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Total syntheses of (+)- and (−)-1,3,4,5-tetragalloylapiitol and revision of absolute configuration of naturally occurring (−)-1,3,4,5-tetragalloylapiitol

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ABSTRACT

The total syntheses of (+)- and (−)-1,3,4,5-tetragalloylapiitol were achieved in seven steps from D- and L-ribose, respectively. By comparing the optical rotations of both enantiomers with those of the natural product, the absolute configuration at C-3 in the naturally occurring 1,3,4,5-tetragalloylapiitol has been revised to *R*. The absolute configurations at C-3 in the synthetic (+)- and (−)-1,3,4,5-tetragalloylapiitol were further confirmed by the circular dichroism exciton chirality method.

1. Introduction

The biological activities of polygalloyl and hexahydroxydiphenoyl glucoses have generated considerable interest because of their anti-HIV, antidiabetic, antiviral, antimicrobial, and antihypertensive effects.[1] 1,3,4,5-Tetragalloylapiitol (**1**) was isolated from the aqueous extract of *Hylodendron gabunensis* by screening for substances that possess HIV ribonuclease H (RNase H) inhibitory activity.[2] Because RNase H is known to participate in the specific hydrolyzation of an RNA strand in an RNA/DNA heteroduplex[3] and is known to be critical for the growth of HIV, activity that counters this enzyme could be an attractive feature of novel drugs for HIV chemotherapy.[4] In addition, the secondary metabolite **1** was shown to inhibit HIV-1, HIV-2, and human RNase H in vitro at the micromolar level. The intriguing structure and characteristic biological activity of **1** have stimulated interest in the synthetic community. The structure of **1** consists of four gallic acids (**3**) and apiitol (**2**), and the acids are connected to the hydroxyl groups at C-1, C-3, C-4, and C-5 of the sugar via ester linkages (Fig. 1). The absolute configuration of **1** was originally assigned as *S* by comparing the optical rotation of the compound, which was obtained through the hydrolysis of the natural product (**1**) under basic conditions, with that of authentic D-apiitol.[5]

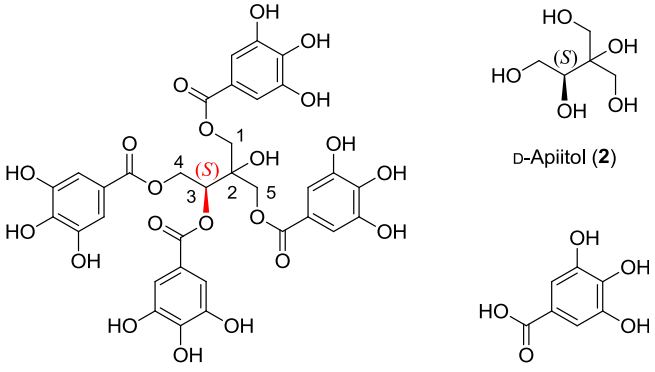

Fig. 1. Structures of 1,3,4,5-tetragalloylapiitol (**1**), D-apiitol (**2**), and gallic acid (**3**).

Recently, Argade's[6] and Kraus's[7] groups reported independently the total synthesis of racemic 1,3,4,5-tetragalloylapiitol from inexpensive and commercially available citraconic anhydride and 1,3-dihydroxy acetone dimer, respectively, using hydroxylation with osmium tetroxide as a key step. More recently, Argade's group also reported the chemoenzymatic total synthesis of (−)-**1** via lipase-catalyzed resolution.[8] However, it has not been demonstrated

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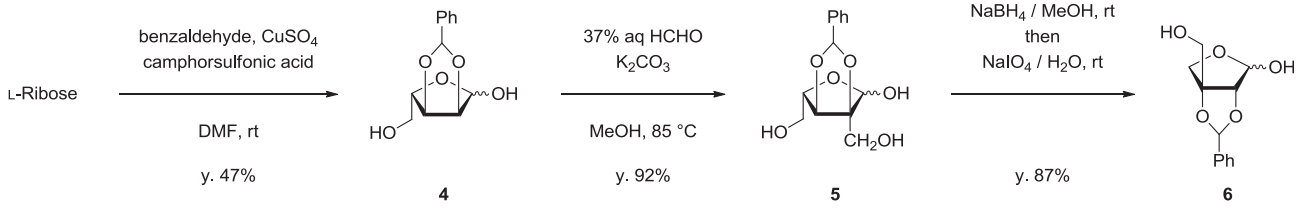
that the absolute configuration of the synthesized product (−)-**1** is unambiguously *S*. That is, the optical rotation of the synthetic intermediate, 2-(*R*)-hydroxy-3-methylenesuccinic acid dimethyl ester ($[\alpha]_D^{25}$ −19.7 (*c* 0.68, EtOH)) differed in magnitude from the published value ($[\alpha]_D$ −11 (*c* 1.0, EtOH)[9a] and $[\alpha]_D^{25}$ −10 (*c* 1.77, EtOH)[9b]). Moreover, Argade's group accomplished the total synthesis of **1** ($[\alpha]_D^{25}$ −23.6 (*c* 0.03, MeOH)) through the reductive removal of benzyl groups on the aromatic rings of its precursor ($[\alpha]_D^{25}$ +26.5 (*c* 0.11, $CHCl_3$)). However, an incomprehensible change in the sign of the optical rotation was not observed upon the synthesis of **1** by hydrogenolysis of the same dextrorotatory precursor in a preliminary examination of our work. Therefore, we decided to undertake the total synthesis of optically active **1** to confirm the absolute configuration at C-3 and to further investigate its biological activity.

In our previous paper, we reported a simple synthetic route for 2,3-*O*-benzylidene-3-*C*-(hydroxymethyl)-D-erythrofuranose (**6**) from L-ribose (Scheme 1).[10] The key step in this synthesis is the selective introduction of the hydroxymethyl group at the C-2 of L-ribose by the aldol reaction of 2,3-*O*-benzylidene-L-ribose with an excess of formaldehyde. Because the functional groups of the branched-chain sugar derivative can be selectively protected and chemically modified, these compounds are often used as chiral building blocks for the asymmetric syntheses of promising biologically active natural and unnatural products.[11,12] These interesting works prompted us to employ 2,3-*O*-benzylidene-3-*C*-(hydroxymethyl)-D-erythrofuranose, which possesses the same configuration as the naturally occurring 1,3,4,5-tetragalloylapiitol (**1**), as the chiral synthon for the expeditious synthesis of optically pure **1**.

D-apiitol ($[\alpha]_D^{26}$ −4.0 (*c* 0.8, MeOH))[5] by Kitajima's group. We next examined an esterification of **8** using 3,4,5-tris(benzyloxy)benzoyl chloride[14] (Table 1). However, the esterification of **8** with acyl chloride (4.4 equiv) in the presence of a catalytic amount of DMAP (0.2 equiv) in pyridine at room temperature gave the desired tetraester **9** in 8% yield and triester **9′**[15] in 68% yield (entry 1). When the reaction was carried out at 60 °C, **9** and **9′** were obtained in 26% and 71% yields, respectively (entry 2). To achieve the complete conversion of intermediate **9′** to the corresponding tetraester **9**, D-apiitol **8** was reacted with an excess amount of acyl chloride (8.0 equiv) at 60 °C. As a result, the desired tetraester **9** was successfully obtained in 90% yield (entry 3). The spectroscopic data for tetraester **9** agreed well with previously reported data except in the assignments of H-1 and H-1′. The careful analysis of the ^1H–^1H COSY spectrum of **9** indicated that all the protons were assigned. The optical rotation ($[\alpha]_D^{26}$ +15.9 (*c* 1.00, $CHCl_3$)) and melting point (159.2–160.9 °C) of **9**, however, differed in magnitude from the published values ($[\alpha]_D^{25}$ +26.5 (*c* 0.11, $CHCl_3$) and mp 130–131 °C).[8] Finally, the debenzylation of the precursor **9** gave the target compound (*S*)-**1** in quantitative yield.

Synthetic (*S*)-**1** was isolated as a pale yellow solid by recrystallization from toluene/EtOAc. Although the ^1H and ^{13}C NMR spectra of the synthetic (*S*)-**1** were identical to those of the natural product, its optical rotation ($[\alpha]_D^{20}$ +20.3 (*c* 1.0, MeOH)[16]) was diametrically opposed to the published values (natural (*S*)-**1**: $[\alpha]_D^{20}$ −18.6 (*c* 0.1, MeOH),[4] synthetic (*S*)-**1**: $[\alpha]_D^{25}$ −23.6 (*c* 0.03, MeOH)[8]). In addition, the ^1H, ^{13}C NMR spectra, and optical rotation of synthetic (*S*)-**1** that was obtained by 10% Pd–C-catalyzed hydrogenolysis of **9** according to Argade's procedure were also identical to those of synthetic (*S*)-**1** by $Pd(OH)_2$-catalyzed hydrogenolysis.



Scheme 1. Synthesis of 2,3-*O*-benzylidene-3-*C*-(hydroxymethyl)-D-erythrofuranose **6**.

Herein, we describe the total synthesis of the originally proposed structure of (*S*)-**1** from L-ribose and show that the absolute configuration at C-3, which is the only chiral center of naturally occurring 1,3,4,5-tetragalloylapiitol, was incorrectly assigned in the original literature. Furthermore, the enantiomer (*R*)-**1** was prepared using the same synthetic route from D-ribose to confirm the correct absolute configuration of the natural 1,3,4,5-tetragalloylapiitol. The stereochemistry of synthetic (+)- and (−)-**1** was confirmed through the application of a dibenzoate chirality method for acyclic alcohols.[13a,b]

2. Results and discussion

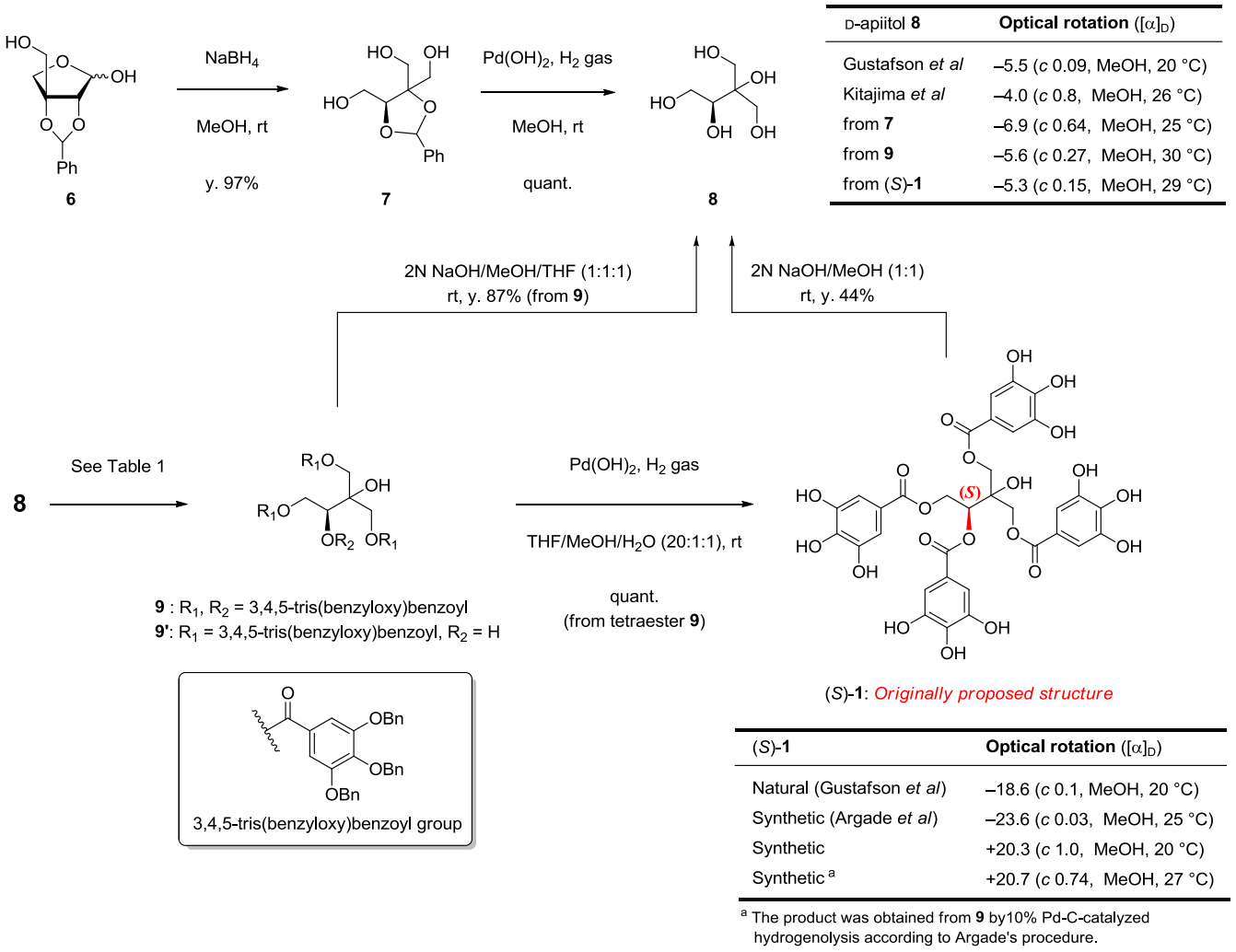
2.1. Total synthesis of (*S*)-1,3,4,5-tetragalloylapiitol

As shown in Scheme 2, 2,3-*O*-benzylidene-3-*C*-(hydroxymethyl)-D-erythrofuranose **6**, which was easily prepared on a multigram scale from L-ribose in three steps according to previously reported procedures (Scheme 1),[10] was converted to the erythritol **7** in 97% yield with $NaBH_4$. The hydrogenolysis of **7** was carried out using $Pd(OH)_2$. The reaction proceeded smoothly to give a D-apiitol **8** in quantitative yield. The synthetic D-apiitol **8** ($[\alpha]_D^{25}$ −6.9 (*c* 0.54, MeOH)) gave data consistent with those reported for

Since our D-apiitol **8** that was recovered from the precursor **9**[17] and (*S*)-**1** by alkaline hydrolysis according to Gustafson's reaction conditions gave data fully consistent with those reported for D-apiitol by Kitajima's group, it was undoubtedly established that the esterification, hydrogenolysis, and hydrolysis proceeded without inversion of the configuration of C-3. Therefore, these experimental results suggest that our synthetic (+)-**1** is actually the enantiomer of naturally occurring 1,3,4,5-tetragalloyapiitol and that correct absolute configuration at C-3 in the natural product should be revised to *R*.

2.2. Total synthesis of (*R*)-1,3,4,5-tetragalloylapiitol

To confirm the revised structure, we employed the above-described route to achieve the first total synthesis of (*R*)-**1** starting from D-ribose (Scheme 3). The resulting synthetic (*R*)-**1** had an optical rotation of $[\alpha]_D^{15}$ −20.5 (*c* 1.03, MeOH), and the spectroscopic data were identical to those of the natural product.[3] Moreover, the (*R*)-synthetic intermediates showed diametrically opposite optical rotations and identical physical data to those of the corresponding (*S*)-intermediates. Based on these results, we concluded that the absolute configuration of the 1,3,4,5-tetragalloylapiitol isolated by Gustafson is *R*.



D-apiitol **8**	**Optical rotation** ($[\alpha]_D$)
Gustafson *et al*	–5.5 (*c* 0.09, MeOH, 20 °C)
Kitajima *et al*	–4.0 (*c* 0.8, MeOH, 26 °C)
from **7**	–6.9 (*c* 0.64, MeOH, 25 °C)
from **9**	–5.6 (*c* 0.27, MeOH, 30 °C)
from (*S*)-**1**	–5.3 (*c* 0.15, MeOH, 29 °C)

(*S*)-**1**	**Optical rotation** ($[\alpha]_D$)
Natural (Gustafson *et al*)	–18.6 (*c* 0.1, MeOH, 20 °C)
Synthetic (Argade *et al*)	–23.6 (*c* 0.03, MeOH, 25 °C)
Synthetic	+20.3 (*c* 1.0, MeOH, 20 °C)
Synthetic [a]	+20.7 (*c* 0.74, MeOH, 27 °C)

[a] The product was obtained from **9** by10% Pd-C-catalyzed hydrogenolysis according to Argade's procedure.

Scheme 2. Synthesis of 1,3,4,5-tetragalloylapiitol (*S*)-**1**.

Table 1
Esterification of D-apiitol **8**

Entry	Reagents and condition	Isolated yield(%)	
		9	**9′**
1	3,4,5-Tris(benzyloxy)benzoyl chloride (4.4 equiv.) DMAP (2.0 equiv) Py, rt, 48 h	8	68
2	3,4,5-Tris(benzyloxy)benzoyl chloride (4.4 equiv.) Py, 60 °C, 48 h	26	71
3	3,4,5-Tris(benzyloxy)benzoyl chloride (8.0 equiv.) Py, 60 °C, 12 h	90	—

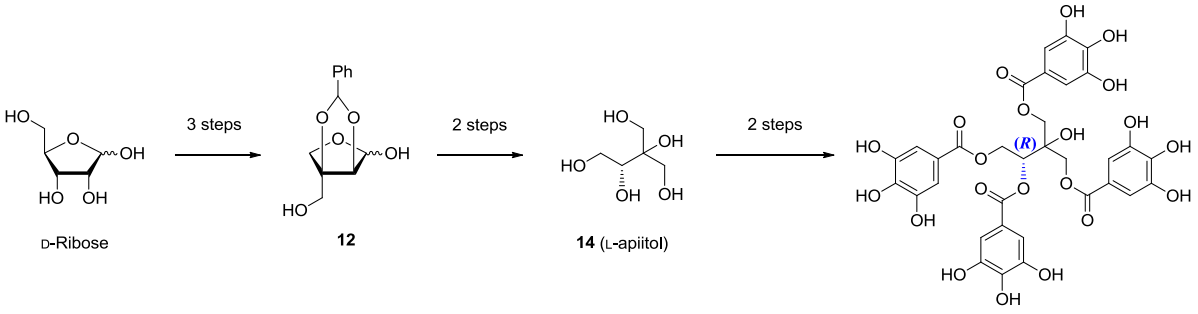
2.3. Further corroboration of absolute configurations at C-3 of tetragalloylapiitol (+)-1 and (−)-1

To confirm the configurations of (+)-**1** and (−)-**1** determined above, we also attempted to clarify the absolute configurations of the synthesized apiitol **8** and **14** by application of the circular dicroism (CD) exciton chirality method.[13a,b] Apiitol **8** and **14** were reacted with benzoyl chloride in pyridine to give tetra-*O*-benzoate (*S*)-**16** and (*R*)-**16** in 99% and quantitative yields, respectively (Scheme 4).[18] As shown in Fig. 2, the CD spectrum of (*S*)-**16** exhibited a negative peak ($\Delta\varepsilon$ −1.2) at a long wavelength (241 nm) and a positive peak ($\Delta\varepsilon$ +4.3) at a short wavelength (227 nm), which indicated a negative exciton chirality in the stable conformation of (*S*)-**16**. Typical acyclic 1,2-di-*O*-benzoates that exhibit negative exciton chirality are shown in Fig. 3. Compound (*S*)-**16** exhibited a CD spectrum very similar to those of the compounds reported by Uzawa,[13a] Harada,[13b] Sakamoto,[13d] Ami,[13e] and Oguri,[13f] while enantiomer (*R*)-**16** showed the opposite positive exciton chirality. The stereochemistry around the chiral centers of the compounds shown in Fig. 3 is the same, although the *R*,*S*-nomenclatures are different. Therefore, the spectroscopic results strongly suggest that the stereochemistry of the chiral center of (*S*)-**16** is actually the (*S*)-configuration.

The configurations at the chiral centers of D-apiitol **8**, tetraester **9**, and tetragalloylapiitol (+)-**1** are the same as that of tetra-*O*-benzoate (*S*)-**16** because, as we have already demonstrated above, the esterification and hydrogenolysis reaction conditions do not affect the configuration during these reactions.

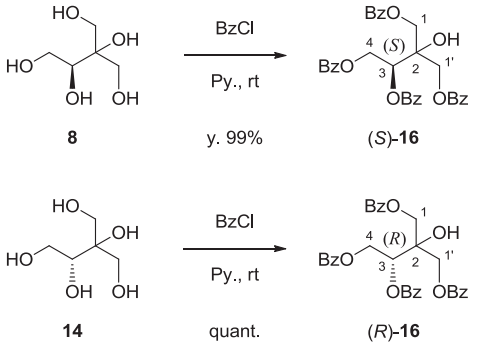
3. Conclusion

The total synthesis of the previously proposed structure of (*S*)-1,3,4,5-tetragalloylapiitol was accomplished from L-ribose in seven steps. The optical rotations of the synthesized product (*S*)-**1** and the natural product exhibited the opposite signs. These results suggested that the absolute configuration at C-3 in the natural product should be revised to *R*. The correct absolute stereochemistry was further confirmed through the first total synthesis of the enantiomer of (*S*)-**1** from inexpensive D-ribose and the analysis of the CD



1,3,4,5-tetragalloylapiitol	Optical rotation ($[\alpha]_D$)
Natural (*S*)-**1** (by Gustafson *et al*)	–18.6 (*c* 0.1, MeOH, 20 °C)
Synthetic (*S*)-**1** (by Argade *et al*)	–23.6 (*c* 0.03, MeOH, 25 °C)
Synthetic (*S*)-**1**	+20.3 (*c* 1.0, MeOH, 20 °C)
Synthetic (*R*)-**1**	–20.5 (*c* 1.03, MeOH, 15 °C)

Scheme 3. Total synthesis of 1,3,4,5-tetragalloylapiitol (*R*)-**1** from D-ribose.



Scheme 4. Syntheses of tetra-*O*-benzoates (*S*)-**16** and (*R*)-**16**.

spectra of both compounds. A comparison of the optical rotations and the CD spectra of tetra-*O*-benzoate (*S*)-**16** and (*R*)-**16** with those published in the literature confirmed that our determination of their absolute configurations at C-3 was correct. The evaluation of

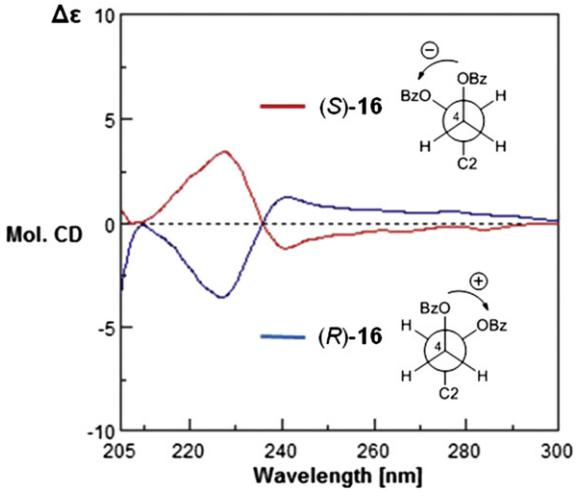


Fig. 2. CD spectra of compounds (*S*)-**16** and (*R*)-**16** in MeOH.

the biological activities of (*R*)- and (*S*)-**1** will be reported in the near future. To demonstrate the versatility of the 3-*C*-(hydroxymethyl)-erythrofuranose derivatives **6** and **12** as chiral synthons, the syntheses of other bioactive compounds are also underway.

4. Experimental section

4.1. General

Melting points were measured using a Yanaco Model MP-J3 micro-melting point apparatus, and these values are uncorrected. IR spectra were recorded using a JASCO FT/IR-460 spectrometer using KBr pellets or liquid film on NaCl. ^{1}H and ^{13}C NMR spectra were measured using a Bruker Avance DPX-250 spectrometer. *J* values were recorded in hertz, and the abbreviations used were s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). Chemical shifts are expressed in δ values relative to the internal standard TMS or the deuterated solvent. Thin-layer chromatography (TLC) was carried out on Merck Silica gel 60 F_{254} plates. Flash column chromatography was carried out on silica gel 60 N (spherical, neutral) (40–100 μm, Kanto). Specific rotations were measured in 1.0-dm tubes using a Perkin–Elmer 241 polarimeter in $CHCl_3$, CH_3OH, or pyridine. CD spectra were measured in CH_3OH (1-cm quartz cell) at 25 °C using a JASCO J-820 spectropolarimeter. ESI-TOF mass spectra were recorded using a JEOL JMS-T100LC AccuTOF mass spectrometer.

4.2. Total synthesis of (*S*)-1,3,4,5-tetragalloylapiitol

*4.2.1. [(5S)-2-Phenyl-1,3-dioxolane-4,4,5-triyl]trimethanol (**7**).* To a solution of **6** (350 mg, 1.48 mmol) in MeOH (3.0 mL) was cautiously added sodium borohydride (67 mg, 1.78 mmol) in small portions. After stirring for 30 min at room temperature, the reaction mixture was quenched with saturated aq NH_4Cl solution (3.0 mL). After the solvent was evaporated, the remaining aqueous solution was extracted with EtOAc (5.0 mL×5). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc) to give **7** (353 mg, 97% yield) as colorless prisms: mp: 108.4–109.4 °C (hexane-EtOAc); $[\alpha]_D^{13}$ –3.7 (*c* 1.0, MeOH); R_f=0.20

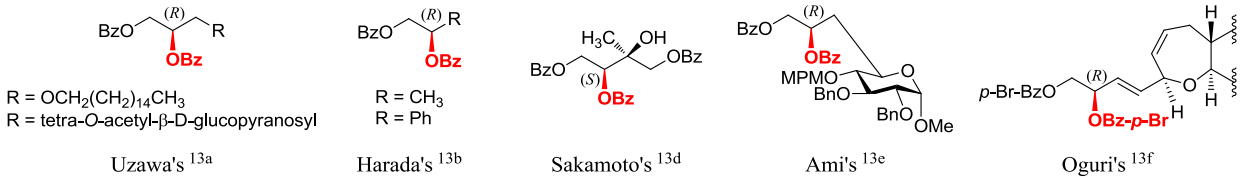


Fig. 3. Structures of acyclic 1,2-di-*O*-benzoates exhibited a negative first and positive second Cotton effects in the CD spectra.

(EtOAc); IR (KBr, disk): 3287, 749, 699 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.46–7.35 (m, 5H, Ar*H*), 5.83 (s, 1H, PhC*H*), 4.11 (t, $J_{3,4}$=5.9 Hz, 1H, H-3), 3.94 (d, $J_{4,3}$=5.9 Hz, 2H, H-4), 3.84, 3.78 (each d, J=11.9 Hz, 2H, H-1), 3.80, 3.74 (each d, J=11.6 Hz, 2H, H-1′), 3.32 (br s, 2H, −O*H*×2), 3.01 (br s, 1H, −O*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ 136.3, 129.7, 128.4, 126.7, 102.6, 83.3, 80.9, 63.5, 61.4, 59.9; ESI-HRMS calcd for $C_{12}H_{16}O_5Na$ *m*/*z* $[M+Na]^+$: 263.0895. Found: 263.0870.

*4.2.2. (3S)-2-Hydroxymethylbutane-1,2,3,4-tetrol (**8**) [D-apiitol].* To a solution of **7** (200 mg, 0.832 mmol) in MeOH (20 mL) was added palladium hydroxide on carbon (palladium 20 wt % on carbon). The suspension was stirred for 24 h at room temperature under H_2 gas. The mixture was filtered through Celite, and the filtrate was concentrated. The residue was loaded onto an octadecyl silica gel column and eluted successively with water and MeOH. The water fraction was concentrated to give D-apiitol **8** (127 mg, quant.) as a colorless syrup. $[\alpha]_D^{25}$ −6.9 (*c* 0.54, MeOH) [lit. $[\alpha]_D^{26}$ −4.0 (*c* 0.8, MeOH)[5]]; R_f=0.31 ($CHCl_3$/MeOH/H_2O=10:10:1 v/v). The ^1H and ^{13}C NMR data for synthetic **8** agreed well with previously reported values.[4,5]

*4.2.3. (3S)-2-Hydroxy-2-[3,4,5-tris(benzyloxy)benzoyloxymethyl]butane-1,3,4-triyl tris[3,4,5-tris(benzyloxy)benzoate] (**9**).* To a solution of **8** (5.4 mg, 0.0355 mmol) in pyridine (1 mL) was added 3,4,5-tris(benzyloxy)benzoyl chloride (130 mg, 0.2839 mmol) at room temperature. After stirring for 12 h at 60 °C, the reaction mixture was quenched with MeOH (0.1 mL). The solvent was evaporated and the residue was coevaporated with toluene (5 mL×3). The residue was purified by silica gel column chromatography (toluene/EtOAc=14:1 then 4:1 v/v) to give **9** (59.1 mg, 90% yield) as colorless needles: mp: 159.2–160.9 °C (hexane/EtOAc) [lit. 130–131 °C]; $[\alpha]_D^{26}$ +15.9 (*c* 1.0, $CHCl_3$) [lit. $[\alpha]_D^{25}$ +26.5 (*c* 0.11, $CHCl_3$)[8]]; R_f=0.51 (toluene/acetone=10:1 v/v); IR (KBr, disk): 3421, 3030, 2868, 1719, 730, 694 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.42–7.18 (m, 68H, Ar*H*), 5.89 (dd, $J_{3,4a}$=3.4 Hz, $J_{3,4b}$=7.6 Hz, 1H, H-3), 5.16–4.87 (m, 24H, PhCH_2×12), 5.01 (dd, $J_{4a,3}$=3.4 Hz, $J_{4a,4b}$=12.4 Hz, 1H, H-4a), 4.70, 4.49 (each d, J=11.9 Hz, 2H, H-1), 4.65 (dd, $J_{4b,3}$=7.6 Hz, $J_{4b,4a}$=12.2 Hz, 1H, H-4b), 4.58, 4.44 (each d, J=11.9 Hz, 2H, H-1′), 3.31 (br s, 1H, −O*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ 166.2, 166.1, 165.7, 165.1, 152.66, 152.64, 152.62, 152.56, 143.2, 143.03, 143.01, 142.7, 137.45, 137.43, 137.42, 137.36, 136.62, 136.59, 136.5, 136.4, 128.50, 128.49, 128.45, 128.39, 128.38, 128.31, 128.15, 128.10, 127.98, 127.87, 127.81, 127.63, 127.54, 127.48, 127.47, 124.5, 124.1, 124.0, 123.9, 109.4, 109.2, 108.9, 75.1, 75.0, 74.4, 72.4, 71.19, 71.14, 71.03, 65.5, 65.4, 62.7; ESI-HRMS calcd for $C_{117}H_{100}O_{21}Na$ *m*/*z* $[M+Na]^+$: 1863.6655. Found: 1863.6660.

*4.2.4. (S)-(+)-1,3,4,5-Tetragalloylapiitol ((S)-**1**).* To a solution of **9** (112 mg, 0.061 mmol) in THF/MeOH/H_2O (22 mL, 20:1:1 v/v) was added palladium hydroxide on carbon (palladium 20 wt % on carbon). The suspension was stirred for 13 h at room temperature under H_2 gas. The mixture was filtered through Celite, and the filtrate was concentrated. After the residue was dissolved with EtOAc, the resulting precipitate was filtered off, and the filtrate was concentrated. The crude crystals were recrystallized from toluene/EtOAc to give (*S*)-**1** (46 mg, 99% yield) as a pale yellow solid: mp: >300 °C (toluene/EtOAc); $[\alpha]_D^{20}$ +20.3 (*c* 1.0, MeOH); R_f=0.39 ($CHCl_3$/MeOH/H_2O=10:10:3 v/v); IR (KBr, disk): 3379, 1701 cm^{-1}; ^1H NMR (250 MHz, C_5D_5N): δ 7.85, 7.81, 7.79, 7.78 (each s, 8H, Ar*H*), 6.43 (dd, $J_{3,4a}$=2.5 Hz, $J_{3,4b}$=8.0 Hz, 1H, H-3), 5.30 (dd, $J_{4a,3}$=2.5 Hz, $J_{4a,4b}$=12.0 Hz, 1H, H-4a), 5.11, 4.87 (each d, J=11.5 Hz, 2H, H-1), 5.06 (dd, $J_{4b,3}$=8.0 Hz, $J_{4b,4a}$=12.0 Hz, 1H, H-4b), 4.97, 4.90 (each d, J=11.7 Hz, 2H, H-1′); ^{13}C NMR (63 MHz, C_5D_5N): δ 166.9, 166.7, 166.6, 166.2, 147.3, 147.2, 140.99, 140.97, 140.92, 120.63, 120.56, 120.45, 110.2, 74.2, 72.6, 65.33, 65.25, 63.6; ESI-HRMS calcd for $C_{33}H_{28}O_{21}Na$ *m*/*z* $[M+Na]^+$: 783.1021. Found: 783.1056.

4.3. Total synthesis of (*R*)-1,3,4,5-tetragalloylapiitol

*4.3.1. 2,3-O-Benzylidene-α/β-D-ribofuranose (**10**).* To a suspension of D-ribose (10.0 g, 66.6 mmol), freshly distilled benzaldehyde (27.0 mL, 266.4 mmol), and $CuSO_4$ (20 g) in dry DMF (30 mL) was added camphor sulfonic acid (7.7 g, 33.3 mmol). After stirring for 48 h at room temperature under argon, the reaction mixture was quenched with triethylamine (30 mL) and diluted with CH_2Cl_2 (70 mL), after which 20 g of Celite was added to the mixture. After stirring for 15 min, the suspension was filtered through Celite. The filter cake was washed with CH_2Cl_2 (20 mL×3), and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/acetone=5:1 then 3:2 v/v) to give **10** (5.18 g, 33% yield, α/β=1:10) as colorless needles: mp 124.8–125.9 °C (hexane/EtOAc) [lit. 123–124 °C (benzene)[19]]; $[\alpha]_D^{17}$ −22.7 (*c* 1.02, $CHCl_3$) [lit. $[\alpha]_D^{20}$ −22.4 (*c* 1.4, $CHCl_3$)[14]]; R_f=0.26 (hexane/EtOAc=1:1 v/v); IR (KBr, disk): 3303, 2937, 767, 697 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, selected β-anomer signal): δ 7.53–7.36 (m, 5H, Ar*H*), 5.77 (s, 1H, PhC*H*), 5.56 (br d, $J_{1,OH}$=3.5 Hz, 1H, H-1), 4.91 (d, $J_{3,2}$=6.2 Hz, 1H, H-3), 4.68 (d, $J_{2,3}$=6.2 Hz, 1H, H-2), 4.64, 3.46 (each br s, 2H, O*H*×2), 4.57 (t, $J_{4,5}$=2.5 Hz, 1H, H-4), 3.77 (m, 2H, H-5); ^{13}C NMR (63 MHz, $CDCl_3$, selected β-anomer signal): δ 135.8, 129.9, 128.4, 126.9, 105.8, 102.7, 87.54, 87.48, 82.6, 63.6; ESI-HRMS calcd for $C_{12}H_{14}O_5Na$ *m*/*z* $[M+Na]^+$: 261.0739. Found: 261.0723.

*4.3.2. 2,3-O-Benzylidene-2-C-(hydroxymethyl)-α/β-D-ribofuranose (**11**).* To a solution of **10** (4.6 g, 19.3 mmol) and potassium carbonate (3.74 g, 27.0 mmol) in MeOH (69.0 mL) was added a 37% aq formaldehyde solution (41.0 mL). After stirring for 8 h at 85 °C, the reaction mixture was neutralized with 1 M aq HCl solution and concentrated. The remaining aqueous solution was extracted with CH_2Cl_2 (20 mL×5), and the combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/acetone=1:1 v/v) to give **12** (4.5 g, 88% yield, α/β=1:3) as colorless needles: mp 145.1–146.7 °C (EtOH); $[\alpha]_D^{18}$ −16.3 (*c* 1.01, MeOH); R_f=0.26 (hexane/acetone=1:1 v/v); IR (KBr, disk): 3331, 2929, 2887, 769, 695 cm^{-1}; ^1H NMR (250 MHz, CD_3OD, selected β-anomer signal): δ 7.64–7.35 (m, 5H, Ar*H*), 6.06 (s, 1H, PhC*H*), 5.36 (s, 1H, H-1), 4.70 (s, 1H, H-3), 4.31 (t, $J_{4,5}$=5.3 Hz, 1H, H-4), 3.94 (s, 2H,H-6), 3.68 (2H, d, $J_{5,4}$=5.3 Hz, H-5); ^{13}C NMR (63 MHz, CD_3OD, selected β-anomer signal): δ 138.7, 130.6, 129.2, 128.1, 107.7, 104.2, 96.3, 88.4, 85.8, 64.1, 62.5; ESI-HRMS calcd for $C_{13}H_{16}O_6Na$ *m*/*z* $[M+Na]^+$: 291.0845. Found: 291.0867.

*4.3.3. 2,3-O-Benzylidene-3-C-(hydroxymethyl)-α/β-L-erythrofuranose (**12**).* To a solution of **11** (3.7 g, 13.8 mmol) in MeOH (60.0 mL) was cautiously added sodium borohydride (1.6 g, 41.5 mmol) in

small portions. After stirring for 30 min at room temperature, the reaction mixture was cooled to 0 °C and then neutralized to pH 7 with a 1 M aq HCl solution. To this mixture was then added a solution of sodium periodate (5.9 g, 27.6 mmol) in H_2O (45.0 mL), and the reaction mixture was stirred for an additional 1 h at room temperature. After the solvent was evaporated, the remaining aqueous solution was extracted with EtOAc (20 mL×3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=3:2 v/v) to give **12** (2.4 g, 73% yield, α/β=1:10) as a colorless syrup: $[\alpha]_D^{17}$ +35.9 (*c* 1.05, $CHCl_3$); R_f=0.56 (hexane/acetone=3:2 v/v); IR (NaCl, neat): 3409, 2939, 760, 699 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, selected β-anomer signal): δ 7.53–7.34 (m, 5H, Ar*H*), 5.89 (s, 1H, PhC*H*), 5.53 (s, 1H, H-1), 4.44 (s, 1H, H-2), 4.12, 4.06 (each d, *J*=10.3 Hz, 2H, H-4), 3.91, 3.85 (each d, *J*=11.7 Hz, 2H, H-5), 3.75, 2.84 (each br s, 2H, O*H*×2); ^{13}C NMR (63 MHz, $CDCl_3$, selected β-anomer signal): δ 136.0, 129.9, 128.4, 127.0, 106.2, 101.2, 91.9, 87.3, 73.3, 63.1. ESI-HRMS calcd for $C_{12}H_{14}O_5Na$ *m*/*z* $[M+Na]^+$: 261.0739. Found: 261.0735.

*4.3.4. [(5R)-2-Phenyl-1,3-dioxolane-4,4,5-triyl]trimethanol (**13**).* This compound was prepared according to the procedure described for **7**, employing **12** (1.0 g, 4.20 mmol) and sodium borohydride (191 mg, 5.04 mmol) to afford the pure compound **13** (1.01 g, quant.) as colorless needles: mp: 81.5–82.6 °C (hexane-EtOAc); $[\alpha]_D^{13}$ +1.8 (*c* 1.0, MeOH); R_f=0.20 (EtOAc); IR (KBr, disk): 3323, 764, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.41–7.27 (m, 5H, Ar*H*), 5.73 (s, 1H, PhC*H*), 4.02 (t, $J_{3,4}$=6.0 Hz, 1H, H-3), 3.82 (d, $J_{4,3}$=5.9 Hz, 2H, H-4), 3.75–3.60 (m, 4H, H-1 and 1′); ^{13}C NMR (63 MHz, $CDCl_3$): δ 136.5, 129.7, 128.4, 126.7, 102.6, 83.3, 81.0, 63.5, 61.5, 60.0; ESI-HRMS calcd for $C_{12}H_{16}O_5Na$ *m*/*z* $[M+Na]^+$: 263.0895. Found: 263.0891.

*4.3.5. (3R)-2-Hydroxymethylbutane-1,2,3,4-tetrol (**14**) [L-apiitol].* - This compound was prepared according to the procedure described for **8**, employing **13** (200 mg, 0.109 mmol) and palladium hydroxide on carbon (palladium 20 wt % on carbon) to afford the pure compound **14** (126.5 mg, quant.) as a colorless syrup: $[\alpha]_D^{26}$ +7.4 (*c* 1.0, MeOH) [lit. $[\alpha]_D^{26}$ +4.3 (*c* 1.2, MeOH)[5]]; R_f=0.31 ($CHCl_3$/MeOH/H_2O=10:10:1 v/v): The ^1H and ^{13}C NMR data for synthetic **14** agreed well with previously reported values.[4,5]

*4.3.6. (3R)-2-Hydroxy-2-[3,4,5-tris(benzyloxy)benzoyloxymethyl]butane-1,3,4-triyl tris[3,4,5-tris(benzyloxy)benzoate] (**15**).* This compound was prepared according to the procedure described for **9**, employing **14** (5.7 mg, 0.0375 mmol), 3,4,5-tris(benzyloxy)benzoyl chloride (138 mg, 0.300 mmol), and pyridine (1.0 mL) to afford the pure compound **15** (61.3 mg, 89% yield) as colorless needles: mp: 158.9–160.1 °C (hexane/EtOAc); $[\alpha]_D^{26}$ −15.1 (*c* 1.0, $CHCl_3$); R_f=0.51 (toluene/acetone=10:1 v/v); IR (KBr, disk): 3423, 3031, 2869, 1717, 731, 694 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.42–7.18 (m, 68H, Ar*H*), 5.88 (dd, $J_{3,4a}$=3.4 Hz, $J_{3,4b}$=7.6 Hz, 1H, H-3), 5.16–4.87 (m, 24H, PhCH_2×12), 5.01 (dd, $J_{4a,3}$=3.4 Hz, $J_{4a,4b}$=12.1 Hz, 1H, H-4a), 4.70, 4.49 (each d, *J*=11.9 Hz, 2H, H-1), 4.65 (dd, $J_{4b,3}$=7.6 Hz, $J_{4b,4a}$=12.2 Hz, 1H, H-4b), 4.58, 4.44 (each d, *J*=11.8 Hz, 2H, H-1′), 3.30 (br s, 1H, −O*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ 166.2, 166.1, 165.7, 165.2, 152.68, 152.65, 152.64, 152.57, 143.3, 143.07, 143.05, 142.7, 137.46, 137.45, 137.40, 137.38, 136.63, 136.61, 136.5, 136.4, 128.50, 128.49, 128.45, 128.39, 128.38, 128.31, 128.15, 128.10, 127.98, 127.87, 127.81, 127.64, 127.54, 127.49, 127.47, 124.5, 124.1, 124.0, 123.9, 109.4, 109.3, 109.0, 75.13, 75.05, 74.4, 72.4, 71.21, 71.17, 71.05, 65.5, 65.4, 62.7; ESI-HRMS calcd for $C_{117}H_{100}O_{21}Na$ *m*/*z* $[M+Na]^+$: 1863.6655. Found: 1863.6615.

*4.3.7. (R)-(−)-1,3,4,5-Tetragalloylapiitol ((R)-**1**).* This compound was prepared according to the procedure described for (*S*)-**1**, employing **15** (200 mg, 0.109 mmol) and palladium hydroxide on carbon (palladium 20 wt % on carbon) to afford the pure compound (*R*)-**1** (82 mg, 99% yield) as a pale yellow solid: mp: >300 °C (toluene/EtOAc); $[\alpha]_D^{15}$ −20.5 (*c* 1.03, MeOH); R_f=0.39 ($CHCl_3$/MeOH/H_2O=10:10:3 v/v); IR (KBr, disk): 3367, 1700 cm^{-1}; ^1H NMR (250 MHz, C_5D_5N): δ 7.84, 7.81, 7.79, 7.77 (each s, 8H, Ar*H*), 6.43 (dd, $J_{3,4a}$=2.6 Hz, $J_{3,4b}$=8.2 Hz, 1H, H-3), 5.30 (dd, $J_{4a,3}$=2.6 Hz, $J_{4a,4b}$=11.8 Hz, 1H, H-4a), 5.10, 4.87 (each d, *J*=11.5 Hz, 2H, H-1), 5.06 (dd, $J_{4b,3}$=8.2 Hz, $J_{4b,4a}$=11.8 Hz, 1H, H-4b), 4.97, 4.91 (each d, *J*=11.7 Hz, 2H, H-1′); ^{13}C NMR (63 MHz, C_5D_5N): δ 166.9, 166.7, 166.6, 166.2, 147.3, 147.2, 140.99, 140.98, 140.92, 120.63, 120.56, 120.46, 110.2, 74.2, 72.6, 65.34, 65.29, 63.6; ESI-HRMS calcd for $C_{33}H_{28}O_{21}Na$ *m*/*z* $[M+Na]^+$: 783.1021. Found: 783.1014.

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15. (3*S*)-2,3-*Dihydroxy*-2-[3,4,5-*tris*(*benzyloxy*)*benzoyloxymethyl*]*butane*-1,4-*diyl bis* [3,4,5-*tris*(*benzyloxy*)*benzoate*] (**9′**). mp: 108.4–109.5 °C (colorless needles, hexane/EtOAc); $[\alpha]_D^{15}$ −2.7 (*c* 1.0, $CHCl_3$); R_f=0.29 (toluene/acetone 10:1 v/v); IR (KBr, disk): 3452, 3031, 2857, 1712, 734, 695 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.39–7.18 (m, 51H, Ar*H*), 5.09–5.00 (m, 18H, PhCH_2×9), 4.85 (dd, $J_{4a,3}$=3.9 Hz, $J_{4a,4b}$=11.8 Hz, 1H, H-4a), 4.61–4.54 (dd, 1H, H-4b, overlapped with H-1 and 1′ signals), 4.60, 4.49 (each d, *J*=11.9 Hz, 2H, H-1), 4.56 (s, 2H, H-1′), 4.08 (br ddd, $J_{3,4a}$=4.0 Hz, $J_{3,4b}$=5.8 Hz, $J_{3,\ OH}$=4.8 Hz, 1H, H-3), 3.20 (br s, 1H, −O*H*), 3.07 (br d, J_{OH3}=4.9 Hz, 1H, −O*H*); ^{13}C NMR (63 MHz, $CDCl_3$): δ 166.5, 166.4, 166.1, 152.59, 152.57, 142.96, 142.92, 142.8, 137.39, 137.37, 137.35, 136.6, 128.48, 128.41, 128.40, 128.37, 128.13, 127.97, 127.88, 127.72, 127.53, 127.47, 127.46, 124.4, 124.1, 109.26, 109.22, 109.19, 75.1, 74.5, 71.2, 65.3, 65.2; ESI-HRMS calcd for $C_{89}H_{78}O_{17}Na$ *m*/*z* $[M+Na]^+$: 1441.5137. Found: 1441.5106.
16. In the cases of low concentration, the optical rotations were $[\alpha]_D^{25}$ +19.8 (*c* 0.1, MeOH) and $[\alpha]_D^{18}$ +20.0 (*c* 0.03, MeOH).
17. Since the precursor **9** bearing four nonpolar 3,4,5-tris(benzyloxy)benzoyl groups was insoluble in 2 N NaOH/MeOH (1:1), the alkaline hydrolysis of **9** was carried out in 2 N NaOH/MeOH/THF (1:1:1).
18. (3*S*)-2-*Hydroxy*-2-(*benzoyloxymethyl*)*butane*-1,3,4-*triyltrisbenzoate* ((*S*)-**16**). To a solution of **8** (35 mg, 0.23 mmol) in pyridine (2.0 mL) was added dropwise benzoyl chloride (159 μL, 1.38 mmol) at 0 °C. After stirring for 12 h at room

temperature, the reaction mixture was quenched with a saturated aq $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL×3), and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc=4: 1 v/v) to give **16** (130 mg, 99% yield) as a colorless amorphous powder. $[\alpha]_D^{20}$ +22.7 (c 1.01, $CHCl_3$); CD (MeOH, *c* 0.018 μmol/mL) λ_{ext} 227 nm ($\Delta\varepsilon$ +3.5), 241 ($\Delta\varepsilon$ −1.2); R_f=0.41 (hexane/EtOAc=3:2 v/v); IR (NaCl, neat): 3470, 1725, 1268, 709 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 8.05–7.32 (m, 20H, *ArH*), 5.97 (dd, $J_{3,4a}$=3.3 Hz, $J_{3,4b}$=7.4 Hz, 1H, H-3), 5.00 (dd, $J_{4a,3}$=3.3 Hz, $J_{4a,4b}$=12.1 Hz, 1H, H-4a), 4.79, 4.68 (each d, *J*=11.8 Hz, 2H, H-1), 4.77 (dd, $J_{4b,3}$=7.5 Hz, $J_{4b,4a}$=11.9 Hz, 1H, H-4b), 4.71, 4.62 (each d, *J*=12.0 Hz, 2H, H-1′), 3.63 (br s, 1H, −OH); ^{13}C NMR (63 MHz, $CDCl_3$): δ 166.6, 166.2, 165.5, 133.5, 133.1, 129.80, 129.78, 129.6, 129.4, 129.15, 129.11, 129.05, 128.5, 128.4, 74.3, 72.3, 65.5, 65.4, 62.9; ESI-HRMS calcd for $C_{33}H_{28}O_9Na$ *m*/*z* $[M+Na]^+$: 591.1631. Found: 591.1637. (3*R*)-2-*Hydroxy*-2-(*benzoyloxymethyl*)*butane*-1,3,4-*triyltrisbenzoate* ((*R*)-**16**) This compound was prepared according to the procedure described for (*S*)-**16**, employing **14** (35 mg, 0.230 mmol), benzoyl chloride (159 μL, 1.380 mmol), and pyridine (1 mL) to afford the pure compound (*R*)-**16** (131 mg, quant.) as a colorless amorphous powder: $[\alpha]_D^{26}$ −23.0 (*c* 1.0, $CHCl_3$); CD (MeOH, *c* 0.018 μmol/mL) λ_{ext} 227 nm ($\Delta\varepsilon$ −3.6), 241 ($\Delta\varepsilon$ +1.3); R_f=0.41 (hexane/EtOAc=3:2 v/v); IR (NaCl, neat): 3461, 1725, 1267, 707 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 8.06–7.33 (m, 20H, ArH), 5.96 (dd, J_{34a}=3.3 Hz, J_{34b}=7.4 Hz, 1H, H-3), 4.99 (dd, $J_{4a,3}$=3.3 Hz, $J_{4a,4b}$=12.1 Hz, 1H, H-4a), 4.79, 4.67 (each d, *J*=11.9 Hz, 2H, H-1), 4.77 (dd, $J_{4b,3}$=7.4 Hz, $J_{4b,4a}$=12.0 Hz, 1H, H-4b), 4.71, 4.61 (each d, *J*=12.0 Hz, 2H, H-1′), 3.54 (br s, 1H, −*OH*); ^{13}C NMR (63 MHz, $CDCl_3$): δ 166.7, 166.2, 165.5, 133.5, 133.1, 129.82, 129.79, 129.7, 129.4, 129.17, 129.12, 129.06, 128.5, 128.4, 74.4, 72.3, 65.5, 65.4, 62.9.

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