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The Tandem Ring-Closing Metathesis–Isomerization Approach to 6-Deoxyglycals

Bernd Schmidt* and Anne Biernat[a]

Abstract: Protected 3,6-dideoxyglycals have been synthesized de novo as single isomers starting from ethyl lactate by using the tandem RCM–isomerization reaction as the key step. Different relative configurations become accessible by addition of vinyl- or allyl–metal compounds to protected lactaldehydes under Cram-chelate or Felkin–Anh control. The concept is exemplified for glycals of L-rhodinose and L-amicetose, as well as for ring-expanded non-natural analogues thereof. This novel approach to glycals is also applicable to the synthesis of disaccharide glycals via a reiterative strategy, as exemplified for the dimer of L-rhodinose and its non-natural ring expanded analogue.

Keywords: carbohydrates · heterocycles · isomerization · metathesis · ruthenium

Introduction

Various deoxygenated carbohydrates are found in nature, and considerable efforts have been made to gain insight into their biological function[1] and the deoxygenation mechanisms leading to their biosynthesis.[2–5] They are frequently constituents of oligosaccharide side chains present in numerous antibiotics and anticancer agents (see examples in Figure 1).[6]

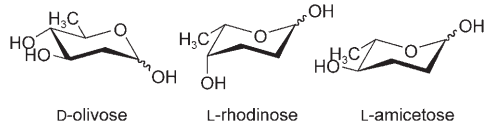

Figure 1. Representative deoxy sugars.

While it was commonly assumed for many years that the glycosylation pattern in these drugs primarily affects their pharmacokinetics, more recent investigations show that the oligosaccharide side chains of glycoconjugates influence molecular recognition. This has, for instance, been demonstrated by co-crystallization of an oligonucleotide with the antitumor agent daunomycin, where the deoxy sugar moiety binds to the minor groove of the DNA duplex.[7] Although deoxygenated carbohydrates, such as D- and L-amicetose, have been accessed by combination of antibiotic gene clusters, and their transfer to the ellaromycin aglycon by an appropriate glycosyltransferase has been demonstrated,[5] the chemical synthesis still remains an important issue. Deoxy sugars can either be synthesized from other more common carbohydrates by deoxygenation, or de novo.[8] For the assembly of oligosaccharide chains and their connection to aglycons by chemical means glycals have evolved as particularly useful building blocks.[9–12] The term glycal, introduced in the literature by Fischer and Zach in their original contribution[13] to describe the chemical resemblance of these compounds to aldehydes, is nowadays used for 1,2-unsaturated sugars. Due to their enol ether structure, they show interesting reactivities that have proven useful in target molecule synthesis, beyond carbohydrate chemistry.[14–16] While most glycal syntheses rely on reductive elimination of glycosides in one way or the other,[17,18] over the past few years transition metal mediated or catalyzed cyclization reactions became more and more important. In particular, the cyclization of alkynols[19–21] and the ring-closing metathesis[22–24] of enol ethers[25–29] has attracted considerable attention. The observation that the well established ruthenium-based metathesis catalysts sometimes catalyze other reactions with comparable efficiency[30,31] has not only stimulated research directed at a deeper understanding of the degradation reactions of these complexes,[32,33] but has also led to the development of new metathesis–non-metathesis tandem sequen-

[a] Prof. Dr. B. Schmidt, Dipl.-Chem. A. Biernat
Universität Potsdam, Institut für Chemie, Organische Chemie II
Karl-Liebknecht-Strasse 24–25, Haus 25, 14476 Golm (Germany)
Fax: (+49) 331-977-5059
E-mail: bernd.schmidt@uni-potsdam.de

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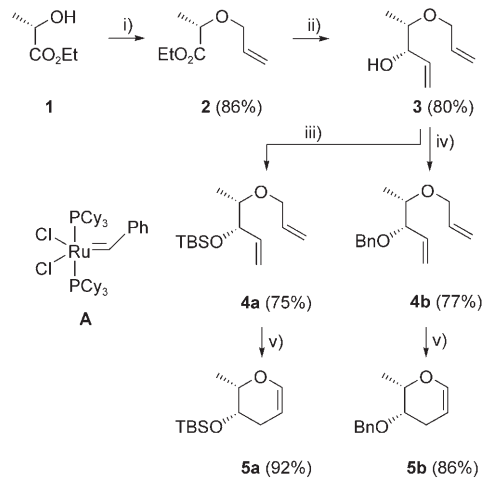
ces.[34] One example for this type of tandem processes is the RCM–isomerization sequence, which has been developed by Snapper et al.[35] and by us.[36–38] In this sequence, a heterocycle is formed by ring-closing metathesis, and—after completion of the metathesis step—the metathesis catalyst is converted to an isomerization catalyst, which induces a subsequent migration of the double bond formed in the metathesis step. It turned out that this method is particularly useful for the synthesis of cyclic enol ethers, because it helps to overcome the difficulties associated with the RCM of enol ethers. These are the sometimes laborious synthesis of appropriate precursors, the necessity to use high dilution conditions and the more active but less conveniently available molybdenum[39] and second-generation ruthenium catalysts.[40] Herein, we report our results on the synthesis of glycals related to important natural or non-natural deoxy sugars using the tandem RCM–isomerization method.

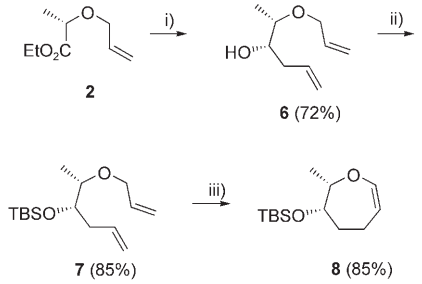
Results and Discussion

L-Rhodinal and its ring-expanded analogue: We started with an approach to the 2,3,6-trideoxy substitution pattern present in rhodinose. Ethyl lactate (**1**) was identified as the starting material of choice,[41] because addition of a vinyl nucleophile to an appropriately O-protected lactaldehyde will either proceed via Cram-chelate control,[42,43] eventually leading to the rhodinal series, or via Felkin–Anh control,[43,44] eventually leading to the amicetal series. With a view to the synthesis of protected L-rhodinals, ethyl lactate (**1**) was first allylated with allyl ethyl carbonate catalyzed by Pd^0.[45] This reaction proceeds without racemization, in contrast to a standard Williamson ether synthesis, and gives enantiomerically pure **2**. As previously reported by us,[42] **2** can be converted to **3** by a one-pot reduction of the ester function, followed by addition of vinyl magnesium chloride. However, this step proceeds with only moderate diastereoselectivity, which might result from insufficient Cram-chelate control due to competing complexation of the ether solvent. Gratifyingly, exchange of the Et_2O solvent by dichloromethane[46] gave (*S*,*S*)-**3** as a single stereoisomer. Alcohol **3** can be protected as a TBS-ether **4a**, or as a benzyl ether **4b** under standard conditions. Both undergo the desired tandem RCM–isomerization cleanly if 2-propanol and solid NaOH are used as additives to induce the conversion of the metathesis catalyst to the isomerization catalyst.[37] TBS-protected (**5a**) and benzyl protected (**5b**) L-rhodinal are identified by their small ^3J(H4,H5) value of 3.0 Hz, which is indicative for a *cis*-arrangement of methyl group and OTBS or OBn group (Scheme 1).

It is also possible to adopt the concept for highly deoxygenated ring-expanded septanose glycals. Septanoses have attracted some attention recently as non-natural analogues of pyranoses which are expected to display significantly different conformational behavior.[47] To this end, the vinyl magnesium chloride used in the sequence outlined above for the protected L-rhodinals was simply replaced by allyl magnesium bromide, under otherwise identical conditions. The resulting alcohol **6** was protected as TBS ether **7**, which gave, under tandem RCM–isomerization conditions, a ring expanded L-rhodinal analogue **8** (Scheme 2). Evidence for the assigned relative configuration of **8** comes, in analogy to protected L-rhodinals **5**, from the small ^3J(H5,H6) value of 2.3 Hz.



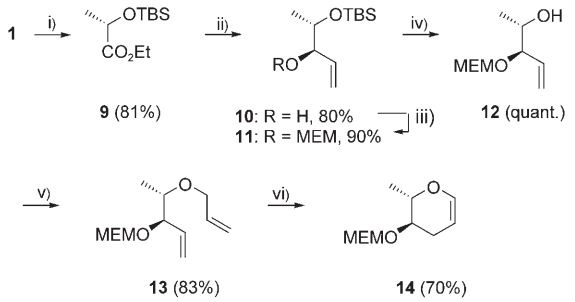
Scheme 1. Protected L-rhodinal. i) $H_2C{=}CHCH_2OCO_2Et$, $[Pd(PPh_3)_4]$ (2.5 mol%), THF, 65°C; ii) DIBAL-H, then $H_2C{=}CHMgCl$, CH_2Cl_2, −90°C; iii) TBSCl, imidazole, DMF; iv) NaH, $PhCH_2Br$, THF, 65°C; v) **A** (5 mol%), toluene, 20°C, then add 2-propanol (20 vol%) and NaOH (30 mol%), 110°C.



Scheme 2. Protected ring-expanded L-rhodinal analogue. i) DIBAL-H, then $H_2C{=}CHCH_2MgBr$, CH_2Cl_2, −90°C; ii) TBSCl, imidazole, DMF; iii) **A** (5 mol%), toluene, 20°C, then add 2-propanol (20 vol%) and NaOH (30 mol%), 110°C.

L-Amicetal and its ring-expanded analogue: As mentioned above, a route to the L-amicetal series starting from ethyl lactate is also feasible: silylation of **1** gives TBS-protected ethyl lactate (**9**). Reduction of **9** with DIBAL-H to the corresponding lactaldehyde[48] and subsequent addition of vinyl magnesium chloride to give **10** have previously been reported.[44] Although we were able to reproduce this two-step procedure with a slightly better diastereoselectivity ((*S*,*R*)-**10**/(*S*,*S*)-**10** 8:1) than reported in the literature, it turned out to be far more convenient to avoid the isolation of the aldehyde and perform reduction and Grignard addition in a one-pot sequence, as described above in the rhodinal series.

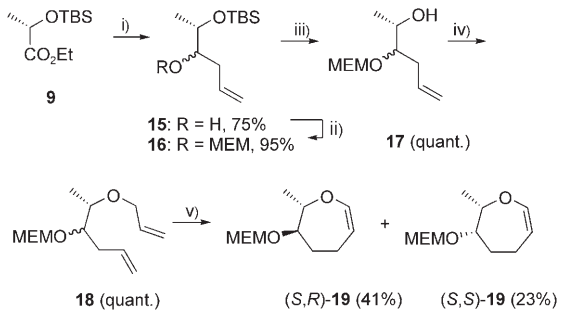
The diastereoselectivities of both reactions are practically identical, but the overall yield is significantly better for the one-pot method. The secondary alcohol in **10** was subsequently protected as MEM-ether **11**, which upon desilylation and O-allylation under standard conditions gave precursor **13**. Subjecting **13** to the same tandem RCM–isomerization conditions mentioned above gives a MEM-protected L-amicetal **14** in 70% yield as a single diastereoisomer after column chromatography. The *trans*-arrangement of methyl group and -OMEM group leads to a larger ^3J(H4,H5) value of 7.8 Hz (Scheme 3).



Scheme 3. Protected L-amicetal. i) TBSCl, imidazole, DMF; ii) DIBAL-H, then $H_2C{=}CHMgCl$, Et_2O, −90°C; iii) MEMCl (2 equiv), NEt_2iPr (3 equiv), CH_2Cl_2, 0→20°C; iv) TBAF (2 equiv), THF, 65°C; v) NaH, $H_2C{=}CHCH_2Br$, THF, 65°C; vi) **A** (5 mol%), toluene, 20°C, then add 2-propanol (20 vol%) and NaOH (30 mol%), 110°C.

The same approach was pursued towards a ring-expanded L-amicetal analogue. Starting from **9**, **15** was obtained via one-pot reduction and addition of allyl magnesium bromide. In contrast to allylic alcohol **10**, the homoallylic derivative **15** was obtained in lower diastereoselectivity (dr 2:1). Separation of the two diastereomers is not possible at this stage and therefore the following steps were conducted for the mixture: MEM protection, followed by desilylation and O-allylation gives the metathesis precursor **18.** **18** is cleanly converted under tandem RCM–isomerization conditions to a mixture of (*S*,*R*)-**19** and (*S*,*S*)-**19** in a 2:1 ratio. These diastereomers are easily separated by column chromatography, and an assignment of the relative configuration is conveniently achieved via the ^3J(H5,H6) value of 2.5 Hz for (*S*,*S*)-**19** (L-rhodinal homologue) and 9.0 Hz for (*S*,*R*)-**19** (L-amicetal homologue). The sequence leading to **19** is outlined in Scheme 4.

6-Deoxy-disaccharide glycals: Oligosaccharides and glycoconjugates containing oligosaccharide side chains may be assembled on solid support. Obviously, it is a prerequisite that efficient reiterative strategies are available. Such a strategy is, for instance, the glycal assembly method, where oligosaccharides result from epoxidation of a glycal, followed by epoxide cleavage with a second selectively deprotected glycal.[12] Another example, where formation of a glycal structure is one of the repetitive steps, has been devised by McDonald and Zhu, who obtained oligosaccharides by repeated application of glycosylation, deprotection and *endo*-cyclization of alkynols.[49] Implementing our glycal synthesis into a reiterative strategy should in principle be possible. In this section, we would like to illustrate the concept for a disaccharide consisting of L-rhodinose and its ring expanded septanose homologue. Related disaccharides containing one heptose and one hexose unit have previously attracted some attention as potential substrates for glycosyl transferases.[50]

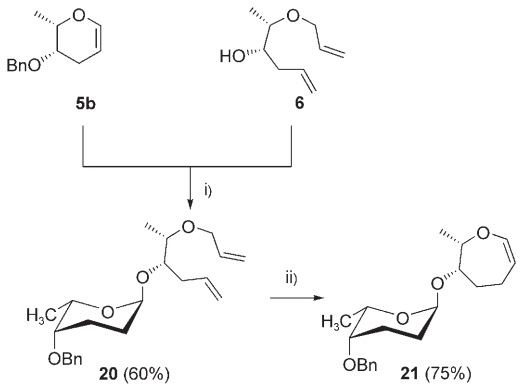


Scheme 4. Protected ring-expanded L-amicetal analogue. i) DIBAL-H, then $H_2C{=}CHCH_2MgBr$, CH_2Cl_2, −90°C; ii) MEMCl (2 equiv), NEt_2iPr (3 equiv), CH_2Cl_2, 0→20°C; iii) TBAF (2 equiv), THF, 65°C; iv) NaH, $H_2C{=}CHCH_2Br$, THF, 65°C; v) **A** (5 mol%), toluene, 20°C, then add 2-propanol (20 vol%) and NaOH (30 mol%), 110°C, then separate by column chromatography.

Starting from L-rhodinal benzyl ether (**5b**) glycosylation with precursor **6** gave the desired glycoside **20**. Different glycosylation procedures were tested: with triphenyl phosphonium bromide[51] the required precursor was obtained, but only as a mixture of epimers and in extremely poor yield. Thiem's iodoglycosylation method[9,52] was tested next. In spite of difficulties that may obviously arise from the presence of three different C–C double bonds, successful application of the method to glycoside formation with an allylic alcohol has been reported in the literature.[53] Unfortunately, in our case the treatment of **5b** with NIS in the presence of alcohol **6** resulted in the formation of a complex mixture. It was not possible to decide whether the electrophilic attack of the C–C double bond was insufficiently selective, or if the problems were caused by insufficient diastereoselectivity of the glycosylation step. Gratifyingly, the required precursor **20** could be obtained in good yield as a separable 5:1 mixture of anomers by using a catalytic amount of *p*-TSA. Conversion of **20** to the disaccharide glycal **21** proceeded smoothly under tandem RCM–isomerization conditions similar to those applied for **8**. This sequence is summarized in Scheme 5.

Conclusion

In summary, we have shown that the tandem RCM–isomerization approach is a useful synthetic method to access various 6-deoxy glycals. We were also able to demonstrate that novel ring-expanded analogues of highly deoxygenated glycals become available via the sequences described herein. For a disaccharide containing one septanose and one hexose



Scheme 5. Disaccharide glycal of L-rhodinose and its ring-expanded analogue. i) *p*-TSA (8 mol%), CH_2Cl_2, 0°C; ii) **A** (5 mol%), toluene, 20°C, then add 2-propanol (20 vol%) and NaOH (30 mol%), 110°C.

unit it was demonstrated that this novel glycal synthesis can in principle be executed in a reiterative manner. Extension to other glycals and applications of these compounds are currently under investigation.

Experimental Section

All experiments were conducted in dry reaction vessels under an atmosphere of dry argon. Solvents were purified by standard procedures. ^{1}H NMR spectra were obtained at 300, 400, 500, or at 600 MHz in $CDCl_3$ with $CHCl_3$ ($\delta = 7.26$ ppm) as an internal standard or in C_6D_6 with C_6D_5H ($\delta = 7.18$ ppm) as an internal standard. Coupling constants are given in Hz. ^{13}C NMR spectra were recorded at 75 MHz, 100 MHz, 125 MHz or at 150 MHz in $CDCl_3$ with $CDCl_3$ ($\delta = 77.0$ ppm) as an internal standard or in C_6D_6 with C_6D_6 ($\delta = 128.0$ ppm) as an internal standard. The number of coupled protons was analyzed by DEPT or APT experiments and is denoted by a number in parentheses following the chemical shift value. Whenever NMR-peak assignments in the ^{13}C NMR spectra are given, these are based on H,H- and H,C-correlation spectroscopy. IR spectra were recorded as films on NaCl or KBr plates. The peak intensities are defined as strong (s), medium (m) or weak (w). Mass spectra were obtained at 70 eV. Ruthenium catalyst **A**[54] was used as purchased without further purification. Compounds **2**,[55] and **9**,[48] were prepared as previously reported in the literature. Compound **10** has previously been reported,[44] but was prepared by a modified procedure (see below).

(3*S*,4*S*)-4-Allyloxy-pent-1-en-3-ol (3): A solution DIBAL-H (1.0 M in CH_2Cl_2, 14.0 mL, 14.0 mmol) was added at −90°C to a solution of **2** (1.62 g, 10.2 mmol) in CH_2Cl_2 (60 mL). After stirring at this temperature for 10 min, TLC (cyclohexane/MTBE 5:1) indicated complete consumption of the starting material. Vinyl magnesium chloride (1.7 M solution in THF, 11.8 mL, 20.0 mmol) was then added via syringe and the mixture was allowed to warm to ambient temperature. It was then poured onto water and diethyl ether, and the precipitate was dissolved with a saturated solution of K/Na tartrate. The organic layer was separated, and the aqueous layer was extracted twice with diethyl ether. The combined organic extracts were dried with $MgSO_4$, filtered and evaporated. Caution: due to the rather high volatility of the product, the minimum pressure during evaporation should be 300 mbar! The residue was distilled (b.p. 45°C/30 mbar) to give **3** (1160 mg, 80%). $[\alpha]_D^{25} = +41.8°$ ($c = 0.79$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.89$ (dddd, 1H, $J = 17.3$, 10.5, 5.5, 5.5 Hz, $OCH_2CH{=}$), 5.79 (ddd, 1H, $J = 17.3$, 10.5, 6.5 Hz, $CH(OH)CH{=}$), 5.34 (dd, 1H, $J = 17.3$, 1.5, 1.5 Hz, $=CH_2$), 5.25 (dm, 1H, $J = 17.3$ Hz, $=CH_2$), 5.19 (ddd, 1H, $J = 10.5$, 1.5, 1.5 Hz, $=CH_2$), 5.15 (dm, 1H, $J = 10.5$ Hz, $=CH_2$), 4.12 (dddd, 1H, $J = 12.8$, 5.5, 1.3, 1.3 Hz, $OCH_2CH{=}$), 3.93 (dddd, 1H, $J = 12.8$, 5.5, 1.3, 1.3 Hz, $OCH_2CH{=}$), 3.89 (dd, 1H, $J = 7.0$, 6.5 Hz, $CH(OH)$), 3.32 (dq, 1H, $J = 7.0$, 6.3 Hz, $CHCH_3$), 2.80 (br s, 1H, O*H*), 1.11 ppm (d, 3H, $J = 6.3$ Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 136.8$ (1), 134.8 (1), 117.4 (2), 117.0 (2), 78.0 (1), 76.5 (1), 70.0 (2), 15.5 ppm (3); IR (film, KBr plates): $\tilde{\nu} = 3372$ (bm), 2933 (m), 1455 (m), 1377 cm^{-1} (m).

(3*S*,4*S*)-4-Allyloxy-3-(*tert*-butyldimethylsilyloxy)pent-1-ene (4a): TBSCl (600 mg, 4.0 mmol) and imidazole (306 mg, 4.5 mmol) was added to a solution of **3** (440 mg, 3.1 mmol) in DMF (20 mL). After stirring for 12 h, the mixture was diluted with water (20 mL) and extracted with pentane. The organic extracts were dried with $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography on silica to yield **4a** (600 mg, 75%). $[\alpha]_D^{26} = -15.3°$ ($c = 1.01$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.90$ (dddd, 1H, $J = 17.3$, 10.3, 5.5, 5.5 Hz, $OCH_2CH{=}$), 5.85 (ddd, 1H, $J = 17.3$, 10.5, 5.3 Hz, $CH(OTBS)CH{=}$), 5.24 (dm, 1H, $J = 17.3$ Hz, $=CH_2$), 5.24 (dm, 1H, $J = 17.3$ Hz, $=CH_2$), 5.13 (dm, 1H, $J = 10.5$ Hz, $=CH_2$), 5.13 (dm, 1H, $J = 10.5$ Hz, $=CH_2$), 4.16 (dd, 1H, $J = 5.5$, 5.3 Hz, $CH(OTBS)$), 4.06 (ddm, 1H, $J = 12.8$, 5.5 Hz, $OCH_2CH{=}$), 4.01 (ddm, 1H, $J = 12.8$, 5.5 Hz, $OCH_2CH{=}$), 3.39 (dq, 1H, $J = 6.3$, 5.5 Hz, $CHCH_3$), 1.03 (d, 3H, $J = 6.3$ Hz, CH_3), 0.88 (s, 9H, *t*Bu), 0.04 (s, 3H, $Si(CH_3)_2$), 0.04 ppm (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 137.3$ (1), 135.4 (1), 116.5 (2), 115.5 (2), 78.0 (1), 75.2 (1), 70.5 (2), 25.8 (3), 18.2 (0), 14.8 (3), −4.7 (3), −4.9 ppm (3); IR (film, KBr plates): $\tilde{\nu} = 2956$ (m), 2929 (m), 2856 (m), 1646 (w), 1472 cm^{-1} (m); LRMS (70 eV, EI): *m*/*z* (%): 279 (30) [M^++Na], 213 (100); HRMS (ESI): *m*/*z*: calcd for $C_{14}H_{28}O_2Si$: 279.1751, found 279.1744 [M^++H].

(3*S*,4*S*)-4-Allyloxy-3-benzyloxy-pent-1-ene (4b): NaH (60% dispersion in mineral oil, 120 mg, 3.0 mmol) was added to a solution of **3** (200 mg, 1.4 mmol) in THF (20 mL) and the mixture was heated to reflux for 30 min. Benzyl bromide (0.36 mL, 3.0 mmol) was added, and the mixture was again heated to reflux for 30 min. Aqueous workup, followed by flash chromatography on silica, yielded **4b** (250 mg, 77%). $[\alpha]_D^{26} = -0.9°$ ($c = 1.55$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.40$–7.25 (5H, Ph), 5.93 (dddd, 1H, $J = 17.0$, 10.5, 5.7, 5.3 Hz, $OCH_2CH{=}$), 5.82 (ddd, 1H, $J = 17.2$, 10.2, 7.2 Hz, $CH(OTBS)CH{=}$), 5.36–5.24 (3H, $=CH_2$), 5.16 (dm, 1H, $J = 10.5$ Hz, $=CH_2$), 4.66 (d, 1H, $J = 12.0$ Hz, -OCH_2Ph), 4.44 (d, 1H, $J = 12.0$ Hz, OCH_2Ph), 4.15–4.05 (2H, $OCH_2CH{=}$), 3.81 (dd, 1H, $J = 7.0$, 6.0 Hz, $CH(OBn)$), 3.58 (dq, 1H, $J = 6.2$, 6.2 Hz, $CHCH_3$), 1.15 ppm (d, 3H, $J = 6.3$ Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 138.6$ (0), 135.4 (1), 135.2 (1), 128.2 (1), 127.6 (1), 127.4 (1), 118.6 (2), 116.4 (2), 83.2 (1), 76.6 (1), 70.8 (2), 70.5 (2), 16.1 ppm (3); IR (film, KBr plates): $\tilde{\nu} = 3065$ (m), 3029 (m), 2978 (m), 2863 (m), 1645 (m), 1454 cm^{-1} (s); LRMS (70 eV, EI): *m*/*z* (%): 233 (40) [M^++H], 131 (100); HRMS (ESI): *m*/*z*: calcd for $C_{15}H_{20}O_2$: 233.1536; found 233.1517; elemental analysis calcd (%) for $C_{15}H_{20}O_2$: C 77.6, H 8.7; found: C 77.1, H, 8.7.

***tert*-Butyldimethyl-[(2*S*)-methyl-3,4-dihydro-2*H*-pyran-(3*S*)-yloxy]silane (5a)**: Ruthenium catalyst **A** (82 mg, 4.8 mol%) was added to a solution of **4a** (550 mg, 2.1 mmol) in toluene (10 mL). The solution was stirred at ambient temperature, until the starting material was fully consumed as indicated by TLC. 2-Propanol (2 mL) and solid NaOH (60 mg) was added, and the mixture was heated to reflux for 30 min. After this time, the intermediate RCM product was completely converted to **5a**, as indicated by TLC. The solution was washed with water, and all volatiles were evaporated. The residue was purified by flash chromatography, followed by Kugelrohr distillation (100°C, 10 mbar) to give **5a** (440 mg, 92%). $[\alpha]_D^{20} = -33.6$ ($c = 0.72$ in CH_2Cl_2); ^{1}H NMR (400 MHz, [D$_6$]benzene): $\delta = 6.33$ (ddd, 1H, $J = 6.0$, 1.8, 1.8 Hz, H1), 4.45 (ddd, 1H, $J = 6.0$, 3.8, 3.8 Hz, H2), 3.96 (qdd, 1H, $J = 6.5$, 3.0, 1.0 Hz, H5), 3.78 (ddd, 1H, $J = 6.3$, 5.5, 3.0 Hz, H4), 2.02 (dm, 1H, $J = 16.8$ Hz, H3), 1.93 (dddd, 1H, $J = 16.8$, 6.3, 3.3, 2.0 Hz, H3′), 1.24 (d, 3H, $J = 6.3$ Hz, CH_3), 0.95 (s, 9H, *t*Bu), 0.00 (s, 3H, $Si(CH_3)_2$), −0.02 ppm (s, 3H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, [D$_6$]benzene): $\delta = 142.6$ (1), 96.7 (1), 73.1 (1), 66.9 (1), 28.0 (2), 25.9 (3), 18.2 (0), 14.2 (3), −4.6 (3), −4.9 ppm (3); IR (film, KBr plates): $\tilde{\nu} = 2956$ (s), 2930 (s), 1651 (s), 1240 (s), 1100 (s), 874 cm^{-1} (s); LRMS (70 eV, EI): *m*/*z* (%): 171 (49) [M^+−*t*Bu], 115 (29), 75 (100); elemental analysis calcd (%) for $C_{12}H_{24}O_2Si$: C 63.1, H, 10.6; found: C 62.6, H 10.6.

(3*S*,2*S*)-3-Benzyloxy-2-methyl-3,4-dihydro-2*H*-pyran (5b):[49] Compound **5b** was obtained from **4b** (218 mg, 0.9 mmol) following the procedure given above for **5a**. Yield: 165 mg (86%). $[\alpha]_D^{26} = -19.6$ ($c = 0.97$ in CH_2Cl_2); ^{1}H NMR (500 MHz, [D$_6$]benzene): $\delta = 7.25$ (d, 2H, $J = 7.2$ Hz, Ph), 7.17 (dd, 2H, $J = 7.2$, 7.2 Hz, Ph), 7.11 (t, 1H, $J = 7.2$ Hz, Ph), 6.33 (d, 1H, $J = 6.0$ Hz, H1), 4.44 (ddd, 1H, $J = 6.2$, 3.5, 3.5 Hz, H2), 4.34 (d, 1H, $J = 12.2$ Hz, OCH_2Ph), 4.19 (d, 1H, $J = 12.2$ Hz, OCH_2Ph), 4.06 (qd, 1H, $J = 6.5$, 2.9 Hz, H5), 3.44 (m, 1H, H4), 2.05–1.95 (2H, H3), 1.28 ppm (d, 3H, $J = 6.5$ Hz, CH_3); ^{13}C NMR (125 MHz, [D$_6$]benzene): $\delta = 142.8$ (1), 139.2 (0), 128.5 (1), 127.7 (1), 127.6 (1), 96.7 (1), 72.9 (1), 71.6 (1), 70.8 (2), 24.0 (2), 14.5 ppm (3); IR (film, KBr plates): $\tilde{\nu} = 3062$ (w), 2979 (w), 2865 (w), 1649 (m), 1453 cm^{-1} (m); LRMS (70 eV, EI): m/z (%): 205 (20) [M^++H], 281 (100); HRMS (ESI): m/z: calcd for $C_{13}H_{16}O_2$: 205.1223, found 205.1228; elemental analysis calcd (%) for $C_{13}H_{16}O_2$: C 76.4, H 7.9; found: C 76.2, H 8.3.

(2*S*)-Allyloxy-hex-5-en-(3*S*)-ol (6): Obtained from **2** (780 mg, 5.0 mmol) and allyl magnesium bromide (1.25 M solution in ether, 12.5 mL, 10 mmol) following the procedure given above for **3**. Compound **6** was purified by column chromatography on silica gel (560 mg, 72%). $[\alpha]_D^{25} = +35.8$ ($c = 0.92$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.94$–5.90 (2H, CH=), 5.24 (dm, 1H, $J = 17.1$ Hz, =CH_2), 5.15 (dm, 1H, $J = 10.3$ Hz, =CH_2), 5.09 (dm, 1H, $J = 17.3$ Hz, =CH_2), 5.06 (dm, 1H, $J = 10.3$ Hz, =CH_2), 4.10 (dd, 1H, $J = 12.6$, 5.3 Hz, OCH_2CH=), 3.90 (dd, 1H, $J = 12.6$, 5.8 Hz, OCH_2CH=), 3.47 (1H, m, CH(OH)), 3.33 (dq, 1H, $J = 6.0$, 6.0 Hz, CH(CH_3)), 2.53 (br s, 1H, OH), 2.32 (dm, 1H, $J = 14.5$ Hz, CH_2), 2.16 (ddd, 1H, $J = 14.5$, 7.5, 7.5 Hz, CH_2), 1.12 ppm (d, 3H, $J = 6.5$ Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 134.9$ (1), 134.7 (1), 117.1 (2), 116.9 (2), 77.4 (1), 74.1 (1), 69.9 (2), 37.4 (2), 15.4 ppm (3); IR (film, KBr plates): $\tilde{\nu} = 3454$ (bw), 3077 (m), 2977 (m), 2867 (m), 1641 cm^{-1} (m); LRMS (70 eV, FAB): m/z (%): 157 (5) [M^+−H], 197 (100); HRMS (FAB): m/z: calcd for $C_9H_{16}O_2$: 157.1223 [M^++H], found 157.1232; elemental analysis calcd (%) for $C_9H_{16}O_2$: C 69.2, H 10.3; found: C 69.1, H 11.3.

[(1*S*,2*S*)-Allyloxyethyl)-but-3-enyloxy]-*tert*-butyl-dimethylsilane (7): Obtained from **6** (300 mg, 1.9 mmol) following the procedure given above for **4a. 7** was purified by column chromatography on silica. Yield: 437 mg (85%). $[\alpha]_D^{25} = -5.02$ ($c = 0.88$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.87$ (dddd, 1H, $J = 17.1$, 10.3, 5.8, 5.5 Hz, OCH_2CH=), 5.83 (dddd, 1H, $J = 17.3$, 10.0, 7.3, 7.0 Hz, CH_2CH=), 5.24 (dm, 1H, $J = 17.1$ Hz, =CH_2), 5.13 (dm, 1H, $J = 10.3$ Hz, =CH_2), 5.03 (dm, 1H, $J = 17.1$ Hz, =CH_2), 5.00 (dm, 1H, $J = 10.0$ Hz, =CH_2), 4.02 (dd, 1H, $J = 12.8$, 5.5 Hz, OCH_2CH=), 3.95 (dd, 1H, $J = 12.6$, 5.8 Hz, OCH_2CH=), 3.68 (m, 1H, CH(OTBS)), 3.39 (qd, 1H, $J = 6.3$, 5.3 Hz, CH(CH_3)), 2.32 (dm, 1H, $J = 14.1$ Hz, CH_2), 2.08 (ddd, 1H, $J = 14.1$, 7.5, 7.3 Hz, CH_2), 1.08 (d, 3H, $J = 6.3$ Hz, CH_3), 0.86 (s, 9H, *t*Bu), 0.02 (s, 3H, Si(CH_3)$_2$), 0.02 ppm (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 136.1$ (1), 135.5 (1), 116.5 (2), 116.4 (2), 77.3 (1), 73.9 (1), 70.2 (2), 36.5 (2), 25.9 (3), 18.1 (0), 14.1 (3), −4.4 (3), −4.5 ppm (3); IR (film, KBr plates): $\tilde{\nu} = 3078$ (w), 2929 (m), 2856 (m), 1642 (w), 1472 cm^{-1} (m); LRMS (70 eV, FAB): m/z (%): 271 (30) [M^+−H], 213 (100); HRMS (FAB): m/z: calcd for $C_{15}H_{30}O_2Si$: 271.2088 [M^++H], found 271.2104.

***tert*-Butyldimethyl-(2*S*-methyl-2,3,4,5-tetrahydro-oxepin-(3*S*)-yloxy)silane (8)**: Obtained from **7** (340 mg, 1.3 mmol) following the procedure given above for **5a**. Compound **8** was purified by column chromatography on silica. Yield: 268 mg (85%). $[\alpha]_D^{25} = -53.9$ ($c = 2.72$ in CH_2Cl_2); ^{1}H NMR (400 MHz, [D$_6$]benzene): $\delta = 6.37$ (d, 1H, $J = 6.4$ Hz, H1), 4.59 (ddd, 1H, $J = 6.4$, 6.4, 4.0 Hz, H2), 4.00 (qd, 1H, $J = 6.5$, 2.3 Hz, H6), 3.53 (ddd, 1H, $J = 8.3$, 5.8, 2.3 Hz, H5), 2.01 (m, 1H, H3/4), 1.94–1.87 (2H, H3/H4), 1.74 (m, 1H, H4/H5), 1.25 (d, 3H, $J = 6.3$ Hz, CH_3), 0.99 (s, 9H, *t*Bu), 0.02 (s, 3H, Si(CH_3)$_2$), 0.01 ppm (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, [D$_6$]benzene): $\delta = 148.6$ (1), 107.9 (1), 80.8 (1), 75.2 (1), 35.0 (2), 26.0 (3), 21.8 (2), 18.3 (0), 17.8 (3), −4.2 (3), −4.8 ppm (3); IR (film, KBr plates): $\tilde{\nu} = 3042$ (w), 2929 (m), 2856 (m), 1647 (m), 1472 (m) cm^{-1}; LRMS (70 eV, EI): m/z (%): 243 (100) [M^++H]; HRMS (ESI): m/z: calcd for $C_{13}H_{26}O_2Si$: 243.1775 [M^++H], found 243.1775.

(3*R*,4*S*)-4-(*tert*-Butyldimethylsilanyloxy)-pent-1-en-3-ol (10): Obtained from **9** (1.75 g, 7.5 mmol) following the procedure given above for **3**, except using ether rather than CH_2Cl_2 for the DIBAL-H reduction. **10** was purified by Kugelrohr distillation (100 °C, 3 mbar). Yield: 1.30 g (80%). $[\alpha]_D^{25} = +19.6$ ($c = 0.65$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.79$ (ddd, 1H, $J = 17.3$, 10.5, 6.3 Hz, CH=), 5.26 (ddd, 1H, $J = 17.3$, 1.5, 1.5 Hz, =CH_2), 5.17 (ddd, 1H, $J = 10.5$, 1.5, 1.5 Hz, =CH_2), 4.00 (m, 1H, CHOH), 3.82 (qd, 1H, $J = 6.3$, 3.8 Hz, OCH(CH_3)), 2.30 (br s, 1H, OH), 1.06 (d, 3H, $J = 6.3$ Hz, CH_3), 0.88 (s, 9H, *t*Bu), 0.06 (s, 3H, Si(CH_3)$_2$), 0.06 ppm (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 136.5$ (1), 116.5 (2), 76.6 (1), 71.3 (1), 25.8 (3), 18.0 (0), 17.6 (3), −4.5 (3), −4.9 ppm (3); IR (film, KBr plates): $\tilde{\nu} = 3443$ (s), 2957 (s), 1472 (s), 1376 (s), 1255 (s), 1097 (s), 1005 (s), 836 (s), 776 cm^{-1} (s); LRMS (70 eV, EI): m/z (%): 159 (58) [M^+−*t*Bu], 75 (100); elemental analysis calcd (%) for $C_{11}H_{24}O_2Si$: C 61.1, H 11.2; found: C 60.8, H 11.4.

(1*S*,2*R*)-*tert*-Butyl-[2-(2-methoxy-ethoxymethoxy)-1-methyl-but-3-enyloxy]-dimethylsilane (11): To a solution of **10** (1.30 g, 6.0 mmol) in dry CH_2Cl_2 was added Et_2NiPr (3.80 mL, 23.0 mmol) and MEM-chloride (1.71 mL, 15.0 mmol) at 0 °C. The mixture was allowed to warm to ambient temperature, and stirring was continued for 12 h. The solution was diluted with MTBE and washed with aqueous Na_2CO_3 solution. The organic layer was separated, dried with $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography on silica to give **11** (1.64 g, 90%). $[\alpha]_D^{26} = -25.8$ ($c = 1.01$ in CH_2Cl_2); ^{1}H NMR (400 MHz, [D$_6$]benzene): $\delta = 5.81$ (ddd, 1H, $J = 17.6$, 10.3, 7.8 Hz, CH=), 5.19 (dm, 1H, $J = 17.6$ Hz, =CH_2), 5.15 (dm, 1H, $J = 10.3$ Hz, =CH_2), 4.81 (d, 1H, $J = 6.5$ Hz, OCHHO), 4.66 (d, 1H, $J = 6.5$ Hz, OCHHO), 3.99 (dd, 1H, $J = 7.8$, 4.5 Hz, CHOMEM), 3.91 (qd, 1H, $J = 6.3$, 4.5 Hz, OCH(CH_3)), 3.78 (dt, 1H, $J = 10.8$, 5.0 Hz, OCHHCH$_2$O), 3.55 (dt, 1H, $J = 10.8$, 5.0 Hz, OCHHCH$_2$O), 3.38 (2H, t, $J = 5.0$ Hz, OCH$_2$CH_2O), 3.14 (s, 3H, OCH_3), 1.20 (d, 3H, $J = 6.3$ Hz, CH_3), 1.01 (s, 9H, *t*Bu), 0.14 (s, 3H, Si(CH_3)$_2$), 0.10 ppm (s, 3H, Si(CH_3)$_2$); ^{13}C NMR (100 MHz, [D$_6$]benzene): $\delta = 135.8$ (1), 118.9 (2), 92.9 (2), 81.6 (1), 72.2 (2), 71.2 (1), 67.4 (2), 58.6 (3), 26.1 (3), 20.2 (3), 18.4 (0), −4.4 (3), −4.5 ppm (3); IR (film, KBr plates): $\tilde{\nu} = 2929$ (m), 2885 (m), 2857 (m), 1472 (w), 1361 (w), 1252 cm^{-1} (m); LRMS (70 eV, EI): m/z (%): 327 (10) [M^++Na], 199 (100); HRMS (ESI): m/z: calcd for $C_{15}H_{32}O_4Si$: 327.1962 [M^++Na], found 327.1973; elemental analysis calcd for $C_{15}H_{32}O_4Si$: C 59.2, H 10.6; found: C 59.2, H 11.0.

(2*S*,3*R*)-3-(2-Methoxyethoxymethoxy)-pent-4-en-2-ol (12): To a solution of **11** (1.16 g, 3.8 mmol) in dry THF (30 mL) was added TBAF (2.37 g, 7.5 mmol) and the solution was heated to reflux. After 30 min, the reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (30 mL), and washed with brine. The organic extracts were dried with $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography on silica using cyclohexane/ethyl acetate 2:1 to give **12** (0.72 g, quant.). $[\alpha]_D^{26} = -65.2$ ($c = 1.01$ in CH_2Cl_2); ^{1}H NMR (400 MHz, [D$_6$]benzene): $\delta = 5.71$ (ddd, 1H, $J = 17.3$, 10.5, 7.5 Hz, CH=), 5.14 (dm, 1H, $J = 17.3$ Hz, =CH_2), 5.08 (dm, 1H, $J = 10.5$ Hz, =CH_2), 4.69 (d, 1H, $J = 7.0$ Hz, OCHHO), 4.57 (d, 1H, $J = 7.0$ Hz, OCHHO), 4.02 (dd, 1H, $J = 7.3$, 3.3 Hz, CHOMEM), 3.87 (m, 1H, CHOH), 3.70 (ddd, 1H, $J = 10.9$, 6.3, 3.5 Hz, OCHHCH$_2$)OCH$_3$), 3.42 (ddd, 1H, $J = 10.9$, 6.3, 3.5 Hz, OCHHCH$_2$)OCH$_3$), 3.31 (ddd, 1H, $J = 10.5$, 6.3, 3.3 Hz, OCH$_2$CHH)OCH$_3$), 3.25 (ddd, 1H, $J = 10.5$, 6.3, 3.3 Hz, OCH$_2$CHH)OCH$_3$), 3.10 (s, 3H, OCH_3), 2.77 (br d, 1H, $J = 3.5$ Hz, OH), 1.20 ppm (d, 3H, $J = 6.3$ Hz, CH_3); ^{13}C NMR (100 MHz, [D$_6$]benzene): $\delta = 135.1$ (1), 118.7 (2), 93.6 (2), 82.7 (1), 72.1 (2), 69.4 (1), 67.6 (2), 58.6 (3), 17.9 ppm (3); IR (film, KBr plates): $\tilde{\nu} = 3438$ (bm), 2976 (m), 2885 (m), 1643 (m), 1452 cm^{-1} (m); LRMS (70 eV, EI): m/z (%): 191 (100) [M^++H]; HRMS (ESI): m/z: calcd for $C_9H_{18}O_4$: 191.1278 [M^++H], found 191.1292; elemental analysis calcd (%) for $C_9H_{18}O_4$: C 56.8, H, 9.5; found: C 56.4, H 9.7.

(3*R*,4*S*)-4-Allyloxy-3-(2-methoxyethoxymethoxy)-pent-1-ene (13): Obtained from **12** (300 mg, 1.6 mmol) following the procedure given above for **4b**, except using allyl rather than benzyl bromide. Compound **13** was purified by flash chromatography on silica. Yield: 300 g (83%). $[\alpha]_D^{26} = -60.1$ ($c = 1.07$ in CH_2Cl_2); ^{1}H NMR (400 MHz, [D$_6$]benzene): $\delta = 5.89$ (dddd, 1H, $J = 17.1$, 10.3, 5.0, 5.0 Hz, CH=), 5.79 (ddd, 1H, $J = 17.3$, 10.5, 7.0 Hz, CH=), 5.30 (d, 1H, $J = 17.1$ Hz, =CH_2), 5.22 (d, 1H, $J = 17.3$ Hz, =CH_2), 5.12 (d, 1H, $J = 10.5$ Hz, =CH_2), 5.05 (d, 1H, $J = 10.3$ Hz, =CH_2), 4.80 (d, 1H, $J = 6.8$ Hz, OCHHO), 4.71 (d, 1H, $J = 6.8$ Hz, OCHHO),

4.21 (dd, 1H, $J=7.0$, 3.5 Hz, C*H*OMEM), 3.99 (dd, 1H, $J=13.3$, 5.0 Hz, OCHHCH=), 3.93 (dd, 1H, $J=13.3$, 5.0 Hz, OCHHCH=), 3.82 (ddd, 1H, $J=10.8$, 5.0, 5.0 Hz, OC*H*HCH$_2$)OCH$_3$), 3.57 (ddd, 1H, $J=10.8$, 5.0, 5.0 Hz, OC*H*HCH$_2$)OCH$_3$), 3.48 (qd, 1H, $J=6.3$, 3.8 Hz, C*H*CH$_3$), 3.39 (t, 2H, $J=5.0$ Hz, OCH$_2$C*H*$_2$)OCH$_3$), 3.14 (s, 3H, OC*H*$_3$), 1.20 ppm (3H, d, $J=6.3$ Hz, C*H*$_3$); ^{13}C NMR (100 MHz, [D$_6$]benzene): $\delta=136.1$ (1), 135.9 (1), 118.2 (2), 115.5 (2), 93.2 (2), 79.6 (1), 77.5 (1), 72.2 (2), 70.3 (2), 67.3 (2), 58.6 (3), 15.9 ppm (3); IR (film, KBr plates): $\tilde{\nu}=2880$ (m), 1646 (w), 1454 (w), 1374 (w), 1105 cm^{-1} (s); LRMS (70 eV, EI): *m*/*z* (%): 231 (10) [M^++H], 186 (100); HRMS (ESI): *m*/*z*: calcd for $C_{12}H_{22}O_4$: 231.1591, found 231.1603 [M^++H]; elemental analysis calcd for $C_{12}H_{22}O_4$: C 62.6, H 9.6; found: C 62.1, H 10.1.

(2*S*,3*R*)-3-(2-Methoxyethoxymethoxy)-2-methyl-3,4-dihydro-2*H*-pyran (14): Obtained from **13** (200 mg, 1.2 mmol) following the procedure given above for **5a. 13** was purified by column chromatography on silica. Yield: 170 mg (70%). $[\alpha]_D^{20}=-89.5$ ($c=1.20$ in CH_2Cl_2); ^{1}H NMR (400 MHz, [D$_6$]benzene): $\delta=6.32$ (d, 1H, $J=6.0$ Hz, H1), 4.65 (d, 1H, $J=6.8$ Hz, OC*H*HO), 4.57 (d, 1H, $J=6.8$ Hz, OC*H*HO), 4.48 (ddd, 1H, $J=6.0$, 5.0, 2.5 Hz, H2), 3.87 (dq, 1H, $J=7.8$, 6.3 Hz, H6), 3.60–3.52 (3H, OMEM + H4), 3.34–3.29 (2H, OMEM), 3.12 (s, 3H, OCH$_3$), 2.25 (ddd, 1H, $J=16.6$, 5.0, 5.0 Hz, H3), 1.98 (dddd, 1H, $J=16.6$, 8.0, 2.5, 2.5 Hz, H3′), 1.33 ppm (d, 3H, $J=6.3$ Hz, CH$_3$); ^{13}C NMR (100 MHz, [D$_6$]benzene): $\delta=143.4$ (1, C1), 97.6 (1, C2), 94.2 (2, OCH$_2$O), 74.0 (1, C5), 74.0 (1, C4), 72.1 (2, *C*H$_2$OCH$_3$), 67.4 (2, *C*H$_2$CH$_2$OCH$_3$), 58.6 (OCH$_3$), 27.2 (2, C3), 17.9 (3, C6); IR (film, KBr plates): $\tilde{\nu}=3063$ (s), 2936 (s), 1656 (s), 1241 (s), 1048 cm^{-1} (s); LRMS (70 eV, EI): *m*/*z* (%): 127 (3) [M^+ −OCH$_2$CH$_2$OCH$_3$], 96 (86), 81 (76), 59 (100); elemental analysis calcd (%) for $C_{10}H_{18}O_4$: C 59.4, H 9.0; found: C 59.4, H 9.3.

2-(*tert*-Butyldimethylsilanyloxy)-hex-5-en-3-ol (15): Obtained from **9** (2.10 g, 9.0 mmol) and allyl magnesium bromide (0.8 M solution in ether, 23.0 mL, 18.0 mmol) following the procedure given above for **10**. Compound **15** was purified by column chromatography on silica. Yield: 1.55 g (75%) of an inseparable 2:1 mixture of diastereoisomers. ^{1}H NMR (400 MHz, CDCl$_3$): $\delta=5.90$–5.75 (1H, CH=), 5.16–5.05 (2H, =CH$_2$), 3.76 (1H, m, CHO (major isomer)), 3.68 (1H, m, CHO (minor isomer)), 3.54 (m, 1H, CHO (major isomer)), 3.36 (m, 1H, CHO (minor isomer)), 2.30–2.10 (2H, CH$_2$), 1.14 (d, 3H, $J=6.2$ Hz, CH$_3$ (minor isomer)), 1.09 (d, 3H, $J=6.2$ Hz, CH$_3$ (major isomer)), 0.89 (s, 9H, *t*Bu (minor isomer)), 0.87 (s, 9H, *t*Bu (major isomer)), 0.09–0.02 ppm (s, 6H, SiMe$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) for major isomer: $\delta=135.1$, 117.3, 74.5, 70.9, 36.7, 25.8, 18.0, 17.3, −4.4, −4.9 ppm; ^{13}C NMR (100 MHz, CDCl$_3$) for minor isomer: $\delta=135.2$, 116.9, 75.2, 70.9, 38.1, 25.8, 20.1, 18.0, −4.4, −4.9 ppm.

***tert*-Butyl-[2-(2-methoxyethoxymethoxy)-1-methyl-pent-4-enyloxy]-dimethylsilane (16)**: Obtained from **15** (1.18 g, 5.1 mmol) following the procedure given above for **11**. Compound **16** was purified by flash chromatography on silica. Yield: 1.54 g (95%) of an inseparable 2:1 mixture of diastereomers. ^{1}H NMR (500 MHz, CDCl$_3$): $\delta=5.88$–5.78 (m, 1H, C*H*=), 5.10–4.98 (2H, =CH$_2$), 4.82–4.68 (2H, OCH$_2$O), 3.90–3.60 (3H), 3.55–3.44 (3H), 3.35 (s, 3H, OCH$_3$), 2.45–2.08 (2H, CH$_2$), 1.10 (d, 3H, $J=6.2$ Hz, CH$_3$ (major isomer), 1.07 (d, 3H, $J=6.2$ Hz, CH$_3$ (minor isomer), 0.85 (9H, s, *t*Bu), 0.02 ppm (s, 6H, SiMe$_2$); ^{13}C NMR (125 MHz, CDCl$_3$) for major isomer $\delta=136.8$ (1), 118.2 (2), 96.7 (2), 82.6 (1), 73.2 (2), 71.4 (1), 68.5 (1), 60.5 (1), 37.1 (2), 27.3 (3), 20.3 (3), −3.0 (3), −3.3 ppm (3); ^{13}C NMR (125 MHz, CDCl$_3$) for minor isomer: $\delta=137.4$ (1), 118.0 (2), 97.3 (2), 83.0 (1), 73.2 (2), 70.9 (1), 68.4 (1), 60.5 (1), 35.6 (2), 27.3 (3), 19.7 (3), −3.0 (3), −3.3 ppm (3).

3-(2-Methoxyethoxymethoxy)-hex-5-en-2-ol (17): Obtained from **16** (1.50 g, 4.7 mmol) following the procedure given above for **12**. After workup, crude **17** (approximately 1.0 g, corresponding to a quantitative yield) was directly used in the next step without further purification. For analytical data the product was purified by flash chromatography on silica, yielding an inseparable 2:1 mixture of diastereomers.^{1}H NMR (300 MHz, CDCl$_3$): $\delta=5.92$–5.71 (1H, C*H*=), 5.19–5.00 (2H, =C*H*$_2$), 4.81 (d, 1H, $J=7.8$ Hz, OC*H*$_2$O), 4.76 (d, 1H, $J=7.8$ Hz, OC*H*$_2$O), 3.85–3.50 (6H), 3.37 (s, 3H, OCH$_3$), 2.45–2.08 (m, 3H), 1.15 (d, $J=6.4$ Hz, 3H, CH$_3$), 1.13 ppm (d, $J=6.5$ Hz, 3H, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) for major isomer: $\delta=134.9$ (1), 117.0 (2), 95.9 (2), 83.7 (1), 71.6 (2), 68.6 (1), 67.5 (2), 58.9 (3), 35.3 (2), 17.1 ppm (3); ^{13}C NMR (75 MHz, CDCl$_3$) for minor isomer: $\delta=134.1$ (1), 118.0 (2), 95.8 (2), 83.7 (1), 71.7 (2), 68.9 (1), 67.6 (2), 59.0 (1), 35.6 (2), 17.1 ppm (3).

5-Allyloxy-4-(2-methoxyethoxymethoxy)-hex-1-ene (18): Obtained from crude **17** (ca 1.0 g, ca 4.7 mmol) following the procedure given above for **13**. Compound **18** (approximately 1.1 g, quantitative yield) was used without further purification in the next step. NMR spectra were obtained from crude reaction mixtures after aqueous workup, extraction, and removal of all volatiles. ^{1}H NMR (500 MHz, CDCl$_3$): $\delta=6.15$–5.78 (2H, C*H*=), 5.30–5.00 (4H, =CH$_2$), 4.86–4.70 (2H, OCH$_2$O), 3.97–3.55 (6H), 3.45–3.33 (2H), 3.13 (s, 3H, OCH$_3$), 2.58–2.43 (1H, CH$_2$), 2.32–2.22 (1H, CH$_2$), 1.16 (d, 3H, $J=6.3$ Hz, CH$_3$ (major isomer), 1.11 (d, 3H, $J=6.3$ Hz, CH$_3$ (minor isomer); ^{13}C NMR (125 MHz, CDCl$_3$) for major isomer: $\delta=136.0$ (1), 135.8 (1), 116.7 (2), 115.5 (2), 95.3 (2), 78.9 (1), 76.8 (1), 72.2 (2), 69.9 (2), 67.5 (2), 58.7 (3), 36.2 (2), 15.2 ppm (3); ^{13}C NMR (125 MHz, CDCl$_3$) for minor isomer: $\delta=136.1$ (1), 135.8 (1), 116.6 (2), 115.6 (2), 95.8 (2), 79.5 (1), 76.2 (1), 70.2 (2), 67.5 (2), 58.7 (3), 34.9 (2), 14.8 ppm (3).

3-(2-Methoxyethoxymethoxy)-2-methyl-2,3,4,5-tetrahydrooxepine [(*S*,*R*)-19] and 3-(2-methoxyethoxymethoxy)-2-methyl-2,3,4,5-tetrahydrooxepine [(*S*,*S*)-19]: Obtained from **18** (0.91 g, 3.7 mmol) following the procedure given above for **14**. The two diastereoisomers were separated by column chromatography on silica using hexane/MTBE mixtures of increasing polarity as eluent. The major isomer (*S*,*R*)-**19** (0.33 g, 41%) was eluted first, followed by a fraction containing the minor isomer (*S*,*S*)-**19** (0.19 g, 23%). Analytically pure samples of both diastereoisomers were obtained by subsequent Kugelrohr distillation (120 °C at 0.02 mbar). (*S*,*R*)-**19**: $[\alpha]_D^{20}=-105.8$ ($c=3.18$ in CH_2Cl_2); ^{1}H NMR (400 MHz, [D$_6$]benzene): $\delta=6.39$ (dd, 1H, $J=6.5$, 1.8 Hz, H1), 4.63 (d, 1H, $J=6.8$ Hz, -OC*H*HO-), 4.62 (m, 1H, H2), 4.52 (d, 1H, $J=6.8$ Hz, -OC*H*HO-), 4.12 (dq, 1H, $J=9.0$, 6.3 Hz, H6), 3.68 (ddd, 1H, $J=9.0$, 3.5, 3.5 Hz, H5), 3.63–3.51 (2H, OMEM), 3.36–3.27 (2H, OMEM), 3.12 (s, 3H, OCH$_3$), 2.48 (ddddd, 1H, $J=17.1$, 12.8, 2.3, 2.3, 2.3 Hz, H3), 2.10 (dddd, 1H, $J=14.5$, 12.8, 4.0, 2.0 Hz, H4), 1.84 (dd, 1H, $J=14.5$, 6.3 Hz, H4′), 1.70 (ddd, 1H, $J=17.1$, 6.5, 6.3 Hz, H3), 1.38 (d, 3H, $J=6.3$ Hz, H7); ^{13}C NMR (100 MHz, [D$_6$]benzene): $\delta=148.6$ (1, C1), 109.3 (1, C2), 94.4 (2, OCH$_2$O), 81.2 (1, C5), 80.8 (1, C6), 72.1 (2, *C*H$_2$OCH$_3$), 67.6 (2, *C*H$_2$CH$_2$OCH$_3$), 58.1 (OCH$_3$), 30.8 (2, C4), 20.9 (2, C3), 19.8 (3, C7); IR (film, KBr plates): $\tilde{\nu}=$ 3042 (s), 2929 (s), 1649 (s), 1264 (s), 1102 (s), 1039 cm^{-1} (s); LRMS (70 eV, EI): *m*/*z* (%): 216 (1) [M^+], 140 (17), 89 (26), 59 (100); elemental analysis calcd for $C_{13}H_{24}O_4$: C 61.1, H 9.3; found: C 61.4, H 9.4.

Product (S,S)-***19***: $[\alpha]_D^{20}=-44.0$ ($c=1.70$ in CH_2Cl_2); ^{1}H NMR (400 MHz, [D$_6$]benzene): $\delta=6.36$ (dd, 1H, $J=6.8$ Hz, H1), 4.69 (d, 1H, $J=7.0$ Hz, OC*H*HO), 4.57 (m, 1H, H2), 4.56 (d, 1H, $J=7.0$ Hz, OC*H*HO), 4.06 (qd, 1H, $J=6.5$, 2.5 Hz, H6), 3.64–3.55 (2H, OMEM), 3.52 (ddd, 1H, $J=8.0$, 5.3, 2.5 Hz, H5), 3.33 ("t", 2H, $J=4.8$ Hz, OMEM), 3.12 (s, 3H, OCH$_3$), 2.04 (dddd, 1H, $J=15.3$, 7.8, 7.8, 7.0 Hz, H4), 1.91–1.82 (3H, H4′, H3′, H3), 1.30 (d, 3H, $J=6.3$ Hz, H7); ^{13}C NMR (100 MHz, [D$_6$]benzene): $\delta=$ 148.5 (1, C1), 108.0 (1, C2), 94.7 (2, OCH$_2$O), 80.2 (1, C5), 79.4 (1, C6), 72.2 (2, *C*H$_2$OCH$_3$), 67.4 (2, *C*H$_2$CH$_2$OCH$_3$), 58.6 (OCH$_3$), 31.6 (2, C4), 21.8 (2, C3), 17.5 (3, C7); IR (film, KBr plates): $\tilde{\nu}=3040$ (s), 2933 (s), 1648 (s), 1269 (s), 1044 cm^{-1} (s); LRMS (70 eV, EI): *m*/*z* (%): 216 (1) [M^+], 140 (15), 89 (25), 59 (100); elemental analysis calcd (%) for $C_{13}H_{24}O_4$: C 61.1, H 9.3; found: C 61.2, H 9.5.

(2*S*,3*S*,6*S*)-6-[(1*S*,2*S*)-Allyloxyethyl)-but-3-enyloxy]-3-benzyloxy-2-methyltetrahydropyran (20): To a solution of **5b** (100 mg, 0.52 mmol) and **6** (162 mg, 1.04 mmol) in dry benzene (20 mL) with MS 4 Å was added *p*-TSA (8 mg, 8 mol%). After stirring for 12 h the solvent was evaporated and the residue was dissolved in ethyl acetate. The organic layer was washed with an aqueous solution of sodium bicarbonate and brine, successively, dried with MgSO$_4$, filtered and evaporated. The residue was purified by flash chromatography on silica using cyclohexane/ethyl acetate 1:1 to give **20** (110 mg, 60%). $[\alpha]_D^{23}=-23.5$ ($c=0.62$ in CH_2Cl_2); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta=7.41$–7.27 (5H, Ph), 5.96–5.80 (2H, C*H*=), 5.25 (dddd, 1H, $J=17.2$, 1.7, 1.7, 1.7 Hz, =C*H*$_2$), 5.19–4.95 (4H, =CH$_2$, OC*H*O), 4.68 (d, 1H, $J=12.3$ Hz, CH$_2$Ph), 4.43 (d, 1H, $J=12.3$ Hz, CH$_2$Ph), 4.12–3.91 (3H, OC*H*$_2$CH=), 3.72 (m, 1H, OC*H*CH$_3$), 3.51 (m, 1H, m, OC*H*CH$_3$), 3.27 (m, 1H, C*H*O), 2.41 (dm, 1H, $J=14.4$ Hz,

C*HH*CH=), 2.20 (ddd, 1H, J=14.4, 7.7, 7.7 Hz, C*HH*CH=), 2.00 (ddd, 1H, J=13.0, 5.3, 3.6 Hz, CH_2CH_2), 1.95–1.85 (2H, CH_2CH_2), 1.51 (dm, J=13.0 Hz, CH_2CH_2), 1.15 (d, 3H, J=6.6 Hz, CH_3), 1.11 ppm (d, 3H, J=6.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ=138.8 (0), 135.8 (1), 135.4 (1), 128.2 (1), 127.8 (1), 127.5 (1), 116.5 (2), 116.3(2), 96.9 (1), 78.1 (1), 75.4 (1), 73.6 (1), 70.8 (2), 70.4 (2), 66.6 (1), 35.2 (2), 24.3 (2), 21.4(2), 17.2 (3), 15.1 ppm (3); IR (film, KBr plates): $\tilde{\nu}$=2932 (m), 2348 (m), 1641 (m), 1496 (m), 1435 (m), 1360 cm^{-1} (m); elemental analysis calcd (%) for $C_{22}H_{32}O_4$: C 73.3, H 8.9; found: C 72.8, H 8.5.

(2*S*,3*S*)-3-((2*S*,5*S*,6*S*)-5-Benzyloxy-6-methyltetrahydropyran-2-yloxy)-2-methyl-2,3,4,5-tetrahydrooxepine (21): Obtained from **20** (100 mg, 0.29 mmol) following the procedure given above for **5a. 21** was purified by column chromatography on silica. Yield: 70 mg (75%). $[\alpha]_D^{23}=-81.1$ (c=1.07 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.40–7.26 (5H, Ph), 6.29 (dd, 1H, J=6.3, 1.5 Hz, H1), 4.85 (brs, 1H, OC*H*O), 4.70 (m, 1H, H2), 4.69 (d, 1H, J=12.3 Hz, CH_2Ph), 4.44 (d, 1H, J=12.3 Hz, CH_2Ph), 4.23 (qd, 1H, J=6.6, 2.4 Hz, H6), 4.03 (qd, 1H, J=6.6, 1.3 Hz, $CHCH_3$, rhodinose), 3.76 (m, 1H, H5), 3.28 (brs, 1H, C*H*OCH_2Ph), 2.24–1.76 (8H, H3, H4, CH_2CH_2 (rhodinose)), 1.25 (d, 3H, J=6.6 Hz, H7), 1.17 ppm (d, 3H, J=6.6 Hz, CH_3 (rhodinose)); ^{13}C NMR (75 MHz, $CDCl_3$): δ=148.2 (1), 138.7 (0), 128.2 (1), 127.8 (1), 127.7 (1), 127.5 (1), 108.3 (1), 99.5 (1), 80.9 (1), 80.4 (1), 73.6 (1), 70.8 (2), 66.8 (1), 33.1 (2), 23.9 (2), 21.9(2), 21.4 (2), 17.3 (3), 17.3 ppm (3); IR (film, KBr plates): $\tilde{\nu}$=3035 (w), 2931 (m), 1647 (m), 1496 (m), 1446 cm^{-1} (m); elemental analysis calcd (%) for $C_{20}H_{28}O_4$: C 72.3, H 8.5; found: C 72.2, H 8.0.

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