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Synthesis of *C*-Glucoside Analogues of Naturally Occurring Phenylethanoid *O*-Glucosides

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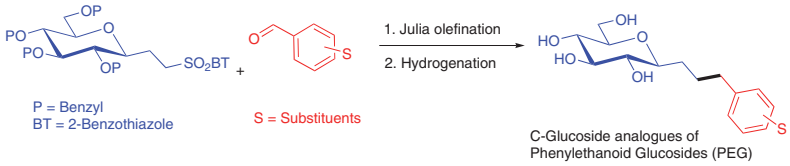

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Abstract Structural modifications of natural products has been a highly effective approach in the search for new leads with improved biological activity, aqueous solubility, and stability. Phenylethanoid glycosides (PEGs), as natural compounds, have attracted great attention due to their promising biological activities. These activities include neuroprotection, antioxidant, immunoregulation, anti-inflammatory, and analgesic effects, as well as antitumor, antiviral, and hepatoprotective abilities. Three potent PEGs, acteoside, echinacoside, and salidroside, are gaining renewed interest in this class of compounds. However, being *O*-glycosides, PEGs have low bioavailability due to factors such as poor intestinal permeability and low hydrolytic stability. The promising pharmacological properties and the limitations have inspired us to synthesize *C*-analogues that are expected to be hydrolytically stable.

Key words phenylethanoid glycosides, *C*-glucosides, *O*-glucosides, *C*-glycosides, *O*-glycosides, Julia olefination

The *O*-glycosides of phenylethyl alcohol **1**, commonly referred to as phenylethanoid glycosides (PEGs), are a water-soluble family of natural products that are widely distributed in several plant species and they display significant bioactivities.[1] Most of the PEGs are isolated from garden plants and medicinal herbs and exhibit diverse pharmacological activities including, antibacterial, antiviral, anti-inflammatory, antioxidant, antitumor, immunomodulatory, hepatoprotective and neuroprotective activity, among others. Three PEGs, namely acteoside **2**,[2] echinacoside **3**,[3] and salidroside **4**[4] have attracted wide attention due to their potency, which has rekindled heightened keen interests in this class of compounds.[5] Salidroside **4**, isolated from the perennial flowering herb of *Rhodiola rosea* with proven protective effects on myocardial injury and liver cancer, has now emerged as a highly promising neuroprotection agent.[4]

Although PEGs have evoked interest, precise mechanisms for their pharmacological activities remain obscure and merit structure-activity relationship studies for their successful therapeutic applications. Furthermore, being *O*-glycosides, they are hydrolytically unstable and have poor bioavailability. Gastric acid and digestive enzymes hydrolyze these glucosides and liberate the aglycone; the half-life of salidroside **4** ranges from 20 minutes to 2 hours. In this context, and given the fact that *C*-glycosides[6] are hydrolytically stable and have successfully contributed towards therapeutic applications, we were emboldened to envision hitherto unknown *C*-glucosides **5** as targets for the synthesis and biological evaluation (Figure 1).

The targeted *C*-glucosides **5** are stable analogues of *O*-glucosides because the glycosidic oxygen atom linking the glycone and the aglycone part is replaced with an isosteric methylene unit (-CH_2). The oxygenation pattern on the aryl ring was inspired by natural products that demonstrate potent antioxidant and anti-inflammatory activities.[7]

A synthesis of targeted *C*-glucoside analogues **5** was envisaged using the Julia–Kocienski reaction between the pyranoside-based sulfone building block **6** and suitably protected aryl aldehydes **7** as a representative example for developing a synthetic route for this class of compounds (Figure 2). A furanoside-based sulfone building block was reported previously.[8]

The sulfone building block **6** was prepared from ester **8**, which, in turn, was prepared in two steps by a known method using tetra-*O*-benzyl-D-gluconolactone as starting material.[9] Reduction of the ester functionality followed by Mitsunobu reaction of alcohol **9** and 2-mercapto benzothiazole provided sulfide **10**. The oxidation of sulfide **10** using *m*-chloroperbenzoic acid furnished the requisite building

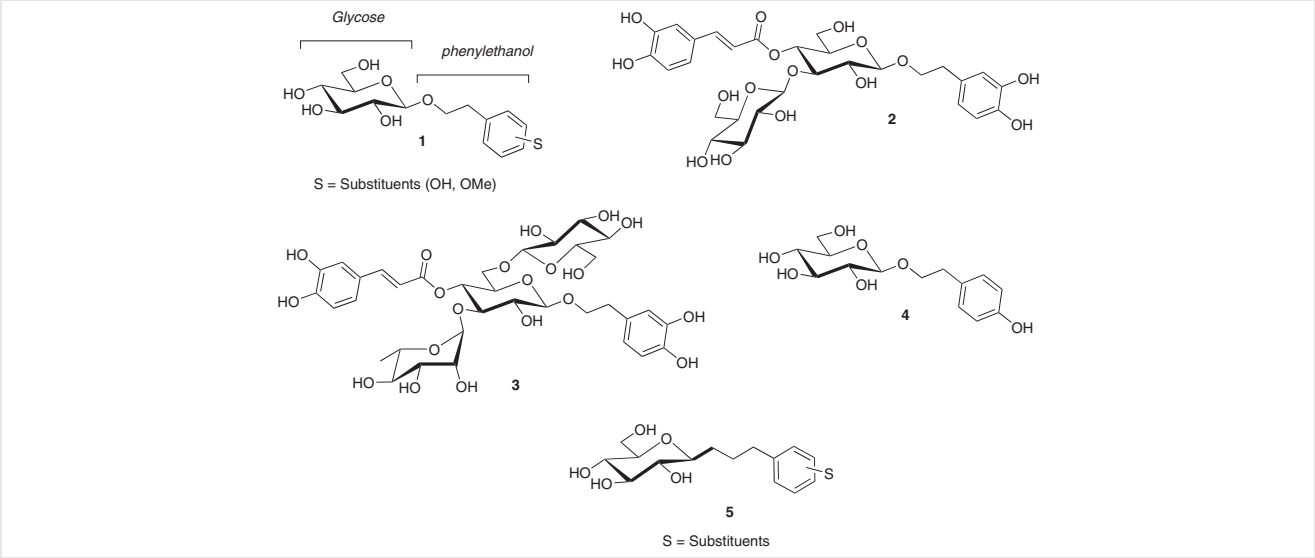


Figure 1 Naturally occurring PEGs and targeted synthetic analogues **5**

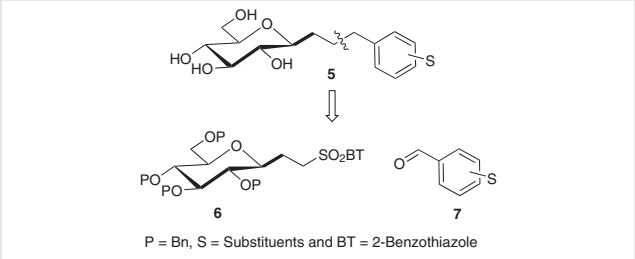


Figure 2 Retrosynthetic analysis of targeted *C*-glucoside analogues **5**

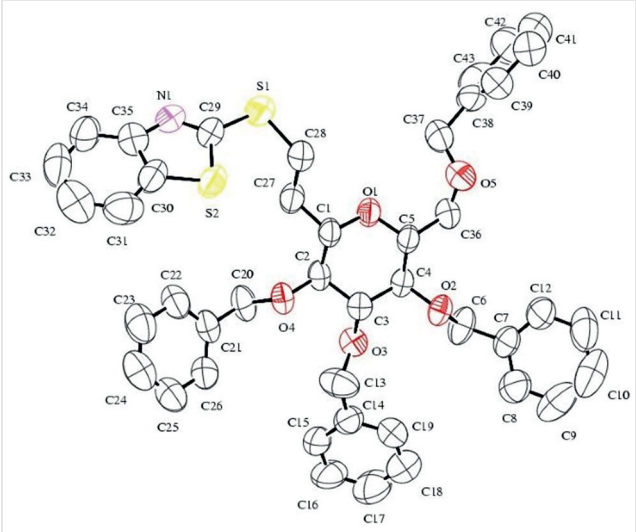
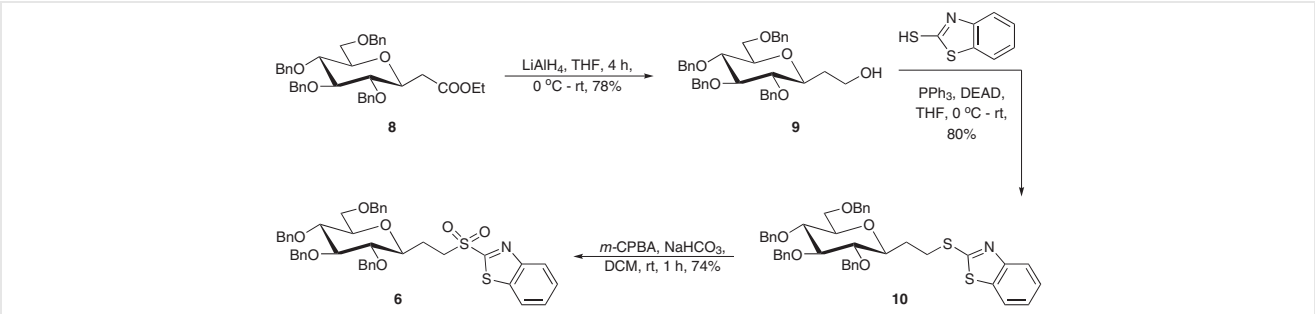


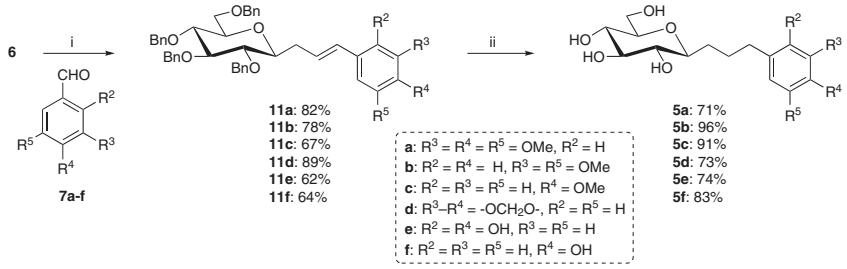
Figure 3 ORTEP diagram of sulfide **10**

block **6** in good yields (Scheme 1). Multigram quantities of **6** can be made by using this scheme. The β-configuration of the substituted alkyl residue at the C-1 position of the D-glucose unit was confirmed through X-ray diffraction data at the sulfide **10** stage (Figure 3).[10]

The carbanion from the sulfone **6** was easily prepared using NaH as a base at –78 °C. The formed carbanion then reacted with aldehydes **7a–f**, leading to the formation of olefinated products **11a–f** in moderate to good yields. The products were predominantly *E*-configured, as indicated



Scheme 1 Synthesis of sulfone building block **6**



Scheme 2 Synthesis of targeted *C*-glucoside analogues **5a–e**. *Reagents and conditions*: (i) NaH, THF, 3 h, –78 °C to r.t.; (ii) $Pd(OH)_2$ (10 mol%), H_2, MeOH, 20–36 h.

from the coupling constant (*J*) value of the benzylic C–H olefinic proton. The olefinated products **11a–f**, after purification over silica-gel chromatography, were directly subjected to hydrogenation. The hydrogenation reaction failed to occur with Pd/C as a catalyst, despite variations in reaction solvent and pressure of hydrogen gas. However, to our satisfaction, facile hydrogenation of the double bond and concomitant debenzylation of the glucosyl residue occurred with the use of 10 mol% $Pd(OH)_2$ in dry MeOH at normal atmospheric pressure. The desired targeted products **5a–f** (71–96%) were obtained after purification over silica-gel-based chromatography using 5% MeOH in dichloromethane as eluent (Scheme 2). The obtained products gave satisfactory spectroscopy and mass spectrometry data.

In conclusion, the work presented in this paper constitutes the first report on the synthesis of *C*-glucoside analogues of naturally occurring *O*-glucoside phenylethanoid glycosides (PEGs). The developed synthetic scheme illustrates the usefulness of the Julia–Kocienski olefination procedure. A small library of such compounds is being generated for assessing their biological activity in a variety of pharmacological applications.

All the reactions that required anhydrous conditions were carried out by standard procedures under a nitrogen atmosphere. Unless otherwise specified, all chemicals were purchased from commercial vendors and used as received. Solvents used for column chromatography were laboratory reagent grade. Solvents were distilled from CaH_2 (CH_2Cl_2, acetonitrile, DMF), Na/benzophenone (THF), and Mg/I_2 (MeOH). Reactions were monitored by thin-layer chromatography (TLC) with silica gel 60 plates under UV light or by dipping into a solution of cerium(IV) sulfate (2.5 g) and ammonium molybdate (6.25 g) in 10% sulfuric acid (250 mL) followed by charring on a hot plate. Melting points were determined for compounds **6**, **9**, and **10**, which were purified by silica gel column chromatography using EtOAc/n-hexane. Compound **10** was recrystallized from CH_2Cl_2/hexanes. Infrared spectra were recorded with a JASCO-FT/IR-4100 spectrophotometer with KBr and reported in wavenumbers (cm^{-1}). ^1H (400 MHz and 500 MHz) and ^{13}C (100 MHz, and 125 MHz) high-resolution NMR experiments were recorded with Brucker AV 400 and 500 FT NMR spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported relative to chloroform (δ = 7.26 ppm), or MeOH (δ = 4.75 ppm) for ^1H NMR and chloroform (δ= 77.2 ppm), or MeOH (δ = 47.65 ppm) for ^{13}C NMR. Multiplicities are given as, s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet, and brs = broad singlet. High-resolution mass spectra were recorded with an LC-QTOF mass spectrometer by using the ESI technique. Optical rotations were recorded with a polarimeter equipped with a sodium lamp source (589 nm). Crystal structures were recorded with a Bruker D8 venture SC-XRD with Cu radiation.

2-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-tetrahydro-2*H*-pyran-2-yl)ethan-1-ol (9)

To a solution of the ester **8** (0.75 g, 1.22 mmol) in anhydrous THF (10 mL) at 0 °C was added $LiAlH_4$ (0.09 g, 2.45 mmol). The reaction mixture was stirred at r.t. for 4 h. The reaction was slowly quenched with saturated NH_4Cl solution (10 mL) and the mixture was filtered. The filtrate was concentrated to remove THF and extracted with EtOAc (3 × 20 mL). The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexanes, 2:8) to afford the alcohol **9**.

Yield: 0.55 g (78%); white solid; mp 71–73 °C (Lit.[11]); $[\alpha]_D^{27}$ –25.44 (*c* = 0.1, $CHCl_3$).

IR (KBr): 3477, 2922, 2857, 1657, 1454, 1373, 1012, 773 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.35–7.23 (m, 18 H), 7.2–7.15 (m, 2 H), 4.92–4.86 (m, 3 H), 4.81 (d, *J* = 10.8 Hz, 1 H), 4.63 (d, *J* = 4.9 Hz, 1 H), 4.57–4.48 (m, 3 H), 3.80–3.74 (m, 2 H), 3.71–3.64 (m, 2 H), 3.61–3.54 (m, 2 H), 3.51–3.44 (m, 2 H), 3.32 (t, *J* = 9.2 Hz, 1 H), 2.62 (brs, 1 H), 2.08–2.01 (m, 1 H), 1.77–1.69 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.5 (1-C), 137.9 (1-C), 137.9 (2-C), 128.5 (3-CH), 128.4 (3-CH), 128.4 (4-CH), 128.0 (2-CH), 128.0 (2-CH), 127.9 (1-CH), 127.8 (2-CH), 127.7 (1-CH), 127.7 (2-CH), 87.0 (1-CH), 81.8 (1-CH), 79.7 (1-CH), 78.6 (1-CH), 78.5 (1-CH), 75.6 (1-CH_2), 75.3 (1-CH_2), 75.0 (1-CH_2), 73.5 (1-CH_2), 69.1 (1-CH_2), 61.4 (1-CH_2-OH), 33.7 (1-CH_2).

MS (ESI): *m*/*z* (%) = 569 (100.0) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{36}H_{41}O_6$: 569.2903; found: 569.2921.

2-((2-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)ethyl)thio)benzo[*d*]thiazole (10)

In an oven-dried, round-bottom flask, alcohol **9** (1.4 g, 2.46 mmol) was dissolved in anhydrous THF (10 mL). PPh_3 (1.29 g, 4.92 mmol) and 2-mercaptobenzothiazole (0.49 g, 2.95 mmol) were added and the solution was stirred at r.t. The solution is then maintained at 0 °C and DEAD (0.77 mL, 4.92 mmol) was added slowly. The reaction mixture was allowed to come to r.t. and stirring was continued for 4 h

(the reaction n was monitored by TLC). Upon completion, the reaction was quenched with saturated NH_4Cl solution (10 mL), and the mixture was extracted with EtOAc (3 × 20 mL), and washed with water (2 × 20 mL) and brine solution (2 × 20 mL). The collected organic layers were dried using anhydrous $NaSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexanes, 1:9) and recrystallized (CH_2Cl_2/*n*-hexane) to afford the sulfide **10**.

Yield: 1.4 g (80%); colorless crystals; mp 101–103 °C; $[\alpha]_D^{27}$ –34.68 (*c* = 0.1, $CHCl_3$).

IR (KBr): 2912, 2857, 1713, 1657, 1459, 1017, 768 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.73 (d, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 7.9 Hz, 1 H), 7.34–7.29 (m, 2 H), 7.29–7.15 (m, 14 H), 7.14–7.01 (m, 6 H), 4.89–4.71 (m, 4 H), 4.65–4.44 (m, 4 H), 3.72–3.54 (m, 4 H), 3.51–3.28 (m, 4 H), 3.28–3.18 (m, 1 H), 2.45–2.28 (m, 1 H), 1.93–1.79 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 165.9 (1-C), 152.3 (1-C), 137.5 (1-C), 137.1 (2-C), 136.7 (1-C), 134.2 (1-C), 127.4 (2-CH), 127.3 (2-CH), 127.3 (3-CH), 127.3 (1-CH), 127.2 (1-CH), 127.0 (2-CH), 126.8 (2-CH), 126.7 (2-CH), 126.7 (1-CH), 126.6 (2-CH), 126.5 (2-CH), 124.9 (1-CH), 123.0 (1-CH), 120.5 (1-CH), 119.8 (1-CH), 86.1 (1-CH), 80.8 (1-CH), 77.8 (1-CH), 77.4 (1-CH), 76.5 (1-CH), 76.2 (1-CH_2), 76.0 (1-CH_2), 75.7 (1-CH_2), 72.5 (1-CH_2), 67.9 (1-CH_2), 30.6 (1-CH_2-S), 28.8 (1-CH_2).

MS (ESI): *m*/*z* (%) = 740 (100.0), 741 (49.1) $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{43}H_{44}NO_5S_2$: 718.2660; found: 718.2642.

2-((2-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)ethyl)sulfonyl)benzo[*d*]thiazole (6)

To a solution of sulfide **10** (1.4 g, 1.95 mmol) in anhydrous CH_2Cl_2 (20 mL), *m*-chloroperbenzoic acid (1.68 g, 9.75 mmol) was added at r.t. To the stirred solution was immediately added $NaHCO_3$ (1.63 g, 19.5 mmol) portion-wise and stirring was continued until precipitation was complete (ca. 30 min). The reaction was quenched with water (20 mL) and the mixture was extracted with EtOAc (2 × 20 mL). Combined organic layers were dried over anhydrous $NaSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexanes, 2:8) to afford the sulfone **6**.

Yield: 1.2 g (85%); white solid; mp 110–112 °C; $[\alpha]_D^{27}$ –32.80 (*c* = 0.1, $CHCl_3$).

IR (KBr): 2922, 2856, 1644, 1458, 1371, 1025 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.16 (d, *J* = 7.6 Hz, 1 H), 8.00 (d, *J* = 7.4 Hz, 1 H), 7.66–7.56 (m, 2 H), 7.36–7.23 (m, 14 H), 7.21–7.12 (m, 6 H), 4.92–4.76 (m, 4 H), 4.59–4.47 (m, 4 H), 3.75–3.52 (m, 6 H), 3.38–3.19 (m, 3 H), 2.47–2.34 (m, 1 H), 2.05–1.92 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.6 (1-C), 152.7 (1-C), 138.4 (1-C), 137.9 (1-C), 137.9 (1-C), 137.4 (1-C), 136.7 (1-C), 128.4 (4-CH), 128.4 (4-CH), 128.1 (2-CH), 128.0 (1-CH), 127.9 (1-CH), 127.9 (2-CH), 127.8 (3-CH), 127.7 (2-CH), 127.6 (3-CH), 125.5 (1-CH), 122.3 (1-CH), 86.9 (1-CH), 81.3 (1-CH), 78.9 (1-CH), 78.2 (1-CH), 76.8 (1-CH), 75.5 (1-CH_2), 75.2 (1-CH_2), 75.0 (1-CH_2), 73.4 (1-CH_2), 68.7 (1-CH_2), 51.4 (1-CH_2-SO_2), 25.1 (1-CH_2).

MS (ESI): *m*/*z* (%) = 750 (100.0), 751 (48.9) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{43}H_{44}NO_7S_2$: 750.2559; found: 750.2522.

Julia–Kocienski Olefination (A); General Procedure

To a solution of sulfone **6** (0.7 g, 0.93 mmol) in anhydrous THF (5 mL) at –78 °C was added NaH (0.07 g, 1.96 mmol). At the same temperature, after 10 minutes a solution of aldehyde **7a–f** (1 equiv) in THF (2 mL) was added, and the reaction mixture was allowed to reach r.t. over 3 h (the reaction was monitored by TLC). The reaction was quenched with saturated NH_4Cl solution (10 mL), the mixture was extracted with EtOAc (3 × 10 mL), and washed with water (2 × 10 mL) and brine solution (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography (EtOAc/hexanes, 1:9) to afford olefin **11a–f**.

(2*R*,3*R*,4*R*,5*S*,6*S*)-3,4,5-Tris(benzyloxy)-2-((benzyloxy)methyl)-6-((*E*)-3-(3,4,5-trimethoxyphenyl)allyl)tetrahydro-2*H*-pyran (11a)

General Procedure A using 3,4,5-trimethoxybenzaldehyde **7a** (0.182 g, 0.93 mmol), with purification by column chromatography (silica gel, EtOAc/hexanes) gave the olefin **11a**.

Yield: 0.56 g (82%); pale-yellow gum; R_f = 0.4 (EtOAc/hexanes, 3:17); $[\alpha]_D^{27}$ –31.12 (*c* = 0.1, $CHCl_3$).

IR (KBr): 2922, 2850, 1577, 1500, 1454, 1412, 1350, 1237, 1123, 1004, 736, 690 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.25–7.16 (m, 18 H), 7.12–7.09 (m, 2 H), 6.44 (s, 2 H), 6.26 (d, *J* = 15.7 Hz, 1 H), 6.19–6.10 (m, 1 H), 4.87–4.72 (m, 4 H), 4.62–4.47 (m, 4 H), 3.75 (s, 3 H), 3.72 (s, 6 H), 3.68–3.62 (m, 3 H), 3.58–3.53 (m, 1 H), 3.40–3.36 (m, 1 H), 3.35–3.28 (m, 2 H), 2.69–2.61 (m, 1 H), 2.44–2.35 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.2 (2-C), 138.5 (1-C), 138.2 (2-C), 138.1 (1-C), 137.4 (1-C), 133.4 (1-C), 132.1 (1-CH), 128.4 (3-CH), 128.4 (3-CH), 128.3 (2-CH), 127.9 (2-CH), 127.9 (1-CH), 127.8 (2-CH), 127.8 (1-CH), 127.7 (1-CH), 127.6 (4-CH), 127.5 (1-CH), 126.0 (1-CH), 103.2 (2-CH), 87.3 (1-CH), 81.6 (1-CH), 79.1 (1-CH), 78.8 (1-CH), 78.6 (1-CH), 75.5 (1-CH_2), 75.1 (1-CH_2), 75.0 (1-CH_2), 73.4 (1-CH_2), 69.0 (1-CH_2), 60.9 (1-CH_3), 56.0 (2-CH_3), 35.3 (1-CH_2).

MS (ESI): *m*/*z* (%) = 731 (100.0) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{46}H_{51}O_8$: 731.3583; found: 731.3585.

(2*R*,3*R*,4*R*,5*S*,6*S*)-3,4,5-Tris(benzyloxy)-2-((benzyloxy)methyl)-6-((*E*)-3-(3,5-dimethoxyphenyl)allyl)tetrahydro-2*H*-pyran (11b)

General Procedure A using 3,5-dimethoxybenzaldehyde **7b** (0.127 g, 0.93 mmol), with purification by column chromatography (silica gel, EtOAc/hexanes) gave olefin **11b**.

Yield: 0.51 g (78%); pale-yellow gum; R_f = 0.4 (EtOAc/hexanes, 3:17); $[\alpha]_D^{27}$ –4.52 (*c* = 0.1, $CHCl_3$).

IR (KBr): 3034, 2873, 1684, 1594, 1480, 1263, 1211, 1079, 980, 806, 730, 696, 634 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.26–7.12 (m, 19 H), 7.11–7.07 (m, 2 H), 6.40–6.37 (m, 2 H), 6.27–6.22 (m, 2 H), 4.85–4.78 (m, 3 H), 4.73 (d, *J* = 10.8 Hz, 1 H), 4.58 (d, *J* = 11.0 Hz, 1 H), 4.56–4.45 (m, 3 H), 3.65 (s, 6 H), 3.64–3.59 (m, 3 H), 3.56–3.51 (m, 1 H), 3.38–3.24 (m, 3 H), 2.70–2.57 (m, 1 H), 2.43–2.31 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 160.9 (2-C), 139.7 (1-C), 138.6 (1-C), 138.3 (1-C), 138.3 (1-C), 138.2 (1-C), 132.3 (1-CH), 128.4 (2-CH), 128.4 (2-CH), 128.4 (2-CH), 128.3 (2-CH), 127.9 (2-CH), 127.9 (2-CH), 127.8 (1-CH), 127.7 (3-CH), 127.6 (2-CH), 127.6 (1-CH), 127.5 (1-CH), 127.1 (1-CH), 104.3 (2-CH), 99.5 (1-CH), 87.4 (1-CH), 81.6 (1-CH), 79.2 (1-CH), 78.8 (1-CH), 78.7 (1-CH), 75.5 (1-CH_2), 75.1 (1-CH_2), 75.0 (1-CH_2), 73.5 (1-CH_2), 69.1 (1-CH_2), 55.3 (2-OCH_3), 35.2 (1-CH_2).

MS (ESI): *m*/*z* (%) = 701.35 (100.0) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{45}H_{48}O_7$: 701.3478; found: 701.3472.

(2*R*,3*R*,4*R*,5*S*,6*S*)-3,4,5-Tris(benzyloxy)-2-((benzyloxy)methyl)-6-((*E*)-3-(4-methoxyphenyl)allyl)tetrahydro-2*H*-pyran (11c)

General Procedure **A** using 4-methoxybenzaldehyde **7c** (0.127 g, 0.93 mmol), with purification by column chromatography (silica gel, EtOAc/hexanes) gave olefin **11c**.

Yield: 0.42 g (67%); pale-yellow gum; R_f = 0.35 (EtOAc/hexanes, 3:17); $[\alpha]_D^{27}$ –74.40 (*c* = 0.1, $CHCl_3$).

IR (KBr): 2922, 2856, 1659, 1458, 1237, 1067, 747, 696 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.25–7.18 (m, 16 H), 7.18–7.15 (m, 4 H), 7.12–7.09 (m, 2 H), 6.76–6.71 (m, 2 H), 6.29 (d, *J* = 12.72 Hz, 1 H), 6.14–6.06 (m, 1 H), 4.87–4.79 (m, 3 H), 4.74 (d, *J* = 8.64 Hz, 1 H), 4.60 (d, *J* = 8.96 Hz, 1 H), 4.58–4.48 (m, 3 H), 3.72 (s, 3 H), 3.71–3.65 (m, 2 H), 3.64–3.60 (m, 2 H), 3.54 (t, *J* = 7.4 Hz, 1 H), 3.39–3.34 (m, 1 H), 3.34–3.27 (m, 2 H), 2.69–2.59 (m, 1 H), 2.42–2.33 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 157.7 (1-C), 137.5 (1-C), 137.3 (1-C), 137.2 (1-C), 137.1 (1-C), 130.5 (2-CH), 129.4 (1-C), 127.4 (2-CH), 127.4 (2-CH), 127.3 (2-CH), 127.2 (2-CH), 126.9 (3-CH), 126.7 (1-CH), 126.7 (1-CH), 126.6 (2-CH), 126.6 (2-CH), 126.5 (1-CH), 126.4 (1-CH), 126.1 (2-CH), 123.2 (1-CH), 112.8 (2-CH), 86.3 (1-CH), 80.5 (1-CH), 78.0 (1-CH), 77.9 (1-CH), 77.6 (1-CH), 74.5 ($1-CH_2$), 74.1 ($1-CH_2$), 73.9 ($1-CH_2$), 72.4 ($1-CH_2$), 68.0 ($1-CH_2$), 54.2 ($1-CH_3$), 34.1 ($1-CH_2$).

MS (ESI): *m*/*z* (%) = 671.34 (100.0) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{44}H_{47}O_6$: 671.3372; found: 671.3396.

5-((*E*)-3-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)prop-1-en-1-yl)benzo[*d*][1,3]dioxole (11d)

General Procedure A using piperonal **7d** (0.14 g, 0.93 mmol), with purification by column chromatography (silica gel, EtOAc/hexanes) gave olefin **11d**.

Yield: 0.57 g (89%); pale-yellow gum; R_f = 0.25 (EtOAc/hexanes, 3:17); $[\alpha]_D^{27}$ +41.84 (*c* = 0.1, $CHCl_3$).

IR (KBr): 2964, 2922, 2856, 1618, 1448, 1360, 1257, 1092, 1041, 793, 696 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.27–7.18 (m, 18 H), 7.13–7.08 (m, 2 H), 6.79 (s, 1 H), 6.68–6.61 (m, 2 H), 6.25 (d, *J* = 15.8 Hz, 1 H), 6.11–6.02 (m, 1 H), 5.85 (s, 2 H), 4.87–4.72 (m, 4 H), 4.62–4.47 (m, 4 H), 3.70–3.60 (m, 3 H), 3.57–3.51 (m, 1 H), 3.39–3.26 (m, 3 H), 2.67–2.58 (m, 1 H), 2.40–2.32 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 146.8 (1-C), 145.7 (1-C), 137.5 (1-C), 137.3 (1-C), 137.2 (1-C), 137.1 (1-C), 131.1 (1-C), 130.7 (1-CH), 127.4 (2-CH), 127.4 (3-CH), 127.3 (2-CH), 127.3 (2-CH), 126.9 (3-CH), 126.7 (1-CH), 126.7 (1-CH), 126.6 (2-CH), 126.6 (2-CH), 126.5 (1-CH), 126.4 (1-CH), 123.7 (1-CH), 119.4 (1-CH), 107.1 (1-CH), 104.5 (1-CH), 99.9 ($1-CH_2$), 86.3 (1-CH), 80.5 (1-CH), 78.0 (1-CH), 77.9 (1-CH), 77.6 (1-CH), 74.5 ($1-CH_2$), 74.0 ($1-CH_2$), 73.9 ($1-CH_2$), 72.4 ($1-CH_2$), 68.0 ($1-CH_2$), 34.1 ($1-CH_2$).

MS (ESI): *m*/*z* (%) = 685.32 (100.0) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{44}H_{45}O_7$: 685.3165; found: 685.3114.

(2*R*,3*R*,4*R*,5*S*,6*S*)-3,4,5-Tris(benzyloxy)-2-((benzyloxy)methyl)-6-((*E*)-3-(2,4-bis(benzyloxy)phenyl)allyl)tetrahydro-2*H*-pyran (11e)

General Procedure A using 2,4-bis(benzyloxy)benzaldehyde **7e** (0.3 g, 0.93 mmol), with purification by column chromatography (silica gel, EtOAc/hexanes) gave olefin **11e**.

Yield: 0.5 g (62%); pale-yellow gum; R_f = 0.2 (EtOAc/hexanes, 3:17); $[\alpha]_D^{27}$ –10.12 (*c* = 0.1, $CHCl_3$).

IR (KBr): 3067, 3036, 2911, 2871, 1608, 1500, 1454, 1366, 1263, 1170, 1103, 830, 731, 696 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.42–7.38 (m, 3 H), 7.38–7.32 (m, 5 H), 7.32–7.28 (m, 9 H), 7.27–7.24 (m, 11 H), 7.23–7.21 (m, 1 H), 7.19–7.16 (m, 2 H), 6.78 (d, *J* = 15.9 Hz, 1 H), 6.55–6.53 (m, 1 H), 6.52–6.48 (m, 1 H), 6.26–6.18 (m, 1 H), 5.02 (s, 2 H), 4.97 (s, 2 H), 4.92–4.87 (m, 2 H), 4.86–4.79 (m, 2 H), 4.67–4.59 (m, 2 H), 4.59–4.52 (m, 2 H), 3.74–3.65 (m, 3 H), 3.62–3.56 (m, 1 H), 3.45–3.35 (m, 3 H), 2.78–2.67 (m, 1 H), 2.55–2.41 (m, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 159.0 (1-C), 156.5 (1-C), 138.7 (1-C), 138.5 (1-C), 138.3 (2-C), 137.0 (2-C), 128.6 (2-CH), 128.5 (2-CH), 128.4 (6-CH), 128.3 (2-CH), 127.9 (3-CH), 127.9 (2-CH), 127.8 (1-CH), 127.7 (4-CH), 127.6 (2-CH), 127.5 (1-CH), 127.4 (2-CH), 127.4 (1-CH), 127.3 (2-CH), 127.1 (1-CH), 126.4 (1-CH), 125.0 (1-CH), 120.5 (1-C), 106.5 (1-CH), 100.8 (1-CH), 87.4 (1-CH), 81.5 (1-CH), 79.2 (1-CH), 79.0 (1-CH), 78.7 (1-CH), 75.4 ($1-CH_2$), 75.1 ($1-CH_2$), 74.9 ($1-CH_2$), 73.5 ($1-CH_2$), 70.3 ($1-CH_2$), 70.2 ($1-CH_2$), 69.1 ($1-CH_2$), 35.6 ($1-CH_2$).

MS (ESI): *m*/*z* (%) = 875 (100.0), 876 (62.6) $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{57}H_{56}O_7Na$: 875.3923; found: 875.3961.

(2*R*,3*R*,4*R*,5*S*,6*S*)-3,4,5-Tris(benzyloxy)-2-((benzyloxy)methyl)-6-((*E*)-3-(4-(benzyloxy)phenyl)allyl)tetrahydro-2*H*-pyran (11f)

General Procedure A using 4-(benzyloxy)benzaldehyde **7f** (0.15 g, 0.93 mmol), with purification by column chromatography (silica gel, EtOAc/hexanes) gave olefin **11f**.

Yield: 0.44 g (64%); white solid, mp 88–90 °C; R_f = 0.4 (EtOAc/hexanes, 3:17); $[\alpha]_D^{27}$ –9.53 (*c* = 1.00, $CHCl_3$).

IR (KBr): 3062, 3031, 2956, 2919, 2856, 1696, 1601, 1509, 1449, 1357, 1246, 1091, 1052, 773, 733, 695 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.45–7.40 (m, 2 H), 7.40–7.35 (m, 3 H), 7.33–7.30 (m, 10 H), 7.28–7.25 (m, 6 H), 7.24–7.20 (m, 3 H), 7.19–7.04 (m, 3 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 6.36 (d, *J* = 15.8 Hz, 1 H), 6.23–6.10 (m, 1 H), 5.05 (s, 2 H), 4.95–4.85 (m, 3 H), 4.81 (d, *J* = 10.7 Hz, 1 H), 4.70–4.65 (m, 1 H), 4.65–4.54 (m, 3 H), 3.79–3.66 (m, 3 H), 3.66–3.56 (m, 1 H), 3.49–3.32 (m, 3 H), 2.78–2.65 (m, 1 H), 2.51–2.39 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.9 (1-C), 138.6 (1-C), 138.3 (1-C), 138.2 (1-C), 138.1 (1-C), 137.0 (1-C), 131.5 (2-CH), 128.6 (2-CH), 128.5 (3-CH), 128.4 (3-CH), 128.3 (2-CH), 127.9 (4-CH), 127.8 (1-CH), 127.7 (3-CH), 127.7 (2-CH), 127.5 (1-CH), 127.4 (2-CH), 127.2 (2-CH), 124.4 (1-CH), 114.8 (2-CH), 87.3 (1-CH), 81.6 (1-CH), 79.1 (1-CH), 79.0 (1-CH), 78.7 (1-CH), 75.5 ($1-CH_2$), 75.1 ($1-CH_2$), 75.0 ($1-CH_2$), 73.4 ($1-CH_2$), 70.0 ($1-CH_2$), 69.0 ($1-CH_2$), 35.2 ($1-CH_2$).

MS (ESI): *m*/*z* (%) = 747.37 (100.0) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{50}H_{51}O_6$: 747.3685; found: 747.3649.

Debenzylation and Reduction; General Procedure B

To an oven-dried, round-bottom flask, olefin **11a–f** (1 equiv) and anhydrous MeOH (5 mL) were added under a nitrogen atmosphere. To the stirred solution, $Pd(OH)_2$ (10 mol%, 0.2 equiv) was added and the nitrogen was replaced with hydrogen using a bladder. Hydrogen was

purged carefully and the mixture was stirred for 20–36 h. The reaction mixture was filtered using MeOH and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:19) to afford **5a–f**.

(2*R*,3*S*,4*R*,5*R*,6*S*)-2-(Hydroxymethyl)-6-(3-(3,4,5-trimethoxyphenyl)propyl)tetrahydro-2*H*-pyran-3,4,5-triol (5a)

General Procedure B using olefin **11a** (170 mg, 0.23 mmol), with purification by column chromatography (silica gel, MeOH/CH_2Cl_2) gave **5a**.

Yield: 62 mg (71%); colorless gum; R_f = 0.5 (MeOH/CH_2Cl_2, 1:9); $[\alpha]_D^{27}$ +5.48 (*c* = 0.1, MeOH).

IR (KBr): 3392, 2922, 2856, 1613, 1515, 1458, 1232, 1164, 1087 cm^{-1}.

^{1}H NMR (MeOH-d_4, 400 MHz): δ = 6.39 (s, 2 H), 3.75 (br s, 1 H), 3.71 (s, 6 H), 3.61 (s, 3 H), 3.60–3.46 (m, 2 H), 3.27–3.01 (m, 7 H), 2.98–2.91 (m, 1 H), 2.53–2.44 (m, 2 H), 1.84–1.75 (m, 2 H), 1.66–1.54 (m, 1 H), 1.41–1.28 (m, 1 H).

^{13}C NMR (MeOH-d_4, 100 MHz): δ = 152.8 (2-C), 138.8 (1-C), 135.6 (1-C), 105.3 (2-CH), 80.2 (1-CH), 79.3 (1-CH), 78.5 (1-CH), 74.1 (1-CH), 70.6 (1-CH), 61.7 (1-CH_2), 59.7 (1-CH_3), 55.1 (2-CH_3), 35.8 (1-CH_2), 31.0 (1-CH_2), 27.0 (1-CH_2).

MS (ESI): *m*/*z* (%) = 373.19 (100.0) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{29}O_8$: 373.1862; found: 373.1934.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-(3,5-Dimethoxyphenyl)propyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (5b)

General Procedure B using olefine **11b** (100 mg, 0.25 mmol), with purification by column chromatography (silica gel, MeOH/CH_2Cl_2) gave **5b**.

Yield: 47 mg (96%); colorless gum; R_f = 0.4 (MeOH/CH_2Cl_2, 1:9); $[\alpha]_D^{27}$ +5.88 (*c* = 0.1, MeOH).

IR (KBr): 3355, 2917, 2237, 2216, 2144, 2067, 1938, 1454, 1397, 1118, 969, 824 cm^{-1}.

^{1}H NMR (MeOH-d_4, 400 MHz): δ = 6.25 (s, 2 H), 6.17 (s, 1 H), 3.75 (s, 1 H), 3.72 (s, 1 H), 3.63 (s, 6 H), 3.56–3.50 (m, 1 H), 3.22–3.19 (m, 1 H), 3.19–3.11 (m, 2 H), 3.10–3.06 (m, 1 H), 3.05–3.01 (m, 1 H), 2.98–2.90 (m, 1 H), 2.45 (t, *J* = 8 Hz, 2 H), 1.82–1.74 (m, 2 H), 1.67–1.50 (m, 2 H), 1.46–1.24 (m, 2 H).

^{13}C NMR (MeOH-d_4, 100 MHz): δ = 160.7 (2-C), 144.8 (1-C), 106.1 (2-CH), 97.2 (1-CH), 80.2 (1-CH), 79.3 (1-CH), 78.4 (1-CH), 74.1 (1-CH), 70.6 (1-CH), 61.7 (1-CH_2), 54.2 (2-OCH_3), 35.8 (1-CH_2), 31.1 (1-CH_2), 26.8 (1-CH_2).

MS (ESI): *m*/*z* (%) = 343.18 (100.0), $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{27}O_7$: 343.1756; found: 343.1755.

(2*R*,3*S*,4*R*,5*R*,6*S*)-2-(Hydroxymethyl)-6-(3-(4-methoxyphenyl)propyl)tetrahydro-2*H*-pyran-3,4,5-triol (5c)

General Procedure B using olefin **11c** (100 mg, 0.23 mmol), with purification by column chromatography (silica gel, MeOH/CH_2Cl_2) gave **5c**.

Yield: 42 mg (91%); white solid, mp 140–142 °C; R_f = 0.3 (MeOH/CH_2Cl_2, 1:9); $[\alpha]_D^{27}$ +7.86 (*c* = 0.1, MeOH).

IR (KBr): 3355, 2922, 2845, 2226, 2067, 1912, 1454, 1381, 1118, 969, 819 cm^{-1}.

^{1}H NMR (MeOH-d_4, 400 MHz): δ = 6.98 (d, *J* = 8.44 Hz, 2 H), 6.69 (d, *J* = 8.52 Hz, 2 H), 3.76–3.70 (m, 1 H), 3.64 (s, 3 H), 3.56–3.49 (m, 1 H), 3.23–3.11 (m, 4 H), 3.09–3.00 (m, 2 H), 2.97–2.88 (m, 1 H), 2.51–2.41 (m, 2 H), 1.81–1.73 (m, 2 H), 1.66–1.44 (m, 2 H),1.42–1.24 (m, 2 H).

^{13}C NMR (MeOH-d_4, 100 MHz): δ = 157.8 (1-C), 134.5 (1-C), 128.9 (2-CH), 113.2 (2-CH), 80.2 (1-CH), 79.3 (1-CH), 78.4 (1-CH), 74.1 (1-CH), 70.6 (1-CH), 61.7 (1-CH_2), 54.2 (1-OCH_3), 34.7 (1-CH_2), 31.1 (1-CH_2), 27.3 (1-CH_2).

MS (ESI): *m*/*z* (%) = 313.17 (100.0) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{25}O_6$: 313.1651; found: 313.1676.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-(Benzo[*d*][1,3]dioxol-5-yl)propyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (5d)

General Procedure B using olefin **11d** (130 mg, 0.18 mmol), with purification by column chromatography (silica gel, MeOH/CH_2Cl_2) gave **5d**.

Yield: 45 mg (73%); colorless gum; R_f = 0.2 (MeOH/CH_2Cl_2, 1:9); $[\alpha]_D^{27}$ –9.84 (*c* = 0.1, MeOH).

IR (KBr): 3370, 2964, 2922, 1649, 1489, 1437, 1241, 1092, 1036, 995, 922, 804 cm^{-1}.

^{1}H NMR (MeOH-d_4, 400 MHz): δ = 6.62–6.65 (m, 2 H), 6.56–6.48 (m, 1 H), 5.75 (s, 2 H), 3.76–3.70 (m, 1 H), 3.57–3.50 (m, 1 H), 3.26–3.0 (m, 6 H), 2.99–2.90 (m, 1 H), 2.48–2.40 (m, 2 H), 1.82–1.71 (m, 2 H), 1.60–1.50 (m, 1 H), 1.37–1.27 (m, 1 H).

^{13}C NMR (MeOH-d_4, 100 MHz): δ = 147.5 (1-C), 145.5 (1-C), 136.4 (1-C), 120.8 (1-CH), 108.4 (1-CH), 107.5 (1-CH), 100.5 (1-CH_2), 80.1 (1-CH), 79.3 (1-CH), 78.4 (1-CH), 74.1 (1-CH), 70.6 (1-CH), 61.7 (1-CH_2), 35.3 (1-CH_2), 31.0 (1-CH_2), 27.3 (1-CH_2).

MS (ESI): *m*/*z* (%) = 327.14 (100.0) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{23}O_7$: 327.1443; found: 327.1426.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-(3-(2,4-Dihydroxyphenyl)propyl)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (5e)

General Procedure B using olefin **11e** (200 mg, 0.23 mmol), with purification by column chromatography (silica gel, MeOH/CH_2Cl_2) gave **5e**.

Yield: 55 mg (74%); colorless gum; R_f = 0.1 (MeOH/CH_2Cl_2, 1:9); $[\alpha]_D^{27}$ –22.13 (*c* = 0.1, MeOH).

IR (KBr): 2927, 2860, 1613, 1520, 1458, 1170, 1092, 995, 839 cm^{-1}.

^{1}H NMR (MeOH-d_4, 400 MHz): δ = 6.74 (d, *J* = 8.1 Hz, 1 H), 6.15 (d, *J* = 2 Hz, 1 H), 6.10 (dd, ^1J = 8 Hz, ^2J = 2 Hz, 1 H), 3.72 (dd, ^1J = 11.8 Hz, ^2J = 1.6 Hz, 1 H), 3.58–3.49 (m, 1 H), 3.28–2.99 (m, 6 H), 2.98–2.91 (m, 1 H), 2.45–2.35 (m, 2 H), 1.82–1.67 (m, 2 H), 1.57–1.44 (m, 1 H), 1.39–1.29 (m, 1 H).

^{13}C NMR (MeOH-d_4, 100 MHz): δ = 155.7 (1-C), 155.4 (1-C), 130.0 (1-CH), 120.0 (1-C), 105.9 (1-CH), 102.0 (1-CH), 80.1 (1-CH), 79.5 (1-CH), 78.5 (1-CH), 74.1 (1-CH), 70.6 (1-CH), 61.7 (1-CH_2), 31.3 (1-CH_2), 29.1 (1-CH_2), 25.8 (1-CH_2).

MS (ESI): *m*/*z* (%) = 315.14 (100.0) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{23}O_7$: 315.1443; found: 315.1452.

(2*R*,3*S*,4*R*,5*R*,6*S*)-2-(Hydroxymethyl)-6-(3-(4-hydroxyphenyl)propyl)tetrahydro-2*H*-pyran-3,4,5-triol (5f)

General Procedure B using olefin **11f** (120 mg, 0.16 mmol), with purification by column chromatography (silica gel, MeOH/CH_2Cl_2) gave **5f**.

Yield: 40 mg (83%); white solid; mp 182–184 °C; R_f = 0.2 (MeOH/CH_2Cl_2, 1:9); $[\alpha]_D^{27}$ –4.44 (*c* = 1.0, MeOH).

IR (KBr): 3375, 2919, 2853, 1635, 1515, 1455, 1220, 1006, 827, 779, 756 cm^{-1}.

^1H NMR (MeOH-d_4, 400 MHz): δ = 6.89 (d, *J* = 7.5 Hz, 2 H), 6.57 (d, *J* = 7.5 Hz, 2 H), 3.72 (d, *J* = 11.7 Hz, 1 H), 3.57–3.48 (m, 1 H), 3.20 (brs, 3 H), 3.18–2.99 (m, 4 H), 2.97–2.87 (m, 1 H), 2.48–2.37 (m, 2 H), 1.82–1.71 (m, 2 H), 1.59–1.48 (m, 1 H), 1.36–1.27 (m, 1 H).

^{13}C NMR (MeOH-d_4, 100 MHz): δ = 154.8 (1-C), 133.3 (1-C), 128.9 (2-CH), 114.5 (2-CH), 80.2 (1-CH), 79.4 (1-CH), 78.4 (1-CH), 74.1 (1-CH), 70.6 (1-CH), 61.7 (1-CH_2), 34.7 (1-CH_2), 31.1 (1-CH_2), 27.3 (1-CH_2).

MS (ESI): *m*/*z* (%) = 299.15 (100.0) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{23}O_6$: 299.1494; found: 299.1504.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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