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First total synthesis of the natural product 1,3-di-*O*-galloyl-4,6-*O*-(*S*)-hexahydroxydiphenoyl-β-D-glucopyranoside

Karamali Khanbabaee* and Mathias Großer

Fachbereich Chemie und Chemietechnik der Universität Paderborn, Warburger Straße 100, 33098 Paderborn, Germany

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Abstract—A straightforward synthesis of the natural product 1,3-di-*O*-galloyl-4,6-*O*-(*S*)-hexahydroxy-diphenoyl-β-D-glucopyranoside (**7**) was achieved based on a regio- and stereoselective galloylation of the 1,3-diol derivative of D-glucopyranose **2** to the β-D-glucopyranoside **3**. Subsequent acylation of monoester **3** to the diester **4** followed by the removal of the benzylidene protecting group led to the formation of the corresponding 4,6-diol derivative of D-glucopyranoside **5**. A further double esterification of the (*rac*)-hexabenzyloxydiphenic acid with the appropriately substituted 4,6-diol derivative of D-glucopyranoside **5** allowed us to assemble the carbon framework of the target **7**. Hydrogenolysis of the tetraester **6** as the precursor of the target compound over palladium on charcoal gave the natural product **7**.

1. Introduction

The natural product 1,3-di-*O*-galloyl-4,6-*O*-(*S*)-hexahydroxydiphenoyl-β-D-glucopyranoside (**7**) was isolated by Yoshida et al. from *Bredita tuberculatata*,[1,2] the flowers of *Tamarix pakistanica*,[1] the leaves of *Reaumuria hirtella* JAUB and sp. (Tamaricaceae)[2] by column chromatography of the ethyl acetate extract and from the leaves of *Acacia raddiana*.[3] Although it is mentioned that this compound was isolated for the first time in 1991,[3] the first isolation of this natural product seems to be from the Nippon Shinyaku Co., Ltd, Japan in 1983.[2] This compound was also obtained by partial degradation of the trimeric natural ellagitannin 'hirtellin T_1' in hot water.[4] Hirtellin T_1 itself was isolated from *R. hirtella*.[4] Sakagami and co-workers investigated the biological activities of natural product **7** along with some other tannins and related compounds for their ability to stimulate monocyte iodination and interleukin-1 production[5] as well as anti-HIV activity.[6] Their anti-HIV activity was demonstrated to be mediated, at least in part, by inhibition of HIV adsorption to the cells.[6] Various tannins and related compounds were compared for their ability to stimulate the iodination (incorporation of radioactive iodine into an acid-insoluble fraction) of human peripheral blood monocytes. The stimulating activity of most of the monomeric and dimeric hydrolyzable tannins was generally higher than that of the trimeric and tetrameric compounds. Compounds that had dehydrohexahydroxydiphenoyl or chebuloyl groups had considerably less activity than those that had other functional groups (hexahydroxydiphenoyl, valoneoyl, dehydrodigalloyl, isodehydrodigalloyl, lactonized valoneoyl, hellinoyl, euphorbinoyl, dehydroeuphorbinoyl or woodfordinoyl group). The methylated derivative, nonacosa-*O*-methylcoriariin A, was essentially inactive, suggesting the requirement of a phenolic hydroxyl group. Three condensed tannins (−)-epicatechin 3-*O*-gallate (ECG)-dimer, ECG-trimer and ECG-tetramer) significantly stimulated both monocyte iodination and their interleukin-1-like factor production. The results suggest the dependence of stimulation of monocyte iodination by tannins and related polyphenols on their molecular weights.[5]

In the preceding review[7] we reported on the synthesis of the ellagitannins strictinin, praecoxin B, pterocarinin C, Mahtabin A and Pariin M, etc., each possessing a (*S*)- or (*R*)-hexahydroxydiphenoyl (HHDP) moiety located at the 2,3 or the 4,6 positions of the D-glucopyranose or D-gluconic acid. For the synthesis of those ellagitannins having one additional galloyl residue at the anomeric center of their D-glucopyranosyl core, we usually used a highly β-stereoselective anomeric esterification[8] of the corresponding α,β-anomeric mixture with tri-*O*-benzylgalloyl chloride[9] in the presence of dried triethylamine (Et_3N). To examine not only the β-selectivity but also the regioselectivity of the galloylation reaction of diol derivatives of D-glucopyranose, we decided to acylate the diol **2** with the tri-*O*-benzylgalloyl chloride under the same reaction conditions as mentioned earlier. For this purpose, we started with *ortho*-nitrobenzyl 2-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranoside (**1**)[10] and removed first the photolytically cleavable *o*-nitrobenzyl protecting group at the anomeric center of the latter by irradiation with UV light at 320 nm in a photochemical apparatus to obtain the corresponding diol **2**. Subsequently,

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* Corresponding author. Fax: +49-525-1603245;
e-mail: kkh@chemie.uni-paderborn.de

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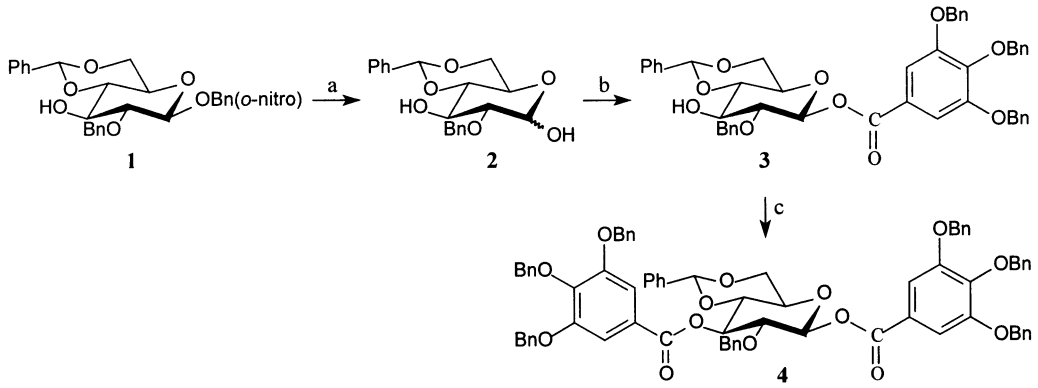


Scheme 1. Synthesis of diester **4**. *Reagents and conditions*: (a) $h\nu$, THF, EtOH, H_2O, 8 h; (b) tri-*O*-benzylgalloyl chloride, dried Et_3N, dried CH_2Cl_2, reflux, 4 h; (c) tri-*O*-benzylgallic acid, DMAP, DCC, dried CH_2Cl_2, reflux, 12 h.

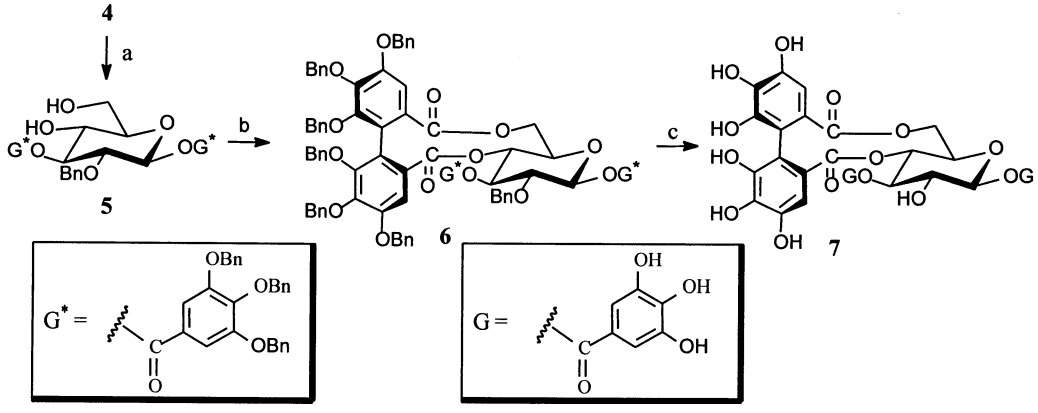
we examined the regio- and stereoselective monogalloylation reaction at the anomeric center of the diol **2** with 3,4,5-tri-*O*-benzylgalloyl chloride under β-selective reaction conditions in the presence of Et_3N. This reaction led exclusively to the formation of the desired compound 1-*O*-(tri-*O*-benzylgalloyl)-2-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**3**) in high yield. The reactivities of both C1–OH and C3–OH groups of the D-glucopyranose seem to be very different, so there was no need to protect first the C3–OH group in order to galloylate the anomeric center of the diol **2**. For the synthesis of natural product **7**, we decided to instal one more galloyl group at the C3–OH of the D-glucopyranosyl core of monoester **3** at this stage, which could be achieved by further esterification of the latter with tri-*O*-benzylgallic acid under Steglich conditions[11] in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) and dicyclohexylcarbodiimide (DCC) (Scheme 1).

Toward the convergent synthesis of natural product **7** it was planed to assemble the carbon framework of the latter by a diastereoselective intramolecular double esterification of the (*rac*)-hexabenzyloxydiphenic acid [(*rac*)-HBODA][12] with the diol **5**. For this purpose, the diester **4** was treated first with diluted HCl to remove the benzylidene protecting group at the 4,6 positions of the diester **4** to generate the 4,6-diol derivative of D-glucopyranoside **5**. As anticipated, the esterification of (*rac*)-HBODA with diol **5** occurred diastereoselectively to furnish the corresponding (*S*)-configured tetraester **6** as the precursor of natural ellagitannin **7** along with a considerable amount of an uncharacterized polar product, which possesses (*R*)-HBODPs. To determine the absolute configuration of the obtained stereoisomer **6**, the tetraester **6** was subjected to hydrolysis using anhydrous potassium hydroxide prepared from potassium *tert*-butoxide and a trace of water in dried THF as proposed by Gassman and Schenk.[13] An optically pure (*S*)-HBODA was obtained from this reaction as shown by comparison of its specific rotation with that reported for (*S*)-HBODA.[12] Thus, the absolute configuration of the observed atropisomer **6** was unambiguously determined to be (*S*). The debenzylation of tetraester **6** was achieved by hydrogenolysis over Pd/C to furnish the natural product **7** as a faintly yellow powder following reversed phase thin layer chromatographic purification (Scheme 2). The identity of the synthetic and natural ellagitannin **7** was evaluated by the comparison of the NMR-data of synthetic ellagitannin **7** with those published for the natural product 1,3-di-*O*-galloyl-4,6-*O*-(*S*)-hexahydroxydiphenoyl-β-D-glucopyranoside.[1,3]

2. Experimental

2.1. General

Nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded by use of a Bruker AMX 300 (300 MHz)



Scheme 2. Total synthesis of **7**. *Reagents and conditions*: (a) 2N HCl, 78°C, 8 h; (b) (*rac*)-HBODA, DMAP, DCC, dried CH_2Cl_2, rt, 24 h; (c) Pd/C–H_2, dried THF, 60°C, 48 h.

and a Bruker ARX 200 (200 MHz) spectrometer. Chemical shifts are reported in ppm (δ) downfield relative to tetramethylsilane as a standard (in $CDCl_3$). The degree of substitution on carbon atoms was determined by DEPT; q, t, d and s designated primary, secondary, tertiary, and quaternary carbon atoms, respectively. HBODP stands for hexabenzyloxydiphenoyl moiety, Gall stands for galloyl moiety and Gluc. stands for D-glucosyl moiety. Melting points were determined by use of a Gallenkamp melting point apparatus and they are uncorrected. Infrared (IR) spectra were obtained by use of a FT-IR spectral photometer Nicolet 510 P (KBr). Ultraviolet/visible (UV/vis) spectra were recorded by use of a Shimadzu UV–vis spectral photometer UV-2101 PC; λ_{max} in nm (log ε). Elemental analyses were perfomed by use of a Perkin–Elmer Elemental Analyser 2400.

2.1.1. 2-*O*-Benzyl-4,6-*O*-benzylidene-D-glucopyranose (2). A solution of *o*-nitrobenzyl protected D-glucopyranoside **1** (4.07 g, 8.25 mmol) in tetrahydrofuran (THF) (150 ml), ethanol (150 ml) and water (0.5 ml) was irradiated under argon for 8 h in a photochemical apparatus (PYREX) at 320 nm. The solvent was removed in vacuo to give a yellow oil. Column chromatography on silica gel [(CH_2Cl_2/AcOEt, 7:3; R_f=0.23] gave diol **2** (56%) as a faintly yellow powder as an α,β-anomeric mixture (α/β ratio in acetone-d_6 6:7, mp 182°C (lit.[14] 180–181°C, lit.[15,16] 175°C), $[\alpha]_D^{21}=-11.2°$ (c=0.53, $CHCl_3$), lit.[14] $[\alpha]_D=-6°$ (c=0.5, $CHCl_3$), lit.[15] $[\alpha]_D^{24}=+6°$ (c=1.0, Py). IR (KBr): $\tilde{\nu}$=3434 cm^{-1}, 3092, 3065, 3032, 2972, 2934, 2874, 1498, 1450, 1384, 1216, 1167, 1085, 1031. UV/vis (MeOH): λ_{max} (log ε)=242 nm (4.32). ^1H NMR (300 MHz, acetone-d_6): δ (ppm)=3.28 (t, J=8.2 Hz, 1H, Gluc.-*H*-2β), 3.39–3.54 (m, 4H, Gluc.-*H*-2α, Gluc.-*H*-4α/β Gluc.-*H*-5β), 3.67–3.84 (m, 3H, Gluc.-*H*-3β, OCH_2Ph), 3.96–4.04 (ddd, J=14.8, 10.0, 4.8 Hz, 1H, Gluc.-*H*-5α), 4.08–4.18 (m, 2H, Gluc.-C-3α, Gluc.-*H*-6α), 4.23 (dd, $J_{6\beta,5\beta}$=4.8 Hz, J_{gem}=10.3 Hz, 1H, Gluc.-*H*-6β), 4.63 (d, J=3.7 Hz, 1H, 3-O*H*α), 4.73 (d, J=4.0 Hz, 1H, 3-O*H*β), 4.79–4.87 (m, 3H, Gluc.-*H*-1β, CH_2Ph), 4.99 (d, J_{gem}=11.5 Hz, 1H, OCH_2Ph), 5.34 (t, $J_{1\alpha,2\alpha}$=3.8 Hz, 1H, Gluc.-*H*-1α), 5.60 (s, 1H, H-7), 5.63 (d, $J_{OH\alpha,1\alpha}$=4.3 Hz, 1H, O*H*), 6.21 (d, $J_{OH\beta,1\beta}$=6.4 Hz, 1H, 1-O*H*β), 7.26–7.52 (m, 10H, Ar-*H*). ^{13}C NMR (50 MHz, acetone-d_6): δ (ppm)= 62.6 (t, Gluc.-*C*-5α), 66.5 (t, Gluc.-*C*-5β), 68.9 (s, Gluc.-*C*-6β), 69.3 (s, Gluc.-*C*-6α), 70.4 (t, Gluc.-*C*-3α), 72.7 (s, OCH_2Phα), 73.8 (t, Gluc.-*C*-3β), 74.7 (s, OCH_2Phβ), 81.0 (t, Gluc.-*C*-2α), 81.8 (t, Gluc.-*C*-4β), 82.5 (t, Gluc.-*C*-4α), 84.7 (t, Gluc.-*C*-2β), 92.1 (t, Gluc.-*C*-1α), 98.3 (t, Gluc.-*C*-1β), 101.7 (t, C-7β), 101.8 (t, C-7α), 126.8 (t), 126.9 (t), 127.5 (t), 127.7 (t), 128.0 (t), 128.1 (t), 128.3 (t), 128.4 (t), 128.5 (t), 129.1 (t), 138.7 (q), 138.8 (q), 139.6 (q), 139.9 (q). MS (FAB/glycerin): m/z (%)=359 (9) [M^++H], 341 (5) [(M^++H)−H_2O], 187 (10), 185 (27), 165 (10), 149 (18), 147 (12), 145 (10), 131 (14), 129 (32), 119 (10), 117 (16), 115 (9), 107 (15) [$C_7H_7O^+$], 105 (11) [$C_7H_5O^+$], 103 (22), 93 (88), 92 (11), 91 (100) [$C_7H_7^+$], 75 (62), 73 (16), 61 (8). Analysis: $C_{20}H_{22}O_6$ (358.39) calcd C, 67.03; H, 6.19; found C, 67.06; H, 6.12.

2.1.2. 1-*O*-(Tri-*O*-benzylgalloyl)-2-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (3). A solution of diol **2** (1.55 g, 4.32 mmol), tri-*O*-benzylgalloyl chloride (2.38 g, 5.19 mmol, 1.2 equiv.), a catalytic amount of dry triethylamine (6 drops) and dry CH_2Cl_2 (50 ml) was refluxed under argon for 4 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed in vacuo. The residue was separated by column chromatography (CH_2Cl_2, R_f=0.33) to give the anomeric acylated monoester **3** (2.40 g, 3.08 mmol, 71%) as a white powder, mp 49–55°C, $[\alpha]_D^{20}=-74.7°$ (c=0.56, $CHCl_3$). IR (CCl_4): $\tilde{\nu}$= 3467 cm^{-1}, 3090, 3064, 3032, 2929, 2878, 1734, 1584, 1502, 1455, 1429, 1372, 1336, 1197, 1088. UV/vis (CH_2Cl_2): λ_{max} (log ε)=259 nm (4.32). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm)=3.00 (s, 1H, 3-O*H*), 3.54–3.56 (m, 2H), 3.61 (t, J=8.4 Hz, 1H), 3.69 (t, 1H), 3.92 (t, J= 8.6 Hz, 1H), 4.31 (dd, J=3.29, 10.6 Hz, 1H), 4.63–4.73 (m, 2H), 5.03– 5.12 (m, 4H, OCH_2Ph), 5.15 (s, 2H, OCH_2Ph), 5.48 (s, 1H, PhC*H*), 5.90 (d, $J_{1,2}$=8.0 Hz, 1H, Gluc.-*H*-1), 7.19–7.48 (m, 27H, Ar-*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm)=67.3 (t), 69.0 (s, Gluc.-*C*-6), 71.8 (s, OCH_2Ph), 74.2 (t), 75.5 (s, OCH_2Ph), 75.6 (s, OCH_2Ph), 80.8 (t), 81.3 (t), 95.2 (t, Gluc.-*C*-1), 102.4 (t), 110.1 (t, Gall-*C*-2 and Gall-*C*-6), 124.3 (q, Gall-*C*-1), 126.9 (t), 127.9 (t), 128.0 (t), 128.5 (t), 128.6 (t), 128.7 (t), 128.9 (t), 129.0 (t), 129.1 (t), 129.8 (t), 137.0 (q), 137.4 (q), 137.8 (q), 138.2 (q), 143.6 (q, Gall-*C*-4), 153.1 (q, Gall-*C*-3 and Gall-*C*-5), 164.7 (q, *C*OOR). MS (FAB/NBA): m/z (%)=781 (0.12) [M^++H], 781 (0.08) [M^+], 673 (0.1) [$M^+-C_7H_7O$], 583 (0.1), 513 (0.12), 423 (26) [tri-*O*-benzylgalloyl ($C_{28}H_{23}O_4^+$)], 331 (4), 304 (2), 271 (1), 255 (1), 241 (8), 197 (6), 181 (12), 107 (6) [$C_7H_7O^+$], 105 (5), 92 (14), 91 (100) [$C_7H_7^+$]. Analysis: $C_{48}H_{44}O_{10}$ (780.87) calcd C, 73.83; H, 5.68; found C, 73.55; H, 5.86.

2.1.3. 1,3-Di-*O*-(tri-*O*-benzylgalloyl)-2-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside (4). A solution of monoester **3** (1.12 g, 1.44 mmol), tri-*O*-benzylgallic acid (0.95 g, 2.16 mmol, 1.5 equiv.), DCC (0.45 g, 2.16 mmol, 1.5 equiv.) and DMAP (0.26 g, 2.16 mmol, 1.5 equiv.) in dry CH_2Cl_2 (50 ml) was refluxed under argon for 12 h. The reaction mixture was allowed to cool to room temperature, and the white solid (dicyclohexylurea) was filtered off. The solvent was removed in vacuo to give a yellow viscous oil. Column chromatography of the crude product on silica gel (CH_2Cl_2, R_f=0.56) gave diester **4** (1.54 g, 1.28 mmol, 89%) as a white powder, mp 151–153°C, $[\alpha]_D^{21}=-31.3°$ (c=1.01, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=3069 cm^{-1}, 3027, 2924, 2878, 1734, 1714, 1584, 1497, 1460, 1429, 1378, 1336, 1197, 1093. UV/vis (CH_2Cl_2): λ_{max} (log ε)=248 nm (3.97). ^1H NMR (200 MHz, $CDCl_3$): δ (ppm)=3.92–4.01 (m, 5H), 4.08 (t, J=8.3 Hz, 1H), 4.56 (d, J=5.5 Hz, 1H, Gluc.-*H*-6), 4.69 (d, J_{gem}=11.8 Hz, 1H, OCH_2Ph), 4.79 (d, J_{gem}=11.8 Hz, 1H, OCH_2Ph), 5.12 (t, 1H, Gluc.-*H*-6), 5.25–5.32 (m, 14H, OCH_2Ph), 5.65 (s, 1H, PhC*H*), 5.88 (t, J= 8.7 Hz, 1H, Gluc.-*H*-3), 6.27 (d, $J_{1,2}$=7.8 Hz, 1H, Gluc.-*H*-1), 7.14–7.24 (m, 4H, Gall-*H*-2 and Gall-*H*-6 or Gall-*H*-2′ and Gall-*H*-6′), 7.39–7.62 (m, 40H, Ar-*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm)=67.4 (t), 69.1 (s, Gluc.-*C*-6), 71.88 (s, OCH_2Ph), 71.93 (s, OCH_2Ph), 74.2 (t), 75.0 (s, OCH_2Ph), 75.7 (s, OCH_2Ph), 79.1 (t), 79.2 (t), 95.6 (t, Gluc.-*C*-1), 102.0 (t, C-7), 110.2 and 110.3 (t, Gall-*C*-2 and Gall-*C*-6 or Gall-*C*-2′ and Gall-*C*-6′), 124.4 (q), 125.3 (q), 126.8 (t), 128.0 (t), 128.1 (t), 128.4 (t), 128.6 (t), 128.7 (t), 128.8 (t), 128.83 (t), 129.1 (t), 129.2 (t), 129.6 (t), 137.0 (q), 137.2 (q), 137.3 (q), 137.6 (q), 137.8 (q), 137.9 (q), 143.3 (q), 143.9 (q), 153.1 (q), 153.3 (q), 164.5 (q, *C*OOR), 165.4 (q, *C*OOR). MS (ESI/acetone): m/z (%)=1225.5 (100)

[(M+Na)$^+$], 1083.4 (25), 997.9 (23), 953.9 (28), 909.9 (34), 865.9 (25), 821.9 (15), 733.7 (11), 306.4 (9). Analysis: $C_{76}H_{66}O_{14}$ (1280.35) calcd C, 75.86; H, 5.53; found C, 74.96; H 5.51.

2.1.4. 1,3-Di-*O*-(tri-*O*-benzylgalloyl)-2-*O*-benzyl-β-D-glucopyranoside (5). To a stirred solution of diester **4** (1.34 g, 1.12 mmol) in THF (30 ml) 2N HCl (30 ml) was added slowly at 60°C. The mixture was stirred at 78°C for 8 h. After cooling to room temperature the reaction mixture was quenched with saturated $NaHCO_3$, extracted 6 times with CH_2Cl_2 (50 ml). Drying of the combined organic extracts (Na_2SO_4) and evaporation under reduced pressure gave an oily residue (CH_2Cl_2/Et_2O 10:1, R_f=0.21). The crystallization of the oily residue (CH_2Cl_2/*n*-hexane) afforded the diol **5** (1.10 g, 0.98 mmol, 88%) as white powder, mp 172°C, $[\alpha]_D^{21}$=+21.6° (*c*=1.07, CH_2Cl_2). IR (KBr): $\tilde{\nu}$=3390 cm^{-1}, 3271, 3069, 3022, 2924, 2862, 1740, 1724, 1590, 1502, 1455, 1424, 1383, 1336, 1202, 1119, 1072. UV/vis (CH_2Cl_2): λ_{max} (log ε)=282 nm (3.89). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)=3.73–3.78 (m, 1H), 3.85–4.02 (m, 5H), 4.58 (d, J_{gem}=11.7 Hz, 1H, OC*H*$_2$Ph), 4.70 (d, J_{gem}=11.7 Hz, 1H, OC*H*$_2$Ph), 5.15–5.22 (m, 16H, OC*H*$_2$Ph), 5.49 (t, *J*=9.0 Hz, 1H), 6.11 (d, $J_{1,2}$=7.9 Hz, 1H, Gluc.-*H*-1), 7.09 (s, 4H, Ar-*H*), 7.34–7.49 (m, 35H, Ar-*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm)=62.3 (s, Gluc.-*C*-6), 69.9 (t), 71.7 (s, O*C*H$_2$Ph), 71.8 (s, O*C*H$_2$Ph), 74.9 (s, O*C*H$_2$Ph), 75.6 (s, O*C*H$_2$Ph), 76.7 (t), 78.4 (t), 78.7 (t), 95.1 (t, Gluc.-*C*-1), 109.9 or 110.1 (t, Gall-*C*-2 and Gall-*C*-6 or Gall-*C*-2′ and Gall-*C*-6′), 124.4 or 124.8 (q, Gall-*C*-1 or Gall-*C*-1′), 127.9 (t), 128.0 (t), 128.3 (t), 128.4 (t), 128.5 (t), 128.6 (t), 128.69 (t), 128.7 (t), 129.0 (t), 136.9 (q), 137.0 (q), 137.6 (q), 137.7 (q), 137.75 (q), 143.3 (q), 143.7 (q), 153.0 (q), 153.1 (q), 164.7 (q, *C*OOR), 167.1 (q, *C*OOR). MS (ESI/acetone): 1137.5 (67) [(M+Na)$^+$], 953.9 (94), 909.8 (100), 625.6 (39), 517.5 (29), 360.5 (29), 306.3 (18), 242.3 (23), 158.1 (82), 100.1 (54). Analysis: $C_{69}H_{62}O_{14}$ (1115.24) calcd C, 74.31; H, 5.60; found C, 74.04; H, 5.68.

2.1.5. 1,3-Di-*O*-(tri-*O*-benzylgalloyl)-2-*O*-benzyl-4,6-*O*-(*S*)-hexabenzyloxydiphenoyl-β-D-glucopyranoside (6). A mixture of diol **5** (1.08 g, 0.96 mmol), racemic hexabenzyloxydiphenic acid (0.84 g, 0.96 mmol), DCC (0.51 g, 2.46 mmol, 2.6 equiv.), and DMAP (0.3 g, 2.49 mmol, 2.6 equiv.) in dry CH_2Cl_2 (20 ml) was stirred under argon at room temperature for 24 h, and the white solid (dicyclohexylurea) was filtered off. The solvent was removed in vacuo to give a viscous oil. Column chromatography of the crude product on silica gel (CH_2Cl_2, R_f=0.53) gave tetraester **6** (0.75 g, 0.38 mmol, 39.5%) as a white powder, mp 58–65°C, $[\alpha]_D^{22}$=−15.0° (*c*=1.15, CH_2Cl_2). IR (CCl_4): $\tilde{\nu}$=3091 cm^{-1}, 3069, 3033, 2929, 2872, 1750, 1590, 1558, 1502, 1460, 1424, 1372, 1336, 1197, 1098, 1005. UV/vis (CH_2Cl_2): λ_{max} (log ε)=285 nm (4.03). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=3.94 (t, *J*=8.1 Hz, 1H), 4.04 (d, *J*=13.2 Hz, 1H), 4.27 (dd, *J*=5.8, 9.8 Hz, 1H), 4.51 (d, J_{gem}=11.8 Hz, 1H, OC*H*$_2$Ph), 4.59 (d, J_{gem}=11.6 Hz, 1H, OC*H*$_2$Ph), 4.75 (d, J_{gem}=11.0 Hz, 1H, OC*H*$_2$Ph), 4.82–5.21 (m, 23H, OC*H*$_2$Ph), 5.29–5.39 (m, 2H), 5.68 (t, 1H), 6.07 (d, $J_{1,2}$=7.7 Hz, 1H, Gluc.-*H*-1), 6.85–7.51 (m, 71H, Ar-*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm)=63.8 (s, Gluc.-*C*-6), 70.9 (t), 71.7 (s, O*C*H$_2$Ph), 71.9 (s, O*C*H$_2$Ph), 72.7 (t), 74.9 (t), 75.4 (s, O*C*H$_2$Ph), 75.7 (s, O*C*H$_2$Ph), 75.7 (s, O*C*H$_2$Ph), 76.0 (s, O*C*H$_2$Ph), 79.0 (t), 95.3 (t, Gluc.-*C*-1), 108.1 (t), 108.5 (t), 110.1 (t), 110.2 (t), 124.1 (q), 124.2 (q), 124.4 (q), 125.1 (q), 128.0 (t), 128.2 (t), 128.5 (t), 128.6 (t), 128.7 (t), 128.7 (t), 128.8 (t), 128.9 (t), 129.0 (t), 129.1 (t), 129.1 (q), 129.2 (t), 129.4 (q), 130.3 (q), 136.9 (q), 137.1 (q), 137.5 (q), 137.9 (q), 138.0 (q), 138.1 (q), 138.2 (q), 138.3 (q), 140.3 (q), 143.5 (q), 143.9 (q), 144.9 (q), 145.3 (q), 152.8 (q), 153.0 (q), 153.1 (q), 153.2 (q), 153.3 (q), 164.6 (q, *C*OOR), 166.1 (q, *C*OOR), 167.8 (q, *C*OOR), 168.0 (q, *C*OOR). MS (ESI/acetone): *m*/*z* (%)=1762.4, 1616, 1100.9. Analysis: $C_{125}H_{104}O_{22}$ (1958.19) calcd C, 76.67; H, 5.35; found C, 76.66; H, 5.42.

2.1.6. 1,3-Di-*O*-galloyl-4,6-*O*-(*S*)-hexahydroxydiphenoyl-β-D-glucopyranoside (7). A suspension of tetraester **6** (160 mg), Pd/C (100 mg, 10%) and dry THF (45 ml) was first degased with argon (3 times) to remove O_2, and hydrogen (H_2) was conducted slowly through the reaction mixture at 60°C for 48 h. The reaction mixture was allowed to cool to room temperature, the solid was filtered off through celite, and the celite was washed with a mixture of acetone/methanol (80:20, 60 ml). The solvent was removed under reduced pressure to give an oily residue, which contains the polyphenolic compound **7** along with some partially debenzylated products. The purification of the ellagitannin **7** was carried out by reversed phased chromatography (H_2O/MeOH, 10:2) to afford natural product **7** (45 mg, 70%) as a brownish powder, decomp. 178°C, $[\alpha]_D^{22}$=+16.2° (*c*=1.0, MeOH), lit.[1] $[\alpha]_D$=+24° (*c*=1.0, MeOH), lit.[3] $[\alpha]_D^{27}$=−60° (*c*=0.61, MeOH). IR (KBr): $\tilde{\nu}$=3340 cm^{-1}, 3005, 2956, 2924, 2873, 2852, 1701, 1616, 1448, 1354, 1319, 1205, 1036. UV (MeOH): λ_{max} (log ε)= 303 nm (4.33), lit.[3] λ_{max} (MeOH)=275 nm. ^{1}H NMR (300 MHz, acetone-d_6/D_2O): δ (ppm)=3.82 (d, J_{gem}=13.2 Hz, 1H, Gluc.-*H*-6), 3.99 (dd, *J*=8.2, 9.2 Hz, 1H, Gluc.-*H*-2), 4.35 (dd, *J*=5.9, 9.9 Hz, 1H, Gluc.-H-5), 5.06 (t, *J*=9.9 Hz, 1H, Gluc.-*H*-4), 5.30 (dd, $J_{6,5}$=6.5 Hz, J_{gem}=13.4 Hz, 1H, Gluc.-*H*-6), 5.48 (t, *J*=9.6 Hz, 1H, Gluc.-*H*-3), 5.90 (d, $J_{1,2}$=8.2 Hz, 1H, Gluc.-*H*-1), 6.47 and 6.62 (s, 2H, HHDP-H-5 or HHDP-H-5′), 7.04 (s, 2H, Gall-*H*-2 or Gall-*H*-6), 7.21 (s, 2H, Gall-*H*-2 or Gall-*H*-6). ^{13}C NMR (50 MHz, acetone-d_6/D_2O): δ (ppm)=62.8 (s, Gluc.-*C*-6), 70.3 (t, Gluc.-*C*-4), 71.9 (t, Gluc.-*C*-2), 72.4 (t, Gluc.-*C*-5), 75.2 (t, Gluc.-*C*-3), 95.4 (t, Gluc.-*C*-1), 107.4 and 107.5 (t, HHDP-*C*-5 and HHDP-*C*-5′), 109.7 and 109.8 (t, Gall-*C*-2 and Gall-*C*-6), 115.4 (q), 115.5 (q), 119.9 (q), 120.7 (q), 125.5 (q), 126.0 (q), 136.0 (q), 136.1 (q), 138.5 (q), 139.2 (q), 144.1 (q), 144.7 (q), 144.75 (q), 145.4 (q), 145.7 (q), 165.1 (q, *C*OOR), 166.5 (q, *C*OOR), 167.5 (q, *C*OOR), 167.9 (q, *C*OOR).

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