Total Synthesis of (±)-1,3,4,5-Tetragalloylapiitol

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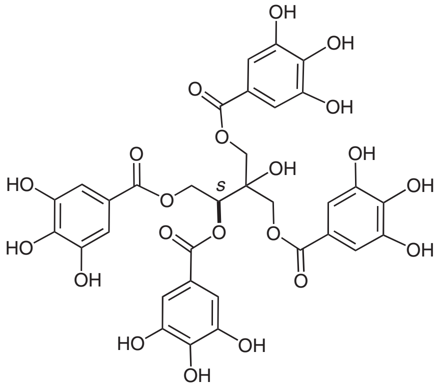
Abstract: Starting from citraconic anhydride, the first total synthesis of (±)-1,3,4,5-tetragalloylapiitol has been demonstrated via a stepwise route involving generation of an apiitol derivative followed by benzoylation.

Key words: allylic hydroxylation, osmium tetroxide, natural products, (±)-1,3,4,5-tetragalloylapiitol

HIV-1 RNase H is an attractive molecular target for the development of new anti-HIV agents as potential chemotherapeutics.[1–3] Very recently, Gustafson et al. isolated a new potent HIV RNase H inhibitor, (–)-1,3,4,5-tetragalloylapiitol (**1**) from an extract of the plant *Hylodendron gabunensis*.[4] The structural features revealed that the natural products (–)-apiitol (**2**)[5] and gallic acid (**3**) could be biogenetic precursors of **1** (Figure 1).

We reasoned that citraconic anhydride (**4**) would be a suitable precursor for the pentahydroxy sugar, apiitol. One of the hydroxy groups can be generated by allylic hydroxylation of the methyl group, two further hydroxy units can be introduced by osmium tetroxide dihydroxylation of the carbon–carbon double bond and finally, the last two hydroxy groups can be installed by reduction of the two carbonyl groups. In this context, we herein report our studies on the synthesis of (±)-**1** (Scheme 1).



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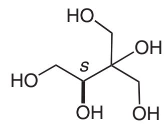

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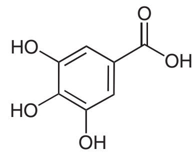

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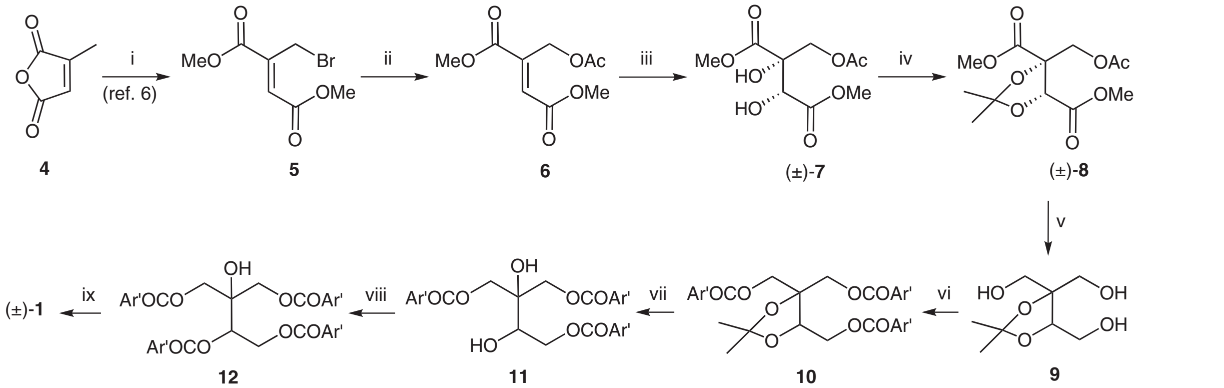
Figure 1 The natural products (–)-1,3,4,5-tetragalloylapiitol (**1**), (–)-apiitol (**2**) and gallic acid (**3**)

Dimethyl bromomethylfumarate (**5**)[6] obtained from citraconic anhydride (**4**) in two steps, on refluxing with sodium acetate in acetic acid underwent a smooth chemoselective allylic nucleophilic substitution reaction with the weakly nucleophilic carboxylate anion to yield dimethyl 2-(acetoxymethylfumarate) (**6**) in 92% yield. The osmium tetroxide induced dihydroxylation of the carbon–carbon double bond in **6**, in the presence of *N*-methylmorpholine *N*-oxide (NMO) as the oxidizing agent, furnished the diol



Scheme 1 *Reagents, conditions and yields*: (i) (a) MeOH, H^+/H_2SO_4, reflux, 8 h, (b) NBS (1.5 equiv), AIBN, CCl_4, reflux, 8 h (90% over 2 steps); (ii) AcOH, NaOAc, reflux, 8 h (92%); (iii) OsO_4, NMO, *t*-BuOH, r.t., 6 h (72%); (iv) $Me_2C(OMe)_2$, PTSA, 4 Å MS, benzene, reflux, 1.5 h (94%); (v) LAH (3.0 equiv), THF, r.t., 8 h (94%); (vi) Ar′COOH (4.5 equiv), EDC (6.0 equiv), DMAP, CH_2Cl_2, reflux, 2 h (96%); (vii) TFA (aq, 90% soln), r.t., 10 min (91%); (viii) Ar′COOH (1.50 equiv), EDC (2.0 equiv), DMAP, CH_2Cl_2, reflux, 2 h (96%); (ix) H_2, 10% Pd/C, EtOAc, MeOH, r.t., 6 h (quant.).

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(±)-**7** in 72% yield. Protection of the *cis*-diol **7** as ketal (±)-**8** (94%), followed by lithium aluminum hydride reduction gave the crystalline triol **9** in 94% yield. The conversion of triol **9** into the sugar apiitol (**2**) is known in the literature.[5] We envisaged the higher propensity of apiitol for intramolecular dehydrative cyclizations. Therefore, we first transformed triol **9** into the triester **10** using 3,4,5-tris(benzyloxy)benzoic acid[7] and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC) as the dehydrating agent, in 96% yield. Aqueous TFA-induced chemoselective cleavage of ketal **10** gave the desired diol **11** in 91% yield. As before, EDC-induced regioselective dehydrative coupling of the secondary alcohol group of **11** with 3,4,5-tris(benzyloxy)benzoic acid yielded tetraester **12** in 96% yield. Finally, catalytic hydrogenation using palladium on charcoal was used for very clean removal of all twelve benzyl protecting groups to afford the desired natural product (±)-**1** in quantitative yield. The analytical and spectral data obtained for (±)-1,3,4,5-tetragalloylapiitol (**1**) were in complete agreement with the reported data.[4] Starting from citraconic anhydride (**4**), racemic **1** was obtained in ten steps in 44% overall yield.

In summary, we have accomplished a straightforward synthesis of the potent anti-HIV compound (±)-1,3,4,5-tetragalloylapiitol in high yield. The use of an anhydride for preparing a sugar derivative is noteworthy.[8]

Melting points were determined using a Mel-Temp apparatus (Barnstead International) and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker AC 200 NMR spectrometer using TMS as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker AC 200 NMR spectrometer (at 50 MHz). The IR spectra were recorded on a Shimadzu FT-IR 8300 spectrometer. Column chromatographic separations were carried out on ACME silica gel (60–120 mesh). Commercially available citraconic anhydride, OsO_4, NMO, $Me_2C(OMe)_2$, TFA, EDC, LAH, DMAP and NBS were used. 3,4,5-Tris(benzyloxy)benzoic acid was prepared using a known procedure.[7] THF was dried over LAH. Petroleum ether (PE) refers to the fraction boiling in the 60–80 °C range.

Dimethyl 2-(Acetoxymethyl)fumarate (6)

A stirred solution of **5** (7.11 g, 30 mmol) and NaOAc (4.92 g, 60 mmol) in AcOH (80 mL) was refluxed for 8 h. The reaction mixture was allowed to reach 25 °C and was concentrated in vacuo. The residue was dissolved in EtOAc (50 mL) and the organic layer was washed with a 5% aq soln of $NaHCO_3$ (25 mL) and brine (25 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue (EtOAc–PE, 1:9) afforded pure **6** as a thick oil; yield: 5.97 g (92%).

IR ($CHCl_3$): 1735, 1732, 1729, 1653 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.05 (s, 3 H), 3.82 (s, 3 H), 3.85 (s, 3 H), 5.22 (s, 2 H), 6.94 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.5, 52.1, 52.7, 57.7, 130.9, 139.8, 164.9, 165.6, 170.2.

Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.59. Found: C, 50.08; H, 5.47.

Dimethyl 2-(Acetoxymethyl)-2,3-dihydroxysuccinate [(±)-7]

To a stirred solution of alkene **6** (5.41 g, 25 mmol) in *t*-BuOH (30 mL) was added a solution of NMO in H_2O (60%, 15 mL) with stirring at 25 °C. The reaction mixture was cooled to 10 °C and a solution of OsO_4 in *t*-BuOH (0.1 M, 0.63 mL, 0.13 mmol) was added with stirring. The reaction mixture was stirred at 10 °C for 6 h and then quenched by the addition of solid Na_2SO_3 (2.00 g). Stirring was continued for 45 min after which the reaction mixture was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with H_2O (20 mL) and brine (30 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue (EtOAc–PE, 2:3) furnished pure (±)-**7** as a dense oil; yield: 4.51 g (72%).

IR ($CHCl_3$): 3499, 3481, 1801, 1747, 1643 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.06 (s, 3 H), 3.62 (br d, *J* = 8 Hz, 1 H), 3.87 (s, 6 H), 4.00 (br s, 1 H), 4.36–4.49 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.5, 53.1, 53.5, 65.5, 72.6, 79.0, 170.3, 170.8, 171.5.

Anal. Calcd for $C_9H_{14}O_8$: C, 43.21; H, 5.64. Found: C, 43.30; H, 5.69.

Dimethyl 4-(Acetoxymethyl)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate [(±)-8]

To a solution of diol (±)-**7** (4.00 g, 16.00 mmol) in benzene (50 mL) was added $Me_2C(OMe)_2$ (3.33 g, 32.00 mmol) and PTSA (0.004 g, 0.02 mmol) and the stirred reaction mixture was refluxed for 1 h using a Dean–Stark apparatus containing freshly activated 4 Å MS (5 g). The reaction mixture was concentrated in vacuo and silica gel column chromatographic purification of the resulting residue (EtOAc–PE, 3:7) afforded (±)-**8** as a thick oil; yield: 4.36 g (94%).

IR ($CHCl_3$): 1751, 1749, 1735, 1215 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 3 H), 1.58 (s, 3 H), 2.03 (s, 3 H), 3.79 (s, 3 H), 3.83 (s, 3 H), 4.34 (s, 2 H), 5.07 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.5, 25.6, 27.1, 52.5, 53.2, 63.5, 77.9, 83.7, 113.1, 167.9, 169.9, 170.0.

Anal. Calcd for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25. Found: C, 49.52; H, 6.33.

(2,2-Dimethyl-1,3-dioxolane-4,4,5-triyl)trimethanol (9)

To a stirred slurry of LAH (1.38 g, 36.00 mmol) in THF (60 mL) at 0 °C, a solution of (±)-**8** (3.50 g, 12.00 mmol) in THF (40 mL) was added dropwise and the reaction mixture was allowed to warm to r.t. After stirring for 8 h at 25 °C, the reaction mixture was cooled to 0 °C and quenched very slowly with a few drops of a sat. aq soln of Na_2SO_4. The reaction mixture was filtered through Celite®. Concentration of the filtrate in vacuo afforded triol **9** as a white solid; yield: 2.32 g (94%); mp 86–88 °C.

IR ($CHCl_3$): 3400–3300 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.46 (s, 3 H), 1.76 (br s, 1 H), 2.54 (br s, 1 H), 2.95 (br s, 1 H), 3.70 (q, *J* = 12 Hz, 2 H), 3.78 (s, 2 H), 3.93 (d, *J* = 6 Hz, 2 H), 4.14 (t, *J* = 6 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.5, 28.3, 60.0, 62.1, 64.8, 78.8, 83.3, 108.5.

Anal. Calcd for $C_8H_{16}O_5$: C, 49.99; H, 8.39. Found: C, 50.07; H, 8.41.

(2,2-Dimethyl-1,3-dioxolane-4,4,5-triyl)tris(methylene)tris[3,4,5-tris(benzyloxy)benzoate] (10)

A suspension of triol **9** (0.48 g, 2.50 mmol), 3,4,5-tris(benzyloxy)benzoic acid (4.95 g, 11.25 mmol), EDC (2.87 g, 15.00 mmol) and DMAP (1.01 g, 8.25 mmol) in CH_2Cl_2 (40 mL) was refluxed for 2 h. The reaction mixture was concentrated in vacuo and the residue was treated with H_2O (50 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with H_2O (50 mL) and brine (50 mL) and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the resulting residue (EtOAc–PE, 3:7) afforded pure product **10** as a white solid; yield: 3.51 g (96%); mp 75–76 °C.

IR ($CHCl_3$): 1719, 1653, 1215 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.48 (s, 3 H), 1.55 (s, 3 H), 4.40–4.66 (m, 6 H), 4.77 (dd, *J* = 10, 4 Hz, 1 H), 4.96–5.07 (m, 16 H), 5.09 (s, 2 H), 7.10–7.45 (m, 51 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.3, 28.1, 70.9, 70.94, 75.0, 77.1, 81.0, 108.68, 108.75, 108.84, 109.9, 124.1, 124.2, 127.41, 127.46, 127.52, 127.9, 128.06, 128.09, 128.12, 128.35, 128.41, 128.5, 136.45, 136.51, 137.29, 137.34, 137.4, 142.4, 142.56, 142.60, 152.44, 152.49, 152.52, 165.2, 165.5, 165.6.

Anal. Calcd for $C_{92}H_{82}O_{17}$: C, 75.70; H, 5.66. Found: C, 75.66; H, 5.48.

2,3-Dihydroxy-2-{[3,4,5-tris(benzyloxy)benzoyloxy]methyl}butane-1,4-diyl Bis[3,4,5- tris(benzyloxy)benzoate] (11)
Compound **10** (2.00 g, 1.37 mmol) was dissolved in TFA (aq, 90% soln, 8 mL) and the resulting mixture was stirred for 10 min at 10 °C. The reaction mixture was evaporated and to the residue was added toluene (15 mL). Concentration in vacuo followed by silica gel column chromatographic purification of the resulting residue (EtOAc–PE, 1:4) furnished pure product **11** as a white solid; yield: 1.77 g (91%); mp 96–98 °C.

IR ($CHCl_3$): 3506, 3423, 1734, 1719, 1703 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.80–4.10 (m, 2 H), 4.30–4.70 (m, 5 H), 4.80–5.10 (m, 18 H), 7.00–7.40 (m, 51 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 65.1, 65.2, 65.3, 71.0, 74.4, 75.1, 77.2, 108.93, 108.98, 109.02, 124.1, 124.3, 127.4, 127.5, 127.7, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 136.5, 137.3, 142.6, 142.68, 142.72, 152.47, 152.50, 166.0, 166.35, 166.43.

Anal. Calcd for $C_{89}H_{78}O_{17}$: C, 75.30; H, 5.54. Found: C, 75.41; H, 5.63.

3-Hydroxy-3-{[(3,4,5-tris(benzyloxy)benzoyloxy]methyl}butane-1,2,4-triyl Tris[3,4,5- tris(benzyloxy)benzoate] (12)
A suspension of diol **11** (1.42 g, 1.00 mmol), 3,4,5-tris(benzyloxy)benzoic acid (0.66 g, 1.50 mmol), EDC (0.38 g, 2.00 mmol) and DMAP (0.13 mg, 1.10 mmol) in CH_2Cl_2 (10 mL) was refluxed for 2 h. The reaction mixture was concentrated in vacuo and the residue was diluted with H_2O (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with H_2O (25 mL) and brine (25 mL) and dried over Na_2SO_4. The organic layer was concentrated in vacuo and silica gel column chromatographic purification of the resulting residue (EtOAc–PE, 1:4) afforded pure product **12** as a white solid; yield: 1.77 g (96%); mp 130–131 °C.

IR ($CHCl_3$): 3447, 1724, 1589, 1215 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.20–4.70 (m, 6 H), 4.60–5.10 (m, 24 H), 5.80 (t, *J* = 6 Hz, 1 H), 7.00–7.40 (m, 68 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 62.7, 65.5, 70.8, 70.9, 72.2, 74.1, 74.9, 75.0, 108.6, 108.9, 109.1, 109.5, 123.86, 123.90, 124.0, 124.3, 127.36, 127.39, 127.44, 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 128.35, 128.37, 136.2, 136.3, 136.4, 136.5, 137.2, 137.3, 142.4, 142.6, 142.7, 142.9, 152.40, 152.44, 152.47, 152.51, 165.1, 165.7, 166.0, 166.1.

Anal. Calcd for $C_{117}H_{100}O_{21}$: C, 76.29; H, 5.47. Found: C, 76.18; H, 5.55.

3-Hydroxy-3-[(3,4,5-trihydroxybenzoyloxy)methyl]butane-1,2,4-triyl Tris(3,4,5-trihydroxybenzoate) [(±)-1,3,4,5-Tetragalloylapiitol, (±)-1]
To a stirred solution of **12** (1.23 g, 0.67 mmol) in EtOAc (10 mL) and MeOH (10 mL) at 25 °C, 10% Pd/C (50 mg) was added and the reaction mixture was subjected to hydrogenation at 65 psi hydrogen pressure for 6 h. The reaction mixture was filtered through Celite®. Concentration of the filtrate in vacuo followed by silica gel column chromatographic purification of the resulting residue (MeOH–$CHCl_3$, 3:1) furnished pure (±)-**1** as a pale yellow solid; yield: 508 mg (quant.); mp > 300 °C (for tabulated ^{1}H and ^{13}C NMR data, see reference 4).

Anal. Calcd for $C_{33}H_{28}O_{21}$: C, 52.11; H, 3.71. Found: C, 52.02; H, 3.65.

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