and **8** could be deacetylated quantitatively (MeOH/MeONa or MeOH/H_2O/Et_3N) to produce the corresponding free *C*-glycodienes either amorphous (**10**) or as colourless crystals (**11**). Deacetylation of the less stable and light-sensitive diene **9** was not attempted.

Chlorides **4**, **5** and **6** lend themselves to further transformations and in particular to free radical reduction with tri-*n*-butyltin hydride. Glycopyranos-1-yl radicals have been shown to react stereoselectively generally from the α-face,[18,19] except for species with bulky substituents at the C-2 position which direct the attack to the β-face.[20] 1-Substituted glycopyranos-1-yl radicals were found to behave similarly as demonstrated by stereocontrolled reductions of either 1-cyano glycosyl bromides[21] or 1-alkoxy glycopyranos-1-yl radicals[22] with tri-*n*-butyltin hydride. As anticipated, allylation of **1**, **2** and **3** and subsequent reduction of crude **4**, **5** and **6** by adding tri-*n*-butyltin hydride and AIBN to the reaction mixture led to the *C*-allyl β-D-glycopyranosides **12**, **13**, and **14** in 25 (unoptimized), 51 and 57 % isolated overall yields, respectively. The only observed byproduct corresponded to *bis*-*C*-allyl glycopyranosides (5-7 %).[23] Therefore, this approach constitutes a new diastereoselective access to *C*-allyl β-D-glycopyranosides. Its major advantages in comparison with other methods and in particular a related one based on the reductive radical-chain decarboxylation by the Barton *O*-acyl thiohydroxamate methodology,[24] lie in the accessibility of sugar *gem* dihalides and in the mildness of the reaction conditions applicable to acetylated sugar derivatives.

In summary, these preliminary results further illustrate the synthetic potential of glycopyranosylidene dihalides[25] which reacted chemoselectively under very mild conditions to afford acetylated *C*-allyl 1-chloro-β-D-glycopyranosides in good yield. Their reduction with tri-*n*-butyltin hydride opened a new stereocontrolled access to acetylated *C*-allyl β-D-glycopyranosides. Moreover, DBU-catalyzed dehydro-



i: C_6H_6, hv, *n*-$Bu_3SnCH_2CH{=}CH_2$; ii: DBU, CH_3CN; iii: C_6H_6, hv, *n*-Bu_3SnH; iv: MeONa, MeOH or NEt_3/MeOH/H_2O.

Scheme 1

chlorination of *C*-allyl 2,3,4,6-tetra-*O*-acetyl-1-chloro-β-D-glycopyranosides led to new unsaturated sugars. Hence, our approach opens a facile access to unknown *C*-glycodienes which will be further investigated in connection with the use of *O*-alkadienyl sugars[26] for performing cycloaddition reactions under variable conditions.

Typical procedure:
Allylation procedure: A mixture of the chlorobromosugar (0.4 g, 0.9 mmol), allyltributyltin (0.6 g, 1.8 mmol) and a catalytic amount of AIBN in dry, deoxygenated benzene (9 mL) was poured in a quartz tube. Argon was flushed into the tube which was mounted besides (~1 cm distance) a medium pressure mercury lamp (450 W). Brief exposure (30-50 min) to unfiltered light resulted in complete transformation of the substrate (TLC). Removal of the organotin derivatives was achieved by stirring the mixture in the presence of aq KF, overnight (**4**) or less (**5**), while hexane/acetonitrile extraction was found more appropriate for **6**. Silica gel chromatography led to pure **4**, **5** and **6** in 86, 51 and 34 % yield, respectively.
Elimination reaction: Treatment of the chloroallyl sugar **4** (0.13 g, 0.3 mmol) for 1.5 h at room temperature in acetonitrile (12 mL) in the presence of DBU (91 mg, 0.6 mmol) led to the corresponding *C*-glucodiene **7** in a 42 % isolated yield. In one-pot type experiments, after the chloroallyl intermediate was formed, benzene was removed under diminished pressure and the residue was taken up in acetonitrile prior treatment with DBU (2 eq). After sonication for ~3 h at ~35 °C, the solid organotin derivatives produced on treatment with aq KF were separated by filtration. Pure glycodienes were obtained by chromatography (yield: 50 % (**7**, **9**), 63 % (**8**)).
One-pot preparation of acetylated C-*allyl* β-D-*glycopyranosides*: After the crude chloroallyl sugar **4**, **5** or **6** was prepared as above, tri-*n*-butyltin hydride (2 eq) was added to the reaction mixture maintained under argon. Irradiation was applied for ~45 min whereupon TLC showed the formation of a major new compound, visible as a less mobile spot on the plates. Removal of organotin derivatives (aq KF), workup and purification by chromatography afforded **12**, **13** or **14** in 25 (unoptimized), 51 and 57 % yield, respectively.

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15 Selected ^{1}H NMR data (δ, $CDCl_3$) for compounds **4**, **5**, and **6** (The chemical shifts of the corresponding protons in related peracetylated glycopyranosylidene dichlorides[14] are italicized): **4**: 5.14, *5.44* (H-2); 5.50, *5.38* (H-3); ~4.3, *4.35* (H-5). **5**: 5.34 (H-2); 5.34 (H-3); 4.47 (H-5). **6**: 5.44, *5.68* (H-2); 5.68, *5.66* (H-3); ~4.2, *4.18* (H-5). Selected ^{1}H NMR data (δ, $CDCl_3$) for compounds **12**, **13**, and **14**: H-1 δ 3.51 (ddd, $J_{1,2}$ 9.5 Hz), lit.[27] 3.50 (ddd, $J_{1,2}$ 9.5 Hz); 3.47 (dt, $J_{1,2}$ 9.5 Hz); 3.64[28] (dt, $J_{1,2}$ 0.85 Hz), respectively. Selected ^{13}C NMR data ($CDCl_3$) for compounds **7**, **8**, and **9**: C-1 δ 145.85, 146.64, 145.27 ppm, respectively.

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