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Indium Chemistry

Ohmic Heating and Ionic Liquids in Combination for the Indium-Promoted Synthesis of 1-Halo Alkenyl Compounds: Applications to Pd-Catalysed Cross-Coupling Reactions

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Abstract: We have explored the combination of ohmic heating (ΩH) with ionic liquids for indium-promoted reactions and report herein the indium-promoted dehalogenation of *gem*-dibromo alkenes and the indium-mediated reductive elimination of chlorohydrins for the synthesis of 1-halo alkenyl derivatives. Heck, Stille, Suzuki, Kumada and Sonogashira couplings of the resulting 1-halo-1-alkenes with appropriate reagents were carried out to give alkenes, dienes and enynes.

Introduction

Ohmic heating is an energy-efficient heating process in which an a.c. electric current of tunable high frequency passes through a conductive reaction medium (which behaves as an electrical heater) with the primary purpose of heating it. Heat is generated directly within the reaction medium by internal energy transformation (from electric to thermal) so it is not transmitted to the medium by means of temperature gradients or hot surfaces.[1,2] The thermal energy transfer occurs mostly between the electrode plates cross-section region (electrodes are in contact with the medium) and the surroundings. Thus, heating is less dependent on the heat transfer to the medium, which results in a high heating rate allowing fast, volumetric and uniform heating and increased dynamics of charged species in solution leading to shorter reaction times and increased yields.[1,2] Ohmic heating is a convenient alternative to classical heating and microwave (MW) irradiation, as demonstrated recently by Silva and co-workers.[2] On the other hand, ionic liquids (ILs) are excellent solvents to use in ohmic heating because they are naturally conductive and they are becoming increasingly popular as solvents in organic synthesis for several reasons;[3] they are practically non-volatile and non-flammable, avoiding the risks associated with volatile organic compounds, and they can be recycled easily without any significant loss of activity.

It was recently reported that ionic liquids improve the performance of several indium-promoted processes, probably through the formation of stable indium(III) complexes with the carbene intermediates. As a result of its low toxicity, environmental benefits and favourable effects on chemical transformations, indium metal has recently attracted considerable attention.[4] It has been used extensively in carbon–carbon bond formation[5] and reductive dehalogenation reactions,[6] and recently our group[7] and others[8] have reported the use of indium in reductive elimination reactions.

Considering the above information, it is reasonable to think that the combination of ohmic heating with ionic liquids for indium-promoted reactions may provide great opportunities for green chemistry. Therefore we applied this idea to the synthesis of 1-halo alkenyl derivatives, of great interest as substrates in palladium-catalysed cross-coupling reactions. In this paper we describe the details of the indium-mediated reduction of 1,1-dibromo-1-alkenes and the reductive elimination of 2,4-dichloro-3-alken-1-ols in ionic liquid media under ohmic heating conditions. The reactions, including their mechanisms, scope, and limitations, and also the usefulness of the resulting 1-halo-1-alkenes for the preparation of conjugated polyenes and enediynes by Pd-catalysed cross-coupling reactions are also discussed.

Results and Discussion

Indium-Mediated Reduction of *gem*-Dibromo Alkenes

Vinyl bromides are extremely useful tools in organic chemistry and their use as coupling partners in a wide range of transition-metal-mediated cross-coupling reactions has sparked a great deal of interest in their stereoselective synthesis.[9]

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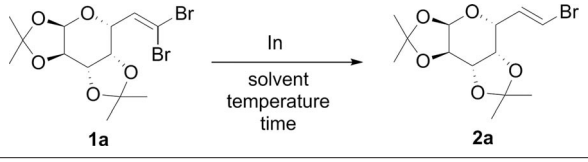
The reduction of *gem*-dibromides, readily available from the simple reaction of an aldehyde with carbon tetrabromide and triphenylphosphine, presents a practical alternative to the synthesis of vinyl bromides. Few examples of the hydrogenolysis of 1,1-dibromo-1-alkenes have been reported in the literature.[10] However, because these methods have some drawbacks (i.e., very low temperatures, highly toxic reagents, limited substrate scope), a simpler, more efficient and environmentally friendly method for the synthesis of 1-halo-1-alkenes is still desirable.

In our preliminary studies, the reduction of galactose-derived dibromo alkene **1a** was assessed under various conditions and the results are reported in Table 1. Thus, the treatment of **1a** (1 mmol) with indium metal (1.1 mmol) in either a mixture of ethanol and water or ethanol and an aqueous saturated ammonium chloride solution under reflux led to complete recovery of the dihalo precursor in both cases (Table 1, entries 1 and 2). These unsatisfactory results were somehow expected, because indium has proven effective in the reduction of aromatic-substituted *gem*-dibromo alkenes, but failed to effectively reduce their alkyl-substituted counterparts.[10e]

Table 1. Reduction of *gem*-dibromo alkene **1a**.



1a **2a**

Entry	Solvent	*T* [°C]	*t* [h]	Yield [%][a]	*E*/*Z*[b]
1	EtOH/H_2O	100	12	n.r.	–
2	EtOH/aq. NH_4Cl	100	12	n.r.	–
3	[bmim]I	95	12	48	91:9
4	[bmim]Br	95	12	45	92:8
5	[bmim]Br	95	36	82	90:10
6	[bmim]Br (second run)	95	36	80	90:10
7	[bmim]Br (third run)	95	36	78	90:10
8	[bmim]PF_6	95	36	n.r.	–
9	[bmim]BF_4	95	36	n.r.	–
10	[bmim]BF_4	95	36	n.r.	–
11	TBAP/H_2O	95	36	n.r.	–
12	[bmim]Br	95	1	n.r.	–
13	[bmim]Br	95[c]	1	46	91:9
14	[bmim]Br	95[c]	3	84	90:10
15	[bmim]Br	95[d]	3	46	61:39

[a] Isolated yield; n.r.: no reaction. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [c] Ohmic heating. [d] Microwave irradiation.

To overcome this limitation, we decided to test the use of ionic liquids (ILs) as the reaction medium. In addition to having well-known properties as green solvents, ILs have also been shown to enhance the rate of many transformations.[11] Thus, we expected that ILs would accelerate single-electron transfer (SET) from indium in the powder form to the dibromo alkenyl substrate.[12] The treatment of **1a** with indium in both [bmim]I (bmim = 1-butyl-3-methylimidazolium) and [bmim]Br at 95 °C afforded bromovinyl **2a** in moderate yields and diastereoselectivity after 12 h along with some recovered starting material (Table 1, entries 3 and 4). The reaction needed 36 h to reach completion (Table 1, entry 5). When other ILs with different counter ions and cations were used, for example, [bmim]PF_6, [bim]BF_4 (bim = 1-butylimidazolium), [mim]BF_4 (mim = 3-methylimidazolium) and TBAP (tetrabutylammonium perchlorate), the reaction did not proceed (Table 1, entries 8–11).

The most appropriate reaction medium is [bmim]Br, because in this IL the product was obtained in good yield and could easily be separated from the water-soluble IL by adding water and extracting with diethyl ether. The ionic liquid can be recovered by evaporation of the aqueous layer followed by filtration and used in subsequent experiments without affecting the yield or selectivity (Table 1, entries 6 and 7).

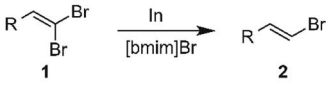
In an attempt to improve the methodology by reducing the reaction time, the reduction of **1a** was performed following the same procedure but by changing the mode of heating of the reaction mixture from classical heating (oil bath) to ohmic heating. With this modification, bromovinyl **2a** was obtained after 3 h in high yield (84 %) and with good (*E*/*Z*) selectivity (90:10; Table 1, entries 13 and 14). Microwave irradiation was not as effective as ohmic heating, affording bromovinyl **2a** in lower yield (46 %) and diastereoselectivity (61:39 *E*/*Z*; Table 1, entry 15). It is interesting to note that in the absence of ohmic heating, no significant amounts of the desired **2a** were detected (Table 1, entry 12).

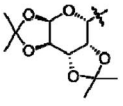
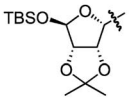
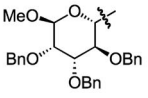
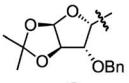
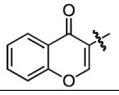
A plausible mechanism for the reductive dehalogenation of dibromo alkenes by In^0 in [bmim]Br would include the formation of an intermediate radical by single-electron transfer (SET) from In^0 to the dibromo alkene followed by hydrogen atom abstraction from [bmim]Br to generate a carbene intermediate, which forms a stable complex with $InBr_3$.[13] The excellent selectivity can be explained by the higher thermodynamic stability of the intermediate conducting to the (*E*)-alkene.

To study the scope of this novel reduction methodology, a series of dibromo alkenes were submitted to the indium-mediated reduction protocol under classical and ohmic heating conditions. As depicted in Table 2, a wide range of structurally varied *gem*-dibromides underwent reduction by this procedure to provide the corresponding (*E*)-vinyl bromides predominantly in high yields. Several functional groups such as OMe, OBn, Cl, Br, CN and CO_2Me remained unaffected under the present reaction conditions. In general, the crude reaction products were obtained in high purity after aqueous work up; it is noteworthy that no column chromatographic purification was necessary to obtain compounds **2** with high purity.

This method offers significant improvements over existing procedures owing to the absence of undesired side-reactions, including over-reduction, the mild conditions required, the wide range of functionalities tolerated, the good results obtained with alkyl-substituted *gem*-dibromides, the good yields and stereoselectivities and the environmentally friendly reaction conditions.

Table 2. Synthesis of vinyl bromides **2**.



				Classical heating[a]			Ohmic heating[a]		
Entry	**1**	R	**2**	*t* (h)	*E*/*Z*[b]	Yield (%)[c]	*t* (h)	*E*/*Z*[b]	Yield (%)[c]
1	**1a**		**2a**	12	91/9	82	1	90/10	84
2	**1b**	Ph	**2b**	12	95/5	93	1	91/9	94
3	**1c**	4-MeO-C_6H_4	**2c**	12	75/25	41	1	75/25	52
4	**1c**	4-MeO-C_6H_4	**2c**	36	75/25	88	3	75/25	92
5	**1d**	3-BnO-C_6H_4	**2d**	12	80/20	85	1	80/20	87
6	**1e**	4-MeO_2C-C_6H_4	**2e**	12	80/20	94	1	78/22	94
7	**1f**	2-Me-C_6H_4	**2f**	12	76/24	90	1	76/24	90
8	**1g**	2-Cl-C_6H_4	**2g**	12	85/15	91	1	82/18	92
9	**1h**	3-Br-C_6H_4	**2h**	12	76/24	93	1	76/24	90
10	**1i**	4-CN-C_6H_4	**2i**	12	72/28	84	1	73/27	79
11	**1j**		**2j**	12	92/8	93	1	65/35	94
12	**1k**	PhCH=CH	**2k**	12	75/25	80	1	72/28	84
13	**1l**	*c*-C_6H_{12}	**2l**	36	57/43	51	3	55/45	62
14	**1m**		**2m**	36	80/20	75	3	80/20	78
15	**1n**		**2n**	36	90/10	83	3	91/9	83
16	**1o**		**2o**	36	75/15	81	3	78/12	85
17	**1p**		**2p**	36	82/18	42	3	82/18	58

[a] Temperature 95 °C. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [c] Isolated yield.

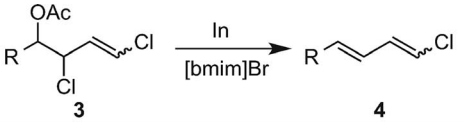
Indium-Promoted Reductive Elimination of Chlorohydrins

We decided to investigate the indium-promoted reductive β-elimination of 2,4-dichloro-3-alken-1-yl acetates for the preparation of 1-chlorodienes, interesting intermediates that undergo a variety of synthetically useful transformations to give unsaturated compounds (e.g., enynes, 1,3-diynes, chloropolyenes, enediynes and polyenes).[14]

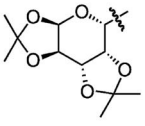
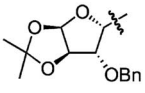
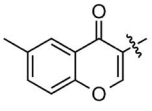
Taking into account our previous experience of dehalogenation reactions, initial studies were focused on the β-elimination reactions of 2,4-dichlorohomoallyl acetates using indium in [bmim]Br under both classical and ohmic heating.

The acetates **3** used as starting materials could be easily prepared from aldehydes by the indium-promoted addition of 3-bromo-1,3-dichloropropene[15] followed by acetylation of the crude alcohols. Under these conditions a collection of 2,4-dichlorohomoallyl acetates **3a**–**j** featuring different substituents and patterns afforded the desired (1*E*)-4-chloro-1-substituted-1,3-dienes **4a**–**j** in good yields and with excellent stereoselectivities (Table 3). Again, ohmic heating was much more efficient than classical heating, leading to an impressive decrease in the reaction time (from 12 to 1 h). The observed (*E*) configuration of the newly formed double bond, obtained through the β-elimination process, can be explained according to a chelation-control model.[7]

Table 3. Synthesis of (1*E*)-4-chloro-1,3-dienes **4**.



3 **4**

				Classical heating[a]			Ohmic heating[a]		
Entry	**1**	R	**2**	*t* (h)	*E*/*Z*[b]	Yield (%)[c]	*t* (h)	*E*/*Z*[b]	Yield (%)[c]
1	**3a**	Ph	**4a**	12	>98/2	86	1	>98/2	88
2	**3b**	4-MeO-C_6H_4	**4b**	12	>98/2	76	1	>98/2	81
3	**3c**	4-MeO_2C-C_6H_4	**4c**	12	>98/2	71	1	>98/2	70
4	**3d**	4-Me-C_6H_4	**4d**	12	>98/2	84	1	>98/2	86
5	**3e**	3-Br-C_6H_4	**4e**	12	>98/2	90	1	>98/2	90
6	**3f**	4-CN-C_6H_4	**4f**	12	>98/2	64	1	>98/2	69
7	**3g**	*c*-C_6H_{12}	**4g**	12	94/6	60	1	95/5	63
8	**3h**		**4h**	12	94/6	80	1	92/8	82
9	**3i**		**4i**	12	91/9	71	1	92/8	75
10	**3j**		**4j**	12	>98/2	41	1	>98/2	43

[a] Temperature 95 °C. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [c] Isolated yield.

Pd-Catalysed Cross-Coupling Reactions

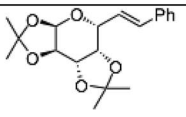
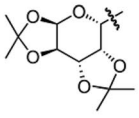
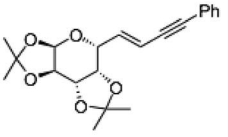
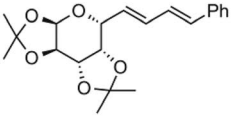
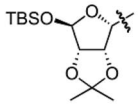
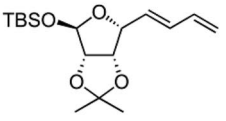
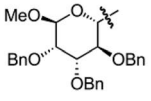
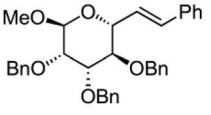
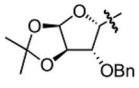
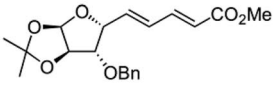
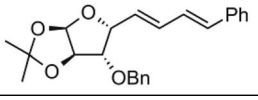
The presence of the halo alkenyl moiety makes sugar halovinyls ideal precursors for palladium-catalysed coupling reactions, which can be exploited for the introduction of new substituents and the elongation of the sugar chain. Accordingly, these derivatives have been used as intermediates in the preparation of natural products,[16] *C*-glycosides,[17] polyols[18] and nucleosides.[19] However, probably as a result of the limited access to these intermediates, this topic has not been extensively investigated.

Taking into account these considerations, we decided to investigate the introduction of new substituents into the alkenyl sugar chain through the palladium-catalysed cross-coupling reactions (Sonogashira, Suzuki, Stille, Kumada, and Heck) of the obtained sugar-derived halovinyl substrates, which yielded highly substituted sugar derivatives of considerable interest for further synthetic elaborations. The results of the cross-coupling reactions between bromovinyls **2** and chlorodienes **4** as precursors are summarized in Table 4.

First, galactose-derived bromovinyl compound **2a** was selected for a Suzuki cross-coupling reaction and subjected to the standard protocol with phenylboronic acid using 5 mol-% $Pd(OAc)_2$ in the presence of 0.2 equiv. of PPh_3 and potassium carbonate as base to afford compound **5a** (Table 4, entry 1). This procedure proved to be successful and hence a Sonogashira reaction with ethynylbenzene was assayed, which provided compound **5b** in excellent yield (Table 4, entry 2). A Kumada cross-coupling reaction of chlorodiene **4h** with phenylmagnesium bromide gave diene **5c** (Table 4, entry 3). Lyxose-derived bromovinyl compound **2m** was submitted to a Stille coupling reaction to give diene **5d** (Table 4, entry 4). Mannose-derived vinyl bromide **2n** was subjected to a Suzuki cross-coupling reaction with phenylboronic acid to afford **5e** (Table 4, entry 5). Xylose-derived bromovinyl compound **2o** and chlorodiene **4i** also underwent smooth palladium-catalysed transformations, as demonstrated by the synthesis of Heck and Kumada coupling products **5f** and **5g**, respectively (Table 4, entries 6 and 7).

Table 4. Pd-catalysed cross-coupling reactions of sugar-derived bromovinyls **2** and (1*E*)-4-chloro-1,3-dienes **4**.

2 or 4 → **5**

Entry	R^1	Y	**2 or 4**	Method[a]	Product	**5**	Yield (%)[b]
1				A		**5a**	87
2		—Br	**2a**	B		**5b**	92
3			**4h**	C		**5c**	77
4		—Br	**2m**	D		**5d**	65
5		—Br	**2n**	A		**5e**	92
6		—Br	**2o**	E		**5f**	86
7			**4i**	C		**5g**	81

[a] Reagents and conditions: A: Phenylboronic acid (1.2 equiv.), $Pd(OAc)_2$ (5 mol-%), PPh_3 (0.2 equiv.), K_2CO_3 (1.5 equiv.), DMF, 70 °C, 12 h. B: Ethynylbenzene (1.2 equiv.), $Pd(OAc)_2$ (5 mol-%), PPh_3 (0.2 equiv.), CuI (5 mol-%), iPr_2NH, DMF, room temp., 10 h. C: PhMgBr, (2 equiv.), $[Pd(PPh_3)_4]$ (5 mol-%), Et_3N (3 equiv.), THF, room temp., 1 h. D: Tributyl(vinyl)stannane (1.1 equiv.), $Pd(OAc)_2$ (10 mol-%), PPh_3 (0.2 equiv.), DMF, 60 °C, 10 h. E: Methyl acrylate (1.5 equiv.), $Pd(OAc)_2$ (5 mol-%), LiCl (3 equiv.), Et_3N (1 equiv.), DMF, 70 °C, 12 h. [b] Isolated yield.

Without any optimization the yields for these coupling reactions were good, which demonstrates that the scope of the chain-elongation of carbohydrate derivatives by the dibromo alkene reduction/cross-coupling reaction sequence is broad and will allow the modification of carbohydrates into libraries of highly diverse compounds.

Conclusions

We have demonstrated that the combination of ohmic heating with ionic liquids for indium-promoted reactions is of considerable synthetic interest and provides convenient alternatives to the existing methodologies for the synthesis of halo alkenyl compounds.

Thus, we have developed a novel, efficient and general methodology for the reduction of aryl- and alkyl-substituted *gem*-dibromides to the corresponding vinyl bromides through the use of ohmic heating. To the best of our knowledge, this is the first report of the indium-promoted reduction of *gem*-dibromides to vinyl bromides that is effective for alkyl-substituted *gem*-dibromides, and certainly it broadens the scope of these indium-mediated reductions.

We have also described a general method for the synthesis of highly functionalized (1*E*)-4-chloro-1-substituted-1,3-dienes from 2,4-dichlorohomoallyl acetates, derived from the indium-promoted allylation of aldehydes with 3-bromo-1,3-dichloropropene and subsequent acetylation. This process was carried out by reductive β-elimination promoted by indium and,

in contrast to previously reported procedures, by using ionic liquid media and ohmic heating there is no need of any additive.

Finally, we prepared a series of sugar-derived alkenes, dienes and enynes of considerable interest for further synthetic elaborations by palladium-catalysed cross-coupling reactions of the obtained sugar halo alkenyl substrates.

In view of the results presented herein, we are sure that the synergy arising from the combined use of indium, ionic liquids and ohmic heating will certainly go a long way to meet the increasing demand for environmentally benign chemical processes.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a 300 MHz NMR spectrometer [300.13 MHz (^{1}H), 75.47 MHz (^{13}C)] with TMS as internal reference and with $CDCl_3$ as solvent. Chemical shifts (δ) are quoted in ppm relative to TMS; coupling constants (J) are quoted in Hz. ESI-MS and ESI-HRMS (70 eV) were carried out with an electrospray ionization mass spectrometer with a micro-TOF analyser. For experiments carried out under ohmic heating, the 10 mL reactor was filled with the reaction mixture, closed and the mixture was heated to 95 °C. For 4 mL of reaction mixture, the length of the electrodes immersed in the reaction medium was 9 mm and the distance between the electrodes was 10 mm. An average magnetic stirring speed of 740 rpm was used in all the experiments carried out in the ohmic heating reactor. The temperature was measured with a type J glass-sheathed thermocouple inside the reactor. For experiments carried out under conventional heating (oil bath), an average magnetic stirring speed of 740 rpm was used. Microwave-assisted reactions were carried out in a circular single-mode cavity instrument (300 W max magnetron power output). The temperature was measured by using an IR sensor. An average stirring speed (ca. 900–1000 rpm) was used in the experiments.

General Procedure for the Preparation of 1-Bromo Alk-1-enes 2: A mixture of the corresponding *gem*-dibromo alkene **1** (0.50 mmol) and indium metal (0.60 mmol) in [bmim]Br (2.00 g) was stirred under ohmic heating at 95 °C for the time specified in Table 2. The reaction mixture was then partitioned between Et_2O (10 mL) and H_2O (10 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined extracts were dried with Na_2SO_4 and evaporated under reduced pressure to afford the products **2**. The physical data of the known 1-bromo alk-1-enes **2a**–**l** are comparable to those in the literature.[10] The physical data of the new 1-bromo alk-1-enes **2m**–**p** are given below.

6-Bromo-1-*O*-*tert*-butyldimethylsilyl-5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enefuranose (2m): Pale-yellow oil. R_f = 0.38 (hexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.37–6.19 (m, 4 H), 5.21 (s, 1 H), 5.17 (s, 1 H), 4.86–4.82 (m, 1 H), 4.73–4.65 (m, 1 H), 4.59–4.56 (m, 1 H), 4.46–4.40 (m, 2 H), 4.36–4.32 (m, 1 H), 1.47 (s, 3 H), 1.33 (s, 3 H), 1.18 (s, 3 H), 1.08 (s, 3 H), 0.77 (s, 9 H), 0.75 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H), –0.01 (s, 3 H), –0.04 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.0, 130.2, 112.7, 112.5, 110.7, 110.3, 101.3, 101.2, 87.1, 81.0, 80.6, 80.3, 79.9, 77.8, 26.1, 26.0, 25.6, 25.6, 24.9, 24.8, 17.9, 15.3, –4.5, –5.4 ppm. MS (ESI$^+$-TOF): *m/z* (%) = 380 (4, ^{81}Br) [M]$^+$, 378 (4, ^{79}Br) [M]$^+$, 317 (100). HRMS (ESI$^+$): calcd. for $C_{15}H_{29}{}^{79}BrNO_7Si$ [M]$^+$ 380.8415; found 380.8400.

Methyl 2,3,4-Tri-*O*-benzyl-7-bromo-6,7-dideoxy-α-D-*manno*-hept-6-enepyranoside (2n): Pale-yellow oil. R_f = 0.24 (hexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 30 H), 6.50–6.31 (m, 4 H), 4.88–4.58 (m, 14 H), 3.99 (dd, J = 9.5, 6.4 Hz, 1 H), 3.99–3.72 (m, 7 H), 3.38 (s, 3 H), 3.28 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 138.4, 138.3, 138.2, 138.1, 134.8, 132.6, 120.5, 128.4, 128.3, 128.2, 128.1, 120.8, 127.9, 127.8, 127.7, 127.6, 112.7, 112.5, 110.7, 110.3, 112.9, 109.4, 99.3, 75.3 (CH_2), 75.1, 74.8, 74.7, 72.9, 72.6, 72.4, 72.1, 63.3, 55.2, 54.9 ppm. MS (ESI$^+$-TOF): *m/z* (%) = 563 (12, ^{81}Br) [M + Na]$^+$, 561 (14, ^{79}Br) [M + Na]$^+$, 487 (100). HRMS (ESI$^+$): calcd. for $C_{29}H_{31}{}^{79}BrNaO_5$ [M + Na]$^+$ 561.1247; found 561.1238.

3-*O*-Benzyl-6-bromo-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enefuranose (2o): Yellow oil. R_f = 0.31 (hexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 10 H), 6.51–6.31 (m, 4 H), 5.98 (d, J = 3.8 Hz, 1 H), 5.94 (d, J = 3.4 Hz, 1 H), 4.69–4.50 (m, 8 H), 4.10 (d, J = 3.2 Hz, 1 H), 3.87 (d, J = 3.1 Hz, 1 H), 1.53 (s, 3 H), 1.48 (s, 3 H), 1.33 (s, 3 H), 1.31 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.3, 137.1, 131.7, 130.6, 128.5, 128.0, 127.9, 127.7, 127.6, 111.9, 111.8, 110.3, 110.3, 104.9, 104.8, 82.8, 82.7, 82.5, 80.3, 78.9, 72.3, 72.2, 26.9, 26.8, 26.4, 26.2 ppm. MS (ESI$^+$-TOF): *m/z* (%) = 374 (74, ^{81}Br) [M + NH_4]$^+$, 372 (75, ^{79}Br) [M + NH_4]$^+$, 314 (34), 274 (12). HRMS (ESI$^+$): calcd. for $C_{16}H_{23}{}^{79}BrNO_4$ [M + NH_4]$^+$ 372.0805; found 372.0795.

3-(2-Bromovinyl)-4*H*-chromen-4-one (2p): White solid; m.p. 107–109 °C (CH_2Cl_2/hexane). R_f = 0.30 (hexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (dd, J = 1.5, 8.0 Hz, 1 H), 7.92 (s, 1 H), 7.74 (d, J = 13.6 Hz, 1 H), 7.69–7.66 (m, 1 H), 7.48–7.41 (m, 2 H), 6.82 (d, J = 13.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.9, 156.0, 154.9, 133.9, 126.2, 125.5, 123.8, 123.0, 119.8, 118.3, 108.5 ppm. MS (ESI$^+$-TOF): *m/z* (%) = 252 (5, ^{81}Br) [M + H]$^+$, 250 (5, ^{79}Br) [M + H]$^+$, 291 (100). HRMS (ESI$^+$): calcd. for $C_{11}H_8{}^{79}BrO_2$ [M + H]$^+$ 250.9702; found 250.9695.

General Procedure for the Preparation of 1-Chloro-1,3-dienes 4: A mixture of the corresponding 2,4-dichlorohomoallyl acetate **3** (0.50 mmol) and indium metal (0.60 mmol) in [bmim]Br (2.00 g) was stirred under ohmic heating at 95 °C for the time specified in Table 3. The reaction mixture was then partitioned between Et_2O (10 mL) and H_2O (10 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined extracts were dried with Na_2SO_4 and evaporated under reduced pressure to afford products **4**. The physical data of the known 1-chloro-1,3-dienes **4a**–**g** are comparable to those in the literature.[14] The physical data of the new 1-chloro-1,3-dienes **4h**–**j** are given below.

9-Chloro-1,2:3,4-di-*O*-isopropylidene-6,7,8,9-tetradeoxy-β-D-*galacto*-non-6(*E*),8-dieno-1,5-pyranose (4h): Pale-yellow oil. R_f = 0.34 (hexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.77–6.68 (m, 1 H, 8-H_Z), 6.66–6.63 (m, 1 H, 8-H_E), 6.34 (dd, J = 11.6, 7.9 Hz, 1 H, 7-H_E), 6.34 (dd, J = 10.4, 7.2 Hz, 1 H, 7-H_Z), 6.21 (d, J = 12.9 Hz, 1 H, 9-H_E), 6.02 (d, J = 7.1 Hz, 1 H, 9-H_Z), 5.93 (dd, J = 15.9, 6.7 Hz, 1 H, 6-H_Z), 5.84–5.75 (m, 1 H, 6-H_E), 5.60–5.57 (m, 2 H, 1-H_E, 1-H_Z), 4.65–4.60 (m, 2 H), 4.39–4.30 (m, 4 H), 4.25–4.19 (m, 2 H), 1.56 (s, 3 H), 1.55 (s, 3 H), 1.47 (s, 3 H), 1.46 (s, 3 H), 1.35 (s, 6 H), 1.35 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): major isomer: δ = 132.1, 129.2, 126.0, 119.0, 109.4, 108.5, 96.4, 73.74, 70.28, 70.3, 68.6, 26.2, 25.9, 24.9, 24.3 ppm. MS (ESI$^+$-TOF): *m/z* (%) = 319 (35, ^{37}Cl) [M + H]$^+$, 317 (100, ^{35}Cl) [M + H]$^+$. HRMS (ESI$^+$): calcd. for $C_{15}H_{22}{}^{35}ClO_5$ [M + H]$^+$ 317.1150; found 317.1150.

3-*O*-Benzyl-8-chloro-1,2-*O*-isopropylidene-5,6,7,8-tetradeoxy-α-D-*xylo*-oct-5(*E*),7-dieno-1,4-furanose (4i): Pale-yellow oil. R_f = 0.32 (hexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.28

(m, 10 H), 6.83–6.74 (m, 1 H), 6.51–6.46 (m, 1 H), 6.39–6.32 (m, 3 H), 6.07–5.96 (m, 4 H), 5.82 (dd, *J* = 15.3, 7.1 Hz, 1 H), 4.73 (dd, *J* = 7.4, 2.6 Hz, 1 H), 4.67–4.63 (m, 5 H), 4.55–4.49 (m, 2 H), 3.90–3.86 (m, 2 H), 1.51 (s, 3 H), 1.49 (s, 3 H), 1.33 (s, 3 H), 1.32 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): major isomer: δ = 137.4, 130.4, 129.0, 128.5, 127.9, 127.6, 127.3, 119.5, 111.7, 104.9, 83.6, 82.7, 80.9, 72.2, 26.8, 26.2 ppm. MS (ESI$^+$-TOF): *m/z* (%) = 339 (35, ^{37}Cl) [M + H]$^+$, 337 (100, ^{35}Cl) [M + H]$^+$. HRMS (ESI$^+$): calcd. for $C_{18}H_{22}{}^{35}ClO_4$ [M + H]$^+$ 337.1201; found 317.1239.

3-[(1*E*)-4-Chlorobuta-1,3-dien-1-yl]-6-methyl-4*H*-chromen-4-one (4j): Yellow oil. R_f = 0.38 (hexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08–7.96 (m, 4 H), 7.79–7.33 (m, 6 H), 6.66–6.31 (m, 5 H), 6.09 (d, *J* = 7.1 Hz, 1 H), 2.46 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): major isomer: δ = 176.5, 159.3, 153.7, 135.4, 134.9, 134.4, 128.3, 125.5, 123.8, 123.7, 121.7, 117.8, 21.0 ppm. MS (ESI$^+$-TOF): *m/z* (%) = 249 (35, ^{37}Cl) [M + H]$^+$, 248 (15), 247 (100, ^{35}Cl) [M + H]$^+$. HRMS (ESI$^+$): calcd. for $C_{14}H_{12}{}^{37}ClO_2$ [M + H]$^+$ 249.0491; found 249.0487.

General Procedure for the Suzuki Reaction (Method A): A reaction flask containing the corresponding bromo alkene **2** (1 equiv.), Ph_3P (0.2 equiv.), $Pd(OAc)_2$ (5 mol-%), K_2CO_3 (1.5 equiv.) and phenylboronic acid (1.2 equiv.) was degassed and filled with argon. DMF (5 mL/mmol) was added and the resulting mixture was stirred at 70 °C. After 12 h, the reaction mixture was diluted with H_2O (8 mL/mmol) and extracted with Et_2O (5 mL/mmol). The combined organic extracts were washed with H_2O (5 mL/mmol) and brine (5 mL/mmol), dried (Na_2SO_4) and concentrated to dryness. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc).

(6*E*)-6,7-Dideoxy-1,2:3,4-di-*O*-isopropylidene-7-*C*-phenyl-β-D-*galacto*-hept-6-enopyranose (5a): $[\alpha]_D^{22}$ = +32.1 (*c* = 2.1, $CHCl_3$). R_f = 0.31 (hexane/EtOAc, 8:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.40 (m, 2 H), 7.32–7.22 (m, 3 H), 6.68 (d, *J* = 15.8 Hz, 1 H, 7-H), 6.31 (dd, *J* = 15.8, 6.7 Hz, 1 H, 6-H), 5.62 (d, *J* = 5.0 Hz, 1 H, 1-H), 4.65 (dd, *J* = 7.8, 2.3 Hz, 1 H, 3-H), 4.35 (dd, *J* = 5.0, 2.3 Hz, 1 H, 2-H), 4.46–4.44 (m, 1 H, 5-H), 4.28 (dd, *J* = 7.8, 2.0 Hz, 1 H, 4-H), 1.57 (s, 3 H), 1.50 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.1, 129.0, 128.7, 128.5, 128.2, 127.8, 111.4, 109.1, 96.2, 73.1, 70.9, 70.2, 69.4, 26.1, 26.0, 25.0, 24.5 ppm. MS (ESI$^+$-TOF): *m/z* (%) = 355 (23) [M + Na]$^+$, 333 (41) [M + H]$^+$. HRMS (ESI$^+$): calcd. for $C_{19}H_{24}NaO_5$ [M + Na]$^+$ 355.1516; found 355.1519.

Methyl (6*E*)-2,3,4-Tri-*O*-benzyl-7-*C*-phenyl-6,7-dideoxy-α-D-*manno*-hept-6-enepyranoside (5e): Pale-yellow oil. $[\alpha]_D^{22}$ = +2.4 (*c* = 0.4, $CHCl_3$). R_f = 0.26 (hexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.20 (m, 20 H), 6.75 (d, *J* = 15.9 Hz, 1 H, 7-H), 6.33 (dd, *J* = 15.9, 7.0 Hz, 1 H, 6-H), 4.84–4.59 (m, 7 H, 3 OC*H*$_2$Ph, 2-H), 4.19 (dd, *J* = 9.0, 7.0 Hz, 1 H, 5-H), 3.94–3.79 (m, 3 H, 2-H, 3-H, 4-H), 3.32 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 138.3, 133.8, 133.1, 128.6, 128.4, 128.3, 128.0, 127.7, 127.6, 127.5, 126.8, 126.6, 99.4, 80.0, 78.9, 75.4, 74.9, 73.0, 72.9, 72.6, 54.9 ppm. MS (ESI$^+$-TOF): *m/z* (%) = 559 (100) [M + Na]$^+$. HRMS (ESI$^+$): calcd. for $C_{35}H_{36}NaO_5$ [M + Na]$^+$ 559.2455; found 559.2423;

General Procedure for the Sonogashira Reaction (Method B): A reaction flask containing the corresponding bromo alkene **2** (1 equiv.), Ph_3P (0.2 equiv.), $Pd(OAc)_2$ (5 mol-%) and CuI (5 mol-%) was degassed and filled with argon. DMF (5 mL/mmol) and *i*Pr_2NH (2.5 mL/mmol) were added followed by ethynylbenzene (1.2 equiv.). After stirring at room temp. for 10 h, the mixture was diluted with H_2O (8 mL/mmol) and extracted with Et_2O (5 mL/mmol). The combined organic extracts were washed with H_2O (5 mL/mmol) and brine (5 mL/mmol), dried (Na_2SO_4) and concentrated to dryness. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc).

(6*E*)-1,2:3,4-Di-*O*-isopropylidene-9-*C*-phenyl-6,7,8,9-tetradeoxy-β-D-*galacto*-nona-6-en-8-ynopyranose (5b): Yellow oil. $[\alpha]_D^{22}$ = +4.6 (*c* = 0.6, $CHCl_3$). R_f = 0.31 (hexane/EtOAc, 8:1). ^{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, 8-H), 5.90 (dd, *J* = 11.0, 1.0 Hz, 1 H, 7-H), 5.58 (d, *J* = 5.0 Hz, 1 H, 1-H), 5.01 (dd, *J* = 8.0, 2.0 Hz, 1 H, 5-H), 4.67 (dd, *J* = 7.9, 2.5 Hz, 1 H, 3-H), 4.39–4.44 (m, 2 H, 2-H, 4-H), 1.57 (s, 3 H), 1.50 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3 H) ppm. ^{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 ppm. MS (ESI$^+$-TOF): *m/z* (%) = 357 (4) [M + Na]$^+$, 241 (100). HRMS (ESI$^+$): calcd. for $C_{21}H_{25}O_5$ [M + H]$^+$ 357.1696; found 357.1707.

General Procedure for the Kumada Reaction (Method C): A reaction flask containing the corresponding chlorodiene **4** (1 equiv.) and $[Pd(PPh_3)_4]$ (5 mol-%) was degassed and filled with argon. DMF (5 mL/mmol) and Et_3N (3 equiv.) were added followed by phenylmagnesium bromide (2 equiv.). After stirring at room temp. for 1 h, the mixture was quenched with an aqueous saturated solution of NH_4Cl (8 mL/mmol) and extracted with Et_2O (5 mL/mmol). The combined organic extracts were washed with H_2O (5 mL/mmol) and brine (5 mL/mmol), dried (Na_2SO_4) and concentrated to dryness. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc).

(6*E*,8*E*)-1,2:3,4-Di-*O*-isopropylidene-9-*C*-phenyl-6,7,8,9-tetradeoxy-β-D-*galacto*-nona-6,8-dieno-1,5-pyranose (5c): Yellow oil. R_f = 0.38 (hexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 10 H), 6.92–6.79 (m, 2 H), 6.59–6.26 (m, 4 H), 5.98–5.90 (m, 2 H), 5.61–5.56 (m, 2 H), 4.63–4.60 (m, 2 H), 4.36–4.30 (m, 4 H), 4.24–4.21 (m, 2 H), 1.56 (s, 3 H), 1.52 (s, 3 H), 1.49 (s, 3 H), 1.46 (s, 3 H), 1.38 (s, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.33 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): major isomer: δ = 137.4, 131.2, 130.5, 129.6, 129.0, 128.2, 127.0, 115.3, 109.3, 108.5, 96.4, 73.5, 70.9, 70.4, 68.7, 26.1, 26.0, 24.9, 24.3 ppm. MS (ESI$^+$-TOF): *m/z* (%) = 359 (100) [M + H]$^+$, 358 (12) [M]$^+$. HRMS (ESI$^+$): calcd. for $C_{21}H_{27}O_5$ [M + H]$^+$ 359.1853; found 359.1853.

(5*E*,7*E*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-8-phenyl-5,6,7,8-tetradeoxy-α-D-*xylo*-oct-5,7-dieno-1,4-furanose (5g): Yellow oil. R_f = 0.38 (hexane/EtOAc, 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 20 H), 6.83–6.74 (m, 1 H), 6.66–6.46 (m, 1 H), 6.39–6.21 (m, 2 H), 6.07–5.94 (m, 5 H), 5.90–5.76 (m, 1 H), 4.74–4.50 (m, 8 H), 3.90 (d, *J* = 3.2 Hz, 1 H), 3.86 (d, *J* = 3.1 Hz, 1 H), 1.51 (s, 3 H), 1.49 (s, 3 H), 1.33 (s, 3 H), 1.32 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): major isomer: δ = 137.4, 130.4, 129.0, 128.5, 127.9, 127.6, 127.3, 119.5, 111.7, 104.9, 83.6, 82.9, 80.9, 72.2, 26.8, 26.2 ppm. MS (ESI$^+$-TOF): *m/z* (%) = 379 (25) [M + H]$^+$, 123 (100). HRMS (ESI$^+$): calcd. for $C_{24}H_{27}O_4$ [M + H]$^+$ 379.1904; found 379.1938.

General Procedure for the Stille Reaction (Method D): A reaction flask containing the corresponding bromo alkene **2** (1 equiv.) in DMF (5 mL/mmol) was degassed and filled with argon. Ph_3P (0.2 equiv.) and $Pd(OAc)_2$ (5 mol-%) were added, followed by tributyl(vinyl)stannane (1.1 equiv.). After stirring at 60 °C for 10 h, the reaction mixture was diluted with H_2O (8 mL/mmol) and extracted with EtOAc (5 mL/mmol). The combined organic extracts were washed with H_2O (5 mL/mmol) and brine (5 mL/mmol), dried (Na_2SO_4) and concentrated to dryness.

(5*E*)-1-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-5,6,7,8-tetradeoxy-α-D-*lyxo*-oct-5,7-dieno-1,4-furanose (5d): Colourless oil. $[\alpha]_D^{22}$ = −27.5 (*c* = 1.2, $CHCl_3$). R_f = 0.27 (hexane/EtOAc, 9:1). ^{1}H

NMR (300 MHz, $CDCl_3$): δ = 6.33–6.20 (m, 2 H), 5.73 (dd, J = 4.8, 8.9 Hz, 1 H), 5.21 (s, 1 H), 5.14 (dd, J = 1.3, 9.8 Hz, 1 H), 5.03 (dd, J = 1.3, 5.9 Hz, 1 H), 4.59 (dd, J = 2.2, 3.5 Hz, 1 H), 4.45 (d, J = 3.5 Hz, 1 H), 4.41 (dd, J = 2.2, 4.8 Hz, 1 H), 1.37 (s, 3 H), 1.20 (s, 3 H), 0.78 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.4, 134.8, 127.4, 118.2, 112.4, 101.3, 87.3, 81.7, 80.5, 26.1, 25.6, 24.9, 17.9, –4.5, –5.4 ppm. MS (ESI$^+$-TOF): m/z (%) = 521 (100) [M + H]$^+$. HRMS (ESI$^+$): calcd. for $C_{28}H_{45}O_7Si$ [2M – OTBS – H]$^+$ 521.2929; found 521.2925.

General Procedure for the Heck Reaction (Method E): A reaction flask containing the corresponding bromo alkene **2** (1 equiv.) in DMF (5 mL/mmol) was degassed and filled with argon. LiCl (3 equiv.) and Et_3N (1 equiv.) were added, followed by $Pd(OAc)_2$ (5 mol-%) and methyl acrylate (1.5 equiv.). After stirring at 70 °C for 12 h, the reaction mixture was diluted with H_2O (8 mL/mmol) and extracted with EtOAc (5 mL/mmol). The combined organic extracts were washed with H_2O (5 mL/mmol) and brine (5 mL/mmol), dried (Na_2SO_4) and concentrated to dryness. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc).

Methyl (5*E*,7*E*)-3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6,7,8-tetradeoxy-α-D-*xylo*-nona-5,7-dienofuranuronate (5f): Yellow oil. $[\alpha]_D^{21}$ = –2.6 (c = 0.4, $CHCl_3$). R_f = 0.21 (hexane/EtOAc, 7:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H), 6.50 (dd, J = 15.4, 11.1 Hz, 1 H), 6.17 (dd, J = 15.4, 6.4 Hz, 1 H), 5.99 (d, J = 3.7 Hz, 1 H), 5.91 (d, J = 15.2 Hz, 1 H), 4.75–4.71 (m, 1 H), 4.66–4.62 (m, 3 H), 4.50 (d, J = 12.2 Hz, 1 H), 3.92 (d, J = 3.1 Hz, 1 H), 3.76 (s, 3 H, OCH_3), 1.50 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4, 143.7, 137.2, 135.8, 130.8, 128.5, 128.0, 127.7, 121.7, 111.8, 104.9, 83.2, 82.8, 80.3, 72.2, 51.6, 26.8, 26.2 ppm. MS (ESI$^+$-TOF): m/z (%) = 361 (100) [M + H]$^+$. HRMS (ESI$^+$): calcd. for $C_{20}H_{25}O_6$ [M + H]$^+$ 361.1646; found 361.1645.

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