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Synthesis of carbohydrate-derived (*Z*)-vinyl halides and silanes: samarium-promoted stereoselective 1,2-elimination on sugar-derived α-halomethylcarbinol acetates

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ABSTRACT

A general and highly selective method for the synthesis of carbohydrate-derived (*Z*)-vinyl halides and silanes is described. This reaction takes place through a β-elimination process of sugar-derived α-halomethylcarbinol acetates promoted by samarium diiodide. Starting materials have been easily prepared in two steps consisting in an initial addition of halomethyllithium compounds to the corresponding galactose-derived aldehyde, followed by acetylation. A mechanism that explains both the formation of (*Z*)-vinyl derivatives and its selectivity is proposed. Finally, the synthetic usefulness of these compounds has been applied in cross-coupling reactions with ethynyl benzene towards the formation of selected enyne derivatives.

1. Introduction

Halovinyl carbohydrate derivatives are compounds of great interest on account of their usefulness as synthetic intermediates.[1] The presence of the haloalkenyl moiety makes halovinyl sugars ideal precursors for palladium catalyzed cross-coupling reactions, which could be exploited for the introduction of new substituents, the elongation of the sugar chain and the formation of *C*-glycosides. Accordingly, these derivatives have been used as intermediates in the preparation of natural products,[2] *C*-glycosides,[3] polyols[4] and nucleosides.[5]

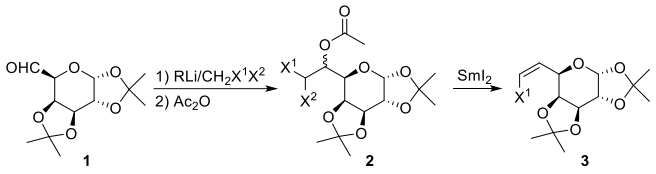
Despite halovinyl sugars have proven to be extremely effective tools for the elongation of the sugar chain and the preparation of very diverse carbohydrate derivatives, this topic has not been extensively investigated. This may be due to the limited access to these intermediates in enantiopure form.

Although various synthetic precursors have been used for the synthesis of sugar-derived halovinyls, one of the most common methods is still the halogenation-reduction of alkynes. Thus, sugar-derived halovinyls have been mostly prepared from sugar acetylenes *via* halogenation and diimide *cis*-hydrogenation.[2b,3] On the other hand, uridine-derived halovinyl compounds have been synthesized from vinyl sulfones *via* vinyltin intermediates.[6] Takai's procedure has been also applied for the preparation of these derivatives.[7] In this sense, it has been reported that treating a sugar-derived aldehyde with iodoform and chromium dichloride, afforded *E*/*Z* mixtures of the corresponding iodoalkenes in moderate yields.[2a,8] Finally, León and co-workers reported the $CrCl_2$-promoted reductive elimination of *gem*-dihalo compounds to obtain alkenyl halides in good yields but with poor stereoselectivity.[9]

In this context, the development of a novel and efficient procedure to obtain sugar-derived halovinyl compounds in good yields and stereoselectivities would be still desirable. Related to that, we have recently described a novel, efficient and general methodology for the indium-promoted reduction of *gem*-dibromides to afford (*E*)-vinyl bromides in ionic liquid media under ohmic heating.[10] This procedure is very effective for the preparation of sugar-derived (*E*)-bromoalkenes, which on Pd-catalyzed cross-coupling reactions (Heck, Stille, Suzuki, Kumada and Sonogashira) afford a wide set of sugar alkenes, dienes and enynes.

Previous work in our laboratory has demonstrated the utility of samarium diiodide to promote stereoselective processes directed towards the synthesis of (*Z*)-unsaturated systems. Thus, we have already reported the synthesis of (*Z*)-allyl[11] and (*Z*)-vinylsilanes,[12] (*Z*)-β,γ-unsaturated nitriles,[13] (*Z*)-alkenes,[14] (*Z*)-vinyl halides[15] and (*Z*)-α,β-unsaturated amides.[16] Herein, we describe a

complementary methodology to the previous work reported by our group for the synthesis of (*E*)-vinyl halides.[10] These initial results prompted us to test the application of samarium diiodide as a versatile reagent for an efficient, simple, and rapid synthesis of carbohydrate-derived (*Z*)-haloalkenes from sugar-aldehydes **1** through a stereoselective 1,2-elimination on their corresponding α-halomethylcarbinol acetates **2** (Scheme 1).



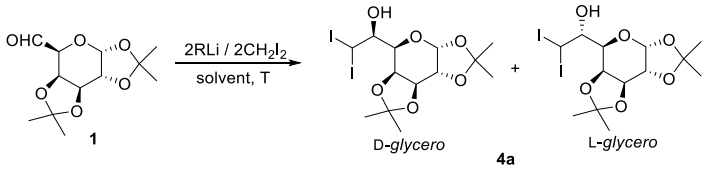
Scheme 1. Synthetic procedure for the preparation of carbohydrate derived (*Z*)-vinyl halides and silanes **3**.

2. Results and discussion

While the importance of polyhalogenated sugars is obvious, stereocontrolled introduction of the polyhalomethyl group in a carbohydrate moiety is not widely achievable. One of the most straightforward pathways to generate α-polyhalomethylcarbinols is the nucleophilic addition of organolithium compounds to aldehydes. The potential difficulties, when applying this approach to sugar aldehydes, rely on the sensitivity of sugar aldehydes to strong bases and the lack of stereocontrol during the addition process. Moreover, organolithium reagents are rather unstable even at low temperature. Accordingly, we have envisioned a strategy for the preparation of sugar α-halomethyl carbinols based on the *in situ* generation of halomethyllithium. Thus, on slow addition of the base over a solution of aldehyde in the presence of an excess of the corresponding dihalomethane or chloromethyltrimethylsilane, the kinetically generated dihalomethyllithium species would react with the aldehyde before side reactions and decomposition take place.

In our preliminary studies, we screened a variety of conditions for the stereoselective addition of diiodomethyllithium to the galactose-derived aldehyde **1** to generate the diiodomethylcarbinol intermediate **4a**, paying special attention to the influence of different bases, solvents and temperatures (Table 1).

Table 1. Screening for diiodomethyllithium addition to sugar aldehyde **1**.



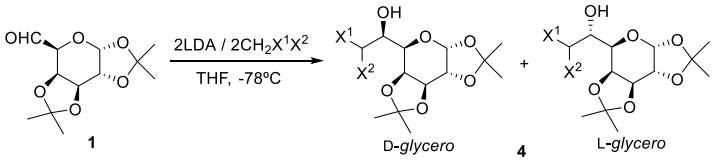
Entry	RLi	Solvent	T (ºC)	D-/L-*glycero*[a]	Yield (%)[b]
1	TMPLi	THF	-78	82/18	64
2	HMDSLi	THF	-78	79/21	70
3	*n*-BuLi	THF	-78	74/26	28
4	*i*-Pr_2NLi	THF	-78	82/18	86
5	*i*-Pr_2NLi	THF	-30	75/25	55
6	*i*-Pr_2NLi	Et_2O	-78	63/37	64

[a] D-/L-*glycero* ratio was determined by ^1H NMR analysis of the crude reaction mixture. [b] Isolated yield of compound **4a** after column chromatography relative to sugar-aldehyde **1**.

Firstly, it was found that the use of TMPLi (TMP = 2,2,6,6-tetramethylpiperidine) as base in THF at -78 °C conducted to good selectivity and yield (Table 1, entry 1). HMDSLi gave similar results (Table 1, entry 2), while *n*-BuLi provided low yields of the desired diiodo compound (Table 1, entry 3). In this case, the epoxide derived from the iodomethylation of the sugar-aldehyde has been obtained as the main product.[17] On the other hand, LDA in THF at -78 °C afforded derivative **4a** in 86% yield and good selectivity (82/18) (Table 1, entry 4). Rising the temperature up to –30 ºC caused a steep decrease in the yield (Table 1, entry 5). Finally, Et_2O was employed as solvent affording similar yield but lower stereoselectivity (Table 1, entry 6). The configuration obtained after the addition of diiodomethyllithium to aldehyde **1** could be easily explained through a Felkin-Ahn model. Thus, diiodomethyllithium would attack the *si* face giving preferentially D-glycero stereoisomer through a model similar to that used to explain the stereoselectivity observed in the addition of nitronates,[18] methyllithium,[19] or halomethyllithium[20] to sugar-derived carbonyl compounds.

LDA in THF at -78 ºC (Table 1, entry 4) showed the best results in terms of yield and selectivity, and these conditions were taken forward. Then, the scope of the reaction was investigated using diiodo-, dibromo-, chloroiodomethyllithium, and (chlorolithiomethyl)trimethylsilane. In all cases, the corresponding addition products **4a-d** were obtained in good yields and moderate selectivities for the D-*glycero* isomer (Table 2).

Table 2. Synthesis of halomethyl carbinols **4**.



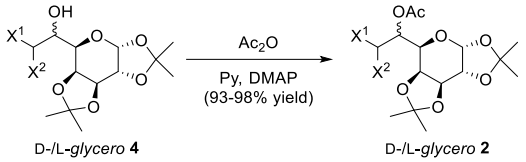
Entry	**4**	X^1	X^2	D-/L-*glycero*[a]	Yield (%)[b]
1	**4a**	I	I	82/18	86
2	**4b**	Cl	I	66/34	64
3	**4c**	Br	Br	84/16	79
4	**4d**	$SiMe_3$	Cl	67/33	70

[a] D-/L-*glycero* ratio was determined by ^1H NMR analysis on the crude reaction mixture. [b] Isolated yield of compounds **4** after column chromatography relative to sugar-aldehyde **1**.

Chloroiodomethyllithium gave the lowest stereoselectivities, producing **4b** as the four possible isomers in 38:28:18:16 ratio (D-/L-*glycero* 66/34; Table 2, entry 2). The use of the bigger dibromomethyl anion led to a significant increase in stereoselectivity generating **4c** in 84/16 D-/L-*glycero* ratio (Table 2, entry 3). Finally, the best D-*glycero* selectivity was reached when the bulkier trimethylsilylchloromethyllithium anion was employed taking into account that a mixture of only two **4d** isomers was obtained out of the four possible ones (Table 2, entry 4).

Owing to we have previously reported several 1,2-elimination processes on 1-halo-2-acetoxy compounds under several

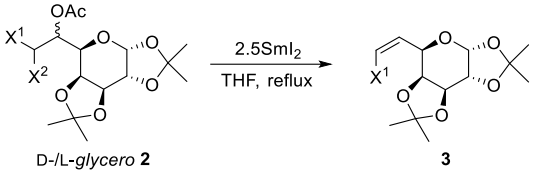
conditions,[11-15] compounds **4** were transformed in the corresponding acetates **2** in excellent yields by treatment with Ac_2O in pyridine and DMAP (Scheme 2).



Scheme 2. Synthesis of D-/L-*glycero* acetate derivatives **2**.

We next decided to explore the β-elimination process of halocarbinol acetates **2** for the preparation of the desired vinyl derivatives **3**. For this purpose, we focused on samarium diiodide, a rather mild reagent widely employed to promote various β-elimination reactions with high or total stereoselectivity.[21] Taking into account our previous results, halocarbinol acetates **2** (as a mixture of D-/L-*glycero* stereoisomers) were treated with 2.5 equiv. of SmI_2 in THF at reflux (Table 3). Under these conditions, the desired (*Z*)-vinyl halides **3a-c** were isolated in very high to excellent yields and selectivities (Table 3, entries 1-3). Similarly, the vinylsilane **3d** was obtained from **2d** in 97% yield although with moderate selectivity (Table 3, entry 4).

Table 3. Synthesis of (*Z*)-vinyl halides **3a-c** and silane **3d**.



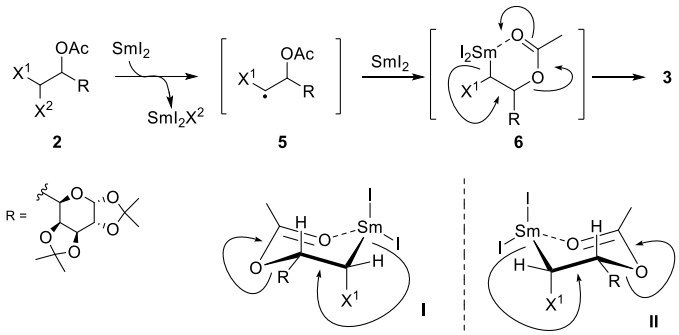
Entry	X^1	X^2	**3**	*Z*/*E*[a]	Yield (%)[b]
1	I	I	**3a**	95/5	90
2	Cl	I	**3b**	96/4	95
3	Br	Br	**3c**	94/6	97
4	$SiMe_3$	Cl	**3d**	81/19	97

[a] *Z*/*E* ratio was determined by ^{1}H NMR analysis on the crude reaction mixture. [b] Isolated yield of compounds **3** after column chromatography relative to starting materials **2**.

The (*Z*)-relative configuration of the C=C bonds in compounds **3** was assigned by analysis of ^{1}H NMR coupling constants between the olefinic protons. Moreover, spectroscopic data for compound (*Z*)-**3c** were compared to the previous values reported in the literature for the corresponding (*E*)-isomer.[10]

The synthesis of (*Z*)-vinyl halides **3a-c** or silane **3d** could be explained as follows: reaction of starting materials **2** with a first equivalent of samarium diiodide would generate a radical intermediate **5**. Then a second equivalent of samarium diiodide would reduce the radical specie **5** to the anionic intermediate **6**, which afforded the corresponding (*Z*)-vinyl compound **3** after 1,2-elimination. The observed (*Z*)-stereochemistry of compounds **3** may be explained as a consequence of the ability of Sm(III) species to form chelates due to their high oxophilicity.[22] Thus, chelation of Sm(III) center with the oxygen atom of the acetyl group leads to a six-membered ring **6** which triggered the 1,2-elimination process by increasing the ability of the acetoxy as a leaving group (as depicted in Scheme 3).

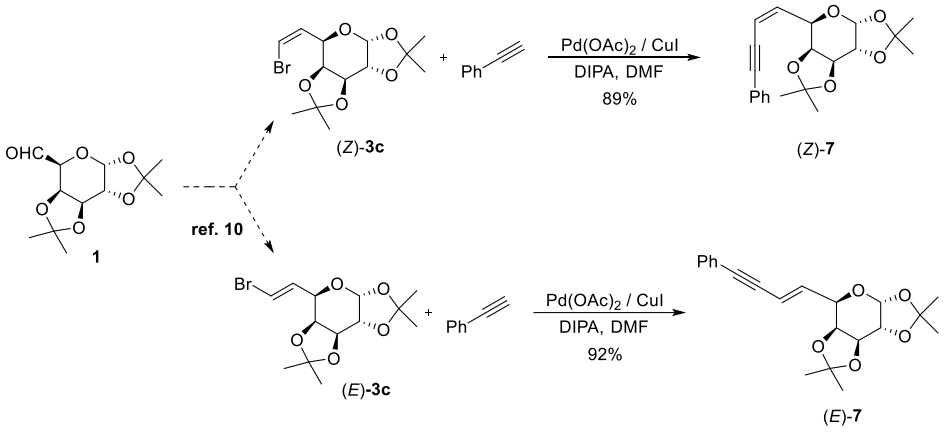
This reaction occurred in a stereoselective fashion but not in a stereospecific manner since the diastereoisomeric ratio rise from compounds **2** to **3**. This may happen as a consequence of a loss of the chiral information contained on the CHX^1X^2 center after the addition of a first equivalent of samarium diiodide and further generation of radical specie **5**. In this sense, the six-membered ring may be formed as the two chairs (see intermediates **I** and **II** in Scheme 3) which structure depends on the spatial disposition of the acetate group.



Scheme 3. Proposed mechanism for the synthesis of (*Z*)-vinyl compounds **3**.

Chelation-control model depicted in Scheme 3 would explain the (*Z*)-selectivity observed in this reaction. Chair-like structure **I-II** is assumed, in which the R (sugar moiety), and X^1 (Cl, Br, I, $SiMe_3$) adopt an equatorial and axial position, respectively. This is due to both, on the one hand, the absence of 1,3-diaxial interactions and, on the other hand, as a consequence that dipoles Sm-I and C-X^1 are opposite. Elimination process, as shown in intermediates **I** and **II**, would afford (*Z*)-vinyl compounds **3**.

As it is shown in Table 3, the lower *Z*/*E* ratio observed in compound **3d**, when compared with **3a-c**, can be explain due to the higher steric requirements of the TMS group. This fact has been already observed in other 1,2-elimination protocols in which 1-halo-2-acetoxyalkylsilanes are involved.[12]



Scheme 4. Synthesis of sugar-derived enyne derivatives (*E*)- and (*Z*)-**7**.

In order to evaluate the usefulness of the aforementioned sugar-vinyls in cross-coupling reactions, bromovinyl **3c** was selected to examine a Sonogashira cross-coupling reaction. Thus, sugar bromoalkene **3c** was subjected to the standard protocol with ethynyl benzene using 5 mol% $Pd(OAc)_2$ and 5 mol% CuI in the presence of 0.2 equiv. of PPh_3 and diisopropylamine as base. Under these conditions, enyne (*Z*)-**7** was obtained (Scheme 4). This enyne is isomeric to the previously we reported from the corresponding (*E*)-bromoalkene (*E*)-**3c**.[10] Taking into account that the (*E*)-bromovinylsugars (*E*)-**3** are easily available from sugar dibromoalkenes on indium promoted debromination on ionic liquid under ohmic heating, both procedures are complementary and give access to both isomers of sugar enyne derivatives **7**.

3. Conclusion

In conclusion, we have described a novel protocol directed towards the synthesis of carbohydrate-derived (*Z*)-vinyl halides and silanes. This process took place with a good control of the stereoselectivity and high yields. Besides, this procedure complements our described methodology for the preparation of sugar-derived (*E*)-vinyl halides. A mechanism that explains both, the formation of compounds **3** and its selectivity is proposed. Sonogashira coupling of both (*E*)- and (*Z*)-vinyl bromides generated the corresponding (*E*)- and (*Z*)-enynes with total stereoselectivity and good yields. Other synthetic applications of both (*E*)- or (*Z*)-vinyl halides are currently under investigation in our laboratory.

4. Experimental section

Reactions that required an inert atmosphere were conducted under dry nitrogen, and the glassware was oven dried (120 ºC). THF was distilled using sodium-benzophenone as desiccant immediately prior to use. All reagents were commercially available and were used without further purification. Silica gel for column chromatography purifications was purchased from Merck (230-400 mesh), and compounds were visualized on analytical thin layer chromatograms (TLC) by UV light (254 nm). ^{1}H NMR spectra were recorded in a Brüker 300 MHz spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane (TMS), which is used as an internal standard, and coupling constants *J* are reported in Hz. The diastereoisomeric ratios were obtained from ^{1}H NMR analysis. GC-MS and HRMS were measured at 70 eV. Only the most important molecular ions and/or base peaks in MS are given.

4.1. General procedure for the synthesis of sugar-derived α-halomethylcarbinols 4: To a solution of the galactose derived aldehyde **1** (10 mmol) and the corresponding dihalomethane or (chloromethyl)trimethylsilane (20 mmol) in THF (20 mL) was added dropwise at -78 ºC, lithium diisopropylamide [prepared from *n*-BuLi (12.5 mL, 1.6 M solution in hexanes, 20 mmol), and diisopropylamine (2.82 mL, 20 mmol) in THF (20 mL) at 0 ºC]. After stirring for 2 h the reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution (10 mL). Standard workup provided crude α-halomethylcarbinols **4** which were purified by column chromatography (silica gel, hexane/EtOAc as eluent).

4.1.a. 7-Deoxy-7,7-diiodo-1,2:3,4-di-O-isopropylidene-D,L-glycero-β-galacto-heptopyranose ***4a***: Yellow oil, $[\alpha]_D^{22}$ -43.7º (c 1.0, $CHCl_3$), yield 86%. Data for major isomer D-*glycero*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.56 (d, *J* 5.1 Hz, 1 H, H-1), 5.42 (d, *J* 3.8 Hz, 1 H, H-7), 4.64 (dd, *J* 7.9, 2.5 Hz, 1 H, H-3), 4.35 (dd, *J* 5.1, 2.5 Hz, 1 H, H-2), 4.24 (dd, *J* 7.9, 2.0 Hz, 1 H, H-4), 3.91 (dd, *J* 5.8, 2.0 Hz, 1 H, H-5), 3.91 (dd, *J* 5.8, 3.8 Hz, 1 H, H-6), 1.59 (s, 3 H), 1.44 (s, 3 H), 1.34 (s, 3 H), 1.33 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.0, 109.2, 96.4, 75.7, 71.0, 70.8, 70.3, 69.4, 26.1, 25.8, 25.0, 24.3, -24.1. MS (ESI^+-TOF, *m/z*, %): 549 ($[M+Na]^+$, 100). HRMS (ESI^+): calcd. for $C_{13}H_{20}I_2O_6Na$ $[M+Na]^+$548.9241, found 548.9215; R_f = 0.33 (hexane/EtOAc 3:1).

4.1.b. 7-Chloro-7-deoxy-7-iodo-1,2:3,4-di-O-isopropylidene-D,L-glycero-β-D-galacto-heptopyranose ***4b***: Yellow oil, $[\alpha]_D^{22}$ -24.2º (c 1.0, $CHCl_3$), yield 64%. Data for major isomer D-*glycero*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.16 (d, *J* 1.3 Hz, 1 H, H-7), 5.49 (d, *J* 4.9 Hz, 1 H, H-1), 4.67 (dd, *J* 8.0, 2.5 Hz, 1 H, H-3), 4.50 (dd, *J* 8.0, 1.9 Hz, 1 H, H-4), 4.34 (dd, *J* 4.9, 2.5 Hz, 1 H, H-2), 4.11 (d, *J* 9.0 Hz, 1 H, H-6), 3.79 (dd, *J* 9.0, 1.9 Hz, 1 H, H-5), 2.66 (br s, 1 H, OH), 1.57 (s, 3 H), 1.47 (s, 3 H), 1.39 (s, 3 H), 1.34 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.3, 109.0, 96.0, 74.5, 70.5, 70.2, 67.9, 51.1, 25.9, 24.9, 24.3. MS (ESI^+-TOF, *m/z*, %): 459 ($[M+Na]^+$, ^{37}Cl, 17), 457 ($[M+Na]^+$, ^{35}Cl, 100). HRMS (ESI^+): calcd. for $C_{13}H_{20}ClIO_6Na$ $[M+Na]^+$ 456.9885, found 456.9883; R_f = 0.35 (hexane/EtOAc 3:1).

4.1.c. 7,7-Dibromo-7-deoxy-1,2:3,4-di-O-isopropylidene-D,L-glycero-β-D-galacto-heptopyranose ***4c***: Yellow oil, $[\alpha]_D^{22}$ -45.7º (c 1.0, $CHCl_3$), yield 79%. Data for major isomer D-*glycero*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.14 (d, *J* 1.3 Hz, 1 H, H-7), 5.48 (d, *J* 4.9 Hz, 1 H, H-1), 4.65 (dd, *J* 8.0, 2.5 Hz, 1 H, H-3), 4.49 (dd, *J* 8.0, 1.8 Hz, 1 H, H-4), 4.32 (dd, *J* 4.9, 2.5 Hz, 1 H, H-2), 4.27 (dd, *J* 9.1, 1.8 Hz, 1 H, H-5), 4.09 (d, *J* 9.1 Hz, 1 H, H-6), 1.55 (s, 3 H), 1.45 (s, 3 H), 1.37 (s, 3 H), 1.32 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.3, 109.0, 95.5, 74.5, 70.4, 70.2, 68.6, 50.8, 25.8,

24.8, 24.3. MS (ESI$^+$-TOF, *m/z*, %): 457 ([M+Na]$^+$, $^{81}Br_2$, 30), 455 ([M+Na]$^+$, $^{81}Br^{79}Br$, 100), 453 ([M+Na]$^+$, $^{79}Br_2$, 39). HRMS (ESI$^+$): calcd. for $C_{13}H_{20}Br_2O_6Na$ [M+Na]$^+$ 452.9519, found 452.9507; R_f = 0.35 (hexane/EtOAc 3:1).

4.1.d. 7-Chloro-7-deoxy-1,2:3,4-di-O-isopropylidene-7-trimethylsilyl-D,L-glycero-β-D-galacto-heptopyranose ***4d***: Yellow oil, $[\alpha]_D^{22}$ -22.5º (c 1.0, $CHCl_3$), yield 70 %. Data for major isomer D-*glycero*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.51 (d, *J* 4.9 Hz, 1 H, H-1), 4.65 (dd, *J* 8.0, 2.5 Hz, 1 H, H-3), 4.46 (dd, *J* 8.0, 1.9 Hz, 1 H, H-4), 4.32 (dd, *J* 4.9, 2.5 Hz, 1 H, H-2), 4.04-4.01 (m, 1 H, H-6), 3.94 (dd, *J* 8.9, 1.9 Hz, 1 H, H-5), 3.87 (d, *J* 1.1 Hz, 1 H, H-7), 1.58 (s, 3 H), 1.45 (s, 3 H), 1.37 (s, 3 H), 1.33 (s, 3 H), 0.17 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.2, 108.9, 96.2, 70.7, 70.6, 69.8, 67.1, 53.6, 25.9, 24.9, 24.3, -2.8. MS (ESI$^+$-TOF, *m/z*, %): 405 ([M+Na]$^+$, ^{37}Cl, 47), 403 ([M+Na]$^+$, ^{35}Cl, 100). HRMS (ESI$^+$): calcd. for $C_{16}H_{29}ClO_6SiNa$ [M+Na]$^+$ 403.1314, found 403.1303; R_f = 0.36 (hexane/EtOAc 3:1).

4.2. General procedure for the synthesis of halocarbinol acetates 2: The corresponding halocarbinol **4** (1.0 mmol) was taken up in pyridine (8 mL) and acetic anhydride (8 mL). DMAP (6 mg) was added and after stirring at room temperature for 6 h, the reaction mixture was poured over ice-cooled water (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (40 mL), a saturated aqueous $CuSO_4$ solution (40 mL), brine (40 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvents were removed under reduced pressure. This allowed the access to halocarbinol acetates **2** in almost quantitative manner (93-98% yield).

4.2.a. 6-O-Acetyl-7-deoxy-7,7-diiodo-1,2:3,4-di-O-isopropylidene-D,L-glycero-β-D-galacto-heptopyranose ***2a***: Yellow oil, yield 93%. Data for major isomer D-*glycero*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.50 (d, *J* 2.8 Hz, 1 H, H-1), 5.47 (d, *J* 5.1 Hz, 1 H, H-7), 5.07 (dd, *J* 7.4, 2.8 Hz, 1 H, H-5), 4.61 (dd, *J* 7.8, 2.8 Hz, 1 H, H-2), 4.30 (dd, *J* 5.1, 2.8 Hz, 1 H, H-6), 4.18 (dd, *J* 7.8, 2.1 Hz, 1 H, H-3), 3.88 (dd, *J* 7.4, 2.1 Hz, 1 H, H-4), 2.20 (s, 3 H), 1.55 (s, 3 H), 1.44 (s, 3 H), 1.32 (s, 3 H), 1.30 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 110.2, 108.9, 96.3, 75.2, 70.8, 70.4, 70.1, 25.9, 25.0, 24.6, 21.0, -31.2. MS (ESI$^+$-TOF, *m/z*, %): 590 ([M+Na]$^+$, 100). HRMS (ESI$^+$): calcd. for $C_{15}H_{22}I_2O_7Na$ [M+Na]$^+$590.9356, found 590.9353; R_f = 0.43 (hexane/EtOAc 3:1).

4.2.b. 6-O-Acetyl-7-chloro-7-deoxy-7-iodo-1,2:3,4-di-O-isopropylidene-D,L-glycero-β-D-galacto-heptopyranose ***2b***: Yellow oil, yield 96%. Data for major isomer D-*glycero*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.14 (d, *J* 1.4 Hz, 1 H, H-7), 5.60-5.56 (m, 1 H, H-6), 5.42 (d, *J* 4.8 Hz, 1 H, H-1), 4.574.52 (m, 1 H, H-3), 4.27-4.25 (m, 1 H, H-2), 4.08-4.01 (m, 1 H, H-4), 3.69-3.66 (m, 1 H, H-5), 2.14 (s, 3 H), 1.47 (s, 3 H), 1.37 (s, 3 H), 1.27 (s, 3 H), 1.26 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 109.5, 108.9, 95.9, 73.2, 69.9, 67.6, 32.2, 25.7, 24.4, 24.2, 20.7. HRMS (ESI+): calcd. for $C_{15}H_{22}ClIO_7Na$ [M+Na]$^+$ 499.9885, found 499.9883;R_f = 0.48 (hexane/EtOAc 3:1).

4.2.c. 6-O-Acetyl-7,7-dibromo-7-deoxy-1,2:3,4-di-O-isopropylidene-D,L-glycero-β-D-galacto-heptopyranose ***2c****:* Yellow oil, yield 98%. Data for major isomer D-*glycero*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.07 (d, *J* 1.4 Hz, 1 H, H-7), 5.54 (dd, *J* 9.2, 1.4 Hz, 1 H, H-6), 5.49 (d, *J* 4.9 Hz, 1 H, H-1), 4.61 (dd, *J* 7.9, 2.5 Hz, 1 H, H-3), 4.33 (dd, *J* 4.9, 2.5 Hz, 1 H, H-2), 4.17 (dd, *J* 7.8, 1.7 Hz, 1 H, H-4), 3.94 (dd, *J* 9.2, 1.6 Hz, 1 H, H-5), 2.20 (s, 3 H), 1.57 (s, 3 H), 1.44 (s, 3 H), 1.33 (s, 3 H), 1.31 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 109.5, 109.0, 95.9, 73.1, 70.4, 69.7, 68.1, 44.6, 25.8, 24.8, 24.3, 20.6. MS (ESI$^+$-TOF, *m/z*, %): 499 ([M+Na]$^+$, $^{81}Br_2$, 55), 497 ([M+Na]$^+$, $^{81}Br^{79}Br$, 100), 495 ([M+Na]$^+$, $^{79}Br_2$, 55). HRMS (ESI$^+$): calcd. for $C_{15}H_{22}Br_2O_7Na$ [M+Na]$^+$ 494.9630, found 494.9641; R_f = 0.50 (hexane/EtOAc 3:1).

4.2.d. 6-O-Acetyl-7-chloro-7-deoxy-1,2:3,4-di-O-isopropylidene-7-trimethylsilyl-D,L-glycero-β-D-galacto-heptopyranose ***2d***: Yellow oil, yield 93%. Data for major isomer D-*glycero*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.51 (d, *J* 5.0 Hz, 1 H, H-1), 5.36 (dd, *J* 9.1, 1.4 Hz, 1 H, H-6), 4.46 (dd, *J* 8.0, 2.0 Hz, 1 H, H-3), 4.32 (dd, *J* 5.0, 2.0 Hz, 1 H, H-2), 4.25-4.12 (m, 1 H, H-4, H-5), 3.87 (d, *J* 1.4 Hz, 1 H, H-7), 2.10 (s, 3 H), 1.52 (s, 3 H), 1.48 (s, 3 H), 1.33 (s, 3 H), 1.27 (s, 3 H), 0.38 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 109.4, 109.0, 96.3, 70.8, 70.7, 70.3, 70.2, 66.0, 50.8, 25.9, 25.8, 24.9, 24.4, 21.0, -3.1. HRMS (ESI+): calcd. for $C_{18}H_{31}ClO_7SiNa$ [M+Na]+ 446.1314, found 446.1311; R_f = 0.46 (hexane/EtOAc 3:1).

4.3. General procedure for the synthesis of (*Z*)-vinyl compounds 3: A solution of the resulting intermediate acetates **2** in THF (20 mL) was added to 0.1 M solution of samarium diiodide in THF (2.5 mmol). After stirring the reaction mixture at reflux for 18 h, an aqueous HCl 0.1 M solution (20 mL) was added and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic layers were then dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography eluting with mixtures of hexane/ethyl acetate to afford (*Z*)-vinyl compounds **3** (90-97% yield).

4.3.a. (Z)-6,7-Dideoxy-1,2:3,4-di-O-isopropylidene-7-iodo-β-D-galacto-hept-6-enopyranose ***3a***: Yellow oil, $[\alpha]_D^{22}$ -75.4º (c 1.0, $CHCl_3$), yield 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.48-6.42 (m, 1 H, H-6, H-7), 5.55 (d, *J* 5.0 Hz, 1 H, H-1), 4.66 (dd, *J* 7.8, 2.5 Hz, 1 H, H-3), 4.60 (dd, *J* 6.0, 2.0 Hz, 1 H, H-5), 4.34 (dd, *J* 5.0, 2.5 Hz, 1 H, H-2), 4.32 (dd, *J* 7.9, 2.0 Hz, 1 H, H-4), 1.67 (s, 3 H), 1.47 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.8, 109.4, 108.9, 96.3, 83.3, 72.1, 71.4, 70.6, 70.1, 26.2, 25.8, 25.0, 24.3. MS (ESI$^+$-TOF, *m/z*, %): 357 ([M+Na]$^+$, 4), 241 (100); HRMS (ESI$^+$): calcd. for $C_{21}H_{25}O_5$ [M+H]$^+$ 357.1696, found 357.1707; R_f = 0.60 (hexane/EtOAc 3:1).

4.3.b. (Z)-7-Chloro-6,7-dideoxy-1,2:3,4-di-O-isopropylidene-β-D-galacto-hept-6-enopyranose ***3b***: Yellow oil, $[\alpha]_D^{22}$ -4.5º (c 0.2, $CHCl_3$), yield 97%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.19 (dd, *J* 7.4, 1.1 Hz, 1 H, H-7), 5.96 (t, *J* 7.4 Hz, 1 H, H-6), 5.53 (d, *J* 5.0 Hz, 1 H, H-1), 4.86 (d, *J* 7.9 Hz, 1 H, H-3), 4.63 (dd, *J* 7.9, 2.5 Hz, 1 H, H-5), 4.32 (dd, *J* 5.0, 2.5 Hz, 1 H, H-2), 4.27 (dd, *J* 7.9, 2.0 Hz, 1 H, H-4), 1.59 (s, 3 H), 1.46 (s, 3 H), 1.34 (s, 3 H), 1.33 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 128.2, 120.2, 109.3, 108.8, 96.3, 72.3, 70.7, 70.2, 64.6, 26.0, 25.9, 24.9, 24.2. MS (ESI$^+$-TOF, *m/z*, %): 313 ([M+Na]$^+$, 100). HRMS (ESI$^+$): calcd. for $C_{21}H_{25}O_5$ [M+Na]$^+$ 313.0819, found 313.0818. R_f = 0.58 (hexane/EtOAc 3:1).

4.3.c. (Z)-7-Bromo-6,7-dideoxy-1,2:3,4-di-O-isopropylidene-β-D-galacto-hept-6-enopyranose ***3c***: Yellow oil, $[\alpha]_D^{22}$ -69.4º (c 0.2, $CHCl_3$), yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.63 (d, *J* = 8.1 Hz, 1 H, H-7), 6.48-6.27 (m, 1 H, H-6), 5.52 (d, *J* = 5.0 Hz, 1 H, H-1), 4.77 (dd, *J* = 6.8, 1.8 Hz, 1 H, H-2), 4.63 (dd, *J* = 5.1, 1.9 Hz, 1 H, H-5), 4.33-4.27 (m, 2 H, H-3, H-4), 1.60 (s, 3 H), 1.45 (s, 3 H), 1.33 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.5, 109.4, 109.3, 108.8, 96.2, 72.1, 70.6, 70.1, 67.1, 26.0, 25.8, 24.9, 24.2. MS (ESI$^+$-TOF, *m/z*, %): 359 ([M+Na]$^+$, ^{81}Br, 96), 357

([M+Na]$^+$, ^{79}Br, 100). HRMS (ESI$^+$) calc. for $C_{13}H_{19}BrO_5Na$ [M+Na]$^+$ 357.0308, found 357.0288; R_f = 0.28 (hexane/EtOAc 9:1).

4.3.d. (Z)-6,7-Dideoxy-1,2:3,4-di-O-isopropylidene-7-trimethylsilyl-β-D-galacto-hept-6-enopyranose ***3d***: Yellow oil, $[\alpha]_D^{22}$ -4.5º (c 0.2, $CHCl_3$), yield 97%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.36 (dd, *J* 14.7, 7.7 Hz, 1 H, H-6), 6.36 (dd, *J* 14.7, 1.1 Hz, 1 H, H-7), 5.58 (d, *J* 5.2 Hz, 1 H, H-1), 4.61 (dd, *J* 7.7, 2.3 Hz, 1 H, H-5), 4.43 (d, *J* 7.1 Hz, 1 H, H-4), 4.31 (dd, *J* 5.2, 2.3 Hz, 1 H, H-2), 4.18 (dd, *J* 7.7, 2.3 Hz, 1 H, H-3), 1.55 (s, 3 H), 1.48 (s, 3 H), 1.34 (s, 6 H), 0.15 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 132.6, 109.1, 108.2, 96.2, 73.8, 70.9, 70.0, 68.1, 26.0, 25.9, 24.7, 24.2, 0.3. MS (ESI$^+$-TOF, *m/z*, %): 351 ([M+Na]$^+$, 100). HRMS (ESI$^+$): calcd. for $C_{16}H_{28}O_5SiNa$ [M+Na]$^+$ 351.1606, found 351.1604. R_f = 0.33 (hexane/EtOAc 3:1).

4.4. General procedure for the synthesis of (*Z*)-1,2:3,4-di-*O*-isopropylidene-9-C-phenyl-6,7,8,9-tetradeoxy-β-D-*galacto*-nona-6-en-8-ynopyranose (*Z*)-7: A reaction flask containing the bromoalkene **3c** (1.0 mmol, 334 mg), PPh_3 (0.2 mmol, 52 mg), $Pd(OAc)_2$ (5.0 mol%, 11 mg), and CuI (5.0 mol%, 10 mg) was degassed and filled with argon. DMF (5 mL) and *i*-Pr_2NH (2.5 mL) were added followed by ethynylbenzene (1.2 mmol, 0.13 mL). After stirring at room temperature for 10 h, the mixture was diluted with H_2O (8 mL) and extracted with Et_2O (5 mL). The combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated to dryness. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc 8:1). Yellow oil, $[\alpha]_D^{22}$ +5.2º (c 0.8, $CHCl_3$), yield 92%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.39 (m, 2 H), 7.33-7.26 (m, 3 H), 6.11 (dd, *J* 11.0, 8.0 Hz, 1 H, H-8), 5.90 (dd, *J* 11.0, 1.0 Hz, 1 H, H-7), 5.58 (d, *J* 5.0 Hz, 1 H, H-1), 5.01 (dd, *J* 8.0, 2.0 Hz, 1 H, H-5), 4.67 (dd, *J* 7.9, 2.5 Hz, 1 H, H-3), 4.39-4.44 (m, 2 H, H-2, H-4), 1.57 (s, 3 H), 1.50 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 131.4, 128.4, 128.3, 122.9, 111.4, 109.3, 108.9, 96.4, 95.1, 85.2, 73.2, 70.8, 70.3, 67.0, 26.1, 25.9, 25.0, 24.3. MS (ESI$^+$-TOF, *m/z*, %): 357 ([M+Na]$^+$, 4), 241 (100); HRMS (ESI$^+$): calcd. for $C_{21}H_{25}O_5$ [M+H]$^+$ 357.1696, found 357.1707; R_f = 0.31 (hexane/EtOAc 8:1).

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