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Domino reactions of 5-deoxy-5-iodo-D-*xylo*- and -L-arabinofuranose derivatives with organometallic reagents. A way towards polyfunctionalized building-blocks

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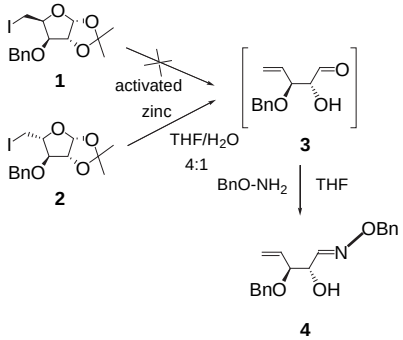
ABSTRACT

Domino reactions involving metal–halogen exchange, furanose ring-opening and nucleophilic addition from 3-*O*-benzyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-xylofuranose and the epimeric L-*arabino* derivative with various organometallic reagents are reported. In anhydrous conditions, with a large excess of organolithium or Grignard reagents, vicinal diols are obtained with good yields and a fair diastereoselectivity. Interestingly, with α-trimethylsilyl organolithium reagents, the fragmentation of the furanose ring to the substituted pent-4-enal is followed by a Peterson olefination giving dienic compounds in a four-step one-pot process.

1. Introduction

As part of a broad research program devoted to the valorization of wheat hemicelluloses, we have been interested in the chemical transformation of their two main components, D-xylose and L-arabinose, into higher added-value products.[1] On the other hand, domino reactions have become a very attractive tool for enhancing synthetic efficiency with the formation of several bonds in a single step.[2] Such a strategy is particularly interesting in carbohydrate chemistry, due to the complexity and the high degree of functionalization of these molecules.[3]

In previous reports,[1] we have described the zinc-mediated ring opening (Vasella–Bernet reaction) of 5-deoxy-5-iodo-D-xylofuranosides and -L-arabinofuranosides, bearing different protecting groups at C-2 and C-3 positions, to produce the same γ,δ-unsaturated aldehyde whatever the starting pentose. Our results have shown that reaction of the D-*xylo*-derived iodo compound **1** with activated zinc was unsuccessful whatever the reaction conditions (Scheme 1). Compound **1** proved to be so inert that even the simple reduction of the carbon–iodine bond, which was previously observed using the Zn/Ag–graphite complex,[4] did not occur. In contrast, the same reaction carried out on the epimeric L-*arabino* derivative **2** surprisingly afforded the target pent-4-enal **3**, isolated as its benzyl oxime ether **4** (Scheme 1). The difference in reactivity of these two iodo pentofuranoses, obviously related to the stereochemistry at C-4, was studied in more details.[1a]



Scheme 1.

As the zinc-mediated reductive elimination was not effective with both these epimeric 5-iodo pentofuranoses, we have attempted to induce the furanose ring-opening with *n*-butyllithium, via a halogen–metal exchange. Such a reaction has been described with halogenated D-glucopyranosides[5] or D-ribofuranosides,[6] but was never reported in D-xylose and L-arabinose series. The results observed led us to a more general study of the domino

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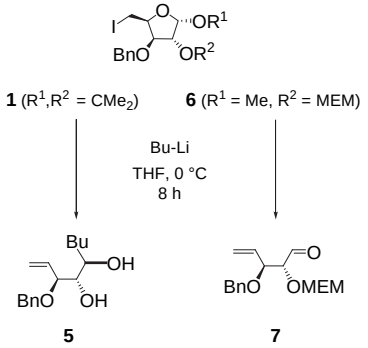
reaction involving metal–halogen exchange–ring opening–alkylation with organolithium and organomagnesium reagents. In addition, we have considered reactions with α-silylated organolithium reagents to extend the domino character of these transformations. We report here a full account of this work.

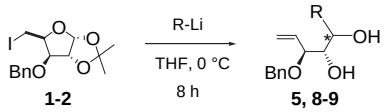
2. Results and discussion

The iodinated 1,2-*O*-isopropylidene D-*xylo* derivative **1** did not react under the reported experimental conditions (*n*-BuLi, 1 equiv, THF, −78 °C),[6] and remained inert at a temperature of −20 °C. At 0 °C, compound **1** was partially transformed (48% conversion) into diol **5** with 33% overall yield as an inseparable 7/1 mixture of diastereomers (Scheme 2 and Table 1, entry 1). The reductive elimination occurred and the released carbonyl group was trapped in situ by the organolithium reagent. Interestingly, treatment under the same conditions of the iodinated methyl D-xylofuranoside **6**,[1b] protected with a MEM group at the 2-position, led to the pent-4-enal **7** without subsequent alkylation (Scheme 2). Several attempts for a selective ring-opening of compound **1** without a subsequent alkylation by using more hindered organolithium reagents such as *sec*-BuLi or *tert*-BuLi failed.



Scheme 2.

Table 1
Tandem reaction of the 5-deoxy-5-iodo pentofuranoses **1**,**2** with organolithium reagents



Entry	Starting material	R-Li	Product	dr[a]	Yield[b] (%)
1	**1**	*n*-BuLi (1 equiv)	**5**	7:1	33[c]
2	**1**	*n*-BuLi (2.5 equiv)	**5**	7:1	64[d]
3	**1**	*n*-BuLi (3.5 equiv)	**5**	7:1	88
4	**1**	MeLi (3.5 equiv)	**8**	4:1	90
5	**1**	PhLi (3.5 equiv)	**9**	6:1	90
6	**2**	*n*-BuLi (3.5 equiv)	**5**	6:1	83

[a] Determined by ^{1}H NMR and HPLC.
[b] Isolated yield, mixture of diastereomers.
[c] Conversion: 48%.
[d] Intermediate aldehyde isolated (15%) as its benzyl oxime.

Hence, the fast nucleophilic addition occurring in the case of compound **1** was probably due to a α-chelation of lithium by the oxygen atoms of the generated alcoholate and of the carbonyl group,[7] enhancing the electrophilicity of the latter. Such a α-chelation should also control the diastereoselectivity of the nucleophilic addition (Fig. 1), as already reported for similar situation of organometallic additions on aldose derivatives.[8–10] Thus the *syn*-configuration (*R* for the new stereogenic center) was assigned to the major diastereomer. Further experimental observations corroborate this assignment (vide infra).

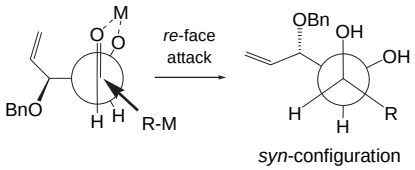


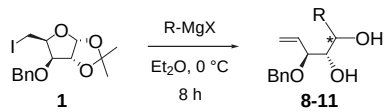
Figure 1. Major diastereomer according to α-chelated model.

The domino zinc-mediated reductive elimination–Barbier-type reaction of ω-iodoglycosides with unsaturated alkyl halides was widely developed by Madsen[3,11] and others.[12] These reactions being performed in aqueous THF, the nucleophilic addition step proceeds via a non-chelated Felkin–Anh transition state,[13] giving selectively the *anti*-epimer.[11a,b] Our domino transformation with organolithium reagents may be considered as a complementary methodology, justifying its optimisation and extension to other organometallics.

Using a 2.5fold-excess of *n*-butyllithium, conversion of **1** was completed and diol **5** was obtained in 64% yield (Table 1, entry 2). Addition of an excess of *O*-benzyl hydroxylamine hydrochloride and 4 Å molecular sieves to the reaction mixture before the work-up showed the presence of remaining pent-4-enal **3** isolated as its *O*-benzyl oxime ether **4** in 15% yield (ratio **5**/**4**: 80:20). This incomplete transformation of the intermediate enal could be due to the presence of two electrophilic by-products in the reaction medium: 1-iodobutane and acetone. Using 3.5 equiv of *n*-BuLi in THF at 0 °C, the overall yield for compound **5** eventually raised to 88% with the same diastereomeric ratio (7:1) (Table 1, entry 3). In the same reaction conditions, two other commercially available organolithium reagents (MeLi and PhLi) were successfully used to afford the corresponding diols **8**,**9** as inseparable mixtures of diastereomers in excellent yields (Table 1, entries 4 and 5). The epimeric 5-iodo L-*arabino* derivative **2** reacted similarly (Table 1, entry 6), and the transformation can therefore be applied to a mixture of epimers.

To the best of our knowledge, the tandem reductive ring-opening–alkylation of 5-deoxy-5-iodo-pentofuranosides with Grignard reagents was not reported so far. However, it has to be mentioned that a somewhat similar transformation was previously described starting from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose derivatives bearing an heteroarylsulfanyl group at the primary position to afford vinyl sulfides in a one-step sequence with acceptable yields.[10] As a wide range of organomagnesium reagents are commercially available, it was relevant to extend the scope of the domino transformation of 5-deoxy-5-iodo-pentofuranosides with Grignard reagents. A larger excess of organomagnesium reagents was required for a complete conversion (Table 2, entries 1–3). Using allylmagnesium bromide as a model, best results were obtained in anhydrous diethyl ether at

Table 2
Tandem reaction of 5-deoxy-5-iodo D-xylofuranose **1** with Grignard reagents



Entry	R-MgX	Conversion (%)	Product	dr[a]	Yield[b] (%)
1	AllMgBr (2.8 equiv)	44	**10**	6:1	33
2	AllMgBr (4 equiv)	78	**10**	6:1	69
3	AllMgBr (5.5 equiv)	98	**10**	6:1	91
4	MeMgCl (5.5 equiv)	94	**8**	4:1	88
5	PhMgBr (5.5 equiv)	95	**9**	6:1	87
6	*i*-PrMgCl(5.5 equiv)	96	**11**	4:1	92

[a] Determined by ^{1}H NMR and HPLC.
[b] Isolated yield, mixture of diastereomers.

0 °C with 5.5 equiv of the Grignard reagent leading to an inseparable mixture of the expected diol **10** with 91% yield and a 6:1 diastereomeric ratio. Under these optimal conditions, the same transformation was achieved with several other organomagnesium reagents (Table 2, entries 4–6). As observed by HPLC and ^{1}H NMR analyses, the major diastereoisomers obtained from PhMgBr and CH_3MgCl were identical to the ones derived from reactions with the corresponding organolithium reagents.

In order to further support the predicted stereochemical outcome of the reaction, we took advantage of the possibility of isolating by HPLC a pure sample of the major diastereomer **11maj** of the diol **11** resulting from the reaction with *i*-PrMgCl. Attempts to obtain X-ray diffraction data from **11maj** or from the corresponding *p*-nitrobenzoyl ester were unsuccessful. Derivatization into a cyclic acetal was expected to afford stereochemical information via the observed coupling constants. Unfortunately, the ^{1}H NMR spectrum of the isopropylidene derivative from **11maj** in various solvents ($CDCl_3$, benzene-d_6, acetone-d_6) exhibited an overlap between protons H_3, H_4 and H_5, preventing any interpretation regarding the configuration. In order to circumvent this problem, the cyclic carbonate **12** was prepared from **11maj**.[14] The resolution of its ^{1}H NMR spectrum allowed to discriminate protons H_4 (δ=4.36 ppm) and H_5 (δ=4.28 ppm) and to read their coupling constant (^3J=4.1 Hz). Owing to the discrepancies of literature NMR data for similar cyclic carbonates,[15] a reliable assignment could not be deduced by a simple comparison of the coupling constants. Thus, correlation was attempted between our experimental result and those resulting from molecular modelling. Optimization[16] of the conformational structure of *syn*-**12** affords the calculated dihedral angle H_4–C_4–C_5–H_5=−111° and a coupling constant J_{syn}=3.6 Hz (Fig. 2). Similar modelisation for *anti*-**12** affords a dihedral angle of 28.9° and J_{anti}=5.7 Hz. The observed coupling constant (J=4.1 Hz) corroborates the anticipated *syn*-configuration for the major diastereomer (Fig. 1).

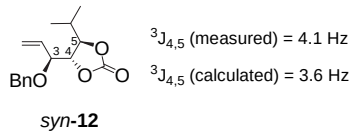
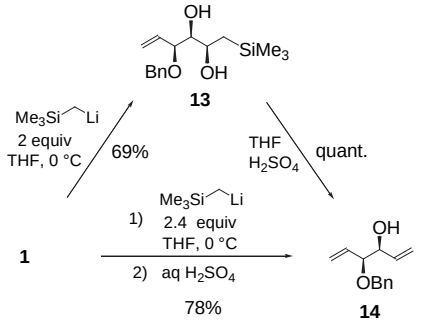


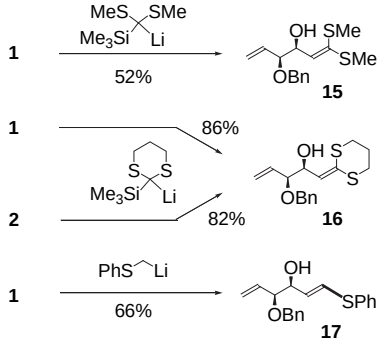
Figure 2. Measured and calculated $^3J_{4,5}$ for the cyclic carbonate **12**.

Finally, the reaction of 5-deoxy-5-iodopentofuranosides with α-silyl organolithium reagents was investigated in order to attempt a domino reaction including a further olefination step. Indeed, in that case, a Peterson reaction should occur after addition on the intermediate aldehyde. When **1** was treated with a commercially available (trimethylsilyl)methyllithium solution (2 equiv) in THF at 0 °C, the domino sequence stopped at the nucleophilic addition stage, giving the vicinal diol **13** in 69% yield and a high diastereomeric excess (Scheme 3). Compound **13** was easily and quantitatively converted into the 1,5-diene **14** under acidic conditions. A better overall yield (78%) of diene **14** was obtained when the transformation was conducted with 2.4 equiv of the lithium reagent and without isolation of the intermediate **13**. Under the same conditions, the lithium reagent derived from methyl trimethylsilylacetate did not react with **1**, probably because the metal–halogen exchange failed.



Scheme 3.

Treatment of **1** with α-lithio-α-trimethylsilyl dithioacetals (2.4 equiv) led directly to the expected γ-unsaturated ketene dithioacetals **15**,**16** in 52–86% yield, as a result of a four-step domino reaction (Scheme 4). Under the same experimental conditions, compound **16** was achieved in 82% yield starting from the 5-deoxy-5-iodo L-arabinofuranoside **2**. A similar reaction sequence took place when compound **1** was reacted with a α-lithio-α-trimethylsilyl thioether, to afford the corresponding enol thioether **17** in 66% yield (Scheme 4).



Scheme 4.

3. Conclusions

A three-step domino transformation of 5-deoxy-5-iodo-pentofuranoside derivatives, involving a halogen–metal exchange with an organolithium or magnesium reagent, a β-fragmentation and a nucleophilic addition was achieved, leading to high yields of 1-vinyl-3-alkyl(aryl)-propanetriol derivatives. The last step is fairly stereoselective towards the (*R*)-diastereomer resulting from a chelated–Cram type transition state model. In contrast to the reductive elimination using zinc metal, which was previously shown to work only with 3-*O*-benzyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-L-arabinofuranose, this organometallic-mediated transformation works with the corresponding D-*xylo* epimer as well, and thus could be applied to the mixture of epimers. Despite their generality and the high yields, the preparative interest of these transformations is somewhat limited by the obtention of a mixture of diastereomers most of them being inseparable. In contrast, α-silylated organolithium reagents afforded, by means of a further Peterson step, diastereo- and enantiopure functionalized 1,5-dienes, which may be viewed as interesting new enantiopure building-blocks.

4. Experimental

4.1. General methods

All air- and moisture-sensitive reactions were carried out under an argon atmosphere. THF and Et_2O were distilled over Na/benzophenone before use. All commercially available chemicals were used as received unless otherwise noted. Commercial organolithium reagents (Acros) were titrated before use with diphenylacetic acid in THF.[17] Commercial Grignard reagents (Acros, Aldrich) were titrated before use in THF against menthol in the presence of 1,10-phenanthroline.[17]

All reported NMR spectra were recorded with a Bruker AC 250. Chemical shifts are reported as δ values relative to $CHCl_3$ peak

defined at δ=7.27 (^{1}H NMR) or δ=77.0 (^{13}C NMR). IR spectra were recorded using NaCl film or KBr pellets on an AVATAR 320 FT-IR (Nicolet) spectrometer. Optical rotations were recorded using a Perkin–Elmer 241 polarimeter with a thermally jacketed 10 cm cell in the specified solvents. HRMS was performed on a Q-TOF Micro micro-mass positive ESI (CV=30 V) instrument. Optical rotations were determined at 23 °C on a Perkin–Elmer Model 241 polarimeter. Analytical TLC was performed on Merck 60 PF_{254} silica gel pre-coated plates. Preparative flash silica gel chromatography was performed using Merck Kieselgel 60 (40–63 μm). Petroleum ether refers to the fraction with bp 40–65 °C. Gas chromatography (GC) analyses were performed on a polydimethylsiloxane HP ultra I column and a flame ionisation detector. High-performance liquid chromatography (HPLC) separations (analytical or semi-preparative) were performed on a LiChrospher Si60 (5 μm) column with mixtures hexane/ethyl acetate as eluents.

Compounds **1**, **2**, **4**, **6** and **7** were previously reported.[1]

4.2. General procedure for the reactions with organolithium reagents

The 5-deoxy-5-iodo pentofuranose **1** or **2** (0.3 g, 0.77 mmol) was dissolved in freshly distilled THF (3 mL) and the mixture was stirred under argon. The organolithium reagent (2.7 mmol, titrated solutions in Et_2O) was then added dropwise at 0 °C. After total disappearance of the starting material (TLC monitoring, 7:3 petroleum ether/EtOAc), the reaction mixture was poured in Et_2O (20 mL) and extracted twice with a saturated NH_4Cl solution (2×5 mL) and water (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by flash chromatography on silica gel (7:3 petroleum ether/EtOAc) to afford the pure unsaturated diol as a mixture of inseparable diastereomers.

4.3. General procedure for the reactions with organomagnesium reagents

The 5-deoxy-5-iodo pentofuranose **1** (0.3 g, 0.77 mmol) was dissolved in freshly distilled Et_2O (4 mL) and the mixture was stirred under argon. The Grignard reagent (4.24 mmol, titrated solutions in Et_2O) was then added dropwise at 0 °C. After total disappearance of the starting material (TLC monitoring, 7:3 petroleum ether/EtOAc), the reaction mixture was poured in Et_2O (20 mL) and extracted twice with a saturated NH_4Cl solution (2×5 mL) and water (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by flash chromatography on silica gel (7:3 petroleum ether/EtOAc) to afford pure unsaturated diols as mixtures of inseparable diastereomers, except for compound **11**.

*4.3.1. (3S, 4S)-3-Benzyloxynon-1-ene-4,5-diol (**5**) (mixture of diastereomers 7:1).* Colourless oil. Yield: 88%. IR (film) ν_{max} cm^{-1}: 3432, 3083, 2955, 2930, 2853, 1378, 1204, 1061; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.37–7.26 (m, 5H, C_6H_5), 5.86–5.80 (m, 1H, H-2), 5.41–5.27 (m, 2H, H-1), 4.57 (d, 1H, *J*=11.6 Hz, C*H*Ph), 4.32 (d, 1H, *J*=11.6 Hz, C*H*Ph), 3.87 (dd, 1H, *J*=14.0, 7.5 Hz, H-3), 3.61–3.55 (m, 1H, H-5), 3.50–3.46 (m, 0.12H, H-4 minor dia.), 3.42–3.38 (m, 0.88H, H-4 major dia.), 2.97 (br s, 1H, OH), 2.91 (br s, 1H, O*H*), 1.67–1.15 (m, 6H, CH_2), 0.92–0.89 (m, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 138.1 (C_q arom.), 135.4 (C-2), 129.0–127.5 (*C*H arom.), 121.1, 120.1 (C-1), 82.6, 81.1 (C-4), 76.2, 75.5 (C-3), 73.2, 71.6 (C-5), 70.8, 70.6 (CH_2Ph), 34.3, 32.9, 28.4, 23.1 (CH_2), 14.5 (CH_3); ESIHRMS calcd for $C_{16}H_{24}O_3Na$ ([M+Na]$^+$) 287.1623; found 287.1631.

*4.3.2. (3S, 4S)-4-Benzyloxyhex-5-ene-2,3-diol (**8**) (mixture of diastereomers 4:1).* Pale yellow oil. Yield: 90%. IR (film) ν_{max} cm^{-1}: 3406, 3078, 2960, 2904, 2838, 1363, 1071; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H, C_6H_5), 5.92–5.86 (m, 1H, H-5), 5.42–5.33 (m, 2H, H-6), 4.53 (d, 1H, *J*=11.7 Hz, C*H*Ph), 4.31 (d, 1H, *J*=11.6 Hz, C*H*Ph), 4.01–3.83 (m, 2H, H-2, H-4), 3.32 (br s, 1H, H-3), 2.86 (br s, 1H, O*H*), 2.64 (br s, 1H, O*H*), 1.13 (d, 3H, *J*=10.3 Hz, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 138.2 (C_q arom.), 135.5, 135.4 (C-5), 129.1–128.2 (*C*H arom.), 120.9, 120.8 (C-6), 82.2, 81.3 (C-3), 70.9 (C-2), 70.8 (C-4), 69.0, 68.0 (CH_2Ph), 23.5, 20.5 (CH_3); ESIHRMS calcd for $C_{13}H_{18}O_3Na$ ([M+Na]$^+$) 245.1154; found 245.1154.

*4.3.3. (2R, 3S)-3-Benzyloxy-1-phenylpent-4-ene-1,2-diol (**9**) (mixture of diastereomers 6:1).* Pale yellow oil. Yield: 90%. IR (film) ν_{max} cm^{-1}: 3426, 3083, 3058, 3022, 2971, 2909, 2863, 1204, 1117, 1055, 1030; ^{1}H NMR (250 MHz, $CDCl_3$+D_2O): δ 7.55–7.23 (m, 10H, C_6H_5), 5.92–5.85 (m, 1H, H-4), 5.39–5.20 (m, 2H, H-5), 4.80 (d, 0.15H, *J*=5.6 Hz, H-1 minor dia.), 4.70 (d, 0.85H, *J*=4.8 Hz, H-1 major dia.), 4.62 (d, 1H, *J*=11.4 Hz, C*H*Ph), 4.29 (d, 1H, *J*=11.4 Hz, C*H*Ph), 3.87–3.82 (m, 0.15H, H-3 minor dia.), 3.79 (dd, 0.85H, *J*=7.9, 4.2 Hz, H-3 major dia.), 3.64–3.58 (m, 1H, H-2); ^{13}C NMR (62.9 MHz, $CDCl_3$+D_2O): δ 141.4, 138.2 (C_q arom.), 135.4 (C-4), 129.1–126.9 (*C*H arom.), 120.6 (C-5), 80.8, 80.7 (C-2), 78.1, 76.7 (C-3), 74.3 (C-1), 71.0, 69.9 (CH_2Ph); ESIHRMS calcd for $C_{18}H_{20}O_3Na$ ([M+Na]$^+$) 307.1310; found 307.1304.

*4.3.4. (3S, 4S)-3-Benzyloxyocta-1,7-diene-4,5-diol (**10**) (mixture of diastereomers 6:1).* Colourless oil. Yield: 91%. IR (film) ν_{max} cm^{-1}: 3442, 3068, 3032, 2976, 2925, 1199, 1061; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.39–7.27 (m, 5H, C_6H_5), 5.79–5.74 (m, 2H, H-2, H-7), 5.42–5.33 (m, 2H, H-1), 5.13–5.05 (m, 2H, H-8), 4.67–4.63 (m, 1H, C*H*Ph), 4.37 (d, 0.15H, *J*=11.6 Hz, C*H*Ph minor dia.), 4.32 (d, 0.85H, *J*=11.6 Hz, C*H*Ph major dia.), 4.07 (dd, 0.85H, *J*=8.0, 6.3 Hz, H-3 major dia.), 4.02 (dd, 0.15H, *J*=7.9, 4.1 Hz, H-3 minor dia.), 3.72–3.64 (m, 1H, H-5), 3.48–3.42 (m, 1H, H-4), 2.95 (d, 1H, *J*=3.9 Hz, O*H*), 2.66 (br s, 1H, O*H*), 2.34–2.25 (m, 2H, H-6); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 138.2, 138.1 (C_q arom.), 135.3, 135.2 (C-2), 129.1–127.5 (*C*H arom.), 121.1, 120.2 (C-1), 118.4, 118.2 (C-8), 82.8, 80.6 (C-4), 76.1, 74.9 (C-3), 72.0, 71.1 (C-5), 71.0 (CH_2Ph), 39.2, 38.1 (C-6); ESIHRMS calcd for $C_{15}H_{20}O_3Na$ ([M+Na]$^+$) 271.1310; found 271.1315. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.56; H, 8.12%. Found: C, 72.52; H, 7.91%.

*4.3.5. (3S, 4S)-3-Benzyloxy-6-methylhept-1-ene-4,5-diol (**11**) (mixture of diastereomers 6:1).* Colourless oil. Yield: 92%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38–7.27 (m, 5H, C_6H_5), 6.05 (ddd, 0.15H, *J*=17.4, 10.1, 8.0 Hz, H-2 minor dia.), 5.91–5.71 (m, 0.85H, H-2 major dia.), 5.52–5.38 (m, 2H, H-1), 4.65 (d, 0.15H, *J*=11.7 Hz, C*H*Ph minor dia.), 4.64 (d, 0.85H, *J*=11.7 Hz, C*H*Ph major dia.), 4.35 (d, 0.85H, *J*=11.5 Hz, C*H*Ph major dia.), 4.33 (d, 0.15H, *J*=11.5 Hz, C*H*Ph minor dia.), 4.07 (dd, 0.15H, *J*=7.8, 2.6 Hz, H-3 minor dia.), 3.95 (t, 0.85H, *J*=7.4 Hz, H-3 major dia.), 3.79–3.70 (m, 0.15H, H-5 minor dia.), 3.61 (dd, 0.85H, *J*=6.6, 3.6 Hz, H-5 major dia.), 3.39 (dd, 0.15H, *J*=12.8, 6.4 Hz, H-4 minor dia.), 3.18 (t, 0.85H, *J*=7.4 Hz, H-4 major dia.), 2.84 (d, 0.85H, *J*=3.6 Hz, O*H* major dia.), 2.57 (d, 0.15H, *J*=8.2 Hz, O*H* minor dia.), 2.46 (d, 0.85H, *J*=7.5 Hz, O*H* major dia.), 2.25 (d, 0.15H, *J*=12.6 Hz, O*H* minor dia.), 1.85–1.80 (m, 1H, H-6), 0.99–0.87 (m, 6H, H-7).

*4.3.6. (3S, 4S, 5R)-3-Benzyloxy-6-methylhept-1-ene-4,5-diol (**11maj**).* The major diastereomer was separated by semi-preparative HPLC (eluent: hexane/EtOAc 75:25). White powder, mp 59 °C; $[\alpha]_D^{23}$−4 (*c* 0.60, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.33–7.29 (m, 5H, C_6H_5), 5.84–5.71 (m, 1H, H-2), 5.44–5.38 (m, 2H, H-1), 4.64 (d, 1H, *J*=11.4 Hz, C*H*Ph), 4.34 (d, 1H, *J*=11.4 Hz, C*H*Ph), 3.94 (t, 1H, *J*=7.3 Hz, H-3), 3.66–3.60 (m, 1H, H-5), 3.18 (t, 1H, *J*=7.3 Hz, H-4), 2.88 (br s, 1H, O*H*), 2.49 (d, 1H, *J*=7.2 Hz, O*H*), 1.85–1.80 (m, 1H, H-6), 0.97 (d, 3H, *J*=13.5 Hz, H-7), 0.88 (d, 3H, *J*=13.5 Hz, H-7); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 138.4 (C_q arom.), 135.1 (C-2), 129.2–128.5 (*C*H arom.), 121.3 (C-1), 83.4 (C-4), 76.6

(C-5), 73.1 (C-3), 71.1 (*C*H$_2$Ph), 31.9 (C-6), 19.6, 19.5 (C-7); ESIHRMS calcd for $C_{15}H_{22}O_3Na$ ([M+Na]$^+$) 273.1467; found 273.1474. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%. Found: C, 71.61; H, 9.29%.

4.4. Reaction with α-lithiotrimethylsilyl reagents

To a solution of the silylated reagent (1.85 mmol) in anhydrous THF (1.5 mL) was added at 0 °C under argon a solution of *n*-butyllithium (2.4 equiv). After stirring for 2 h at 0 °C, a solution of the iodofuranose **1** (or **2**) in THF (1.5 mL) was slowly added. The mixture was left at rt until completion of the reaction (TLC monitoring; petroleum ether/EtOAc 70/30). Diethyl ether (15 mL) was added and the resulting mixture was washed with a saturated aqueous NH_4Cl solution (2 mL) then with water (2×2 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated and the crude product was purified on silica gel chromatography (75:25 petroleum ether/EtOAc).

*4.4.1. (3S,4S)-4-Benzyloxy-1-trimethylsilylhex-5-ene-2,3-diol (**13**).* Colourless oil. Yield: 69%. Single isomer (only traces of the other diastereomer were detected in the ^{1}H NMR spectrum). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38–7.27 (m, 5H, C_6H_5), 5.86 (ddd, 1H, *J*=16.8, 10.8, 7.9 Hz, H-5), 5.43–5.32 (m, 2H, H-6), 4.63 (d, 1H, *J*=11.6 Hz, C*H*Ph), 4.31 (d, 1H, 11.6 Hz, C*H*Ph), 3.88 (dd, 1H, *J*=8.2, 5.7 Hz, H-4), 3.80 (ddd, 1H, *J*=8.2, 5.7, 2.4 Hz, H-2), 3.28 (dd, 1H, *J*=5.7, 2.4 Hz, H-3), 2.74 (br s, 1H, O*H*), 2.37 (d, 1H, *J*=5.7 Hz, O*H*), 0.92 (dd, 1H, *J*=14.4, 5.7 Hz, H-1), 0.75 (dd, 1H, *J*=14.4, 9.1 Hz, H-1), 0.01 (s, 9H, Si(*CH*$_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 138.4 (C_q arom.), 136.3 (C-5), 129.8, 129.3, 129.2 (C arom), 121.6 (C-6), 83.1 (C-4), 78.7 (C-3), 71.6 (*C*H$_2$Ph), 70.5 (C-2), 23.8 (C-1), 0.4 (Si(*C*H$_3$)$_3$). Anal. Calcd for $C_{16}H_{26}O_3Si$: C, 65.31; H, 8.84. Found C, 65.05; H, 9.03.

*4.4.2. (3S,4S)-3-Benzyloxyhexa-1,5-dien-4-ol (**14**).* Compound **13** (110 mg, 0.37 mmol) was treated for 48 h at rt in THF (4 mL) containing H_2SO_4 (80 μL). Then, THF was removed under vacuum, the residue was dissolved in DCM (20 mL) and the resulting solution was neutralized with a saturated aqueous $NaHCO_3$ solution, then with water. After drying over Na_2SO_4, filtration and evaporation, the product was purified by chromatography over silica gel (85:15 petroleum ether–EtOAc), yielding the diene **14** (85 mg, 100%) as an oil. Diene **14** was obtained in 78% overall yield (two steps from **1**) starting from 2.4 equiv of (trimethylsilyl)methyllithium without purification of the intermediate **13**.

Oil. Yield: quantitative. $[\alpha]_D^{23}$ +10 (*c* 1.10, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.33–7.20 (m, 5H, C_6H_5), 5.83–5.61 (m, 2H, H-2, H-5), 5.34–5.11 (m, 4H, H-1, H-6), 4.57 (d, 1H, *J*=11.6 Hz, C*H*Ph), 4.29 (d, 1H, *J*=11.6 Hz, C*H*Ph), 3.99 (m, 1H, H-4), 3.61 (t, 1H, *J*=7.8 Hz, H-3), 2.81 (br s, O*H*); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 138.4 (C_q arom.), 136.7, 135.2 (C-2, C-5), 128.9, 128.5, 128.4, 128.3 (*C*H arom.), 120.7, 117.4 (C-1, C-6), 84.5 (C-4), 75.2 (C-3), 71.0 (*C*H$_2$Ph); ESIHRMS calcd for $C_{13}H_{16}O_2Na$ ([M+Na]$^+$) 227.1048; found 227.1044.

*4.4.3. (3S,4S)-4-Benzyloxy-1,1-bis(methylsulfanyl)hexa-1,5-dien-3-ol (**15**).* Yellow oil. Yield: 52%. $[\alpha]_D^{23}$ +62 (*c* 1.20, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H, C_6H_5), 5.74 (m, 1H, H-5), 5.66 (d, 1H, *J*=8.5 Hz, H-2), 5.37–5.27 (m, 2H, H-6), 4.79 (ddd, 1H, *J*=8.5, 7.0, 2.9 Hz, H-3), 4.68 (d, 1H, *J*=11.7 Hz, C*H*Ph), 4.38 (d, 1H, *J*=11.7 Hz, C*H*Ph), 3.72 (t, 1H, *J*=7.0 Hz, H-4), 2.84 (d, 1H, 2.9 Hz, O*H*), 2.32 (s, *CH*$_3$), 2.28 (s, *CH*$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 138.3 (C_q arom.), 134.8 (C-5), 134.5 (C-1), 129.3 (C-2), 129.2, 128.7, 128.4, 127.4 (*C*H arom.), 121.0 (C-6), 83.2 (C-4), 71.3 (C-3), 70.5 (*C*H$_2$Ph), 16.5 (*C*H$_3$), 15.0 (*C*H$_3$); ESIHRMS calcd for $C_{15}H_{20}O_2S_2Na$ ([M+Na]$^+$) 319.0802; found 319.0796.

*4.4.4. (2S,3S)-3-Benzyloxy-1-(1,3-dithian-2-ylidene)pent-4-en-2-ol (**16**).* Yellow oil. Yield: 86%. $[\alpha]_D^{24}$ +103 (*c* 0.60, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H, C_6H_5), 5.85 (d, 1H, *J*=8.6 Hz, H-1), 5.71 (ddd, 1H, *J*=17.0, 10.5, 7.3 Hz, H-4), 5.37–5.26 (m, 2H, H-5), 4.57 (d, 1H, *J*=11.7 Hz, C*H*Ph), 4.53 (dd, 1H, *J*=8.6, 7.3 Hz, H-2), 4.38 (d, 1H, *J*=11.7 Hz, C*H*Ph), 3.65 (t, 1H, *J*=7.3 Hz, H-3), 2.94–2.63 (m, 5H, S*CH*$_2$, O*H*), 2.10–1.95 (m, 2H, *CH*$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 138.1 (C_q arom.), 134.3 (C-4), 133.4 (S*C*S), 128.9 (C-1), 128.3, 127.8, 127.6 (*C*H arom.), 119.9 (C-5), 83.4 (C-3), 70.6 (C-2), 70.5 (*C*H$_2$Ph), 29.4, 29.1 (*C*H$_2$-S), 24.4 (*C*H$_2$); ESIHRMS calcd for $C_{16}H_{20}O_2S_2Na$ ([M+Na]$^+$) 331.0802; found 331.0793.

*4.4.5. (3S,4S)-4-Benzyloxy-1-(phenylsulfanyl)hexa-1,5-dien-3-ol (**17**).* Mixture 1:1 of stereomers. Yellow oil. Yield: 66%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H, C_6H_5), 6.51 (d, 0.5H, *J*=15.1 Hz, H-1$_E$), 6.42 (d, 0.5H, *J*=9.6 Hz, H-1$_Z$), 5.88–5.67 (m, 2H, H-2, H-5), 5.42–5.32 (m, 2H, H-6), 4.70 (d, 0.5H, *J*=8.5 Hz, C*H*Ph), 4.66 (d, 0.5H, *J*=8.5 Hz, C*H*Ph), 4.59 (m, 1H, H-3), 4.41 (d, 0.5H, *J*=9.7 Hz, C*H*Ph), 4.36 (d, 0.5H, *J*=9.7 Hz, C*H*Ph), 3.77 (t, 0.5H, *J*=7.7 Hz, H-4), 3.66 (t, 0.5H, *J*=7.6 Hz, H-4), 2.84 (d, 1H, 14.4 Hz, O*H*); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 138.4, 137.5 (C_q arom.), 134.0, 133.8 (C-5), 129.5–126.0 (C-2, *C*H arom.), 120.1, 119.9 (C-6), 83.2, 83.1 (C-4), 73.7, 70.7 (C-3), 70.1, 70.0 (*C*H$_2$Ph).

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Supplementary data

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