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A Convenient Route to *cis*- and *trans*-Fused Bicyclic Ethers by Ruthenium Mediated Ring-Closing Metathesis of Diene and Enyne Carbohydrate Derivatives

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Abstract: A general approach towards the construction of highly functionalised pyranopyran and pyranofuran systems *via* Grubbs [Ru] catalysed ring-closing metatheses of neighbouring vinyl-*O*-allyl and vinyl-*O*-propargyl functions on monosaccharide scaffolds is described.

INTRODUCTION

Carbohydrates are widely recognised as versatile building blocks in synthetic organic chemistry due to the wealth of functional, conformational and stereochemical information. The diversity and easy availability of these relatively cheap chiral compounds has led to a plethora of applications in the design and synthesis of naturally occurring compounds.[1] The accessibility of carbohydrates in the acyclic (open chains) or cyclic form (five- or six-membered rings) not only allows specific manipulations of the individual asymmetric centers, but also at either of the extremities (*i.e.* the reducing or non-reducing end). In addition, the functional groups in monosaccharides offer the opportunity to install a number of neighbouring vinyl-*O*-allyl functions. The latter diene arrangements may present a suitable platform for ring-closing metathesis (RCM) under catalytic conditions, which are compatible with a broad range of protecting as well as other functionalities. For example, olefination of the hydroxymethyl substituent at the non-reducing end (C-6 in pyranoses) and allylation of the neighbouring hydroxyl function will afford dienes of type **A**, RCM of which may give access to annulated carbohydrate derivatives of the type **B** (see Scheme 1). On the other hand, RCM of a 1-vinyl-2-*O*-allyl arrangement **C**, obtained after introduction of an olefinic group at the anomeric center (*i.e.*, formation of a *C*-glycoside) and consecutive allylation of the neighbouring hydroxyl function, may lead to annulated pyrans **D**.

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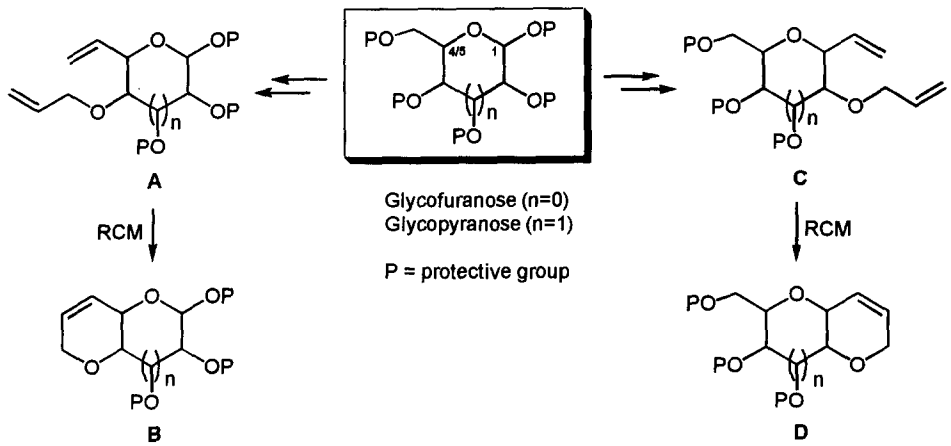
Scheme 1

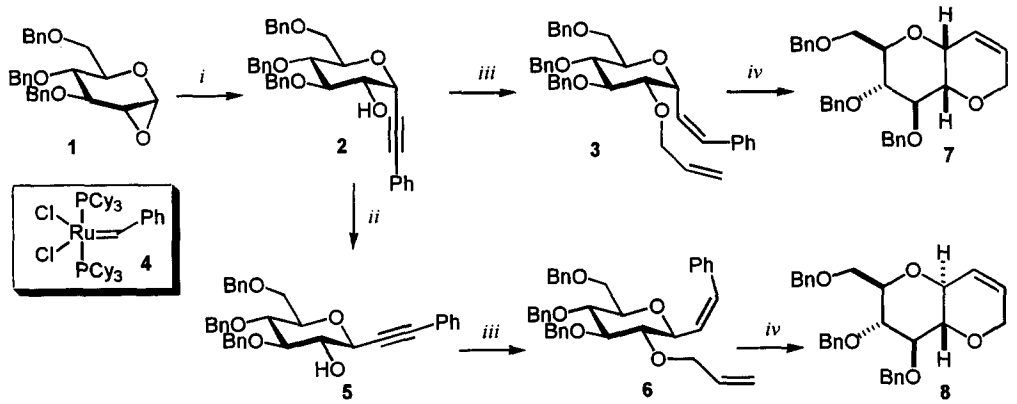


In this paper, we wish to report that highly functionalised annulated dihydropyrans can be prepared by metathesis of vinyl-*O*-allyl or vinyl-*O*-propargyl functions attached to pyranoid and furanoid systems.

RESULTS AND DISCUSSION

We recently showed[2] that *cis*- and *trans*-fused pyranopyrans **7** and **8** (see Scheme 2) can be attained by performing RCM on the corresponding *cis*- and *trans*-1-vinyl-2-*O*-allyl systems **3** and **6**, respectively. Both dienes were readily accessible from the same intermediate α-*C*-phenylethynyl-glucoside **2**, which in turn was synthesised by zinc chloride mediated ring opening[3] of known α-1,2-anhydro-3,4,6-tri-*O*-benzyl-D-glucose (**1**)[4] with lithium phenylacetylide. Epimerisation of **2** to the β-phenylethynyl-*C*-glucoside **5** proceeded smoothly *via* the following known[5] three-step sequential procedure: *i.e.* complexation of the triple bond with $Co_2(CO)_8$, acid-catalysed epimerisation and decomplexation with iodine. Transformation of the intermediate hydroxyalkynes **2** and **5** into the RCM precursors **3** and **6** was effected by sequential Lindlar reduction of the triple bond and allylation of the free 2-position hydroxyl function. Metathesis of **3** and **6** under the influence of Grubbs catalyst **4**[6] (7 mol%) in toluene at 60 °C gave rise to the expected *cis*- and *trans*-fused bicyclic ethers **7** and **8**, respectively. The identity and homogeneity of both compounds were firmly ascertained by NMR-spectroscopy and mass spectrometry.

Scheme 2



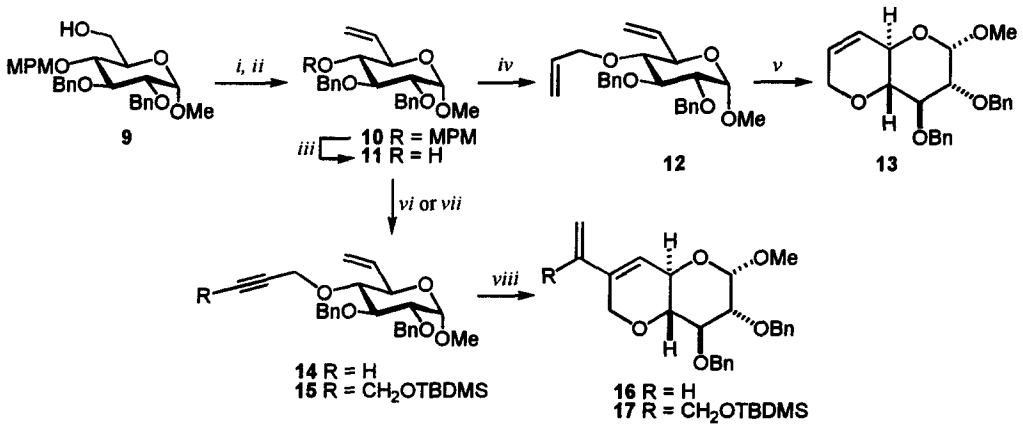
Reagents and conditions: i) phenylacetylene, *n*-BuLi, $ZnCl_2$, THF, -70 °C to r.t., 78%. *ii)* a. $Co_2(CO)_8$, CH_2Cl_2; b. TfOH (0.1 equiv.), CH_2Cl_2; c. I_2, THF, 76% three steps. *iii)* a. H_2, Lindlar, quinoline, EtOAc; b. allyl bromide, NaH, DMF, 90% **3**, 92% **6** (two steps). *iv)* **4** (7 mol%), toluene, 60 °C, 82% **7**, 60% **8**.

It was also established[2] that *trans*-5-vinyl-4-*O*-allyl system **12** could be converted *via* olefin metathesis into *trans*-fused **13**, as depicted in Scheme 3. To this end, known[7] methyl 2,3-di-*O*-benzyl-4-*O*-(4-methoxybenzyl)-α-D-glucopyranoside (**9**) was transformed into the diene system **12** *via* a four-step sequence. Thus, consecutive Swern oxidation of **9** and Wittig olefination gave, after removal of the *p*-methoxybenzyl (MPM) group in **10** with DDQ,[8] the partially protected glucose derivative **11**. Allylation of HO-4 in **11** furnished the diene **12** having the required 5-vinyl-4-*O*-allyl geometry. In this particular case, the RCM reaction proceeded smoothly at ambient temperature, to give the *trans*-fused oxacycle **13** in 93% yield. The latter result clearly indicates that a terminal olefin is more prone to RCM than a 1,2-disubstituted olefin (*cf.* **3** and **6**).

Having hydroxyalkene **11** in hand, we next investigated whether compound **14** bearing a vinyl-*O*-propargyl, instead of a vinyl-*O*-allyl motif, could function as a substrate for an enyne ring-closing metathesis.[9] It was established that RCM of **14**, readily prepared by propargylation of **11**, proceeded very slowly and in low yield under the same conditions as applied for the metathesis of **12**→**13**. Even after stirring for 3 days at elevated temperature with 10 mol% of **4**, a considerable amount of starting compound was still present in the reaction mixture. Moreover, the metathesis product **16** could not be separated from the starting material **14** by silica gel chromatography. The unsatisfactory outcome of the RCM of **14** is probably due to the absence of a substituent on the alkyne moiety.[9,10] Indeed, RCM of substituted alkyne derivative **15**, synthesised by reaction of **11** with 4-bromo-1-(*tert*-butyldimethylsilyl-oxy)methyl-2-butyne[11] under the influence of sodium hydride, went to completion within 24 hours at 60 °C to give highly substituted pyranopyran **17** in 73% yield. The latter result is in agreement with

earlier findings[9,10] that a substituent on the alkyne moiety has a beneficial effect on the yield of the enyne metathesis.

Scheme 3



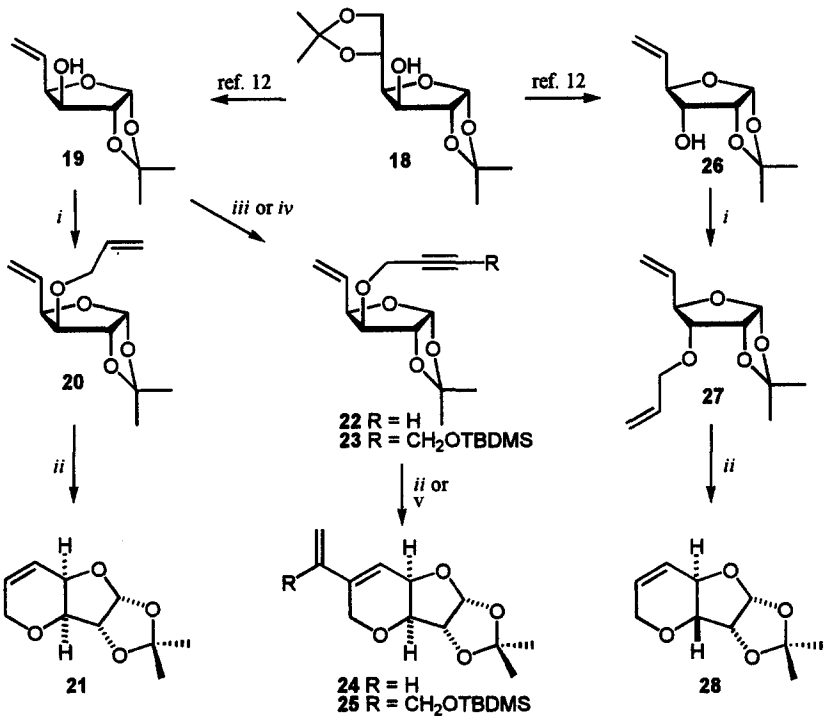
Reagents and conditions: i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to r.t. *ii)* $MePh_3P^+Br^-$, *n*-BuLi, THF, -40 °C to r.t., 80% (two steps). *iii)* DDQ, H_2O, CH_2Cl_2, 85%. *iv)* allyl bromide, NaH, DMF, 94%. *v)* **4** (4 mol%), toluene, r.t., 93%. *vi)* propargyl bromide, NaH, DMF (90%). *vii)* $BrCH_2C{\equiv}CCH_2OTBDMS$, NaH, TBAI (cat), DMF (63%). *viii)* **4** (10 mol%), toluene, 60 °C. a. 3 d, 24% **16** (determined by ^{1}H-NMR), b. 24 h, 73% **17**.

The results obtained so far indicate that glycopyranoid rings, having *cis* or *trans* orientated vinyl-*O*-allyl or vinyl-*O*-propargyl groups present an appropriate setting for an ensuing RCM event. Therefore, it would be of interest to find out whether the same geometrical motif in furanoid rings could also undergo RCM. With the objective to assess this question, we first prepared the *cis*-vinyl-*O*-allyl furanose derivative **20** (see Scheme 4), setting the stage for the ensuing RCM. To this end, commercially available 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (**18**), was transformed according to a well established procedure[12] into hydroxyalkene **19**, allylation of which afforded diene **20** in an excellent yield. Ring closure of diene **20** under the influence of catalyst **4** (3 mol%) proceeded readily at room temperature in dichloromethane to give the homogeneous *cis*-fused pyranofuran **21** in 98% yield.

In the next stage, we examined the RCM of the epimeric *trans*-vinyl-*O*-allyl derivative **27**, which was also readily accessible from **18**. Thus, consecutive oxidation and reduction of **18**, followed by olefination as applied for the synthesis of **19** gave, after allylation of the thus obtained *trans*-hydroxyalkene **26**,[12] RCM precursor **27**. Unfortunately, RCM of **27** under the same conditions used for the conversion of **20**→**21** led to the predominant formation of a dimeric product, as based on NMR spectroscopy and mass spectrometry. However, the unwanted dimerisation could be substantially

suppressed by lowering the concentration of the substrate from 0.2 to 0.02 M, resulting in the isolation of the homogeneous *trans*-fused pyranofuran **28** in an acceptable yield of 63%. The low yield of *trans*-fused **28**, as compared to *cis*-fused **21**, may be ascribed to the formation of the relatively more constrained *trans*-fused 5+6 ring system.

Scheme 4



Reagents and conditions: i) allyl bromide, NaH, DMF, 95%. *ii)* **4** (3-5 mol%), CH_2Cl_2, 98% **21**, 94% **25**, 63% **28**. *iii)* propargyl bromide, NaH, DMF (94%). *iv)* $BrCH_2C{\equiv}CCH_2OTBDMS$, NaH, TBAI, DMF (81%). *v)* **4** (10 mol%), toluene, 60 °C, 51% **24**.

The feasibility of executing an enyne metathesis on a neighbouring allyl-*O*-propargylic furanoid arrangement is illustrated in the synthesis of the highly functionalised *cis*-fused oxacycles **24** and **25**. It was expected that RCM of the *cis*-4-vinyl-3-*O*-propargyl arrangement in the glucofuranoid derivative **22**, prepared by reaction of **19** with propargyl bromide, could only be effected under rather strenuous conditions (*cf.* **14**→**16**). Indeed, the *cis*-fused oxacycle **23** was obtained in a yield of 51% by heating **22** at 60 °C in the presence of **4** (10 mol%) for 24 h in toluene. In contrast, metathesis of the corresponding non-terminal alkyne derivative **23**, obtained by reaction of **19** with 4-bromo-1-(*tert*-butyldimethyl-silyloxy)-2-butyne,[11] proceeded smoothly under the same conditions applied for the conversion of **20** into **21** to give the highly functionalised *cis*-fused oxacycle **25** in a yield of 94%.

CONCLUSION

The RCM approach described in this paper clearly shows that glycopyranoids as well as glycofuranoids having neighbouring vinyl-*O*-allyl or vinyl-*O*-propargyl functionalities can be used as starting compounds for the synthesis of highly substituted *cis*- or *trans*-fused oxacycles. As such, our methodology nicely complements previously reported RCM-mediated syntheses of fused bicyclic ethers.[13] It is also of interest to note that pyranopyran systems as in compounds **8** and **13** occur as repeating structural elements in many marine biotoxins,[14] *e.g.* the ciguatoxins[15] and brevetoxins.[16] In addition, the *cis*- and *trans*-fused pyranofuran frameworks of compounds **21** and **28** are present in a number of annulated nucleoside antibiotics, such as the herbicidins and octosyl acids,[17] respectively. The implementation of our strategy to the construction of naturally occurring fused oxacycles is currently under investigation.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Jeol JNM-FX-200 (200/50.1 MHz) or a Bruker WM-300 (300/75.1 MHz) spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard. Mass spectra were recorded with PE Sciex API 165 with ion spray interface. Toluene and dimethylsulfoxide were boiled under reflux with CaH_2 for 3 h, distilled and stored over molecular sieves (4 Å). 1,2-Dichloroethane (DCE, Biosolve, HPLC-grade), tetrahydrofuran (THF, Baker, HPLC grade), *N,N*-dimethylformamide (DMF, Baker, p.a.), dichloromethane (DCM, Baker, p.a.) were stored over molecular sieves (4 Å). Methanol (Rathburn, HPLC-grade) was stored over 3 Å molecular sieves. Column chromatography was performed either on Baker silicagel (0.063-0.200 mm) or Merck silicagel 60 (0.040-0.063 mm). TLC-analysis was conducted on DC-fertigfolien (Schleicher & Schuell, F1500, LS254) or HPTLC aluminium sheets (Merck, silicagel 60, F254) with detection by UV-absorption (254 nm) where applicable and charring with 20% H_2SO_4 in ethanol. Reactions were run at ambient temperature, unless stated otherwise.

(3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-phenylethyne (2): To a solution of phenylacetylene (6.0 mmol, 0.66 mL) in THF (4 mL) at -78 °C was added, under a constant stream of nitrogen, a solution of *n*-BuLi (6 mmol, 3.75 mL 1.6 M in hexanes). After stirring for 0.5 h, a solution of **1**[4] (3.40 mmol, 1.47 g, dried by coevaporation with DCE) in THF (4 mL) was added, followed by a 1M solution of $ZnCl_2$ in THF (6 mL). The mixture was allowed to warm up to r.t. and stirring was continued for 1 h, after which, TLC-analysis (50% EtOAc/light petroleum) showed complete consumption of the starting compound. The mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The organic layer was washed with NH_4Cl and brine, followed by drying ($MgSO_4$) and evaporation. Column chromatography (20 to 50% EtOAc/light petroleum) afforded **2** as a colourless syrup (1.42 g, 2.65 mmol, 78%). ^{1}H-NMR ($CDCl_3$): δ 7.46-7.14 (m, 20H), 5.04 (d, 1H, J=5.1 Hz), 4.97-4.49 (m, 6H), 4.07 (m, 1H), 3.85-3.65 (m, 5H). ^{13}C-NMR ($CDCl_3$): δ 138.4, 137.9, 137.7, 131.9, 128.7-127.6, 121.8, 89.9, 83.5, 83.3, 77.6, 75.2, 75.0, 73.9, 73.4, 71.4, 68.9, 68.4. MS: m/z = 557 ($M+Na^+$), 573 ($M+K^+$).

***cis*-1-(2-*O*-allyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-2-phenylethene (3):** Compound **2** (0.48 g, 0.90 mmol) was dissolved in EtOAc (5 mL) and quinoline (50 mg) and Lindlar catalyst (50 mg) were added. Hydrogen gas was bubbled through the mixture for 15 min. after which the mixture was left to stir overnight under an atmospheric pressure of hydrogen. The catalyst was filtered over Hyflo and rinsed with EtOAc, after which the filtrate was evaporated *in vacuo*. The crude product, dissolved in DMF (5 mL) was treated with allyl bromide (1.6 mmol, 0.14 mL) and NaH (1.6 mmol, 65 mg, 60 wt% in mineral oil). After stirring overnight at 60 °C, TLC analysis (25% EtOAc/light petroleum) showed clean conversion of the starting compound. Excess reagent was destroyed with methanol and the solvent was removed by evaporation. The residue was taken up in Et_2O and water, followed by consecutive washing of the organic

layer with water and brine, drying ($MgSO_4$) and evaporation. Column chromatography (10 to 30% EtOAc/light petroleum) afforded pure **3** (0.47 g, 0.81 mmol, 90%) as a colourless oil. ^{1}H-NMR ($CDCl_3$): δ 7.55-7.14 (m, 20H), 6.86 (d, 1H, J=11.9 Hz), 6.04 (dd, 1H, J=8.2 Hz), 5.81 (m, 1H), 5.14 (m, 2H), 4.93 (ddd, 1H, J_1=1.0 Hz, J_2=7.6 Hz), 5.01-4.44 (m, 6H), 4.02-3.68 (m, 7H), 3.49 (d, 1H).

(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-phenylethyne (5): To a solution of compound **2** (2.60 mmol, 1.39 g) in DCM (10 mL) under nitrogen, was added $Co_2(CO)_8$ (2.9 mmol, 1.04 g). Stirring for 1.5 h resulted in complete formation of the cobalt complex (TLC: 10% EtOAc/light petroleum). In order to oxidise excess reagent, air was bubbled through the solution for 15 min, after which the solvent was removed *in vacuo*. The complex was purified by flash column chromatography (5% EtOAc/light petroleum). The dark red complex was then dissolved in DCM (10 mL) and, under a stream of nitrogen, TfOH (0.1 equiv., 24 μL) was added. TLC-analysis (10% EtOAc/light petroleum) after 1.5 h revealed clean conversion of the starting complex into a slightly higher running complex. After addition of saturated $NaHCO_3$ and Et_2O, the organic layer was washed with water and brine, followed by drying ($MgSO_4$). Concentration *in vacuo* gave the crude β-alkynyl-cobalt complex, which was dissolved in THF (10 mL). I_2 was added (5 equiv., 2.90 g) and the solution was stirred for 3 h. Then, a 10% solution of Na_2SO_3 was added, followed by saturated $NaHCO_3$ and Et_2O. The layers were separated and the organic layer was washed with 10% Na_2SO_3 and brine. Drying ($MgSO_4$) and evaporation of the solvents, followed by column chromatography (10 to 40% EtOAc/light petroleum) gave **5** as a white solid (1.06 g, 1.98 mmol, 76% overall). ^{1}H-NMR ($CDCl_3$): δ 7.52-7.13 (m, 20H), 4.91-4.51 (m, 6H), 4.18 (d, 1H, J=9.4 Hz), 3.81-3.50 (m, 6H). ^{13}C-NMR ($CDCl_3$): δ 138.5, 137.9, 132.0, 128.7-127.7, 121.9, 86.6, 85.6, 84.9, 79.1, 77.3, 75.2, 75.0, 74.5, 73.5, 71.5, 68.6.

***cis*-1-(2-*O*-allyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-2-phenylethene (6):** Lindlar reduction of **5** was executed as described for compound **3**. Allylation was conducted with the same excess of reagents, but in this case the reaction was complete at r.t. after 3 h. Diene **6** was obtained in 92% yield from **5**. ^{1}H-NMR ($CDCl_3$): δ 7.50-7.12 (m, 20H), 6.80 (d, 1H), 5.89 (m, 1H), 5.75 (dd, 1H), 5.15 (m, 2H), 4.98-4.46 (m, 7H), 4.26-4.17 (m, 3H), 3.74-3.59 (m, 5H), 3.46-3.37 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 138.5, 137.8, 137.5, 136.4, 134.5, 134.3, 128.6-127.3, 116.6, 86.2, 82.0, 77.9, 77.6, 75.2, 74.5, 74.4, 73.2, 73.0, 68.6.

(1*R*, 6*R*, 8*R*, 9*R*, 10*S*)-9,10-bis(benzyloxy)-8-benzyloxymethyl-2,7-dioxabicyclo[4.4.0]dec-4-ene (7): Residual water was removed from compound **3** (0.23 g, 0.40 mmol) by coevaporation with dry toluene, after which **3** was dissolved in dry toluene (2 mL). The solution was degassed by bubbling through with argon for 20 min. Catalyst **4** (23 mg, 7 mol%) was added and degassing was continued for 20 min, after which the solution was warmed up to 60 °C. Stirring was continued overnight under argon atmosphere, after which TLC (25% EtOAc/light petroleum) showed complete consumption of the starting material. Evaporation of the solvent, followed by column chromatography (20 to 40% EtOAc/light petroleum) gave **7** (0.15 g, 0.33 mmol, 82%). ^{1}H-NMR ($CDCl_3$): δ 7.45-7.19 (m, 15H), 5.93 (m, 1H), 5.83 (m, 1H), 5.00-4.54 (m, 6H), 4.64 (m, 1H), 4.14-4.08 (m, 3H), 3.94 (t, 1H), 3.74-3.66 (m, 4H). ^{13}C-NMR ($CDCl_3$): δ 138.6, 138.2, 138.0, 129.6, 128.3-127.6, 125.9, 77.9, 77.6, 74.8, 74.3, 74.0, 73.5, 72.7, 69.1, 67.4, 60.5.

(1*R*, 6*S*, 8*R*, 9*R*, 10*S*)-9,10-bis(benzyloxy)-8-benzyloxymethyl-2,7-dioxabicyclo[4.4.0]dec-4-ene (8): prepared as described for compound **7** in 60% yield. ^{1}H-NMR ($CDCl_3$): δ 7.38-7.13 (m, 15H), 5.91 (m, 1H), 5.76 (m, 1H), 5.02-4.45 (m, 6H), 4.25 (m, 2H), 3.81 (m, 1H), 3.75-3.58 (m, 5H), 3.34 (t, 1H). ^{13}C-NMR ($CDCl_3$): δ 138.8, 138.1, 138.0, 128.3-127.6, 126.1, 83.7, 79.5, 78.9, 77.9, 75.1, 74.7, 73.4, 72.2, 69.1, 66.0. MS: m/z = 473 ($M+H^+$), 490 ($M+NH_4^+$), 495 ($M+Na^+$).

methyl 2,3-di-*O*-benzyl-6,7-dideoxy-4-*O*-(4-methoxybenzyl)-α-D-*gluco*-hept-6-enopyranoside (10): To a solution of oxalyl chloride (0.82 mL, 9.45 mmol) in dry DCM (10 mL) at -65 °C was added, under a stream of nitrogen, a solution of DMSO (1.56 mL, 22.1 mmol) in dry DCM (5 mL) over 5 min. After stirring for 5 min. at -65 °C, a solution of alcohol **9**[7] (2.59 g, 6.3 mmol) in dry DCM (5 mL) was added and stirring was continued for 5 min. Warming to -50 °C was followed by addition of dry Et_3N (3.69 mL, 26.5 mmol). The mixture was allowed to warm up to r.t and TLC analysis (50% EtOAc/light petroleum) showed complete conversion. The mixture was poured into water and diluted with Et_2O, after which the organic layer was washed with water and brine. Drying ($MgSO_4$) and evaporation of the solvents gave the aldehyde, which was used without further purification. Methyltriphenylphosphonium bromide (2.32 g, 6.5 mmol, dried *in vacuo* overnight at 140 °C) was suspended in THF at -40 °C under a nitrogen atmosphere. *n*-BuLi (6.4 mmol, 4.0 mL 1.6 M in hexanes) was added and the mixture was allowed to warm up to 0 °C. A solution of the aldehyde (dried by coevaporation 2x with toluene) in THF (5 mL) was added and the inhomogeneous mixture was stirred for a further 4 h at r.t. Pouring the mixture into saturated NH_4Cl and dilution with Et_2O was followed by consecutive washing the organic layer with H_2O and brine. Drying ($MgSO_4$) and concentration *in vacuo* gave the crude alkene,

which was purified on silicagel (0 to 25% EtOAc/light petroleum) to give pure **10** (2.07 g, 5.0 mmol, 80%) as a white solid. ^{1}H-NMR ($CDCl_3$): δ 7.36-6.81 (m, 14H), 5.89 (m, 1H), 5.45-5.24 (m, 2H), 4.99-4.51 (m, 6H), 4.59 (d, 1H), 4.10-3.93 (m, 2H), 3.79 (s, 3H), 3.52 (dd, 1H), 3.38 (s, 3H), 3.23 (t, 1H).

methyl 2,3-di-*O*-benzyl-6,7-dideoxy-α-D-*gluco*-hept-6-enopyranoside (11): MPM ether **10** (2.53 g, 5.2 mmol) was dissolved in DCM/water (18/1, 25 mL) and DDQ (7.8 mmol, 1.77 g) was added.[8] Stirring was continued for 6 h, after which TLC analysis (EtOAc/toluene 1/2) showed complete disappearance of the starting compound. Saturated aqueous $NaHCO_3$ and Et_2O were added and the organic layer was washed with saturated $NaHCO_3$ and brine. Drying ($MgSO_4$) and evaporation of the solvents, followed by column chromatography furnished pure **11** (1.64 g, 4.44 mmol, 85%). ^{1}H-NMR ($CDCl_3$): δ 7.47-7.26 (m, 10H), 5.85 (m, 1H), 5.45-5.22 9 (m, 2H), 5.00-4.62 (m, 4H), 4.61 (d, 1H), 3.95 (dd, 1H), 3.79 (t, 1H), 3.51 (dd, 1H), 3.36 (s, 3H), 3.28 (t, 1H). 2.41 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 138.6, 138.4, 134.8, 128.5-127.3, 118.2, 98.0, 81.0, 79.5, 75.5, 73.5, 73.0, 71.6, 55.1.

methyl 4-*O*-allyl-2,3-di-*O*-benzyl-6,7-dideoxy -α-D-*gluco*-hept-6-enopyranoside (12): prepared as described for **6**. ^{1}H-NMR ($CDCl_3$): δ 7.39-7.25 (m, 10H), 5.97-5.77 (m, 2H), 5.43-5.11 (m, 4H), 4.95-4.63 (m, 4H), 4.58 (d, 1H), 4.17 (m, 2H), 4.08-3.87 (m, 2H), 3.48 (dd, 1H), 3.38 (s, 3H), 3.11 (t, 1H). ^{13}C-NMR ($CDCl_3$): δ 138.8, 138.2, 135.2, 134.9, 128.3-127.5, 117.6, 116.7, 98.0, 82.0, 81.5, 79.7, 75.7, 73.8, 73.2, 71.2, 55.1.

(1*R*, 6*R*, 8*S*, 9*R*, 10*S*)-9,10-bis(benzyloxy)-8-methoxy-2,7-dioxabicyclo[4.4.0]dec-4-ene (13): prepared analogous to **7** in 2 h at room temperature in toluene with 4 mol% of **4** in 93 % yield. ^{1}H-NMR ($CDCl_3$): δ 7.43-7.25 (m, 10H), 5.77 (m, 2H), 4.94-4.64 (m, 4H), 4.59 (d, 1H), 4.25 (m, 2H), 4.18 (m, 1H), 3.90 (t, 1H), 3.53 (dd, 1H), 3.39 (s, 3H), 3.24 (t, 1H). ^{13}C-NMR ($CDCl_3$): δ 139.0, 138.2, 128.3-127.8, 127.4, 125.9, 99.1, 79.6, 79.1, 78.7, 75.1, 73.6, 66.2, 63.8, 55.1.

methyl 2,3-di-*O*-benzyl-6,7-dideoxy-4-*O*-propargyl-α-D-*gluco*-hept-6-enopyranoside (14): To a mixture of **11** (0.30 g, 0.80 mmol) and propargyl bromide (0.98 mmol, 98 μL) in DMF (5 mL) was added NaH (0.98 mmol, 39 mg, 60 wt% in mineral oil). After stirring for 3 h, the reaction was quenched by adding MeOH and the solvents were removed *in vacuo*. The resulting slurry was taken up in Et_2O and water and the organic layer was washed with water and brine. The solution was dried ($MgSO_4$) and concentrated. Silicagel chromatography (0 to 20% EtOAc/light petroleum) afforded **14** (0.30 g, 0.72 mmol, 90%). ^{1}H-NMR ($CDCl_3$): δ 7.40-7.26 (m, 10H), 5.92 (m, 1H), 5.45-5.22 (m, 2H), 4.98-4.62 (m, 4H), 4.59 (d, 1H), 4.32 (m, 2H), 4.09-3.90 (m, 2H), 3.50 (dd, 1H), 3.39 (s, 3H), 3.21 (t, 1H), 2.42 (t, 1H). ^{13}C-NMR ($CDCl_3$): δ 138.1, 137.5, 134.5, 127.8-127.1, 117.3, 97.3, 80.9, 80.7, 79.2, 75.1, 74.1, 72.1, 70.2, 59.3, 54.6.

methyl 2,3-di-*O*-benzyl-4-*O*-(4-*tert*-butyldimethylsilyloxy-2-butyn-1-yl)-6,7-dideoxy-α-D-*gluco*-hept-6-enopyranoside (15): Traces of water were removed from a mixture of **11** (0.41 g, 1.11 mmol) and 4-bromo-1-(*tert*-butyldimethylsilyloxy)-2-butyne[11] (1.67 mmol, 0.44 g) by coevaporation twice with dry toluene. The mixture was then dissolved in DMF (8 mL) and NaH (1.67 mmol, 70 mg, 60 wt% in mineral oil) and a catalytic amount of TBAI were added. After stirring for 3 h, TLC analysis (25% EtOAc/light petroleum) revealed a complete conversion. Quenching excess reagent with MeOH was followed by evaporation of the solvents. Work-up procedure and purification proceeded as described for compound **14**, to give pure enyne **15** (0.38 g, 0.69 mmol, 63%). ^{1}H-NMR ($CDCl_3$): δ 7.27-7.17 (m, 10H), 5.85 (m, 1H), 5.34-5.11 (m, 2H), 4.86-4.51 (m, 4H), 4.49 (d, 1H), 4.27 (t, 2H), 4.20 (t, 2H), 3.95-3.79 (m, 2H), 3.39 (dd, 1H), 3.27 (s, 3H), 3.10 (t, 1H). ^{13}C-NMR ($CDCl_3$): δ 138.5, 137.9, 134.9, 127.7-127.2, 117.5, 97.8, 84.8, 81.4, 81.0, 80.7, 79.5, 75.5, 73.1, 70.6, 60.1, 55.0, 51.5, 25.6, 18.1.

(1*R*, 6*R*, 8*S*, 9*R*, 10*S*)-9,10-bis(benzyloxy)-8-methoxy-4-vinyl-2,7-dioxabicyclo[4.4.0]dec-4-ene (16): Enyne **14** (0.29 g, 0.53 mmol) was stirred in toluene (2 mL) for 3 days at 60 °C with 0.1 equiv of **4**. HPTLC analysis (25% EtOAc/light petroleum or toluene/EtOAc/MeOH 19/0.9/0.1 or 2.5% acetone/DCM) showed a considerable amount of starting compound, comigrating with the product. The number of lower running spots proved to be an intractable mixture of products. Column chromatography (silicagel 60, 5 to 25% EtOAc/light petroleum) afforded a mixture of product and starting compound (0.16 g, 55%), in a ratio of 3:4, as gauged by ^{1}H-NMR. Representative signals of product **16**: ^{1}H-NMR ($CDCl_3$): δ 6.28 (m, 1H), 5.79 (bs, 1H). ^{13}C-NMR ($CDCl_3$): δ 138.8, 138.0, 136.4, 134.6, 125.9, 113.1, 99.1, 79.5, 79.0, 78.9, 75.0, 73.6, 65.8, 64.1, 55.0.

(1*R*, 6*R*, 8*S*, 9*R*, 10*S*)-9,10-bis(benzyloxy)-4-(1-*tert*-butyldimethylsilyloxy-2-propen-2-yl)-8-methoxy-2,7-dioxabicyclo[4.4.0]dec-4-ene (17): RCM was executed as described for compound **7** with 10 mol% of catalyst. HPTLC: 2/1 toluene/EtOAc. Column chromatography on silicagel 60 gave **17** in 73% yield. ^{1}H-NMR ($CDCl_3$): δ 7.48-7.28 (m, 10H), 5.82 (d, 1H, J=1.5 Hz), 5.36 (s, 1H), 5.03 (s, 1H), 5.00-4.69 (m, 4H), 4.65 (d, 1H), 4.51 (m, 2H), 4.43-4.29 (m, 3H), 3.97

(t, 1H), 3.58 (dd, 1H), 3.45 (s, 3H), 3.27 (t, 1H), 0.97 (s, 9H), 0.13, 0.12 (2x s, 6H). ^{13}C-NMR ($CDCl_3$): δ 141.8, 138.9, 138.1, 135.2, 128.3-127.4, 121.3, 110.2, 99.3, 79.5, 79.1, 78.7, 75.0, 73.7, 66.9, 64.1, 61.9, 55.2, 25.8, 18.3.

3-*O*-allyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (20): Allylation of **19**[12] was performed as described for **6**. Diene **20** was isolated in 95% yield. ^{1}H-NMR ($CDCl_3$): δ 6.06-5.76 (m, 3H), 5.47-5.16 (m, 4H), 4.64-4.58 (m, 2H), 4.06 (m, 2H), 3.84 (d, 1H). ^{13}C-NMR ($CDCl_3$): δ 133.9, 132.3, 118.3, 116.7, 110.9, 104.5, 83.1, 82.6, 81.2, 70.7, 26.5, 25.9.

(1*S*, 6*R*, 8*R*, 9*R*)-8,9-dihydroxy-8,9-*O*-isopropylidene-2,7-dioxabicyclo[3.4.0]non-4-ene (21): RCM was executed analogous to **13** in 2 h in DCM with 3 mol% of **4** in 98% yield. ^{1}H-NMR ($CDCl_3$): δ 6.10-6.06 (m, 2H), 5.98 (d, 1H, J=3.7 Hz), 4.59 (d. 1H), 4.38 (m, 1H), 4.16 (m, 2H), 3.95 (d, 1H, J=2.2 Hz), 1.52 (s, 3H), 1.37 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ 131.7, 121.1, 111.0, 104.9, 84.1, 78.4, 70.6, 64.2, 26.5, 25.9.

5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-*xylo*-hex-5-enofuranose (22): A cooled (0 °C) solution of **15** (9.1 mmol, 1.69 g) in DMF (20 mL) was subsequently treated with propargyl bromide (11 mmol, 1.0 mL) and NaH (11 mmol, 0.44 g, 60 wt% in mineral oil). The mixture was then allowed to warm up to r.t. and stirring was continued for 4 h. Excess of reagent was destroyed by adding MeOH and the solvent was removed. The residue was taken up in Et_2O and water, after which the organic layer was washed with water and brine. Drying ($MgSO_4$) and evaporation of the solvent gave the crude enyne, which was purified by column chromatography (20 to 40% EtOAc/light petroleum) to afford **22** (1.92 g, 8.5 mmol, 94%). ^{1}H-NMR ($CDCl_3$): δ 6.03-5.86 (m, 2H), 5.49-5.30 (m, 2H), 4.65 (m, 2H), 4.22 (t, 2H), 4.16 (d, 1H), 2.46 (t, 1H), 1.50 (s, 3H), 1.32 (s, 3H). ^{13}C-NMR ($CDCl_3$): δ 131.2, 118.5, 111.0, 104.2, 82.5, 82.2, 80.7, 79.3, 75.0, 57.1, 26.3, 25.9.

3-*O*-(4-*tert*-butyldimethylsilyloxy-2-butyn-1-yl)-5,6-dideoxy-1,2-*O*-isopropylidene- α-D-*xylo*-hex-5-enofuranose (23): prepared as described for **15** in 81% yield. ^{1}H-NMR ($CDCl_3$): δ 6.04-5.87 (m, 2H), 5.49-5.28 (m, 2H), 4.68-4.63 (m, 2H), 4.35 (t, 2H), 4.27 (t, 2H), 4.05 (d, 1H), 1.53 (s, 3H), 1.32 (s, 3H), 0.91 (s, 9H), 0.11 (s, 6H). 131.9, 118.5, 111.1, 85.2, 82.5, 82.4, 80.9, 57.6, 51.3, 26.5, 25.9, 25.5, 18.0.

(1*S*, 6*R*, 8*R*, 9*R*)-8,9-dihydroxy-8,9-*O*-isopropylidene-4-vinyl-2,7-dioxabicyclo[3.4.0]non-4-ene (24): prepared as described for **7** with 10 mol% of **4**. TLC: toluene/EtOAc/MeOH 19/0.9/0.1. Silicagel chromatography (15 to 40% EtOAc/light petroleum) afforded **24** in 51% yield. ^{1}H-NMR ($CDCl_3$): δ 6.31 (dd, 1H, J_1=11.2, J_2=17.9 Hz), 5.98 (d, 1H, J=3.9 Hz), 5.15 (d, 1H), 5.13 (d, 1H), 4.62 (d, 1H), 4.49 (dd, 1H, J_1=4.8 Hz, J_2=2.1 Hz), 4.47 (d, 1H, J=15.2 Hz), 4.18 (dt, 1H, J_1=1.8 Hz, J_2=15.7 Hz), 3.94 (d, 1H), 1.52, 1.34 (2x s, 2x 3H).

(1*S*, 6*R*, 8*R*, 9*R*)-4-(1-*tert*-butyldimethylsilyloxy-2-propen-2-yl)-8,9-dihydroxy-8,9-*O*-isopropylidene-2,7-dioxabicyclo-[3.4.0]non-4-ene (25): prepared as described for **13** in DCM after stirring for 6 h with 5 mol% of **4**. HPTLC: 10% EtOAc/light petroleum. Column chromatography (silicagel 60, 5 to 10% EtOAc/light petroleum) gave **25** as a white solid in 94%. ^{1}H-NMR ($CDCl_3$): δ 5.94 (d, 1H, J=4.9 Hz), 5.92 (d, 1H, J=3.9 Hz), 5.32 (s, 1H), 5.01 (s, 1H), 4.56 (d, 1H), 4.41 (m, 1H), 4.40 (dd, 1H, J_1=14.5 Hz, J_2=1.1 Hz), 4.28 (t, 2H, J=1.5 Hz), 4.15 (dt, 1H, J_1=15.6 Hz, J_2=1.9 Hz), 3.88 (d, 1H, J=1.6 Hz), 1.47 (s, 3H), 1.28 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C-NMR ($CDCl_3$): δ 142.3, 138.7, 116.0, 111.4, 111.2, 104.9, 84.1, 78.6, 71.2, 65.2, 62.8, 26.6, 26.0, 25.7, 18.2, -5.6. MS: m/z=391.1 ($M+Na^+$).

3-*O*-allyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (27): Allylation of **26**[12] was performed as described for **6** in 95% yield. ^{1}H-NMR ($CDCl_3$): δ 5.90 (m, 2H), 5.76 (d, 1H, J=4.4 Hz), 5.48-5.19 (m, 4H), 4.62 (t, 1H), 4.41 (dd, 1H, J_1=6.7 Hz, J_2=8.8 Hz), 4.14 (m, 2H), 3.51 (dd, 1H), 1.60 (s, 3H), 1.36 (s, 3H).

(1*R*, 6*R*, 8*R*, 9*R*)-8,9-dihydroxy-8,9-*O*-isopropylidene-2,7-dioxabicyclo[3.4.0]non-4-ene (28): prepared as described for **21** with 0.02 M diene concentration in 63% yield. ^{1}H-NMR ($CDCl_3$): δ 6.21 (m, 1H), 5.87 (d, 1H, J=3.9 Hz), 5.69 (m, 1H), 4.68 (t, 1H), 4.48-4.40 (m, 3H), 3.31 (dd, 1H, J_1=8.4 Hz, J_2=3.6 Hz), 1.60 (s, 3H), 1.37 (s, 3H).

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