EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201400028

Synthesis of glyco-Fused Bicyclic Compounds; Conformationally Constrained Scaffolds and Useful Polyfunctional Building Blocks

Francisco Cardona,[a,b] Giuseppe D'Orazio,[a] Artur M. S. Silva,[b] Francesco Nicotra,[a] and Barbara La Ferla*[a]

Keywords: Chiral pool / Diastereoselectivity / Synthetic methods / Annulation / Glycoconjugates / Cycloaddition

We synthesized fused bicyclic polyfunctional compounds containing a highly hydroxylated pyran ring starting from commercially available methyl glucopyranoside and adopting a RCM annulation approach. The versatile α,β-unsaturated ketone group was introduced on the newly formed ring and, as an example of the potential of these polyfunctionalized building blocks, a tetracyclic compound was synthesized through a Diels–Alder cycloaddition reaction.

Introduction

The fused-bicyclic moiety containing a pyranose ring is a very common structural feature in a vast range of naturally occurring and biologically relevant compounds such as cyclic terpenes and flavonoids. The structure of the pyran ring is similar to the cyclic structure of glycopyranoses, thus directly suggesting the use of monosaccharides as potential starting materials. Monosaccharides are readily available and abundant compounds with high chirality content and with multiple hydroxyl functionalities, which makes them useful materials for the preparation of complex optically pure compounds, adopting the so called "chiron approach".[1]

The generation of carbohydrate annulated products has been explored with different synthetic approaches including ring-closing metathesis (RCM),[2] Robinson annulation,[3] intramolecular aldol condensation,[4] radical cyclization,[5] and Diels–Alder cycloadditions.[6] The insertion of a glyco-structure allows the physicochemical properties and consequently the pharmacokinetics of the molecules to be tuned.[7]

Our aim was to prepare a set of fused bicyclic compounds containing a highly hydroxylated pyran ring and high chirality content determined by the monosaccharide starting material. To allow further functionalization and, in particular, generate fused cycles, an α,β-unsaturated ketone group, which represents a key functionality for Diels–Alder cycloadditions and Michael–Dickman reactions, was introduced in the second cycle. We show, as a demonstrative example, the synthesis of a tetracyclic derivative **30** (Scheme 4), which was obtained in good yield through Diels–Alder cycloaddition reaction from **1**.

Results and Discussion

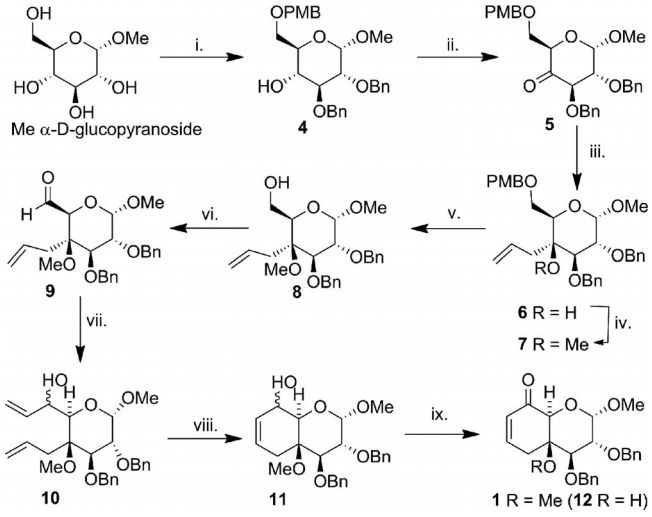
Our approach was based on RCM reaction of glucopyranose derivatives containing a C-1,2- or C-4,5-bis-allyl moiety and further oxidation for the generation of the carbonyl group. This approach allowed construction of the fused cycle on both sides of the sugar moiety. Compounds **1** and **2** were designed to have different stereochemistry and functionality on the ring junction, and both compounds were obtained from the common precursor alcohol **4** (Scheme 1), which was readily obtained according to a published procedure[8] from commercially available methyl α-D-glucopyranoside.

The synthesis of compound **1** is reported in Scheme 1. Alcohol **4** was subjected to Swern oxidation, affording ketone **5**, which was immediately reacted with allylmagnesium bromide to afford **6**, with a yield of 60% (over two steps) as a single diastereoisomer. The absolute configuration was determined by NOE NMR experiments (see the Supporting Information). The stereoselectivity of this reaction can be ascribed to the formation of a Cram chelated intermediate in which the magnesium ion coordinates the carbonyl group and the benzylic oxygen at C-3. The chelated oxo-sugar assumes a $^4C_1$ conformation (Figure 1), and the equatorial attack of the nucleophile dominates over the sterically hindered axial attack.[9]

The tertiary hydroxyl group of **6** was methylated (MeI) to afford **7** in 92% yield. Selective deprotection of the primary hydroxyl group of **7** by using cerium(IV) ammonium nitrate (CAN) (82% yield), followed by selective oxidation of the

[a] Dept. of Biotechnology and Bioscience, & Consorzio Interuniversitario Nazionale Metodologie e Processi Innovativi di Sintesi C.I.N.M.P.I.S.
Piazza della Scienza 2, 20126 Milano, Italy
E-mail: barbara.laferla@unimib.it
www.unimib.it
[b] Dept. of Chemistry & QOPNA, University of Aveiro, Campus Universitário de Santiago,
3810-193 Aveiro, Portugal

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201400028.



Scheme 1. *Reagents and conditions:* (i) Ref.[8], see also the Supporting Information; (ii) $(COCl)_2$, DMSO, Et_3N, –78 °C, 2 h; (iii) AllylMgBr, THF, –78 °C, 3 h, 60% (two steps); (iv) MeI, NaH, DMF, r.t., 2 h, 92%; (v) CAN, H_2O, CH_3CN, room temp., 20 min, 82%; (vi) Dess–Martin, CH_2Cl_2, room temp., 1 h, 89%; (vii) VinylMgBr, THF, –78 °C, 1 h, 94%; (viii) Hoveyda–Grubbs 2nd gen., CH_2Cl_2, 40 °C, 2 h, 97%; (ix) MnO_2, EtOAc, reflux, 2 h, 95%.

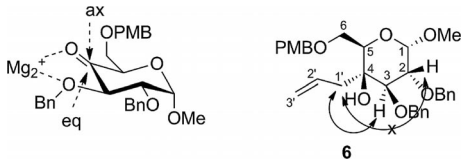
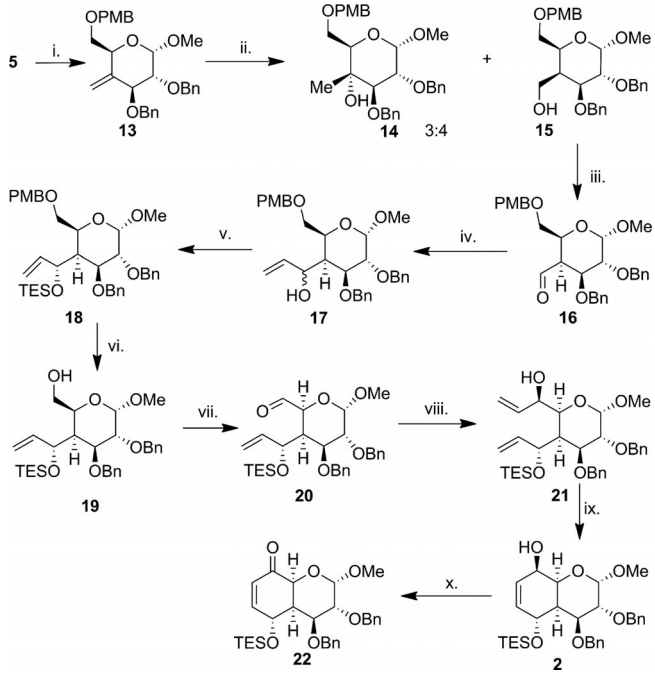


Figure 1. Cram chelate model and NOE contacts of **6**.

primary hydroxyl group of **8** with Dess–Martin periodinane led to aldehyde **9** in good yield (89%). Compound **9** was then reacted with vinylmagnesium bromide to afford **10** (94%), as a mixture of diastereomers. This mixture was subject to RCM by using Hoveyda–Grubbs 2nd generation catalyst to afford **11**, which were oxidized to produce the α,β-unsaturated ketone **1** in 95% yield. We also carried out the synthesis directly from **6** without introducing the methyl group (data not shown), which afforded the final bicyclic product **12** containing a free and more versatile hydroxyl group, but with significantly lower yield (26% from **6** vs. 58% of **1**).

The synthesis of **2** (Scheme 2) took advantage of the known aldehyde **16**, which was prepared from ketone **5** through a slightly modified literature procedure. This transformation requires Wittig methylenation to give olefin **13** and hydroboration by using $BH_3{\cdot}Me_2S$ followed by oxidation (H_2O_2) to afford a separable mixture of alcohols **14** and **15** in 3:4 ratio and 49% yield for the desired primary alcohol. A more hindered borane such as 9-borabicyclo[3.3.1]nonane (9-BBN-H), which could favor the formation of the desired product was tried; unfortunately, 9-BBN-H did not react at all with olefin **13**, probably due to steric hindrance of the substrate. Swern oxidation of **15** afforded the corresponding aldehyde **16** in 98% yield, which, upon treatment with vinylmagnesium bromide in tetrahydrofuran (THF) at –78 °C, gave alcohol **17** as mixture of diastereomers in a 7:3 ratio, which could be isolated in 84% yield.



Scheme 2. *Reagents and conditions:* (i) $MePh_3PBrBuLi$, THF, –78 °C, 12 h, 80%; (ii) $BH_3{\cdot}Me_2S$, H_2O_2 30%, NaOH, THF, room temp., 12 h, 49% for **15**; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 2 h, 98%; (iv) vinylMgBr, THF, –78 °C, 90 min, 84%; (v) TESCl, imidazole, THF, 60 °C,1 h, 85%; (vi) DDQ, CH_2Cl_2/H_2O (20:1), 0 °C, 3 h, 87%; (vii) $(COCl)_2$, DMSO, Et_3N, –78 °C, 2 h; (viii) vinylMgBr, THF, –78 °C, 1 h, 69% over two steps; (ix) Hoveyda–Grubbs 2nd gen. cat., CH_2Cl_2, 40 °C, 2 h, 84%; (x) MnO_2, EtOAc, reflux, 2 h, 70%.

The stereochemistry of the major isomer was determined for the cyclized product **22** on the basis of 2D NOESY NMR experiments, and was consistent with Grignard attack according to a Cram chelate model involving the oxygen at C-3 (see the Supporting Information). Protection of the allyl alcohol **17** with TESCl (85% yield) allowed the isolation of the major isomer. Selective removal of the *p*-methoxybenzyl protecting group by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (87% yield) gave primary alcohol **19**, which was then smoothly oxidized under Swern conditions to aldehyde **20**. Treatment of the latter with vinylmagnesium bromide gave allylic alcohol **21**, as a single diastereomer, in 69% yield over two steps. RCM of diene **21** by using Hoveyda–Grubbs 2nd generation catalyst afforded compound **22**, isolated in 84% yield, which was oxidized by using MnO_2 to give the desired product **2** in 70% yield. The ^1H NMR spectrum of the bicyclic product **22** and the corresponding 2D NOESY (Figure 2 and the Supporting Information) were used to establish the stereochemistry of the new stereocenter formed during the addition of vinylmagnesium bromide on aldehyde **16**. The observation of a small vicinal coupling constant ($J < 1$ Hz) in the ^1H NMR spectrum between H-7 and H-7a confirmed the *cis* orientation of these two protons. The doublet of

doublet of proton H-2 at δ = 3.71 ppm (J = 9.1 and 3.7 Hz) present an NOE cross-peak with the proton signal of H-4 at δ = 4.39 ppm, which corresponds to the *R* configuration at C-4. Further evidence is the absence of cross-peaks between proton H-4 and proton H-3 at δ = 3.94 ppm (Figure 2).

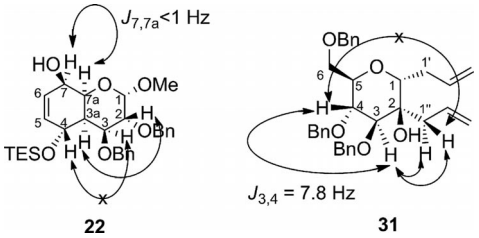
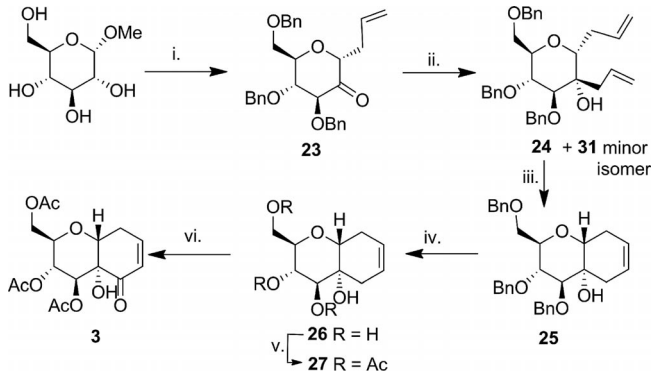


Figure 2. NOE contacts and coupling constants of **22** and **31**.

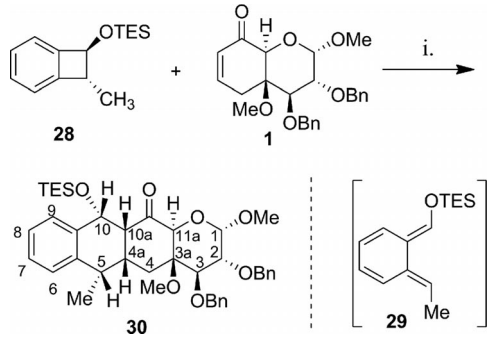
For the synthesis of scaffold **3**, in which the fused ring is constructed on the C-1,2 of the starting monosaccharide, the commercially available methyl α-D-glucopyranoside was readily converted into the allyl ketone **23**, in five steps, according to a published procedure (Scheme 3).[10] Grignard reaction of **23** with allylmagnesium bromide in toluene/CH_2Cl_2 (2:1)[11] afforded a separable mixture of tertiary alcohols **24** and its epimer at C-2 (68:32 ratio, 85% overall, 58% for **24**), in favor of isomer **24** with a D-*gluco* configuration; the absolute configuration was determined for the minor isomer on the basis of NMR experiments (see the Supporting Information).



Scheme 3. *Reagents and conditions:* (i) Ref.[10] (ii) AllylMgBr, toluene, CH_2Cl_2, –78 °C, 3 h, 58%; (iii) Hoveyda–Grubbs 2nd gen. cat., CH_2Cl_2, 40 °C, 1.5 h, 88%; (iv) BCl_3, CH_2Cl_2, –78 °C to r.t., 12 h, 71%; (v) Ac_2O, DMAP, Py, room temp., 80%; (vi) $Mn_3(OAc)_9$, tBuO$_2$H, EtOAc, 48 h, 52%.

RCM of **24** by using a second-generation Grubbs' catalyst at 40 °C in CH_2Cl_2 afforded the expected cyclized product **25** (88% yield). Debenzylation of **25** with BCl_3 at –78 °C in CH_2Cl_2, followed by acetylation, afforded compound **27** in 80% yield. Protecting group interconversion was necessary to avoid possible oxidation of the benzylic carbon atoms. Allylic oxidation of **27** was achieved by using commercially available manganese(III) acetate dihydrate as the catalyst and *tert*-butyl hydroperoxide (TBHP) as the cooxidant at room temperature.[12] Molecular sieves (3 Å) were added to remove the trace amount of water. After 48 h the α,β-unsaturated compound **3** was obtained in 52% yield. The stereochemistry of the diene was determined on the basis of ^{1}H and 2D NOESY NMR experiments for the minor isomer **31** (see the Supporting Information). The ^{1}H NMR spectrum of **31** showed a clean doublet at δ = 3.60 ppm with J = 7.8 Hz, indicating that proton H-3 couples only with H-4 and thus indicating a *trans*-diaxial orientation (Figure 2). The 2D NOESY spectrum showed a cross-peak between the signals of H-3 and those of H-1a′′ and H-1b′′; also evident is the absence of cross-peaks between the signal of H-4 and those of H-1a′′ and H-1b′′.

To demonstrate the synthetic potential of the synthesized polyfunctionalized building blocks, we undertook the synthesis of the highly functionalized tetracyclic derivative **30** (Scheme 4).



Scheme 4. *Reagents and conditions:* (i) 1,2-Dichlorobenzene, 160 °C, 90 min, 74%.

Compound **1** was reacted through Diels–Alder cycloaddition reactions with the very reactive diene *ortho*-quinodimethane **29**, produced in situ from benzocyclobutenol **28**,[13] affording tetracyclic compound **30** in 74% yield, along with traces of the other diastereomer.

Once again the stereochemistry of the new stereocenters was determined on the basis of ^{1}H NMR and 2D NOESY experiments. ^{1}H NMR spectrum showed H-10 signal at δ = 4.85 ppm as a doublet with J = 2.8 Hz, thus H-10 and H-10a are in a *cis*-orientation. The 2D NOESY experiment showed cross-peaks between the signal of H-5 and those of H-4a, H-5 and of the H-10a and H-5 and H-10 (see the Supporting Information), indicating a common facial disposition of all these protons. The absence of a cross-peak between the signals of H-10a and H-11a is consistent with the *anti* conformation of these protons.

Conclusions

We have synthesized polyfunctional glyco-fused bicyclic compounds from methyl α-D-glucopyranoside. The conformational rigidity, high chirality content, presence of an α,β-unsaturated ketone and multiple hydroxyl groups makes these compounds useful building blocks for the preparation of complex optically pure compounds.

Experimental Section

General Remarks: All solvents were dried with molecular sieves for at least 24 h prior to use. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates (Merck) with detection using UV light when possible, or by charring with a solution of concd. H_2SO_4/EtOH/H_2O (5:45:45) or a solution of $(NH_4)_6Mo_7O_{24}$ (21 g), $Ce(SO_4)_2$ (1 g), and concd. H_2SO_4 (31 mL) in water (500 mL). Flash column chromatography was performed on silica gel 230–400 mesh (Merck). ^1H and ^{13}C NMR spectra were recorded at 25 °C unless otherwise stated, with a Varian Mercury 400 MHz instrument. Chemical shift assignments, reported in ppm, are referenced to the corresponding solvent peaks (omitted in the peak assignment). HRMS were recorded with a QSTAR elite LC/MS/MS system with a nanospray ion source. Optical rotations were measured at room temperature with an Atago Polax-2L polarimeter and are reported in units of 10^{-1} deg cm^2 g^{-1}.

Methyl 2,3-Di-*O*-benzyl-6-*O*-(*p*-methoxybenzyl)-α-D-*xylo*-hexopyranosid-4-ulose (5): To a solution of $(COCl)_2$ (46 mmol, 3.97 mL) in anhydrous CH_2Cl_2 (92 mL) at –78 °C under an argon atmosphere, a solution of anhydrous DMSO (92 mmol, 6.51 mL) in anhydrous CH_2Cl_2 (20 mL) was added dropwise, and the resulting solution was stirred for 30 min. A solution of **4** (5.693 g, 11.5 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise at –78 °C and the final reaction mixture was stirred for 1 h at –78 °C. Anhydrous Et_3N (115 mmol, 13.91 mL) was added and the reaction was stirred for 30 min at –78 °C, and then warmed to 0 °C. A saturated solution of NH_4Cl was added, and the reaction mixture was extracted with CH_2Cl_2 (×3). The organic extracts were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was used without further purification.

Methyl 4-*C*-Allyl-2,3-di-*O*-benzyl-6-*O*-(*p*-methoxybenzyl)-α-D-galactopyranoside (6): To a solution of **5** (2.03 g, 4.12 mmol) in anhydrous THF (20 mL) at –78 °C under an argon atmosphere, a solution of allylmagnesium bromide (1 M in Et_2O, 8.24 mmol, 8.24 mL) was added dropwise. The resulting solution was stirred d concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc, 8.5:1.5) to give **6** (1.32 g, 60%; over two steps) as a pale-green oil. $[\alpha]_D^{25}$ = +21.4 (*c* = 2.9, $CHCl_3$). ^1H NMR (400 MHz, [D$_6$]benzene): δ = 7.28–7.00 (m, 12 H, Ar-H), 6.75–6.71 (m, 2 H, Ar-H), 5.75–5.62 (m, 1 H, CH_2-C*H*=CH_2), 5.03 (d, *J* = 11.2 Hz, 1 H, C*H*Ph), 4.94–4.87 (m, 2 H, CH_2-CH=CH_2), 4.75 (d, *J* = 3.4 Hz, 1 H, 1-H), 4.56 (d, *J* = 11.2 Hz, 1 H, C*H*Ph), 4.43–4.29 (m, 4 H, CH_2Ph), 4.12–4.06 (m, 2 H, 5-H, 2-H), 4.04–3.95 (m, 2 H, 3-H, 6-Ha), 3.88 (dd, *J* = 10.6, 5.8 Hz, 1 H, 6-Hb), 3.23 (s, 3 H, ArOMe), 3.20 (s, 3 H, OMe), 2.66 (dd, *J* = 14.0, 7.7 Hz, 1 H, C*H*H-CH=CH_2), 2.34 (dd, *J* = 14.0, 7.4 Hz, 1 H, C*H*H-CH=CH_2) ppm. ^{13}C NMR (101 MHz, [D$_6$]-benzene): δ = 159.6, 139.2, 139.1, 133.4, 130.8, 129.4, 128.4, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 118.5, 113.9, 98.0, 79.4, 77.1, 76.1, 75.4, 73.2, 72.4, 70.8, 55.0, 54.6, 40.7 ppm. HRMS: calcd. for [M + H]$^+$ 535.2696; found 535.2691.

Methyl 4-*C*-Allyl-2,3-di-*O*-benzyl-6-*O*-(*p*-methoxybenzyl)-4-*O*-methyl-α-D-galactopyranoside (7): To a solution of **6** (500 mg, 0.96 mmol) in anhydrous DMF (2.5 mL), NaH (76 mg, 1.92 mmol) and MeI (70 μL, 1.15 mmol) were added. The reaction mixture was stirred for 2 h at room temperature under an argon atmosphere, then MeOH was added and the reaction was stirred for 10 min. This solution was partitioned between saturated aqueous $NaHCO_3$ (8 mL) solution and EtOAc (4 mL), the phases were separated, and the aqueous phase was further extracted with EtOAc (4 mL). The organic extracts were combined and the combined solution was dried with anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The product was purified by flash chromatography (petroleum ether/EtOAc, 7:3) to afford **7** (8 mg, 92%) as a pale-yellow oil. $[\alpha]_D^{25}$ = +33.3 (*c* = 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.20 (m, 12 H, Ar-H), 6.86 (d, *J* = 8.6 Hz, 2 H, Ar-H), 5.88–5.63 (m, 1 H, CH_2-C*H*=CH_2), 5.12–4.98 (m, 3 H, CH_2-CH=CH_2, CH_2Ph), 4.79–4.70 (m, 2 H, CH_2Ph, 1-H), 4.67–4.60 (m, 2 H, CH_2Ph), 4.55 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.41 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.00 (dd, *J* = 10.1, 3.5 Hz, 1 H, 2-H), 3.94–3.85 (m, 2 H, 3-H, 5-H), 3.82–3.76 (m, 4 H, 6-H, ArOMe), 3.55–3.47 (m, 4 H, 6-H, OMe), 3.42 (s, 3 H, OMe), 3.09 (dd, *J* = 13.6, 7.8 Hz, 1 H, C*H*H-CH=CH_2), 2.14 (dd, *J* = 13.6, 7.1 Hz, 1 H, C*H*H-CH=CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.3, 139.4, 138.4, 132.5, 129.4, 128.6, 128.5, 128.4, 128.0, 127.5, 127.2, 119.6, 113.9, 98.3, 79.7, 79.4, 78.5, 76.1, 73.5, 73.3, 72.4, 55.5, 55.5, 53.2, 34.1 ppm. HRMS: calcd. for [M + H]$^+$ 549.2852; found 549.2866.

Methyl 4-*C*-Allyl-2,3-di-*O*-benzyl-4-*O*-methyl-α-D-galactopyranoside (8): To a solution of **7** (450 mg, 0.84 mmol) in CH_3CN (35 mL) at 0 °C, a solution of CAN (2.3 g, 4.21 mmol) in water (10 mL) was added. The reaction mixture was stirred at room temperature for 20 min, then diluted with CH_2Cl_2 (20 mL) and wash with water (2× 20 mL). The combined organic phases were dried, concentrated, and purified by flash chromatography (petroleum ether/EtOAc, 6:4) to give **8** (295 mg, 82%) as a pale-yellow oil. $[\alpha]_D^{25}$ = +45.5 (*c* = 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.20 (m, 10 H, Ar-H), 5.75–5.59 (m, 1 H, CH_2-C*H*=CH_2), 5.20–5.03 (m, 3 H, CH_2-CH=CH_2, CH_2Ph), 4.79–4.71 (m, 2 H, 1-H, CH_2Ph), 4.65 (d, *J* = 8.1 Hz, 1 H, CH_2Ph), 4.62 (d, *J* = 7.6 Hz, 1 H, CH_2Ph), 4.02 (dd, *J* = 10.0, 3.6 Hz, 1 H, 2-H), 3.96–3.87 (m, 2 H, 3-H, 6-H), 3.77–3.67 (m, 2 H, 6-H, 5-H), 3.53 (s, 3 H, OMe), 3.39 (s, 3 H, OMe), 3.13 (dd, *J* = 13.9, 7.2 Hz, 1 H, C*H*H-CH=CH_2), 2.21 (dd, *J* = 13.9, 7.6 Hz, 1 H, C*H*H-CH=CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.1, 138.3, 132.0, 128.7, 128.6, 128.4, 128.1, 127.7, 127.3, 119.9, 98.7, 80.6, 79.4, 78.2, 76.3, 73.6, 71.9, 61.3, 55.7, 53.2, 34.0 ppm. HRMS: calcd. for [M + H]$^+$ 429.2277; found 429.2281.

Methyl 4-*C*-Allyl-2,3-di-*O*-benzyl-6-formyl-4-*O*-methyl-α-D-galactopyranoside (9): Alcohol **8** (250 mg, 0.59 mmol) in CH_2Cl_2 (1 mL) was added to a stirred solution of Dess–Martin periodinane (371 mg, 0.88 mmol) in CH_2Cl_2 (5 mL) at 0 °C, then the mixture was warmed to room temperature. The reaction was completed after 2 h, and the excess of oxidant was destroyed by addition of a saturated solution of $Na_2S_2O_3$ (10 mL). After 5 min vigorous stirring, the mixture was diluted with CH_2Cl_2 (10 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2× 5 mL). The combined extracts were dried with Na_2SO_4, filtered, and concentrated. The product was purified by flash chromatography (petroleum ether/EtOAc, 8.5:1.5) to afford **8** (221 mg, 89%) as a yellow oil. $[\alpha]_D^{25}$ = +62.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.61 (s, 1 H, C*H*O), 7.40–7.21 (m, 10 H, Ar-H), 5.87–5.72 (m, 1 H, CH_2-C*H*=CH_2), 5.26–5.14 (m, 2 H, CH_2-CH=CH_2), 5.07 (d, *J* = 11.4 Hz, 1 H, CH_2Ph), 4.82–4.75 (m, 2 H, 1-H, CH_2Ph), 4.66 (d, *J* = 11.4 Hz, 1 H, CH_2Ph), 4.64 (d, *J* = 11.9 Hz, 1 H, CH_2Ph), 4.08 (dd, *J* = 10.0, 3.5 Hz, 1 H, 2-H), 4.03 (br. s, 1 H, 5-H), 3.93 (d, *J* = 10.0 Hz, 1 H, 3-H), 3.45 (s, 3 H, OMe), 3.39 (s, 3 H, OMe), 3.07 (dd, *J* = 13.5, 7.9 Hz, 1 H, C*H*H-CH=CH_2), 2.46 (dd, *J* = 13.5, 7.2 Hz, 1 H, C*H*H-CH=CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.7, 139.0, 138.3, 132.3, 128.7, 128.6, 128.4, 128.2, 127.7, 127.4, 120.7, 99.0, 82.1, 78.4, 78.1, 76.2, 75.8, 73.7, 56.2, 53.5, 33.0 ppm. HRMS: calcd. for [M + H]$^+$ 427.2121; found 427.2141.

Methyl 7,8-Dideoxy-4-*C*-allyl-2,3-di-*O*-benzyl-4-*O*-methyl-α-D-galacto-L/D-*glycero*-7-enopyranoside (10): Allylmagnesium bromide

(1 M in THF, 1.17 mmol, 1.17 mL) was added to a solution of **9** (200 mg, 0.47 mmol) in anhydrous THF (3 mL) at –78 °C and the reaction was stirred at –78 °C for 2 h. The reaction mixture was warmed to 0 °C, a solution of NH_4Cl (15 mL) was slowly added, and the mixture was diluted with EtOAc (10 mL). The aqueous phase was back-extracted with EtOAc (3× 5 mL) and the organic fractions were combined and dried with anhydrous Na_2SO_4. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give **10** (0.200 g, 94% yield) as a mixture of diastereomers (62:38) as a pale-yellow oil. $[\alpha]_D^{25}$ = +24.0 (*c* = 0.5, $CHCl_3$). NMR characterization of the major isomer partially CH=CH_2, 2.38 (dd, *J* = 13.8, 7.6 Hz, 1 H, C*H*H-CH=CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.8, 138.1, 138.0, 131.6, 128.4, 128.4, 128.2, 127.9, 127.5, 127.1, 119.9, 115.5, 98.3, 82.2, 78.9, 77.6, 76.1, 73.3, 72.1, 71.3, 55.5, 52.9, 34.0 ppm. HRMS: calcd. for $[M + H]^+$ 455.2434; found 455.2424.

Compound 11: To a solution of **10** (77 mg, 0.17 mmol) in anhydrous CH_2Cl_2 (10 mL), Hoveyda–Grubbs 2nd generation catalyst (5% weight), was added. The reaction mixture was stirred at 40 °C for 90 min, then the crude product was concentrated and purified by flash chromatography (petroleum ether/EtOAc, 6:4) to give **10** (70 mg, 97%) as a pale-brown oil. ^1H NMR (400 MHz, $CDCl_3$): δ (major isomer) = 7.41–7.21 (m, 10 H, Ar-H), 5.71–5.63 (m, 1 H, 6-H), 5.63–5.54 (m, 1 H, 5-H), 5.01 (d, *J* = 11.5 Hz, 1 H, CH_2Ph), 4.82–4.75 (m, 2 H, 1-H, CH_2Ph), 4.66 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 4.60 (d, *J* = 11.5 Hz, 1 H, CH_2Ph), 4.46–4.40 (m, 1 H, 7-H), 4.03 (dd, *J* = 10.0, 3.6 Hz, 1 H, 2-H), 3.76 (d, *J* = 10.0 Hz, 1 H, 3-H), 3.64 (d, *J* = 8.1 Hz, 1 H, 7-Ha), 3.44 (s, 3 H, OMe), 3.42 (s, 3 H, OMe), 2.91 (dd, *J* = 19.3, 4.5 Hz, 1 H, 4-Ha), 2.10–2.03 (br., 1 H, OH), 1.88 (br. d, *J* = 19.3 Hz, 1 H, 4-Hb) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.1, 138.5, 129.2, 128.6, 128.6, 128.3, 128.1, 127.8, 124.1, 98.9, 83.3, 78.1, 76.4, 75.9, 73.6, 68.9, 55.5, 54.0, 29.2 ppm. HRMS: calcd. for $[M + H]^+$ 427.2121; found 427.2113.

Compound 1: Compound **11** (693 mg, 1.62 mmol) and activated MnO_2 (988 mg, 11.37 mmol) were slurried in EtOAc (20 mL), and the mixture was heated to reflux for 4 h. After consumption of the starting material, the reaction mixture was hot-filtered though Celite and the residual black solid was washed copiously with EtOAc (40 mL). The filtrate was concentrated in vacuo, to give **1** (656 mg, 95%yield) as pale-brown oil. $[\alpha]_D^{25}$ = +66.7 (*c* = 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.24 (m, 10 H, Ar-H), 6.71–6.66 (m, 1 H, 5-H), 6.06 (dd, *J* = 10.1, 3.1 Hz, 1 H, 6-H), 5.04 (d, *J* = 11.2 Hz, 1 H, CH_2Ph), 4.84 (d, *J* = 3.4 Hz, 1 H, 1-H), 4.79 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.65 (d, *J* = 11.2 Hz, 1 H, CH_2Ph), 4.62 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.35 (s, 1 H, 7-Ha), 4.05 (dd, *J* = 10.0, 3.4 Hz, 1 H, 2-H), 3.90 (d, *J* = 10.0 Hz, 1 H, 3-H), 3.42 (s, 3 H, OMe), 3.38 (s, 3 H, OMe), 3.16 (dd, *J* = 19.6, 5.9 Hz, 1 H, 4-H), 2.20–2.11 (m, 1 H, 4-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 193.8, 142.2, 138.7, 138.2, 129.7, 128.7, 128.7, 128.4, 128.2, 128.0, 99.2, 82.2, 80.5, 77.5, 76.3, 76.3, 73.8, 56.3, 54.4, 30.3 ppm. HRMS: calcd. for $[M + H]^+$ 425.1964; found 425.1954.

Methyl 2,3-Di-*O*-benzyl-4-deoxy-4-*C*-(methylene)-6-*O*-*p*-methoxybenzyl-α-D-*xylo*-hexopyranoside (13): To a suspension of methyltriphenylphosphonium bromide (10.6 g, 29.84 mmol) in anhydrous THF (50 mL) was added *n*BuLi (1.6 M in hexane, 17.31 mL) at –78 °C with stirring under an argon atmosphere. After warming to 0 °C for 30 min, the solution was re-cooled to –78 °C and treated with a solution of ketone **5** (2.1 g, 4.26 mmol) in anhydrous THF (90 mL). The mixture was stirred for 2 h and warmed to room temperature, then poured in a saturated solution of NH_4Cl (100 mL) and extracted with Et_2O (3× 30 mL). The organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc, 8.5:1.5) to give **13** (1.67 g, 80%) as a yellow oil. $[\alpha]_D^{25}$ = +62.5 (*c* = 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.23 (m, 10 H, Ar-H), 6.90–6.85 (m, 2 H, Ar-H), 5.35 (br. s, 1 H, C*H*H=), 4.96 (s, 1 H, C*H*H=), 4.85 (d, *J* = 12.2 Hz, 1 H, CH_2Ph), 4.80 (d, *J* = 11.3 Hz, 1 H, CH_2Ph), 4.72 (d, *J* = 11.3 Hz, 1 H, CH_2Ph), 4.71–4.63 (m, 2 H, 1-H, CH_2Ph), 4.55 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.51 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.35–4.27 (m, 2 H, 5-H, 3-H), 3.80 (s, 3 H, OMe), 3.76 (dd, *J* = 10.0, 4.9 Hz, 1 H, 6-H), 3.65 (dd, *J* = 10.0, 5.9 Hz, 1 H, 6-H), 3.48 (dd, *J* = 9.6, 3.6 Hz, 1 H, 2-H), 3.43 (s, 3 H, OMe) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 142.6, 138.5, 138.4, 130.0, 129.4, 128.4, 128.1, 127.8, 127.7, 127.6, 127.6, 113.8, 107.8, 98.8, 81.5, 79.2, 73.9, 73.6, 73.2, 69.2, 67.7, 55.4, 55.3 ppm. HRMS: calcd. for $[M + H]^+$ 491.2434; found 491.2424.

Methyl 2,3-Di-*O*-benzyl-4-deoxy-4-*C*-(hydroxymethylene)-6-*O*-(*p*-methoxybenzyl)-α-D-galactopyranoside (15): A solution of $BH_3{\cdot}Me_2S$ (7.3 mmol, 0.7 mL) was added dropwise to a solution of **13** (2.9 g, 5.86 mmol) in anhydrous THF (54 mL) at room temperature, under an argon atmosphere and stirred for 90 min. The reaction mixture was cooled to 0 °C, aqueous NaOH 3 M (2.9 mL) then aqueous H_2O_2 (30%, 2.9 mL) were added dropwise. After 12 h, the reaction mixture was diluted with H_2O (200 mL) and extracted with EtOAc (3× 70 mL), dried with Na_2SO_4, filtered, and concentrated under vacuum. The resulting residue was purified by flash chromatography (petroleum ether/EtOAc, 7.5:2.5) to give **15** (1.82 g, 49%) as a pale-brown oil. $[\alpha]_D^{25}$ = +33.3 (*c* = 1.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 12 H, Ar-H), 6.87 (d, *J* = 8.6 Hz, 2 H, Ar-H), 4.82 (d, *J* = 12.1 Hz, 1 H, CH_2Ph), 4.75 (d, *J* = 11.5 Hz, 1 H, CH_2Ph), 4.70 (d, *J* = 11.5 Hz, 1 H, CH_2Ph), 4.66 (d, *J* = 12.1 Hz, 1 H, CH_2Ph), 4.64 (d, *J* = 3.9 Hz, 1 H, 1-H), 4.52 (d, *J* = 11.5 Hz, 1 H, CH_2Ph), 4.48 (d, *J* = 11.5 Hz, 1 H, CH_2Ph), 4.09–4.01 (m, 2 H, 5-H, 3-H), 3.94 (dd, *J* = 11.5, 5.5 Hz, 1 H, 6-H), 3.83–3.75 (m, 4 H, ArOMe, 6-H), 3.68 (dd, *J* = 10.2, 3.9 Hz, 1 H, 2-H), 3.61–3.54 (m, 2 H, CH_2OH), 3.37 (s, 3 H, OMe), 2.37–2.30 (m, 1 H, 4-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.4, 138.3, 138.3, 129.5, 129.4, 128.4, 128.4, 128.0, 127.8, 127.7, 113.9, 98.7, 78.5, 76.7, 73.4, 73.1, 70.2, 67.8, 57.8, 55.2, 55.2, 43.7 ppm. HRMS: calcd. for $[M + H]^+$ 509.2539; found 509.2530.

Compound 14 (Minor Byproduct): $[\alpha]_D^{25}$ = +8.3 (*c* = 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.17 (m, 12 H, Ar-H), 6.87 (d, *J* = 8.6 Hz, 2 H, Ar-H), 4.94 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.81 (d, *J* = 11.9 Hz, 1 H, CH_2Ph), 4.78 (d, *J* = 11.8 Hz, 1 H, CH_2Ph), 4.62 (d, *J* = 11.9 Hz, 1 H, CH_2Ph), 4.59 (d, *J* = 3.8 Hz, 1 H, 1-H), 4.51 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.45 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 3.88 (br. t, *J* = 6.1 Hz, 1 H, 5-H), 3.82–3.78 (m, 4 H, 3-H, ArOMe), 3.68 (dd, *J* = 9.8, 6.1 Hz, 1 H, 6-H), 3.55 (dd, *J* = 9.8, 6.1 Hz, 1 H, 6-H), 3.46–3.36 (m, 4 H, 2-H, OMe), 1.18 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 139.2, 138.3, 129.8, 129.3, 128.4, 128.4, 128.0, 127.8, 127.8, 127.6, 113.8, 98.0, 83.5, 78.5, 75.7, 74.3, 73.4, 73.2, 70.7, 68.6, 55.3, 55.1, 15.8 ppm.

Methyl 2,3-Di-*O*-benzyl-4-deoxy-4-*C*-(formyl)-6-*O*-(*p*-methoxybenzyl)-α-D-galactopyranoside (16): To a solution of $(COCl)_2$ (7.86 mmol, 0.7 mL) in anhydrous CH_2Cl_2 (16 mL) at –78 °C under an argon atmosphere, a solution of anhydrous DMSO (15.76 mmol, 1.1 mL) in anhydrous CH_2Cl_2 (6 mL) was added dropwise, and the resulting solution was stirred for 30 min. To the reaction flask, a solution of **15** (1 g, 1.97 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise at –78 °C. This final reaction mixture was stirred for 1 h at –78 °C, then anhydrous Et_3N

(19.7 mmol, 2.76 mL) was added and the reaction was stirred for 30 min, and then warmed to 0 °C. A saturated solution of NH_4Cl (150 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc, 7.5:2.5) to give **16** (977 mg, 98%) as a pale-green oil. $[\alpha]_D^{25}$ = +36.7 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.90 (d, *J* = 5.3 Hz, 1 H, C*H*O), 7.37–7.14 (m, 12 H, Ar-H), 6.86 (d, *J* = 8.6 Hz, 2 H, Ar-H), 4.85 (d, *J* = 12.1 Hz, 1 H, CH_2Ph), 4.78 (d, *J* = 3.8 Hz, 1 H, 1-H), 4.73–4.66 (m, 2 H, CH_2Ph), 4.63 (d, *J* = 11.5 Hz, 1 H, CH_2Ph), 4.44 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.39 (d, *J* = 11.7 Hz, 1 H, CH_2Ph), 4.17–4.05 (m, 2 H, 3-H, 5-H), 3.98 (dd, *J* = 10.0, 3.8 Hz, 1 H, 2-H), 3.80 (s, 3 H, OMe), 3.56 (dd, *J* = 10.4, 4.2 Hz, 1 H, 6-H), 3.47 (dd, *J* = 10.4, 5.0 Hz, 1 H, 6-H), 3.37 (s, 3 H, OMe), 3.00–2.95 (m, 1 H, 4-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.5, 159.4, 138.3, 138.1, 129.7, 129.6, 128.6, 128.5, 128.5, 128.2, 127.9, 113.9, 99.2, 76.6, 76.6, 73.8, 73.4, 72.3, 69.9, 67.8, 55.5, 55.4, 54.8 ppm. HRMS calcd. for $[M + H]^+$ 507.2383; found 507.2555.

Methyl 2,3-Di-*O*-benzyl-4-deoxy-4-*C*-(1*R*/*S*-1-hydroxyallyl)-6-*O*-(*p*-methoxybenzyl)-α-D-galactopyranoside (17): To a solution of **16** (720 mg, 1.42 mmol) in anhydrous THF (30 mL) at –78 °C under an argon atmosphere, a solution of vinylmagnesium bromide (1M in THF, 3.55 mmol, 3.6 mL) was added dropwise. The resulting solution was stirred for 90 min, then warmed to 0 °C. A saturated solution of NH_4Cl (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 35 mL). The organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc, 7:3) to give **17** (637 mg, 84%) as a pale-brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.12 (m, 12 H, Ar-H), 6.97–6.78 (m, 2 H, Ar-H), 6.02 [m, 1 H, CH(OH)-C*H*=CH_2], 5.22 [d, *J* = 17.2 Hz, 0.7 H, CH(OH)-CH=CH_2 *trans* major isomer], 5.29 [d, *J* = 17.2 Hz, 0.3 H, CH(OH)-CH=CH_2 *trans* minor isomer], 5.09–5.03 [m, 1 H, CH(OH)-CH=CH_2 *cis*], 4.81–4.40 [m, 8 H, 1-H, C*H*(OH)-CH=CH_2, 6 CH_2Ph], 4.20–4.00 (m, 3 H, 2-H, 3-H, 5-H), 3.80 (s, 3 H, OMe), 3.67–3.60 (m, 1 H, 6-H), 3.57–3.51 (m, 1 H, 6-H), 3.38 (s, 3 H, OMe), 2.45–2.39 (m, 1 H, 4-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.2, 139.2, 138.3, 129.8, 129.3, 128.4, 128.4, 128.0, 127.8, 127.8, 127.6, 113.8, 98.0, 83.5, 78.5, 75.7, 74.3, 73.4, 73.2, 70.7, 68.6, 55.3, 55.1, 15.8 ppm. HRMS: calcd. for $[M + H]^+$ 535.2696; found 535.2702.

Methyl 2,3-Di-*O*-benzyl-4-deoxy-4-*C*-[(1*R*)-1-(triethylsilyloxyallyl)]-6-*O*-(*p*-methoxybenzyl)-α-D-galactopyranoside (18): To a solution of **17** (588 mg, 1.10 mmol) and imidazole (249 mg, 1.65 mmol) in anhydrous DMF (7 mL) was added TESCl (1.65 mmol, 0.25 mL). The reaction mixture was heated at 60 °C for 90 min then cooled to room temperature and a saturated aqueous solution of $NaHCO_3$ was added. The reaction mixture was extracted with EtOAc (× 3) and the organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc, 8:2) to give **18** (605 mg, 85%) as a light-green oil. $[\alpha]_D^{25}$ = +33.6 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.16 (m, 12 H, Ar-H), 6.86 (d, *J* = 8.6 Hz, 2 H, Ar-H), 6.19–6.06 [m, 1 H, CH(OTES)-C*H*=CH_2], 5.08 [d, *J* = 17.2 Hz, 1 H, CH(OTES)-CH=CH_2], 4.94 [d, *J* = 10.5 Hz, 1 H, CH(OTES)-CH=CH_2], 4.77–4.49 [m, 7 H, C*H*(OTES)-CH=CH_2, 5 C*H*Ph, 1-H], 4.42 (d, *J* = 11.6 Hz, 1 H, C*H*Ph), 4.16–4.11 (m, 1 H, 5-H), 4.04–3.97 (m, 2 H, 2-H, 3-H), 3.89–3.81 (m, 1 H, 6-Ha), 3.79 (s, 3 H, ArOMe), 3.72–3.64 (m, 1 H, 6-Hb), 3.40 (s, 3 H, OMe), 2.38 (br. s, 1 H, 4-H), 0.88 (t, *J* = 7.8 Hz, 9 H, CH_3CH$_2$Si), 0.51 (q, *J* = 7.8 Hz, 6 H, CH$_3$CH_2Si) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.1, 139.0, 138. 7, 130.7, 129.2, 128.4, 128.4, 128.3, 127.7, 127.5, 127.4, 113.7, 77.7, 74.5, 73.2, 72.9, 72.8, 72.7, 72.4, 55.3, 55.1, 7.0, 5.0 ppm. HRMS: calcd. for $[M + H]^+$ 649.3561; found 649.3545.

Methyl 2,3-Di-*o*-benzyl-4-deoxy-4-*C*-[(1*R*)-1-(triethylsilyloxyallyl)]-α-D-galactopyranoside (19): DDQ (300 mg, 1.31 mmol) was added to an ice-cooled solution of **18** (609 mg, 0.94 mmol) in H_2O/CH_2Cl_2 (1:20) (42 mL), and the mixture was stirred for 2 h. The reaction mixture was then diluted with a saturated aqueous solution of $NaHCO_3$ (80 mL) and extracted with CH_2Cl_2 (× 3). The extracts were washed with H_2O and brine, dried, and concentrated under reduce pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc, 8:2) to give **19** (432 mg, 87%) as a green oil. $[\alpha]_D^{25}$ = +53.7 (*c* = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.22 (m, 10 H), 6.24–6.09 [m, 1 H, CH(OTES)-C*H*=CH_2], 5.14 [d, *J* = 17.1 Hz, 1 H, CH(OTES)-CH=CH_2], 4.98 [d, *J* = 8.7 Hz, 1 H, CH(OTES)-CH=CH_2], 4.82–4.67 [m, 4 H, 3 C*H*Ph, C*H*(OTES)-CH=CH_2], 4.61 (d, *J* = 12.2 Hz, 1 H, C*H*Ph), 4.55 (d, *J* = 3.4 Hz, 1 H, 1-H), 4.05–3.94 (m, 3 H, 2-H, 3-H, 5-H), 3.85–3.74 (m, 2 H, 6-Ha, 6-Hb), 3.34 (s, 3 H, OMe), 2.63–2.48 (m, 1 H, 4-H), 0.92 (t, *J* = 7.9 Hz, 9 H, CH_3CH$_2$Si), 0.58 (q, *J* = 7.9 Hz, 6 H, CH$_3$CH_2Si) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.5, 138.7, 138.4, 128.3, 128.3, 128.2, 127.3, 117.1, 98.7, 74.3, 73.0, 72.9, 72.9, 69.1, 62.7, 55.1, 47.5, 6.7, 4.7 ppm. HRMS: calcd. for $[M + H]^+$ 529.2985; found 529.2993.

Methyl 2,3-Di-*O*-benzyl-4-deoxy-6-formyl-4-*C*-[(1*R*)-1-(triethylsilyloxyallyl)]-α-D-galactopyranoside (20): To a solution of $(COCl)_2$ (1.51 mmol, 0.13 mL) in anhydrous CH_2Cl_2 (2 mL) at –78 °C under an argon atmosphere, a solution of anhydrous DMSO (2.96 mmol, 0.2 mL) in anhydrous CH_2Cl_2 (3 mL) was added dropwise, and the resulting solution was stirred for 30 min. To the reaction flask, a solution of **19** (200 mg, 0.37 mmol) in anhydrous CH_2Cl_2 (4 mL) was added dropwise at –78 °C. This final reaction mixture was stirred for 1 h at –78 °C, then anhydrous Et_3N (3.7 mmol, 0.52 mL) was added and the reaction was stirred for 30 min, and then warmed to 0 °C. A saturated solution of NH_4Cl (15 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (× 3). The organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was used without further purification.

Methyl 2,3-Di-*O*-benzyl-4,7,8-trideoxy-4-*C*-[(1*R*)-1-triethylsilyloxyallyl)]-α-D-*galacto*-D-*glycero*-7-enopyranoside (21): To a solution of **20** (380 mg, 0.72 mmol) in anhydrous THF (18 mL) at –78 °C under an argon atmosphere, a solution of vinylmagnesium bromide (1 M in THF, 1.8 mmol, 1.8 mL) was added dropwise. The resulting solution was stirred for 90 min, then warmed to 0 °C. A saturated solution of NH_4Cl (15 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (× 3). The organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc, 8.5:1.5) to give **21** (275 mg, 69% over two steps) as a pale-green oil. $[\alpha]_D^{25}$ = +54.0 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 77.40–7.24 (m, 10 H), 6.39–6.25 [m, 1 H, CH(OTES)-C*H*=CH_2], 6.10–5.94 (m, 1 H, 7-H), 5.39 (d, *J* = 17.5 Hz, 1 H, 8-H), 5.18 (d, *J* = 10.4 Hz, 1 H, 8-H), 5.11 [d, *J* = 17.0 Hz, 1 H, CH(OTES)-CH=CH_2], 4.95 [d, *J* = 9.6 Hz, 1 H, CH(OTES)-CH=CH_2], 4.82–4.68 [m, 4 H, 3 CH_2Ph, C*H*(OTES)-CH=CH_2], 4.61–4.54 (m, 2 H, CH_2Ph, 1-H), 4.40 (br. s, 1 H, 6-H), 4.07 (dd, *J* = 10.0, 3.7 Hz, 1 H, 2-H), 3.98 (dd, *J* = 10.0, 5.9 Hz, 1 H, 3-H), 3.79 (br. s, 1 H, 5-H), 3.34 (s, 3 H, OMe), 2.46 (br. s, 1 H, 4-H), 0.92 (t, *J* = 7.9 Hz, 9 H, CH_3CH$_2$Si), 0.59 (q, *J* = 7.9 Hz, 6 H, CH$_3$CH_2Si) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.1, 138.3,

138.1, 136.6, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 117.5, 116.4, 99.1, 79.1, 75.3, 73.5, 73.1, 72.9, 71.9, 71.8, 71.7, 55.6, 45.6, 6.8, 6.4 ppm. HRMS: calcd. for $[M + H]^+$ 555.3142; found 555.3155.

Compound 22: To a solution of **21** (50 mg, 0.09 mmol) in anhydrous CH_2Cl_2 (4 mL), Hoveyda–Grubbs 2nd generation catalyst (5% weight), was added. The reaction mixture was stirred at 40 °C for 2 h, then the crude product was concentrated and purified by flash chromatography (petroleum ether/EtOAc, 8:2) to give **22** (40 mg, 84%) as a pale-brown oil. $[\alpha]_D^{25}$ = +60.0 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.22 (m, 10 H, Ar-H), 5.82 (dd, J = 10.2, 3.7 Hz, 1 H, 6-H), 5.77 (dd, J = 10.2, 2.2 Hz, 1 H, 5-H), 4.89 (d, J = 12.6 Hz, 1 H, C*H*Ph), 4.80 (d, J = 12.6 Hz, 1 H, C*H*Ph), 4.75 (d, J = 12.7 Hz, 1 H, C*H*Ph), 4.63–4.58 (m, 2 H, C*H*Ph, 1-H), 4.39 (br. d, J = 6.3 Hz, 1 H, 4-H), 4.10–4.05 (m, 1 H, 7-H), 4.00–3.90 (m, 2 H, 7-Ha, 3-H), 3.71 (dd, J = 9.1, 3.7 Hz, 1 H, 2-H), 3.38 (s, 3 H, OMe), 2.62–2.49 (m, 1 H, 3-Ha), 0.92 (t, J = 7.9 Hz, 9 H, CH_3CH_2Si), 0.58 (q, J = 7.9 Hz, 6 H, CH_3CH_2Si) ppm. ^{13}C NMR (101 MHz, [D$_6$]acetone): δ = 140.1, 139.6, 133.5, 129.3, 129.1, 128.8, 128.6, 128.6, 128.3, 126.9, 99.2, 80.2, 78.7, 74.4, 72.8, 70.6, 66.7, 65.7, 55.2, 41.3, 7.2, 7.1 ppm. HRMS: calcd. for $[M + H]^+$ 527.2829; found 527.2822.

Compound 2: Compound **22** (10 mg, 0.019 mmol) and MnO_2 (12 mg, 0.132 mmol) were slurried in EtOAc (2 mL), and the mixture was heated to reflux for 2 h. After consumption of the starting material, the reaction mixture was hot-filtered though Celite and the residual black solid was washed copiously with EtOAc. The filtrate was concentrated in vacuo, and the crude product was purified by flash chromatography (petroleum ether/EtOAc, 8.5:1.5) to give **22** (7 mg, 70%) as a pale-brown oil. $[\alpha]_D^{25}$ = +63.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.38–7.24 (m, 8 H, Ar-H), 7.13 (d, J = 6.9 Hz, 2 H, Ar-H), 6.62 (dd, J = 9.8, 3.0 Hz, 1 H, 5-H), 5.89 (d, J = 9.8 Hz, 1 H, 6-H), 4.75–4.70 (m, 2 H, C*H*Ph, 1-H), 4.61–4.47 (m, 3 H, 2C*H*Ph, 7-Ha), 4.33 (d, J = 12.5 Hz, 1 H, C*H*Ph), 4.20–4.08 (m, 1 H, 4-H), 3.78–3.74 (m, 1 H, 3-H), 3.72–3.67 (m, 1 H, 2-H), 3.43 (s, 3 H, OCH_3), 2.69–2.63 (m, 1 H, 3-Ha), 0.85 (t, J = 7.9 Hz, 9 H, CH_3CH_2Si), 0.51 (q, J = 7.9 Hz, 6 H, CH_3CH_2Si) ppm. ^{13}C NMR (101 MHz, DMSO): δ = 200.9, 138.7, 138.7, 138.0, 137.9, 128.2, 127.4, 96.5, 75.7, 73.3, 72.7, 71.1, 70.8, 67.5, 56.3, 43.0, 6.7, 4.1 ppm. HRMS: calcd. for $[M + H]^+$ 525.2672; found 525.2665.

***C*-Allyl-3,4,6-tri-*O*-benzyl-2-*C*-allyl-α-D-glucopyranoside (24):** Allylmagnesium bromide (1 M in THF, 1.6 mmol, 1.6 mL) was added to a solution of **23** (293 mg, 0.62 mmol) in anhydrous toluene/CH_2Cl_2 (2:1, 3 mL) at –78 °C. The reaction was stirred at –78 °C for 2 h, then the mixture was warmed to 0 °C, a solution of NH_4Cl (20 mL) was slowly added and the mixture was diluted with EtOAc (8 mL). The aqueous phase was back-extracted with EtOAc (3 × 8 mL) and the organic fractions were combined and dried with anhydrous Na_2SO_4. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9.5:0.5) to give **24** and **31** (0.271 g, 85%) as a mixture of diastereomers (68:32) as a yellow oil. $[\alpha]_D^{25}$ = +12.1 (c = 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer **24**) = 7. 7.40–7.16 (m, 15 H, Ar-H), 6.02–5.81 (m, 2 H, 2′-H, 2′′-H), 5.21–5.00 (m, 4 H, 3′-Ha,b, 3′′-Ha,b), 4.63 (d, J = 11.5 Hz, 1 H, CH_2Ph), 4.61–4.47 (m, 4 H, 4 CH_2Ph), 4.45 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.11–4.04 (m, 1 H, 4-H), 3.79–3.72 (m, 3 H, 1-H, 5-H, 6-Ha), 7.72–3.65 (m, 2 H, 3-H, 6-Hb), 2.52–2.31 (m, 4 H, 1′-Ha,b, 1′′-Ha,b) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.5, 138.2, 137.6, 136.1, 133.7, 128.7, 128.7, 128.6, 128.3, 128.2, 128.0, 127.9, 127.8, 119.2, 116.5, 79.3, 74.4, 73.9, 73.8, 73.7, 73.4, 73.4, 73.0, 68.6, 38.3, 31.8 ppm. HRMS: calcd. for $[M + H]^+$ 408.2301; found 408.2298.

Compound 25: To a solution of **24** (768 mg, 1.49 mmol) in anhydrous CH_2Cl_2 (45 mL), Hoveyda–Grubbs 2nd generation catalyst (5% weight) was added. The reaction mixture was stirred at 40 °C for 2 h, then the crude product was concentrated and purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give the corresponding cyclized product **25** (642 mg, 88%) as a green oil. $[\alpha]_D^{25}$ = +9.6 (c = 2.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.23 (m, 15 H, Ar-H), 5.61–5.50 (m, 2 H, 2′-H, 3′-H), 4.61 (d, J = 11.8 Hz, 1 H, CH_2Ph), 4.56 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.53–4.37 (m, 4 H, 4 CH_2Ph), 4.34–4.26 (m, 1 H, 6-Ha), 3.96–3.83 (m, 2 H, 1-H, 5-H), 3.76–3.72 (m, 1 H, 6-H), 3.66–3.58 (m, 1 H, 3-H), 3.43–3.36 (m, 1 H, 4-H), 2.62 (br. d, J = 17.2 Hz, 1 H, 4′-H), 2.37–2.15 (m, 2 H, 1′-H), 1.94 (br. d, 1 H, 4′-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.3, 137.3, 137.1, 128.8, 128.7, 128.6, 128.3, 128.2, 127.9, 127.8, 123.8, 75.6, 74.7, 73.3, 73.12, 71.7, 69.5, 67.8, 67.3, 33.1, 28.2 ppm. HRMS: calcd. for $[M + H]^+$ 380.1988; found 380.1982.

Compound 26: To a solution of **25** (439 mg, 0.90 mmol) in anhydrous CH_2Cl_2 (12 mL) was added BCl_3 (11 mmol, 11 mL) at –78 °C under argon. The reaction mixture was stirred for 3 h at –78 °C, and overnight at room temperature, then diluted by the addition of a solution MeOH/H_2O (20:1, 6 mL). The reaction mixture was then concentrated under reduced pressure and the crude product was purified by flash chromatography (EtOAc) to give **26** (0.138 g, 71%) as a colorless oil. $[\alpha]_D^{25}$ = +73.3 (c = 0.3, CH_3OH) ppm. ^{1}H NMR (400 MHz, CD_3OD): δ = 5.59–5.47 (m, 2 H, 2′-H, 3′-H), 4.13 (dd, J = 12.1, 8.6 Hz, 1 H, 6-H), 4.02 (dd, J = 9.5, 6.9 Hz, 1 H, 1-H), 3.92 (dd, J = 8.6, 4.2 Hz, 1 H, 5-H), 3.73 (d, J = 2.2 Hz, 1 H, 4-H), 3.59 (dd, J = 12.1, 4.2 Hz, 1 H, 6-H), 3.50 (d, J = 2.5 Hz, 1 H, 3-H), 2.61 (br. d, J = 18.4 Hz, 1 H, 4′-Ha), 2.31–2.17 (m, 2 H, 1′-Ha,b), 1.87 (dd, J = 18.1, 3.7 Hz, 1 H, 4′-Hb) ppm. ^{13}C NMR (101 MHz, CD_3OD): δ = 124.8, 124.7, 81.8, 71.6, 71.5, 70.8, 67.2, 60.9, 34.6, 29.0 ppm. HRMS: calcd. for $[M + H]^+$ 217.1076; found 217.1081.

Compound 27: To a solution of **26** (200 mg, 0.92 mmol) in anhydrous Py (5 mL), Ac_2O (4.62 mmol, 0.5 mL) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) were added at room temperature. The reaction mixture was stirred overnight at room temperature, then the reaction was quenched by the addition of a solution of HCl (5%). The aqueous layer was extracted with EtOAc (3×) and the combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 3:7) to give **27** (297 mg, 80%) as a yellow oil. $[\alpha]_D^{25}$ = +45.5 (c = 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.64–5.58 (m, 1 H, 2′-H), 5.55–5.49 (m, 3′-H), 4.92 (br. d, J = 2.0 Hz, 1 H, 4-H), 4.82 (d, J = 2.4 Hz, 1 H, 3-H), 4.69 (dd, J = 10.3, 7.3 Hz, 1 H, 6-Ha), 4.20–4.10 (m, 2 H, 5-H, 6-Hb), 4.07 (t, J = 8.1 Hz, 1-H), 2.28–2.21 (m, 2 H, 1′-Ha,b), 2.15 (s, 3 H, CH_3CO), 2.14 (s, 3 H, CH_3CO), 2.10 (s, 3 H, CH_3CO), 2.08–1.99 (m, 2 H, 4′-Ha,b) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.8, 170.4, 169.8, 123.7, 123.5, 75.7, 71.5, 71.5, 69.6, 68.2, 63.0, 34.1, 25.6, 20.8, 20.7 ppm. HRMS: calcd. for $[M + H]^+$ 343.1393; found 343.1387.

Compound 3: To a solution of **27** (20 mg, 0.058 mmol) in anhydrous EtOAc (1 mL) was added *tert*-butyl hydroperoxide (5.5 M in decane, 0.304 mmol, 56 μL) and molecular sieves (3 Å). The mixture was stirred for 30 min under argon at room temperature, then manganese(III) acetate dihydrate (0.006 mmol, 1.6 mg) was added and the mixture was stirred for 48 h at room temperature. The solution was filtered through a Celite pad and concentration of the filtrate followed by flash chromatography (petroleum ether/EtOAc, 6:4) gave **3** (0.011 g, 52%) as a colorless oil. $[\alpha]_D^{25}$ = +20.0 (c = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.63 (d, J = 10.0 Hz, 1 H, 3′-H), 6.10 (br. d, J = 10.0 Hz, 1 H, 2′-H), 5.21 (br. s, 1 H, 3-H), 4.85 (d, J = 2.4 Hz, 1 H, 4-H), 4.66 (dt, J = 12.6, 6.3 Hz, 1 H, 6-Ha), 4.31 (dd, J = 12.1, 5.0 Hz, 1 H, 1-H), 4.22–4.14 (m, 2 H, 5-H, 6-H), 2.86 (dd, J = 16.3, 12.1 Hz, 1 H, 1′-H), 2.59 (dd, J = 16.3, 5.0 Hz, 1 H, 1′-H), 2.17 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.4, 170.5, 168.7, 168.5, 144.9, 133.6, 74.6, 68.8, 67.9, 66.4, 66.1, 59.7, 29.7, 20.9, 20.8, 20.7 ppm. HRMS: calcd. for $[M + H]^+$ 357.1186; found 357.1195.

Compound 30: To a solution of **1** (45 mg, 0.106 mmol) in 1,2-dichlorobenzene (4 mL), benzocyclobutenol **29**[13] (203 mg, 0.817 mmol) was added. The reaction mixture was stirred at 160 °C for 90 min, then the crude product was concentrated and purified by flash chromatography (petroleum ether/EtOAc, 8:2) to give **30** (53 mg, 74%) as a pale-yellow oil. $[\alpha]_D^{25}$ = +74.4 (c = 0.91, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.21 (m, 13 H, Ar-H), 7.12 (d, J = 7.3 Hz, 1 H, Ar-H), 4.91–4.83 (m, 2 H, 10-Ha, CHPh), 4.78 (d, J = 3.5 Hz, 1-H), 4.72 (d, J = 12.1 Hz, 1 H, CHPh), 4.61 (d, J = 12.1 Hz, CHPh), 4.41 (d, J = 11.7 Hz, CHPh), 3.95 (s, 1 H, 11-Ha), 3.88 (dd, J = 10.1, 3.5 Hz, 1 H, 2-H), 3.50 (d, J = 10.1 Hz, 1 H, 3-H), 3.39 (s, 3 H, OMe), 3.35 (s, 3 H, OMe), 3.21 (t, J = 8.2 Hz, 1 H, 10-Ha), 2.91–2.84 (m, 1 H, 5-H), 2.44–2.35 (m, 1 H, 4-H), 2.23 (dd, J = 15.0, 5.4 Hz, 1 H, 4-Ha), 1.30 (d, J = 7.0 Hz, 3 H, CH_3), 0.90 (t, J = 7.9 Hz, 9 H, CH_3CH$_2$Si), 0.61 (m, 7 H, 4-H, CH$_3$CH_2Si) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.3, 140.2, 138.7, 138.3, 138.1, 128.4, 127.4, 126.1, 125.8, 125.0, 98.5, 81.8, 80.4, 78.0, 76.9, 76.1, 73.3, 68.3, 63.4, 55.5, 55.5, 34.9, 34.7, 29.7, 26.3, 17.1, 6.8, 4.7 ppm. HRMS: calcd. for $[M + H]^+$ 673.3561; found 673.3576.

Supporting Information (see footnote on the first page of this article): 2D NOESY spectra and NOE contacts of compounds **6**, **22**, **30** and **31** are available.

Acknowledgments

The research leading to these results has received funding from the Regione Lombardia (project number 4779, Network-Enabled Drug Design, NEDD). Thanks are due to the European Union (EU), the Quadro de Referência Estratégico Nacional (QREN), the Fundo Europeu de Desenvolvimento Regional (FEDER) and the Programa Operacional Temático Factores de Competitividade (COMPETE) for funding the Organic Chemistry Research Unit (QOPNA) (project PEst-C/QUI/UI0062/2013). Thanks are also due to the Portuguese Fundação para a Ciência e a Tecnologia (FCT) for the PhD grant to F. C. (grant number SFRH/44888/2008).

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Received: January 7, 2014
Published Online: February 19, 2014

