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Chemoenzymatic total synthesis of potent HIV RNase H inhibitor (−)-1,3,4,5-tetragalloylapiitol

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ABSTRACT

Starting from racemic dimethyl 2-acetoxy-3-methylenesuccinate, the chemoenzymatic facile total synthesis of (−)-1,3,4,5-tetragalloylapiitol has been demonstrated via an efficient lipase catalyzed resolution followed by a DIBAL reduction–double gallyolation, osmium tetroxide dihydroxylation–double gallyolation, and reductive global *O*-benzyl deprotection pathway.

1. Introduction

Polygalloylated sugars have recently been isolated as bioactive natural products and they possess anti-HIV, antiviral, antitumor and antidiabetic activities (Fig. 1).[1–3] HIV-1 RNase H is an attractive molecular target for the development of new anti-HIV agents as potential chemotherapeutics.[4–6] Gustafson et al. isolated a new potent HIV RNase H inhibitor (−)-1,3,4,5-tetragalloylapiitol **1a** from an extract of the plant *Hylodendron gabunensis*.[1] The structural features revealed that the natural products (−)-apiitol[7] and gallic acid could be the biogenetic precursors of **1a**. Starting from citraconic anhydride, we designed the pentahydroxy sugar apiitol and reported the first total synthesis of (±)-1,3,4,5-tetragalloylapiitol **1a**.[8] Very recently, Kraus and Kempema also accomplished a flexible racemic synthesis of **1a** using the 1,3-dihydroxyacetone dimer as the starting material.[9] The chemoenzymatic synthesis provides a powerful approach and new opportunities for accessing chemical diversity.[10] In continuation of our studies on both cyclic anhydrides and derivatives to bioactive natural and unnatural products,[11] and efficient enzymatic resolutions,[12] starting from (±)-dimethyl 2-acetoxy-3-methylenesuccinate **4**, we herein report our results on the first total synthesis of enantiomerically pure (−)-**1a** (Schemes 1 and 2).

2. Results and discussions

We reasoned that (±)-dimethyl 2-acetoxy-3-methylenesuccinate **4** could be a potential precursor for the chemoenzymatic total synthesis of (−)-1,3,4,5-tetragalloylapiitol **1a** via lipase catalyzed resolution followed by reduction of two ester units and the consequent carbon–carbon double bond dihydroxylation route. We started our synthesis with the selenium dioxide allylic oxidation of dimethyl itaconate **2** and obtained the desired product (±)-**4**, but only in 37% yield (Scheme 1). All our attempts to further improve the yield were ineffective and under the forced reaction conditions, we always ended up with the formation of decomposed materials and polymeric gums. Even the use of a catalytic amount of SeO_2 and *t*-BuOOH at room temperature for the conversion of **2** to (±)-**4** was not effective and the starting material remained unreacted. Finally starting from dimethyl tartarate **3**, the required precursor (±)-**4** was synthesized in three steps with very good overall yield by using the known Baylis–Hillman reaction between the methyl 2-oxoacetate and methyl acrylate, followed by an O-acylation step.[13]

On the basis of the higher acidity of the methine proton in (−)-**4** and the anticipated propensity for racemization, an enzymatic resolution of (±)-**4** appeared more appropriate. Hence systematic studies on the biphasic hydrolytic enzymatic resolution of (±)-**4** using the promising enzymes *Pig pancreas* lipase (PPL), *Candida cylindracea* lipase (CCL), and *Pseudomonas cepacia* lipase (Amano PS) for the preparation of enantiomerically pure (−)-**4** were planned.[12–14] The enzyme PPL was ineffective in recognizing our racemic substrate **4**, while we obtained very low enantiomeric excess when using the enzyme CCL (Table 1, entry 4). Fortunately, the readily available and relatively inexpensive enzyme Amano PS, which is specific for the secondary alcohols, better recognized our starting material (±)-**4**. The Amano PS catalyzed resolutions of (±)-**4** at 25 °C and 35 °C were found to be slow (Table 1, entries 5 and 6). The same Amano PS catalyzed biphasic resolution of (±)-**4** at 50 °C furnished the desired unhydrolyzed enantiomerically pure (−)-**4** in 42% yield with 97% ee (by chiral HPLC) in 84 h (Table 1, entry 7). In the above mentioned enzymatic resolution the hydrolyzed alcohol (+)-**5** was obtained in 58% yield, but with only 53% ee. The same reaction at about 40% conversion also provided the product (+)-**5** in very good yield with 87% ee (by chiral HPLC).[15] We can infer that both the multifunctional enantiomerically pure products (−)-**4** and

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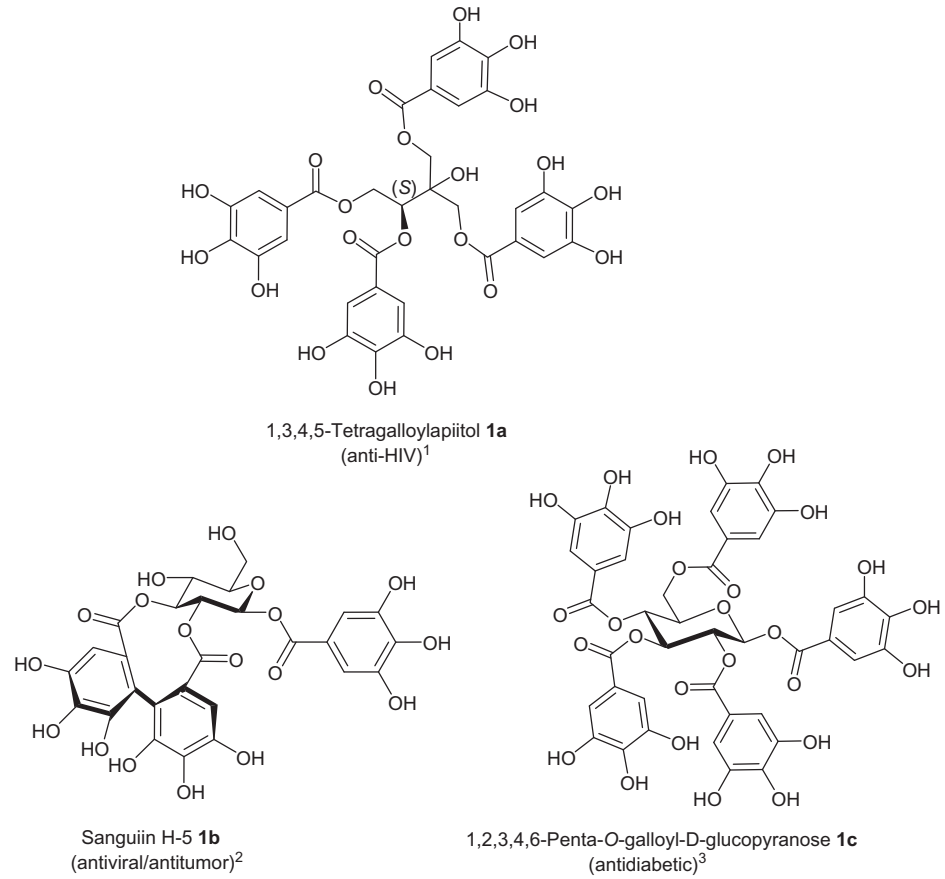
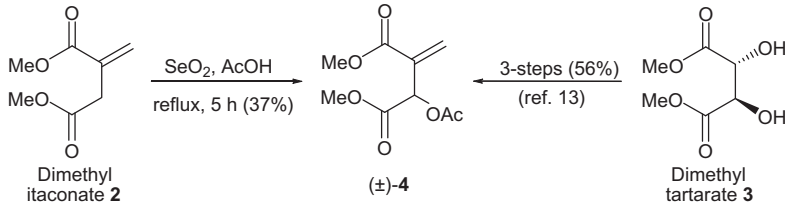
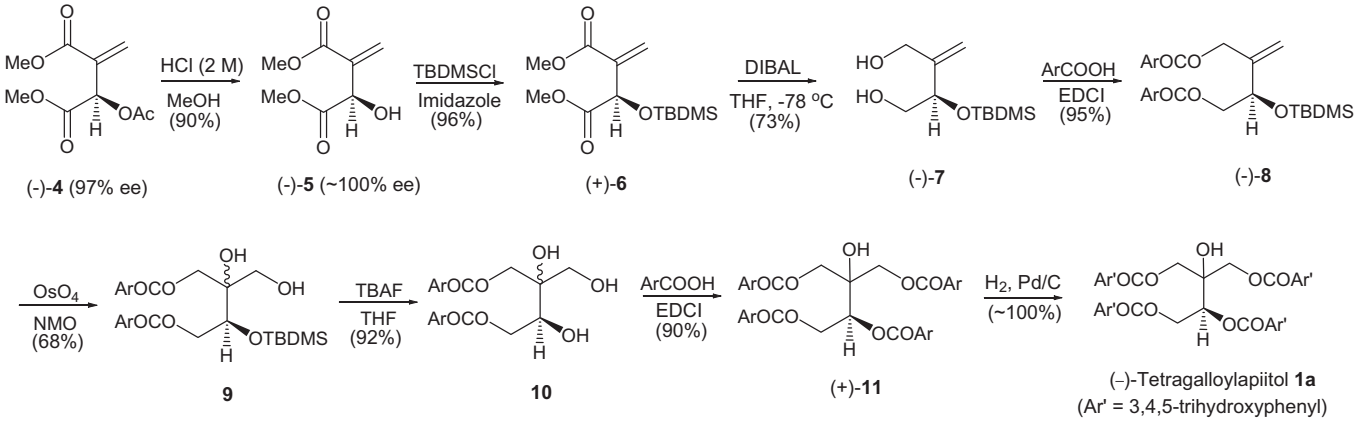


Figure 1. Recently isolated bioactive natural products with the polygalloylated sugar architectures.[1–3]

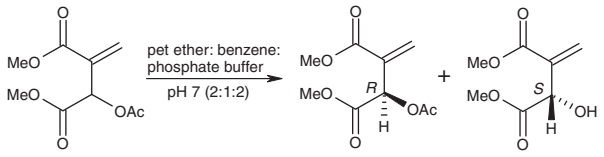


Scheme 1. Synthesis of (±)-dimethyl 2-acetoxy-3-methylenesuccinate **4**.



Scheme 2. Total synthesis of (−)-1,3,4,5-tetragalloylapiitol from (*R*)-dimethyl 2-hydroxy-3-methylenesuccinate.

Table 1
Lipase catalyzed resolution of (±)-**4**



(±)-**4** (-)-**4** (+)-**5**

Entry	Enzyme	Temp/time[a]	(−)-**4**:% yield/ee
1	PPL	25 °C, 48 h	NR[b]
2	PPL	35 °C, 48 h	NR
3	CCL	25 °C, 48 h	NR
4	CCL	35 °C, 48 h	57/25
5	Amano PS	25 °C, 96 h	83/ND[c]
6	Amano PS	35 °C, 8 days	44/95[d]
7	Amano PS	50 °C, 84 h	42/97[d]

[a] Reactions were monitored by HPLC.
[b] NR: no reaction.
[c] ND: not determined.
[d] Chiral HPLC, the (+)-**5** was obtained in 58% yield with only 53% ee.

(+)-**5** would serve as important building blocks for the total synthesis of several desired bioactive natural and unnatural products.

The enantiomerically pure (−)-dimethyl 2-acetoxy-3-methylenesuccinate **4** on acid catalyzed methanolysis delivered the desired alcohol (−)-**5** in 90% yield with ~100% ee (by chiral HPLC), which on treatment with TBDMSCl gave the corresponding silyl ether (+)-**6** in 96% yield (Scheme 2). To avoid the foreseen difficulty of possible intramolecular cyclization upon dihydroxylation to form the γ-lactone, we first considered the reduction of both the ester moieties in (+)-**6** to the corresponding primary alcohols. The DIBAL (6.00 equiv) reduction of diester (+)-**6** at −78 °C exclusively provided the expected diol (−)-**7** in 73% yield. At this stage we decided to carry out the double gallyolation of diol (−)-**7** rather than the immediate dihydroxylation of the carbon–carbon double bond to form the corresponding tetrol for two obvious reasons; (i) to keep the polarity of our intermediate compounds under control for convenient column chromatographic purifications and (ii) to avoid any plausible intramolecular shuffling of our TBDMS protecting group.[16] The *N*-ethyl *N*′-(3-dimethylpropyl)carbodiimide (EDCI) induced dehydrative double coupling of diol (−)-**7** with the triple benzyl protected gallic acid[17] to furnish the required diester (−)-**8** in 95% yield. The osmium tetroxide induced dihydroxylation of the carbon–carbon double bond in compound (−)-**8** in the presence of *N*-methylmorpholine *N*-oxide (NMO) as the oxidizing agent yielded a diastereomeric mixture of the desired diol **9** in 68% yield with a ~3:2 ratio (by NMR). The TBAF-deprotection of silyl ether **9** provided the expected diastereomeric mixture of triol **10** in 92% yield. It should be noted that triol **10** contains free the 1°, 2°, and 3° alcohol units, but we did not notice any intramolecular acyl migration under our reaction conditions.[16] The second EDCI induced selective dehydrative double coupling of 1° and 2° alcohol units in triol **10** with the tri-benzyl protected gallic acid yielded the required enantiomerically pure dodecabenzyl protected tetraester (+)-**11** in 90% yield. The final product **1a** is very polar in nature as it contains the free 12-phenolic and an alcoholic hydroxyl groups. Hence, we decided to check the enantiomeric purity of the penultimate step product (+)-**11**; all attempts to resolve a sample of (±)-**11** from our earlier racemic synthesis[8] on suitable chiral columns were unsuccessful. Finally, hydrogenolysis using palladium on charcoal was used for the global deprotection of benzyl groups in (+)-**11** to obtain the desired natural product (−)-**1a** in ~100% yield. The analytical and spectroscopic data obtained for (−)-1,3,4,5-tetragalloylapiitol **1a** were in complete agreement with the reported data.[1,8] Starting from enantiomerically pure (−)-dimethyl 2-acetoxy-3-methylenesuccinate **4** the (−)-1,3,4,5-tetragalloylapiitol **1a** was obtained in 8-steps with 34% overall yield.

3. Conclusion

In conclusion, we have accomplished a straightforward chemoenzymatic total synthesis of the naturally occurring potent anti-HIV compound (−)-1,3,4,5-tetragalloylapiitol in very good overall yield. In the present synthesis an efficient enzymatic resolution for the preparation of enantiomerically pure dimethyl acetoxyitaconate, DIBAL reduction of two different ester functions, and very clean simultaneous deprotections of the twelve benzyl groups were the key steps. In our present synthesis the stepwise double gallyolation demanded one extra step and was essential for the smooth handling of the intermediate compounds. We feel that the use of dimethyl itaconate/tartarate for the synthesis of a sugar moiety is noteworthy.

4. Experimental

4.1. General

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR spectrometer, 400 MHz NMR spectrometer, and 500 MHz NMR spectrometer using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 NMR spectrometer (50 MHz), 400 NMR spectrometer (100 MHz), and 500 NMR spectrometer (125 MHz). Mass spectra were taken on MS-TOF mass spectrometer. The IR spectra were recorded on an FT-IR spectrometer. Elemental analyses were taken at NCL. HRMS (ESI) were taken on mass spectrometer at IICT, Hyderabad. Column chromatographic separations were carried out on silica gel (60–120 mesh). Commercially available TBDMCl, DIBAL, EDCI, DMAP, aqueous solution of NMO (60%), OsO_4, TBAF solution in THF (1.0 M), and Pd on charcoal (10 wt %) were used. 3,4,5-Tris(benzyloxy)benzoic acid was prepared using the known procedure.[17]

4.2. (±)-Dimethyl 2-acetoxy-3-methylenesuccinate 4

To a stirred solution of dimethyl itaconate (2.00 g, 12.66 mmol) in glacial acetic acid (25 mL) was added SeO_2 (1.55 g, 13.92 mmol) and the reaction mixture was refluxed for 5 h. The deposited selenium metal was filtered off and the residue was washed with acetic acid (5 mL). The filtrate was concentrated in vacuo and the residue obtained was dissolved in ethyl acetate (30 mL). The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 15% ethyl acetate/petroleum ether as an eluent afforded pure product (±)-**4** as a colorless oil (1.01 g, 37%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.18 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 6.00 (s, 1H), 6.02 (s, 1H), 6.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.6, 52.3, 52.7, 70.2, 130.7, 134.6, 164.8, 168.3, 169.6; ESIMS (*m*/*z*) 217 $[M+H]^+$, 239 $[M+Na]^+$, 255 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1755, 1747, 1732, 1638 cm^{-1}.

4.3. (*R*)-Dimethyl 2-acetoxy-3-methylenesuccinate 4

To a stirred solution of acetate (±)-**4** (1.00 g, 4.63 mmol) in a mixture of petroleum ether and benzene (15 mL, 1:2) were successively added the phosphate buffer (pH 7, 10 mL) and enzyme Amano PS (100 mg). The resulting reaction mixture was stirred at 50 °C for 84 h, with monitoring the reaction progress by chiral HPLC. The

reaction mixture was filtered through Celite bed and washed with ethyl acetate (50 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 15% ethyl acetate/petroleum ether as an eluent afforded pure product (−)-**4** as a colorless oil (421 mg, 42% yield, 97% ee). $[\alpha]_D^{25} = -49.9$ (*c* 0.50, EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.18 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 6.00 (s, 1H), 6.02 (s, 1H), 6.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.6, 52.3, 52.7, 70.2, 130.7, 134.6, 164.8, 168.3, 169.6; ESIMS (*m*/*z*) 217 $[M+H]^+$, 239 $[M+Na]^+$, 255 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 1755, 1747, 1732, 1638 cm^{-1}. In the aforementioned enzymatic resolution the hydrolyzed opposite isomer (+)-**5** was obtained in 58% yield with only 53% ee. *HPLC conditions*: column: Kromasil 5-CelluCoat (250 × 4.6 mm), wavelength: 220 nm, flow rate: 0.5 mL/min, retention time: 19.8 min (+)-isomer, 25.2 min (−)-isomer.

4.4. (*R*)-Dimethyl 2-hydroxy-3-methylenesuccinate 5

To a stirred solution of acetate (−)-**4** (400 mg, 1.85 mmol) in methanol (10 mL) at 0 °C was added 2 M HCl (10 mL) and the reaction mixture was further stirred for 2 h. The reaction mixture was concentrated in vacuo and the residue obtained was diluted with ethyl acetate (20 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 25% ethyl acetate/petroleum ether as an eluent afforded pure product (−)-**5** as a colorless oil (290 mg, 90%). $[\alpha]_D^{25} = -19.7$ (*c* 0.68, EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.58 (br s, 1H), 3.79 (s, 6H), 4.88 (br s, 1H), 5.97 (s, 1H), 6.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.1, 53.0, 71.2, 129.2, 137.8, 165.6, 172.7; ESIMS (*m*/*z*) 175 $[M+H]^+$, 197 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3503, 1746, 1726, 1636 cm^{-1}.

4.5. (*R*)-Dimethyl 2-((*tert*-butyldimethylsilyl)oxy)-3-methylenesuccinate 6

To a stirred solution of alcohol (−)-**5** (250 mg, 1.44 mmol) in dichloromethane (10 mL) at 0 °C were added imidazole (108 mg, 1.58 mmol) and TBDMSCl (239 mg, 1.58 mmol). The reaction mixture was allowed to return to room temperature and stirred for a further 6 h. The reaction mixture was concentrated in vacuo and the residue obtained was diluted with ethyl acetate (20 mL). The organic layer was washed with water and brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 5% ethyl acetate/petroleum ether as an eluent afforded pure product (+)-**6** as a colorless oil (397 mg, 96%). $[\alpha]_D^{25} = +23.9$ (*c* 0.60, EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.10 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 3.72 (s, 3H), 3.78 (s, 3H), 5.08 (dd, *J* = 2 and 2 Hz, 1H), 6.07 (dd, *J* = 2 and 2 Hz, 1H), 6.38 (dd, *J* = 2 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.4, −5.2, 18.3, 25.6, 52.0, 52.3, 70.9, 126.4, 138.7, 165.9, 171.2; ESIMS (*m*/*z*) 289 $[M+H]^+$, 311 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1759, 1736, 1686 cm^{-1}.

4.6. (*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylenebutane-1,4-diol 7

To a stirred solution of diester (+)-**6** (350 mg, 1.22 mmol) in THF (10 mL) at −78 °C was dropwise added a DIBAL solution in toluene (1 M, 7.30 mL, 7.30 mmol) and the reaction mixture was stirred for 2 h at the same temperature. The reaction was quenched with saturated NH_4Cl solution and then concentrated in vacuo. The obtained residue was diluted with ethyl acetate (20 mL) and washed with brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 40% ethyl acetate/petroleum ether as an eluent afforded pure product (−)-**7** as a colorless oil (206 mg, 73%). $[\alpha]_D^{25} = -7.0$ (*c* 0.16, EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.07 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 2.46 (br s, 2H), 3.54–3.70 (m, 2H), 4.10 (d, *J* = 12 Hz, 1H), 4.21 (d, *J* = 12 Hz, 1H), 4.34 (t, *J* = 6 Hz, 1H), 5.18 (br s, 1H), 5.20 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.1, −4.8, 18.1, 25.7, 63.1, 66.5, 75.2, 114.2, 148.1; ESIMS (*m*/*z*) 255 $[M+Na]^+$; HRMS (ESI) calcd for $C_{11}H_{24}O_3NaSi$ 255.1392, found 255.1383; IR ($CHCl_3$) ν_{max} 3456, 1652 cm^{-1}.

4.7. (*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylenebutane-1,4-diyl bis(3,4,5-tris(benzyloxy)benzoate) 8

To a stirred solution of mixture of diol (−)-**7** (150 mg, 0.65 mmol), 3,4,5-tris(benzyloxy)benzoic acid (tribenzylgallic acid) (626 mg, 1.42 mmol), and a catalytic amount of DMAP in dichloromethane (10 mL) at room temperature was added dropwise a solution of EDCI (371 mg, 1.94 mmol) in dichloromethane (3 mL). The reaction mixture was stirred for a further 3 h and then quenched with water (10 mL). The reaction mixture was extracted with dichloromethane (2 × 25 mL) and the combined organic layer was washed with water and brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 15% ethyl acetate/petroleum ether as an eluent afforded pure product (−)-**8** as a white solid (662 mg, 95%). Mp 59–61 °C; $[\alpha]_D^{25} = -4.2$ (*c* 0.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 4.38 (d, *J* = 6 Hz, 2H), 4.62 (t, *J* = 6 Hz, 1H), 4.80–5.00 (m, 2H), 5.05 (s, 4H), 5.09 (s, 8H), 5.34 (s, 1H), 5.40 (s, 1H), 7.15–7.45 (m, 34H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −4.9, −4.8, 18.1, 25.7, 64.4, 68.2, 71.04, 71.06, 72.3, 75.1, 108.9, 117.1, 125.0, 127.46, 127.49, 127.86, 127.94, 128.1, 128.4, 128.5, 136.56, 136.62, 137.4, 142.36, 142.41, 143.4, 152.49, 152.53, 165.7, 165.9; ESIMS (*m*/*z*) 1100 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 1716, 1590 cm^{-1}. Anal. Calcd for $C_{67}H_{68}O_{11}Si$: C, 74.70; H, 6.36. Found: C, 74.37; H, 5.84.

4.8. 3-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-2-(hydroxymethyl)butane-1,4-diyl bis(3,4,5-tris(benzyloxy)benzoate) 9 [diastereomeric mixture (3:2)]

To a stirred solution of diester (−)-**8** (600 mg, 0.56 mmol) and an aqueous solution of NMO (60%, 3 mL) in *t*-butanol (10 mL) at room temperature was added OsO_4 solution in *t*-butanol (0.22 mL, 1 M, 0.22 mmol) and the reaction mixture was further stirred for 6 h. The reaction was quenched with a saturated solution of sodium sulfite and concentrated in vacuo. The obtained residue was diluted with ethyl acetate (25 mL) and washed with water and brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 35% ethyl acetate/petroleum ether as an eluent afforded product **9** as a colorless oil (421 mg, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.07–0.13 (m, 12H), 0.92 (s, 18H), 2.42 (br s, 4H), 3.65–3.83 (m, 4H), 4.05–4.10 (m, 2H), 4.35–4.70 (m, 8H), 5.02–5.15 (m, 24H), 7.20–7.45 (m, 68H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.6, 18.2, 25.8, 64.1, 64.3, 64.9, 65.0, 65.4, 65.9, 71.06, 71.12, 72.5, 74.0, 74.3, 75.1, 108.96, 109.01, 109.07, 109.10, 124.3, 124.6, 124.68, 124.71, 127.4, 127.5, 127.9, 127.96, 127.98, 128.2, 128.5, 136.6, 137.32, 137.34, 142.4, 142.57, 142.62, 152.5, 152.6, 166.1, 166.25, 166.31, 166.6; ESIMS (*m*/*z*) 1134 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3463, 1716, 1590 cm^{-1}. Anal. Calcd for $C_{67}H_{70}O_{13}Si$: C, 72.41; H, 6.35. Found: C, 72.11; H, 6.78.

4.9. 2,3-Dihydroxy-2-(hydroxymethyl)butane-1,4-diyl bis(3,4,5-tris(benzyloxy)benzoate) 10 [diastereomeric mixture (3:2)]

To a stirred solution of diol **9** (400 mg, 0.36 mmol) in THF (10 mL) at 0 °C was added TBAF solution in THF (1 M, 0.43 mL, 0.43 mmol) and the reaction mixture was further stirred at the same temperature for 20 min. The reaction was then quenched with saturated solution of NH_4Cl and concentrated in vacuo. The residue obtained was diluted with ethyl acetate (25 mL) and the organic layer was washed with brine and dried over Na_2SO_4. The concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 65% ethyl acetate/petroleum ether as an eluent afforded product **10** as a colorless oil (330 mg, 92%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.22 (br s, 4H), 3.56–3.90 (m, 4H), 4.00–4.12 (m, 2H), 4.35–4.70 (m, 8H), 4.92–5.00 (m, 2H), 5.00–5.15 (m, 24H), 7.15–7.45 (m, 68H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 63.6, 64.1, 65.1, 65.3, 65.65, 65.69, 71.20, 71.24, 72.1, 72.2, 74.3, 74.8, 75.12, 75.14, 109.2, 109.25, 109.33, 109.4, 127.46, 127.48, 127.5, 127.6, 127.95, 127.97, 128.0, 128.1, 128.2, 128.3, 128.4, 128.46, 128.48, 128.50, 128.53, 136.56, 136.59, 137.31, 137.33, 152.58, 152.61, 166.5, 166.56, 166.58, 166.7; ESIMS (m/z) 1020 $[M+Na]^+$; IR ($CHCl_3$) ν_{max} 3462, 1716, 1590 cm^{-1}. Anal. Calcd for $C_{61}H_{56}O_{13}$: C, 73.48; H, 5.66. Found: C, 73.08; H, 5.33.

4.10. (*S*)-3-Hydroxy-3-(((3,4,5-tris(benzyloxy)benzoyl)oxy) methyl)butane-1,2,4-triyl tris(3,4,5-tris(benzyloxy)benzoate) 11

To a stirred solution of a mixture of triol **10** (300 mg, 0.30 mmol), 3,4,5-tris(benzyloxy)benzoic acid (tribenzylgallic acid) (291 mg, 0.66 mmol), and DMAP (4 mg, 0.03 mmol) in dichloromethane (15 mL) was added dropwise a solution of EDCI (172 mg, 0.90 mmol) in dichloromethane (5 mL) at room temperature. The reaction mixture was stirred for 5 h and then quenched with water (15 mL). The reaction mixture was extracted with dichloromethane (2 × 30 mL). The combined organic layer was washed with water and brine and dried over Na_2SO_4. The concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue using 40% ethyl acetate/petroleum ether as an eluent afforded pure product (+)-**11** as a white solid (499 mg, 90%). Mp 130–131 °C; $[\alpha]_D^{25} = +26.5$ (c 0.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.42 (br s, 1H), 4.46 (dd, J = 25 and 15 Hz, 2H), 4.58 (d, J = 10 Hz, 1H), 4.62–4.68 (m, 1H), 4.70 (d, J = 10 Hz,1H), 4.87–5.15 (m, 25H), 5.87–5.93 (m, 1H), 7.15–7.45 (m, 68H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 62.7, 65.4, 65.5, 70.9, 71.0, 71.1, 72.3, 74.3, 75.0, 75.1, 108.8, 109.1, 109.3, 123.9, 123.95, 124.03, 124.4, 127.4, 127.46, 127.52, 127.6, 127.8, 127.9, 127.96, 127.98, 128.09, 128.14, 128.3, 128.39, 128.40, 128.45, 128.47, 128.5, 136.3, 136.4, 136.5, 136.6, 137.3, 137.37, 137.38, 142.5, 142.8, 142.9, 143.1, 152.5, 152.56, 152.58, 152.61, 165.1, 165.7, 166.1, 166.2; ESIMS (m/z) 1859 $[M+NH_3]^+$, 1865 $[M+Na]^+$, 1881 $[M+K]^+$; IR ($CHCl_3$) ν_{max} 3447, 1724, 1589, 1215 cm^{-1}.

4.11. (*S*)-3-Hydroxy-3-(((3,4,5-trihydroxybenzoyl)oxy)methyl)-butane-1,2,4-triyl tris(3,4,5-trihydroxybenzoate) 1a [(−)-tetragalloylapiitol]

To a stirred solution of (+)-**11** (450 mg, 0.24 mmol) in a mixture of ethyl acetate and methanol (20 mL, 1:1) at room temperature was added 10% Pd/C (50 mg) and the reaction mixture was subjected to hydrogenation at 65-psi hydrogen pressure for 8 h. The reaction mixture was filtered through a Celite bed and washed with methanol. The concentration of the filtrate in vacuo followed by silica gel column chromatographic purification of the resulting residue using methanol/chloroform (3:1) as an eluent furnished pure product (−)-**1a** as a pale purple solid (185 mg, ~100%). The analytically pure sample was obtained by reversed-phase C_{18} HPLC (Grace Denali id 4 × 250 mm) with an isocratic elution from 30% aqueous MeOH. Mp >300 °C; $[\alpha]_D^{25} = -23.6$ (c 0.03, MeOH); ^{1}H NMR (C_5D_5N, 400 MHz) δ 4.88 (d, J = 12 Hz, 1H), 4.92 (d, J = 12 Hz, 1H), 4.98 (d, J = 12 Hz, 1H), 5.06 (dd, J = 12 and 8 Hz, 1H), 5.12 (d, J = 12 Hz, 1H), 5.31 (br d, J = 12 Hz, 1H), 6.45 (dd, J = 8 and 4 Hz, 1H), 7.80 (s, 2H), 7.82 (s, 2H), 7.84 (s, 2H), 7.87 (s, 2H); ^{13}C NMR (C_5D_5N, 100 MHz) δ 63.8, 65.5, 72.7, 74.3, 110.3, 120.5, 120.66, 120.71, 141.1, 141.2, 147.4, 147.5, 166.4, 166.8, 166.9, 167.1; ESIMS (m/z) 759 $[M-H]^-$ (calcd for $C_{33}H_{27}O_{21}$); IR (Nujol) ν_{max} 3432, 1742, 1682 cm^{-1}.

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