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Synthesis of 3-Deoxy Glycals via Tandem Metathesis Sequences and Their Use in an Intermolecular Heck Arylation

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Dedicated to the memory of Professor Peter Welzel

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Deoxy glycals can be synthesized from a mannitol-derived C_2-symmetric diene diol by using the tandem RCM/isomerization approach. Incorporation of a ruthenium-catalyzed dehydrogenative silylation step into the reaction sequence is possible. Thus, an orthogonally protected 3-deoxy glycal results via a tandem RCM/hydrosilylation/isomerization sequence. All ruthenium-catalyzed steps of this tandem sequence occur under distinct conditions, allowing for the selective synthesis of the intermediates. The 3-deoxy glycals obtained via this route undergo a regio- and stereoselective Heck reaction, as exemplified by the synthesis of a *C*-aryl glycoside.

Introduction

The enormous importance of carbohydrates for the regulation of many biological processes has been widely recognized.[1] In particular, deoxygenated carbohydrates have attracted considerable attention for many years, both from the biochemical[2] and the synthetic[3] point of view. For instance, deoxy carbohydrates are frequently found as constituents of oligosaccharide side chains in antibiotics,[4] and incorporation of novel substitution and deoxygenation patterns might help to overcome resistance of certain pathogenic bacteria to these antibiotics. Thus, an important goal is the elucidation of the mechanisms used by nature to make certain deoxygenation patterns accessible.[5] Eventually, this could lead to deoxygenated carbohydrates with hitherto unknown substitution patterns. This approach, proceeding via modified biosynthetic pathways, is indeed very attractive. However, chemical synthesis is in certain cases a useful alternative due to better opportunities for generalization.[6] Two examples for less common substitution patterns are 3-deoxygalactose (**1**) and 3-deoxyglucose (**2**) (Figure 1). Although they do not occur in nature, synthetic routes were investigated. Most of these rely on a Ferrier rearrangement[7] of acetylated galactal or glucal, followed by hydrogenation of the C=C bond.[8–12] More recently, O'Doherty described a de novo approach, starting from 2-vinylfuran using an enantioselective dihydroxylation and subsequent Achmatowicz rearrangement.[13] This was applied to the synthesis of desoxygenated analogues of mannopeptimycin E antibiotics.[14,15] Phthalimido derivatives of **1** and **2** were tested for antiinflammatory[16] and hypolipidemic activity.[17] Utilization as a building block for the synthesis of non-carbohydrate target molecules has also been reported: examples are the amino acid vigabatrin,[18] trans-fused polyether toxins,[19] and conformationally constrained *C*-glycoside amino acids.[20] Finally, TBS-protected **2** has very recently been used as a chiral auxiliary in Nazarov cyclizations of allenes.[21]

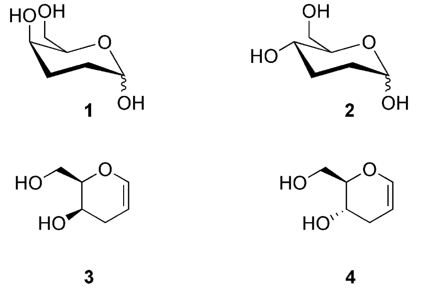

Figure 1. 3-Deoxygalactose (**1**) and 3-deoxyglucose (**2**) and their corresponding glycals.

Particularly useful building blocks for the introduction of glycosyl moieties are glycals,[22] 1,2-unsaturated derivatives of carbohydrates. In this particular case, the corresponding glycals **3** and **4** have been obtained by Pd-catalysed allylic reduction of the corresponding galactal or glucal, albeit in moderate to low yields.[23] More recently, the

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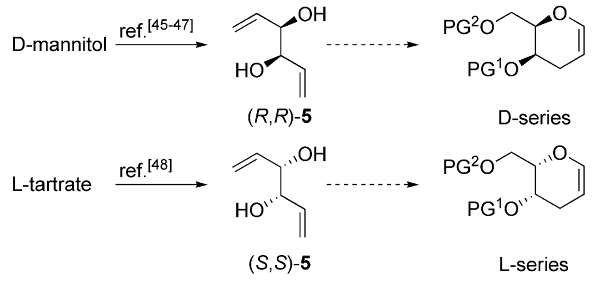
cyclization of alkynols,[24] reductive Ferrier rearrangement followed by rhodium-catalyzed isomerization,[25] and the reductive elimination of 2-deoxy-2-iodothio glycosides have been devised as alternatives.[26] Several synthetic applications of protected glycals **3** and **4** have been described in the literature: hexose nucleic acids have been synthesized using 2,3-dideoxy glycals,[27] upon treatment of the glycals with nucleic acids a ring contraction occurs, leading to cyclopropanated analogues of deoxy nucleosides as potential antiviral agents,[28,29] and the formation of 1-azides[30] and 2-iodo-1-azides[31] has also been investigated. A synthesis of 3-deoxy-3-azido glycals from TBS-protected **2** was reported by Kirschning et al. with a view to 3-deoxy-3-amino glycals.[32]

We have recently embarked on a project directed at the utilization of the tandem RCM[33–35]/isomerization sequence, developed by Snapper et al.[36] and by us,[37–39] for the synthesis of deoxy glycals.[40–42] We describe our method as catalysis at the interface of Ru-carbene and Ru-hydride chemistry,[43,44] as it relies on the in situ conversion of the metathesis-active carbene to an isomerization-active Ru-hydride species, which is induced by additives. A major advantage of the method is that the drawbacks of enol ether metathesis, such as the necessity for high dilution conditions and low reactivity can be avoided. In this contribution we describe a new synthesis of 3-deoxygalactal using the tandem RCM/isomerization approach.

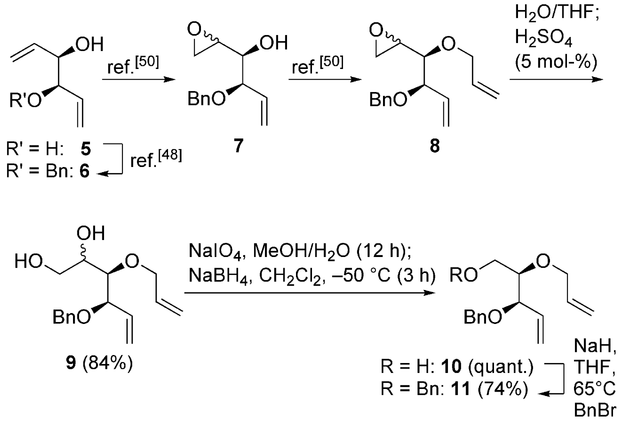
Results and Discussion

It has previously been reported that chiral C_2-symmetric (*R*,*R*)-hexa-1,5-diene-3,4-diol [(*R*,*R*)-**5**][45–47] is conveniently available from D-mannitol in few steps. Interestingly, the (*S*,*S*)-enantiomer of this compound is also available in few steps from L-tartrate.[48] A major advantage of a route starting from **5** would be the opportunity for independent access to both D- and L-3-deoxy glycals via an identical sequence of steps (Scheme 1).



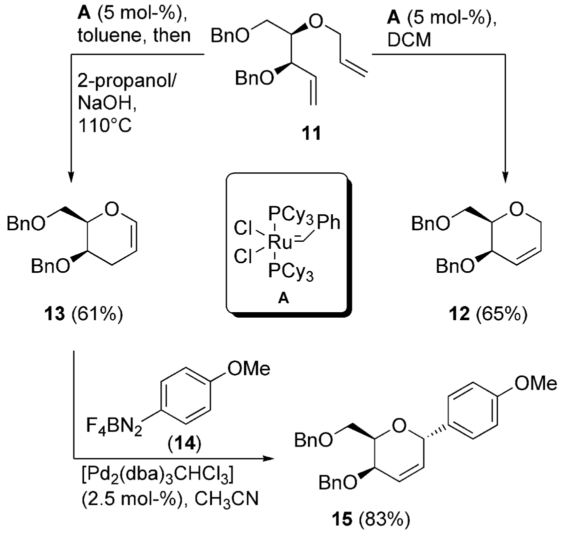
Scheme 1. Ex-chiral pool starting materials for D- and L-3-deoxy glycals.

Our route starts with a selective monobenzylation of **5** via a stannylene acetal. Formation of benzyl ether **6** has previously been described in the literature.[47,49] Vanadium-catalysed epoxidation of **6** was investigated in different context by us.[50] The reaction yields epoxide **7**[50] in good yield and perfect regioselectivity within short periods of time. The only drawback is a diastereomeric ratio of 2:1, which is, however, irrelevant for our purposes: in a subsequent step, the alcohol was allylated to give allyl ether **8**[50] using either a Pd-catalysed reaction or a conventional Williamson ether synthesis at 0 °C. Under these basic conditions low temperatures (and consequently longer reaction times) are required to prevent undesired epoxide rearrangement reactions.[51] **8** was then (as a mixture of diastereomers) subjected to an acid-catalyzed hydrolysis of the epoxide, resulting in diol **9** as a mixture of diastereomers. In the following step the *vic*-diol was oxidatively cleaved with periodate, followed by reductive work-up. After this step, the metathesis precursor **10** required for the D-3-deoxygalactose pattern was obtained as a single isomer in quantitative yield. Occasionally, difficulties arising from undesired transfer hydrogenation reactions were observed when conducting tandem RCM/isomerization reactions with unprotected alcohols.[52] Therefore, **10** was protected as a benzyl ether **11** (Scheme 2).



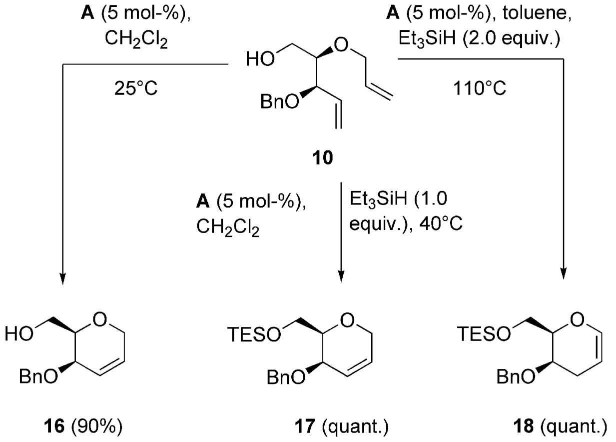
Scheme 2. Access to RCM and tandem RCM/isomerization precursors.

As expected, **11** smoothly undergoes RCM with the first generation ruthenium catalyst **A**,[53] giving the dihydropyran **12**. Tandem RCM/isomerization of **11** was achieved using the 2-propanol/NaOH protocol developed by us.[38] Thus, after completion of the metathesis step, transformation of the metathesis catalyst to a Ru-hydride species was induced with 2-propanol in the presence of hydroxide. Under these conditions, dibenzylated D-3-deoxygalactal **13** was obtained in 61% yield after column chromatography on silica. NMR spectroscopy of the crude reaction mixture reveals that the RCM/isomerization sequence is selective, confirming that the reduced yield can be attributed to loss of material during purification. As a representative example for stereo- and regioselective functionalization, **13** was used for the synthesis of a *C*-aryl glycoside. Characteristic structural feature of these compounds is an aromatic moiety directly attached to a carbohydrate via a C–C rather than a C–O bond. *C*-aryl glycosides are frequently found in the aglycon part of various antitumor antibiotics[54] and as natural products originating from various plants.[55] Consequently, many syntheses have been published and the subject of *C*-aryl glycoside synthesis has been extensively reviewed.[56–59] A classical method for obtaining *C*-aryl glycosides involves an *O*-glycosylation of phenols with glycosyl fluorides, followed by a Fries-type O→C rearrangement.[60] Palladium-mediated couplings of a 3-pyranoid glycal with aryl iodides (Heck reaction)[61] or an organomercury compound leading to a *C*-aryl glycoside have been reported by Daves and co-workers.[62] A major obstacle in these intermolecular Heck arylations of cyclic enol ethers is the occasionally low reactivity, resulting in long reaction times at elevated temperatures, high catalyst loadings and the necessity to use one coupling partner in excess. In addition, undesired double bond migrations may occur, leading to mixtures of isomers. We have previously shown that arene diazonium salts[63] are highly reactive electrophiles in the intermolecular Heck reaction with cyclic enol ethers[64] and that the problems mentioned above can be avoided with these arylating agents.[65,66] Thus, **13** was treated with the electron-rich arene diazonium salt **14** in the presence of 2.5 mol-% $Pd_2(dba)_3$·$CHCl_3$. Gratifyingly, the *C*-aryl glycoside **15** was obtained as a single α-isomer in good yield, and no undesired double bond migration was observed (Scheme 3).



Scheme 3. RCM and tandem RCM/isomerization of precursor **11** and formation of a *C*-aryl glycoside.

Selective deprotection of the hydroxy groups in **12**, **13** or products derived from one of these two can sometimes be challenging.[67,68] We thought that our metathesis precursor **10** would be well suited to access dihydropyrans or glycals with two orthogonal protecting groups at C4 and C6 position, for instance one benzyl ether and one silyl ether. While conventional silylation of **10** with a silyl halide or triflate would be an obvious solution, we pursued an alternative route that relies on the ability of ruthenium carbenes to activate Si–H bonds: for instance, Grubbs' catalysts are known to catalyze the hydrosilylation of alkynes[69–71] or the hydrogenation of alkenes with silanes.[72] In addition, we had previously reported that triethylsilane is also a suitable additive to promote the double bond migration step of the tandem RCM/isomerization sequence.[39] Silylation of alcohols or carboxylic acids[73] can be achieved with silanes in a dehydrogenative manner, using either Lewis acids[74] or transition metal catalysts.[75] The combination of these observations initiated a project directed at the synthesis of mono-protected or orthogonally diprotected dihydropyrans and glycals from a single precursor, the alcohol **10**: while RCM of **10** in dichloromethane gave the expected dihydropyran **16** at ambient temperature, addition of 1 equivalent of Et_3SiH to the reaction mixture and heating to reflux inititated the dehydrogenative silylation, resulting in the formation of orthogonally diprotected dihydropyran **17**. This reaction can be described as a tandem RCM/dehydrogenative silylation sequence. Notably, under these conditions (refluxing CH_2Cl_2) no isomerized product was detected. If, however, toluene is used as a solvent and the mixture is heated to reflux for several hours, subsequent isomerization occurs and glycal **18** is obtained in quantitative yield. The formation of **18** is an example of a tandem RCM/dehydrogenative silylation/isomerization sequence, where three ruthenium-catalyzed transformations occur under distinct conditions in a defined order of events (Scheme 4).



Scheme 4. RCM and RCM/isomerization coupled with dehydrogenative silylation of alcohols.

Conclusions

In conclusion, a route to enantiopure protected 3-deoxy glycals and isomeric dihydropyrans was developed that makes use of conventional ring closing metathesis or the tandem RCM/isomerization sequence. We showed that incorporation of a dehydrogenative alcohol silylation into the sequence is possible, and that the ruthenium catalyzed steps occur at distinct temperatures. Regio- and stereoselective Heck arylation with an arene diazonium salt opens up a route to *C*-aryl gycosides. Further applications of 3-deoxy glycals and their isomeric dihydropyrans is currently underway.

Experimental Section

General Remarks: 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 MHz, 400 MHz or 500 MHz in CDCl$_3$ with CHCl$_3$ (δ = 7.26 ppm) as an internal standard or in C$_6$D$_6$ with C$_6$D$_5$H (δ = 7.18 ppm) as an internal standard. Coupling constants are given in Hz. Signal assignments are based on H,H-correlation spectroscopy. ^{13}C NMR spectra were recorded at 75 MHz, 100 MHz, or at 125 MHz in CDCl$_3$ with CDCl$_3$ (δ = 77.0 ppm) as an internal standard or in C$_6$D$_6$ with C$_6$D$_6$ (δ = 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 parantheses following the chemical shift value. NMR-peak assignment for cyclic products refers to carbohydrate numbering (i.e. positions –O*CH$_2$*CH = in compounds **12**, **16**, **17** and –O*CH*=CH– in compounds **13** and **18** are numbered H1 or C1, respectively). 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. Optical purities were determined by HPLC using a HP-LC-1050 system equipped with a Daicel Chiralcel OD column. The following compounds have been prepared following procedures described in the literature: **6**,[47,49] **7**,[50] **8**,[50] **14**.[76]

(2*RS*,3*R*,4*R*)-3-Allyloxy-4-(benzyloxy)hex-5-ene-1,2-diol (9): To a solution of **8** (780 mg, 3.00 mmol, mixture of diastereomers) in a 1:1 mixture of THF (20 mL) and water (20 mL) was added a catalytic amount of H$_2$SO$_4$. After complete conversion the solution was neutralized with saturated solution of sodium hydrogen carbonate and the aqueous layer was extracted with diethyl ether. The organic layers were dried with MgSO$_4$ and the solvent was removed in vacuo. After filtration through a short pad of silica, **9** (720 mg, 86%) was obtained as an inseparable mixture of diastereomers. Diol **9** was used without further purification. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.40–7.28 (5 H), 6.02–5.81 (2 H), 5.45–5.33 (2 H), 5.30–5.12 (2 H), 4.70–4.63 (1 H), 4.42–3.97 (4 H), 3.85–3.40 (4 H), 3.15 (br. d, *J* = 4.4 Hz, 0.5 H), 2.65 (br. d, *J* = 6.1 Hz, 0.5 H), 2.33 (br. dd, *J* = 6.3 Hz, 0.5 H), 2.29 (br. dd, *J* = 6.0 Hz, 0.5 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = (*ipso*-C not observed) 134.8, 134.5, 134.4, 134.2 (1), 128.5, 128.4, 127.9, 127.8, 127.7 (1), 119.4, 119.3, 117.6, 117.5 (2), 81.2, 80.9, 80.4, 80.1 (1), 73.6, 73.1, 70.8, 70.7 (2), 71.1 (1), 64.1, 63.4 (2) ppm.

(2*R*,3*R*)-2-(Allyloxy)-3-(benzyloxy)pent-4-en-1-ol (10): To a solution of **9** (180 mg, 0.70 mmol) in MeOH (40 mL) and H$_2$O (6 mL) was added NaIO$_4$ (1.39 g, 6.50 mmol) and the reaction mixture was stirred for 12 h. Excess NaIO$_4$ was destroyed by adding ethylene glycol, and the mixture was stirred for 2 h and filtered through silica. The solvent was removed, and the residue was dissolved in dry DCM and cooled to –50 °C. NaBH$_4$ (490 mg, 12.90 mmol) was added and the reaction mixture was stirred for 3 h. After aqueous workup, the organic layer was extracted with diethyl ether, dried with MgSO$_4$ and the solvent was evaporated. After column chromatography on silica, **10** (160 mg, quant.) was obtained. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.37–7.27 (5 H, Ph), 6.00–5.75 (2 H, -C*H*=CH$_2$), 5.35–5.27 (2 H, =C*H$_2$*), 5.26 (dddd, *J* = 17.3, 1.7, 1.7, 1.7 Hz, 1 H, =C*H$_2$*), 5.17 (dm, *J* = 10.5 Hz, 1 H, =C*H$_2$*), 4.64 (d, *J* = 11.8 Hz, 1 H, -C*H$_2$*Ph), 4.40 (d, *J* = 11.8 Hz, 1 H, -C*H$_2$*Ph), 4.25 (ddt, *J* = 12.6, 5.6, 1.5 Hz, 1 H, -C*H$_2$*CH=), 4.13 (ddt, *J* = 12.6, 6.0, 1.3 Hz, 1 H, -C*H$_2$*CH=), 3.97 (dd, *J* = 6.6, 5.9 Hz, 1 H, -C*H*OBn), 3.76–3.44 (3 H, -C*H$_2$*OH, -C*H*OAll), 1.74 (br. s, 1 H, -O*H*) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 138.2 (0, *ipso*-C, Ph), 134.9, 134.6 (1, -*C*H=CH$_2$), 128.4, 127.8, 127.6 (1, Ph), 119.1, 117.1 (2, -CH=*C*H$_2$), 81.2, 80.9 (1, -*C*HO-), 72.4, 70.6, 62.1 (2, -O*C*H$_2$-) ppm. $[\alpha]_D^{24}$ = –7.0 (*c* = 0.88, CH$_2$Cl$_2$). IR (film, KBr plates): $\tilde{\nu}$ = 3454 (br., w), 3065 (w), 2868 (m), 1736 (w), 1454 (m). LRMS (EI): *m*/*z* (%) = 249 (M$^+$ + H, 60%) 117 (100). HRMS (ESI): calcd. for C$_{15}$H$_{21}$O$_3$$^+$ (M$^+$ + H) 249.1485, found 249.1492.

(2*R*,3*R*)-2-(Allyloxy)-1,3-bis(benzyloxy)pent-4-ene (11): To a solution of **10** (360 mg, 1.40 mmol) in THF (40 mL) was added NaH (60% dispersion in mineral oil, 120 mg, 3.00 mmol) and the mixture was heated to reflux for 30 min. Benzyl bromide (0.36 mL, 3.00 mmol) was added, and the mixture was again heated to reflux for 30 min. Aqueous workup, followed by flash chromatography on silica, yielded **11** (350 mg, 74%). ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.48–7.18 (10 H, Ph), 6.00–5.80 (2 H, -C*H*=CH$_2$), 5.35–5.21 (3 H, =C*H$_2$*), 5.14 (dm, *J* = 10.4 Hz, 1 H, =C*H$_2$*), 4.64 (d, *J* = 12.1 Hz, 1 H, -C*H$_2$*Ph) 4.49 (s, 2 H, -C*H$_2$*Ph) 4.41 (d, *J* = 12.1 Hz, 1 H, -C*H$_2$*Ph), 4.22 (dddd, *J* = 12.9, 5.2, 1.3, 1.3 Hz, 1 H, -C*H$_2$*CH=), 4.16 (dddd, *J* = 12.9, 5.2, 1.3, 1.3 Hz, 1 H, -C*H$_2$*CH=), 3.98 (dd, *J* = 7.5, 4.9 Hz, 1 H, -C*H*OBn) 3.71–3.48 (3 H, -C*H$_2$*OBn, -C*H*OAll) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 138.4, 138.4 (0, *ipso*-C, Ph), 135.4, 135.3 (1, -*C*H=CH$_2$), 128.3, 128.2, 127.8, 127.6, 127.5, 127.4 (1, Ph), 118.3, 116.7 (2, -CH=*C*H$_2$), 80.4, 80.3 (1, -*C*HO-), 73.4, 72.5, 70.8, 70.4 (2, -*C*H$_2$O-) ppm. $[\alpha]_D^{25}$ = –7.5 (*c* = 0.83, CH$_2$Cl$_2$). IR (film, KBr plates): $\tilde{\nu}$ = 3064 (w), 3029 (w), 2863 (m), 1645 (w), 1453 (m). LRMS (EI 361 (M$^+$ + Na, 100%)*m*/*z* HRMS (ESI): calcd. for C$_{22}$H$_{27}$O$_3$$^+$ (M$^+$ + H) 339.1955, found 339.1945.

(2*R*,3*R*)-3-(Benzyloxy)-2-(benzyloxymethyl)-3,6-dihydro-2*H*-pyran (12): To a solution of **11** (100 mg, 0.30 mmol) in dry DCM (10 mL) was added ruthenium catalyst **A** (12 mg, 5 mol-%). The solution was stirred at ambient temperature, until the starting material was fully consumed as indicated by TLC. All volatiles were evaporated, and the residue was purified by flash chromatography to give **12** (60 mg, 65%). ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.40–7.27 (10 H, Ph), 6.10–5.96 (2 H, H2, H3), 4.68 (d, *J* = 12.0 Hz, 1 H, -OC*H$_2$*Ph), 4.66 (d, *J* = 12.0 Hz, 1 H, -OC*H$_2$*Ph), 4.57 (d, *J* = 12.0 Hz, 1 H, -OC*H$_2$*Ph), 4.56 (d, *J* = 12.0 Hz, 1 H, -OC*H$_2$*Ph), 4.36 (dm, *J* = 16.6 Hz, 1 H, H1), 4.19 (dm, *J* = 16.6 Hz, 1 H, H1′), 3.86–3.73 (4 H, H4, H5, H6, H6′) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 138.7, 138.2 (0, *ipso*-C, Ph), 131.4, 128.3, 128.2, 127.7, 127.6, 127.5, 127.4, 123.5 (1, Ph, C2, C3), 76.7, 68.5 (1, C4, C5), 73.5, 70.6, 69.9, 65.8 (2, -O*C*H$_2$Ph, C1, C6) ppm. $[\alpha]_D^{25}$ = –178.6 (*c* = 0.69, CH$_2$Cl$_2$). IR (film, KBr plates): $\tilde{\nu}$ 3030 (w), 2861 (m), 1496 (m), 1453 (m). LRMS (EI): *m*/*z* 311 (M$^+$ + H, 100%). HRMS (ESI): calcd. C$_{20}$H$_{23}$O$_3$$^+$ (M$^+$ + H) 311.1642, found 311.1633.

(2*R*,3*R*)-3-(Benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2*H*-pyran (13): To a solution of **11** (100 mg, 0.30 mmol) in toluene (20 mL) was added ruthenium catalyst **A** (12 mg, 5 mol-%). The solution was stirred at ambient temperature, until the starting material was fully consumed as indicated by TLC. 2-Propanol (300 µL) and solid NaOH (10 mg) were added, and the mixture was heated to reflux for 30 min. After this time, the intermediate RCM product was completely converted to **13**, as indicated by TLC. The solution was washed with water, and all volatiles were evaporated. The residue was purified by flash chromatography to yield **13** (57 mg, 61%). ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.40–7.27 (10 H, Ph), 6.41 (ddd, *J* = 6.4, 1.9, 1.9 Hz, 1 H, H1), 4.67 (d, *J* = 11.3 Hz, 1 H, -C*H$_2$*Ph), 4.66 (m, 1 H, H2), 4.58 (d, *J* = 11.3 Hz, 1 H, -C*H$_2$*Ph), 4.50 (d, *J* = 11.3 Hz, 1 H, -C*H$_2$*Ph), 4.49 (d, *J* = 11.3 Hz, 1 H, -C*H$_2$*Ph), 4.13 (ddm, *J* = 7.1, 5.3 Hz, 1 H, H5), 3.86 (m, 1 H, H4), 3.74 (dd, *J* = 9.5, 7.1 Hz, 1 H, H6), 3.66 (dd, *J* = 9.5, 5.3 Hz, 1 H, H6′), 2.28–2.06 (2 H, H3, H3′) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 143.0 (1, C1), 138.3, 138.1 (0, *ipso*-C, Ph), 128.3, 128.3, 127.8, 127.7, 127.6, 127.6 (1, Ph), 97.7 (1, C2), 75.2, 69.9 (1, C4, C5), 73.4, 71.1, 68.7 (2, -*C*H$_2$Ph, C6), 24.6 (2, C3) ppm. $[\alpha]_D^{25}$ = –7.0 (*c* = 0.80, CH$_2$Cl$_2$). IR (film, KBr plates): $\tilde{\nu}$ 3062 (w), 3029 (w), 2865 (w), 1654 (m), 1496 (m). LRMS (EI): *m*/*z* 311 [M$^+$ + H, 100%]. HRMS (ESI): calcd. for C$_{20}$H$_{23}$O$_3$$^+$ (M$^+$ + H) 311.1642, found 311.1664.

(2*R*,3*R*,6*S*)-3-(Benzyloxy)-2-(benzyloxymethyl)-6-(4-methoxyphenyl)-3,6-dihydro-2*H*-pyran (15): **13** (120 mg, 0.80 mmol) was dissolved in dry acetonitrile (5 mL) and [$Pd_2(dba)_3 \cdot CHCl_3$] (10 mg, 2.5 mol-%) was added. Diazonium salt **14** (106 mg, 0.50 mmol) was subsequently added over a period of 20 minutes. After complete conversion, the solvent was evaporated. After column chromatography on silica (cyclohexane/MTBE), **15** (276 mg, 83%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.20 (12 H, Ph, Ar), 6.89 (d, J = 8.8 Hz, 2 H, *p*-OMe-Ph), 6.26 (dd, J = 10.5, 3.1 Hz, 1 H, H2), 6.14 (ddd, J = 10.3, 4.5, 1.8 Hz, 1 H, H3), 5.33 (br. s, 1 H, H1), 4.72 (d, J = 11.9 Hz, 1 H, -CH_2Ph), 4.64 (d, J = 11.9 Hz, 1 H-CH_2Ph), 4.54 (d, J = 11.8 Hz, 1 H, -CH_2Ph), 4.49 (d, J = 11.8 Hz, 1 H, -CH_2Ph), 3.97 (ddd, J = 6.6, 6.0, 2.9 Hz, 1 H, H5), 3.89 (dd, J = 4.2, 3.0 Hz, 1 H, H4), 3.81 (s, 3 H, -OMe), 3.81 (signal not resolved due to overlap with singlet at 3.81, 1 H, H6), 3.72 (dd, J = 10.1, 6.8 Hz, 1 H, H6′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3 (0, *C*-OMe), 138.7, 138.4 (0, *ipso*-C, Ph), 132.4 (1, C2/3), 131.2 (0, *ipso*-C, *p*-OMe-Ph), 129.3, 128.3, 128.2, 127.8, 127.6, 127.5, 127.4, 125.0 (1, Ph, C2/3), 113.7 (1, *p*-OMe-Ph), 73.4, 70.8, 69.1 (2, C6, -CH_2Ph), 73.2, 70.9, 68.3 (1, C1, C4, C5), 55.2 (3, -OMe) ppm. $[\alpha]_D^{28}$ = –135.7 (c = 1.67, CH_2Cl_2). IR (film, KBr plates): $\tilde{\nu}$ = 3030 (w), 2862 (w), 1607 (m), 1509 (s), 1453 (m). HRMS (EI): calcd. for $C_{27}H_{28}O_4$ (M^+) 416.1988, found 416.1949.

(2*R*,3*R*)-3-(Benzyloxy)-2-(hydroxymethyl)-3,6-dihydro-2*H*-pyran (16): Obtained from **10** (50 mg, 0.20 mmol) following the procedure given above for **12**. After column chromatography, **16** (40 mg, 90%) was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.37–7.27 (5 H, Ph), 6.00–5.75 (2 H, H2, H3), 4.69 (d, J = 11.9 Hz, 1 H, -CH_2Ph), 4.54 (d, J = 11.9 Hz, 1 H, -CH_2Ph), 4.34 (dm, J = 17.4 Hz, 1 H, H1), 4.26 (dm, J = 17.4 Hz, 1 H, H1′), 3.96 (dd, J = 11.8, 7.2 Hz, 1 H, H6), 3.83 (m, 1 H, H4), 3.75 (br. dm, J = 11.8 Hz, 1 H, H6′), 3.63 (ddd, J = 7.1, 4.2, 2.7 Hz, 1 H, H5), 2.29 (br. s, 1 H, -OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2 (0, *ipso*-C, Ph), 131.6 (1, C2/3), 128.4, 127.7, 127.7 (1, Ph), 123.2 (1, C2/3), 77.6, 68.9 (1, C4, C5), 70.4, 65.8, 62.8 (2, -OCH_2Ph, C1, C6) ppm. $[\alpha]_D^{24}$ = –15.5 (c = 1.70, CH_2Cl_2). IR (film, KBr plates): $\tilde{\nu}$ = 3421 (br. m), 3032 (w), 2864 (m), 1435 (w), 1454 (m). LRMS (EI): *m*/*z* 249 [M^+ + H, 60%], 117 (100). HRMS (ESI): calcd. for $C_{15}H_{21}O_3^+$ (M^+ + H) 249.1485, found 249.1492.

(2*R*,3*R*)-3-(Benzyloxy)-2-(triethylsilyloxymethyl)-3,6-dihydro-2*H*-pyran (17): 10 (100 mg, 0.30 mmol) and ruthenium catalyst **A** (12 mg, 5 mol-%) were dissolved in dry CH_2Cl_2. After full conversion of the starting material, Et_3SiH (35 mg, 0.3 mmol) was added and heated to reflux until the primary metathesis product was fully consumed (TLC). Yield of **17** (93 mg, quant.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.26 (5 H, Ph), 6.06–5.94 (2 H, H2, H3), 4.69 (d, J = 12.0 Hz, 1 H, -CH_2Ph), 4.61 (d, J = 12.0 Hz, 1 H, -CH_2Ph), 4.31 (dd, J = 16.8, 2.6 Hz, 1 H, H1), 4.14 (dm, J = 16.8 Hz, 1 H, H1′), 3.90 (dd, J = 10.6, 6.2 Hz, 1 H), 3.86–3.80 (2 H, H4, H6′), 3.59 (ddd, J = 6.3, 6.3, 2.4 Hz, 1 H, H5), 0.97 [t, J = 7.9 Hz, 9 H, -Si(CH_2CH_3)$_3$], 0.63 [q, J = 7.4 Hz, 6 H, -Si(CH_2CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.9 (0, *ipso*-C, Ph), 131.3 (1, C2/3), 128.2, 127.8, 127.5 (1, Ph), 123.9 (1, C2/3), 78.6 (1, C4/5), 70.9 (2, -OCH_2Ph), 68.2 (1, C4/5), 65.9, 62.4 (2, C1, C6), 6.7 [3, -Si(CH_2CH_3)$_3$], 4.44 [2, -Si(CH_2CH_3)$_3$] ppm. $[\alpha]_D^{24}$ = –156.7 (c = 1.07, CH_2Cl_2). IR (film, KBr plates): $\tilde{\nu}$ 3033 (w), 2952 (m), 2875 (m), 1496 (w), 1455 (m), 1098 (s). LRMS (EI): *m*/*z* 335 [M^+ + Na, 100%]. HRMS (ESI): calcd. for $C_{19}H_{31}O_3Si^+$ (M^+ + H) 335.2037, found 335.2038.

(2*R*,3*R*)-3-Benzyloxy-2-triethylsilyloxymethyl-3,4-dihydro-2*H*-pyran (18): 10 (100 mg, 0.3 mmol) and ruthenium catalyst **A** (12 mg, 5 mol-%) were dissolved in dry toluene (10 mL). After complete conversion, Et_3SiH (70 mg, 0.6 mmol) were added and the solution was heated to reflux until formation of **18** was complete. Yield **18** (93 mg, quant.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.25 (5 H, Ph), 6.39 (dt, J = 6.1, 1.8 Hz, 1 H, H1), 4.68 (d, J = 12.1 Hz, 1 H, -CH_2Ph), 4.63 (m, 1 H, H2), 4.55 (d, J = 12.1 Hz, 1 H, -CH_2Ph), 3.99–3.87 (2 H, H4, H5), 3.87–3.82 (2 H, H6, H6′), 2.31–2.05 (2 H, H3, H3′), 0.96 [t, J = 7.9 Hz, 9 H, -Si(CH_2CH_3)$_3$], 0.63 [q, J = 7.9 Hz, 6 H, -Si(CH_2CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.9 (1, C1), 138.5 (0, *ipso*-C, Ph), 128.3, 127.7, 127.6 (1, Ph), 97.7 (1, C2), 77.1 (1, C4/5), 71.2 (2, -OCH_2Ph), 69.7 (1, C4/5), 61.2 (2, C6), 24.4 (2, C3), 6.7 [3, -Si(CH_2CH_3)$_3$], 4.4 [2, -Si(CH_2CH_3)$_3$] ppm. $[\alpha]_D^{30}$ = –1.4 (c = 1.16, CH_2Cl_2). IR (film, KBr plates): $\tilde{\nu}$ 3064 (w), 2952 (w), 2875 (m), 1654 (m), 1455 (m). LRMS (EI): *m*/*z* 335 [M^+ + Na, 100%]. HRMS (EI): calcd. for $C_{19}H_{31}O_3Si^+$ (M^+ + H) 335.2037, found 335.2045.

Supporting Information (see also the footnote on the first page of this article): Characterization data of **9** and copies of ^{1}H and ^{13}C NMR spectra of new compounds.

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