A Direct Synthesis of Racemic 1,3,4,5-Tetragalloylapiitol

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Abstract: A direct and flexible synthesis of racemic 1,3,4,5-tetragalloylapiitol is described.

Key words: apiitol, HIV, osmium tetroxide, deprotection

Plant derived natural products are increasingly being investigated as leads for pharmaceutical development. Using bioactivity-guided fractionation of plants reported to be useful as folk medicines, valuable bioactive compounds have been discovered.[1] As part of a screening campaign to find natural products that actively inhibit RNase H activity, natural product extracts were screened by a group at the National Institutes of Health.[2] They isolated and determined the structure of a new compound from an extract of the plant *Hylodendron gabunensis* Taub. (Fabaceae). The compound was the tetragallate ester of apiitol, a rare carbohydrate.[2] This compound exhibits potent activity against HIV RNase H. The apiitol derivative inhibited HIV-1, HIV-2, and human RNase H with IC_{50} values of 0.24, 0.13, and 1.5 mM, respectively. Significantly, it did not show inhibition of *E. coli* RNase H at 10 mM. Recently, Patel and Argade reported[3] a ten-step synthesis of racemic 1,3,4,5-tetragalloylapiitol (**1**) (Figure 1).

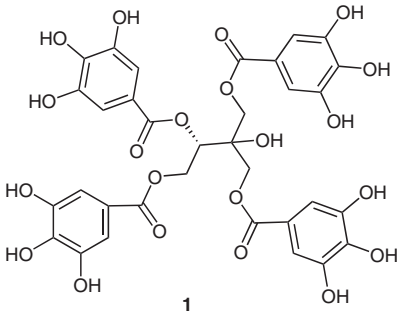
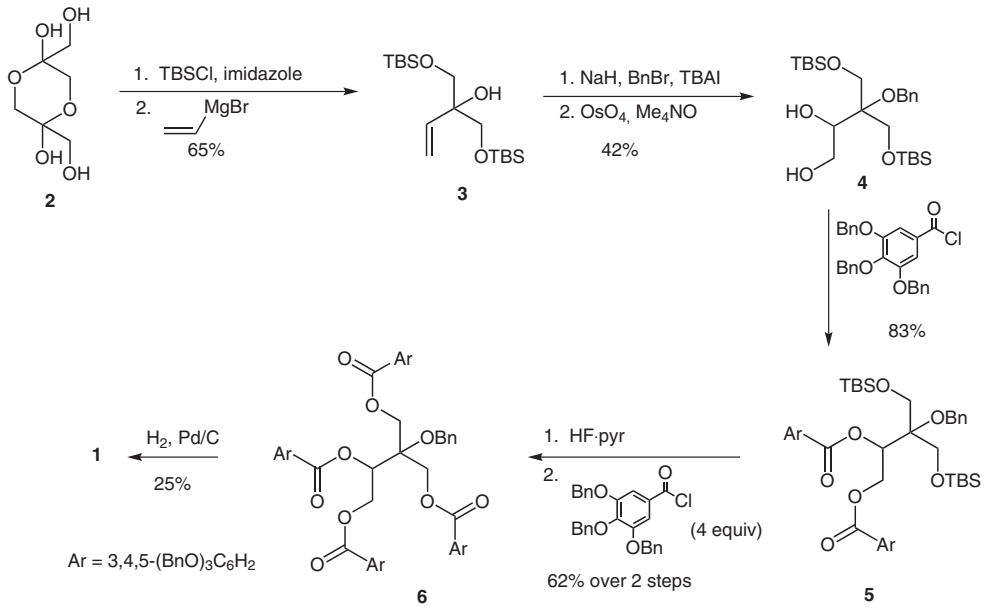


Figure 1 1,3,4,5-Tetragalloylapiitol (**1**)

Herein, we report a direct synthesis of 1,3,4,5-tetragalloylapiitol (**1**). Commercially available 1,3-dihydroxyacetone dimer **2** was readily protected as the bis-TBS ether using TBSCl and imidazole in DMF as shown in Scheme 1.[4] After the addition of vinylmagnesium bromide (THF, –30 °C), the benzyl group was introduced using sodium hydride and benzyl bromide. The benzyl group was chosen as the protecting group, since the gallic acid phenols also had to be protected and it would be convenient to remove all of the protecting groups at one time at the end of the synthesis. Additionally, the benzyl group is not subject



Scheme 1 Synthesis of **1** from dihydroxyacetone dimer

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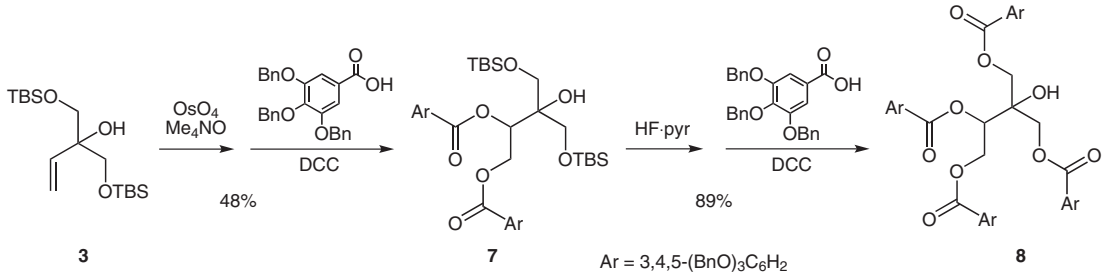

Scheme 2 Alternate synthesis of **1**

to protecting group translocation under basic conditions as sometimes happens with an ester protecting group or a silyl ether protecting group.[5] Moreover, the benzyl group will enhance the solubility of polyhydroxy intermediates in organic solutions. The resulting benzyl ether was hydroxylated using catalytic osmium tetroxide and tetramethylammonium *N*-oxide in aqueous acetone in high yield. The resulting diol **4** was treated with the tribenzyl ether of galloyl chloride[6] to form the bis-galloylated material **5** in 83% yield. Removal of the silyl ether protecting groups with HF·pyridine[7] followed by a second galloylation gave the protected material **6** in 19% yield over seven steps. Removal of the benzyl groups afforded a polar material that was purified by recrystallization from toluene–ethyl acetate. The ^{1}H and ^{13}C NMR spectra of our synthetic material were identical to that of the natural product **1**.

In an alternate synthetic route to tetragalloylapiitol (**1**), the known intermediate alcohol **8**[3] was prepared by hydroxylation of **3** using osmium tetroxide, followed by the acylation using 3 equivalents of tri-*O*-benzylgallic acid and DCC. This gave the diacylated product as the main product **7** in 48% yield (Scheme 2). The mono- and bis-galloylated products proved difficult to separate because of their surprisingly similar polarity. Since both of the compounds could in principle be converted to **8** by desilylation and acylation, the mixture was treated with HF–pyridine and acylated. Alcohol **8** was produced in 89% yield over two steps, which had been quantitatively debenzylated to **1**.[3]

The synthesis of tetragalloylapiitol described by us is direct and flexible. It will be possible to prepare other galloyl-substituted apiitols using our route. For example, the deprotection of the bis-galloylated intermediate **5** will provide a bis-galloylapiitol. The biological evaluation of selected derivatives will be reported in the future.

Commercially available dihydroxyacetone dimer, imidazole, TBSCl, vinylmagnesium bromide solution (1 M in THF), NaH (60% dispersion in mineral oil), TBAI, BnBr, TMNO·2H$_2$O, OsO$_4$, DMAP, DCC, HF·pyridine, and Pd/C were used. THF was dried over sodium. NMR experiments were performed with either a Varian 300 MHz or a 400 MHz instrument. LRMS were performed with a Shimaduzu LC–MS 2010 mass spectrometer. Standard grade silica gel (60 Å) was used for flash column chromatography. All reactions were performed under an argon atmosphere. Thin-layer chromatography was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm).

4-*tert*-Butyldimethylsilyloxy-3-(*tert*-butyldimethylsilyloxymethyl)but-1-en-3-ol (3)

To a stirred solution of dihydroxyacetone dimer **2** (4.000 g, 22.20 mmol) in DMF (30 mL) were added imidazole (7.558 g, 111.0 mmol) and *tert*-butyldimethylsilyl chloride (16.73 g, 111.0 mmol) at 0 °C. The mixture was stirred at r.t. for 1 h and then H$_2$O (30 mL) was added at 0 °C. The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine (30 mL), dried (MgSO$_4$), filtered, and concentrated. The residue was purified by flash column chromatography (hexanes) to give the protected intermediate (12.56 g, 89%) as a colorless oil. To a stirred solution of vinylmagnesium bromide (1 M in THF; 9.41 mL, 9.41 mmol) in THF (15 mL) was added the above protected intermediate (1.000 g, 3.138 mmol) in THF (10 mL) dropwise at –30 °C. The mixture was stirred at –30 °C for 3 h and then treated with sat. aq NH$_4$Cl (20 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried (MgSO$_4$), filtered, and concentrated. The residue was purified by flash column chromatography over silica gel (hexanes–EtOAc, 10:1) to give **3** (0.794 g, 73%) as a colorless oil.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.06 (s, 12 H), 0.90 (s, 18 H), 2.71 (s, 1 H), 3.54 (dd, *J* = 29.7, 9.3 Hz, 4 H), 5.19 (dd, *J* = 11.1, 1.8 Hz, 1 H), 5.42 (dd, *J* = 17.4, 1.8 Hz, 1 H), 5.96 (dd, *J* = 17.5, 10.8 Hz, 1 H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = –5.24, 18.5, 26.1, 65.9, 75.0, 114.9, 138.7.

MS (ESI): *m*/*z* calcd for C$_{17}$H$_{38}$O$_3$Si$_2$ (M$^+$): 347; found: 347.

3-Benzyloxy-4-*tert*-butyldimethylsilyloxy-3-(*tert*-butyldimethylsilyloxymethyl)butane-1,2-diol (4)

To a suspension of NaH (60% dispersion in mineral oil; 0.243 g, 6.07 mmol) in THF (20 mL) was added a solution of alcohol **3** (1.915 g, 5.522 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min. Bu$_4$NI (204 mg, 0.552 mmol) and benzyl bromide (0.72 mL, 6.1 mmol) were added. The mixture was allowed to warm to r.t. and was stirred for 18 h. The reaction was quenched with sat. aq NH$_4$Cl (20 mL) and diluted with EtOAc (20 mL). After extraction with EtOAc (3 × 10 mL), the combined organic extracts were washed with brine (20 mL), dried (MgSO$_4$), filtered, and concentrated. The residue was purified by flash chromatography over silica gel (hexanes) to give the intermediate benzyl ether (1.665 g, 69%) as a colorless oil. A solution of the intermediate benzyl ether (1.401 g, 3.207 mmol), trimethylamine *N*-oxide dihydrate (0.713 g, 6.41 mmol), and OsO$_4$ (0.160 mmol, 4.07 mL of a 100 mg/10 mL stock solution) in acetone (90 mL) and H$_2$O (45 mL) was stirred at r.t. for 7 h. The reaction was quenched with sat. aq Na$_2$SO$_3$ (100 mL), stirred for 0.5 h, concentrated, and extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO$_4$), filtered, and concentrated. The residue was purified by flash chromatography over silica gel (hexanes–EtOAc, 5:1) to give **4** (0.911 g, 61%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 12 H), 0.92 (s, 18 H), 2.87 (m, 1 H), 3.27 (d, *J* = 29.7, 9.3 Hz, 1 H), 3.91 (m, 7 H), 4.71 (dd, *J* = 17.4, 1.8 Hz, 2 H), 7.32 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.44, 18.3, 26.0, 62.6, 63.0, 63.1, 66.1, 72.9, 80.0, 127.6, 128.5, 139.1.

MS (ESI): *m*/*z* calcd for $C_{24}H_{46}O_5Si_2$ + Na (M + Na)$^+$: 493; found: 493.

3-Benzyloxy-4-*tert*-butyldimethylsilyloxy-3-(*tert*-butyldimethylsilyloxymethyl)butane-1,2-diyl Bis[3,4,5-tris(benzyloxy)benzoate] (5)

To a solution of diol **4** (0.456 g, 0.972 mmol) and DMAP (0.475 g, 3.89 mmol) in CH_2Cl_2 (40 mL) was added 3,4,5-tris(benzyloxy)benzoyl chloride (1.784 g, 3.886 mmol). The mixture was stirred at r.t. for 8 h. The solvent was evaporated and chromatography of the residue over silica gel (hexanes, EtOAc, 10:1) to give **5** (1.094 g, 83%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 12 H), 0.94 (s, 18 H), 3.83–4.08 (m, 4 H), 4.81–5.13 (m, 16 H), 6.05 (dd, *J* = 8.6, 3.6 Hz, 1 H), 7.27–7.39 (m, 39 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4, 18.4, 26.1, 61.6, 62.5, 66.3, 71.1, 71.2, 72.7, 75.2, 75.3, 80.6, 109.0, 109.3, 109.3, 125.2, 125.3, 127.5, 127.8, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 136.6, 136.8, 137.6, 137.7, 139.1, 142.3, 142.8, 152.6, 152.7, 165.4, 166.1.

MS (ESI): *m*/*z* calcd for $C_{80}H_{90}O_{13}Si_2$ + Na (M + Na)$^+$: 1339; found: 1339.

3-Benzyloxy-3-[3,4,5-tris(benzyloxy)benzoyloxymethyl]butane-1,2,4-triyl Tris[3,4,5-tris(benzyloxy)benzoate] (6)

To a solution of **5** (0.459 g, 0.350 mmol) in anhyd THF (6 mL) and pyridine (6 mL) cooled to 0 °C was added HF·pyridine (2.0 mL). The mixture was warmed to r.t. and stirred for 18 h. The mixture was then diluted with EtOAc (5 mL) and washed with 10% aq $CuSO_4$ (5 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organics were washed with sat. aq $NaHCO_3$ (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to afford a yellow oil. To a solution of the obtained intermediate diol (0.350 mmol) and DMAP (0.228 g, 1.86 mmol) in CH_2Cl_2 (20 mL) was added 3,4,5-tris(benzyloxy)benzoyl chloride (0.855 g, 1.86 mmol). The mixture was stirred at r.t. for 8 h. The solvent was evaporated and chromatography of the residue over silica gel (CH_2Cl_2–EtOAc, 10:1) gave **6** (0.554 g, 86% over 2 steps) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.39–5.16 (m, 32 H), 6.17 (dd, *J* = 7.0, 3.0 Hz, 1 H), 7.26–7.43 (m, 73 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.1, 63.1, 63.3, 66.5, 71.2, 71.3, 71.7, 75.3, 78.6, 109.0, 109.1, 109.3, 124.3, 124.4, 124.7, 127.5, 127.6, 127.7, 127.9, 128.2, 128.3, 128.4, 128.6, 128.7, 136.5, 136.6, 136.7, 136.8, 137.5, 137.6, 137.7, 137.8, 142.7, 142.8, 143.0, 143.2, 151.0, 152.7, 152.8, 165.2, 165.4, 165.6, 165.9.

MS (ESI): *m*/*z* calcd for $C_{124}H_{106}O_{21}$ (M^+): 1933; found: 1933.

1,3,4,5-Tetragalloylapiitol (1)

A suspension of benzyl-protected tetragalloylapiitol **6** (0.249 g, 0.129 mmol), 10% Pd/C (25 mg) in anhyd THF (15 mL) was stirred at 40 °C under H_2 for 16 h. The mixture was cooled and filtered through Celite, and the filtrate was evaporated. The residue was crystallized from toluene–EtOAc. Compound **1** (26 mg, 26%) was obtained as colorless crystals. Characterization matched perfectly with literature values.[2]

4-*tert*-Butyldimethylsilyloxy-3-(*tert*-butyldimethylsilyloxymethyl)-3-hydroxybutane-1,2-diyl Bis[3,4,5-tris(benzyloxy)benzoate] (7)

To a solution of olefin **3** (1.500 g, 4.326 mmol), trimethylamine *N*-oxide dihydrate (0.962 g, 8.65 mmol), and OsO_4 (4.40 mL, 0.216 mmol of a 100 mg/10 mL stock solution) in acetone (80 mL) and H_2O (40 mL) was stirred at r.t. for 7 h. The reaction was quenched with sat. aq Na_2SO_3 (100 mL) and stirred for 0.5 h, concentrated, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography over silica gel (hexanes–EtOAc) to give (0.9052 g, 55%) as a colorless oil. To a solution of the diol (0.401 g, 1.053 mmol) was added 3,4,5-tris(benzyloxy)benzoic acid (0.401 g, 1.053 mmol), DCC (0.861 g, 4.21 mmol), and DMAP (0.283 g, 2.32 mmol) in CH_2Cl_2 (20 mL). The solution was refluxed for 2 h. The solvent was evaporated and chromatography of the residue over silica gel (hexanes–EtOAc, 5:1) furnished **7** (1.035 g, 80%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.11 (s, 12 H), 0.89 (s, 18 H), 2.89 (m, 1 H), 3.62–4.74 (m, 4 H), 4.98–5.10 (m, 14 H), 6.05 (dd, *J* = 96, 2.4 Hz, 1 H), 7.27–7.38 (m, 34 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3, 18.4, 26.0, 60.6, 63.4, 63.3, 64.2, 71.2, 71.3, 73.2, 75.3, 75.3, 109.1, 109.4, 125.1, 125.3, 127.7, 127.9, 128.1, 128.3, 128.6, 128.7, 136.7, 136.8, 137.6, 137.7, 142.5, 142.9, 152.6, 152.7, 165.6, 166.1.

MS (ESI): *m*/*z* calcd for $C_{73}H_{84}O_{13}Si_2$ +Na (M + Na)$^+$: 1248; found: 1248.

3-Hydroxy-3-[3,4,5-tris(benzyloxy)benzoyloxymethyl]butane-1,2,4-triyl Tris[3,4,5-tris(benzyloxy)benzoate] (8)

A solution of bis-TBS protected alcohol **7** (0.160 g, 0.130 mmol) in anhyd THF (2.0 mL) and pyridine (2.0 mL) was cooled to 0 °C, and HF·pyridine (0.67 mL) was added. The mixture was warmed to r.t. and stirred for 18 h. The mixture was then diluted with EtOAc (2 mL) and washed with 10% aq $CuSO_4$ (2 mL). The aqueous phase was extracted with EtOAc (3 × 2 mL) and the combined organics were washed with sat. aq $NaHCO_3$ (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to afford a yellow oil. To the obtained intermediate diol (0.130 mmol) was added 3,4,5-tris(benzyloxy)benzoic acid (0.172 g, 0.391 mmol), DCC (0.106 g, 0.521 mmol), and DMAP (0.035 g, 0.286 mmol) in CH_2Cl_2 (5 mL). The solution was refluxed for 2 h. The solvent was evaporated and chromatography of the residue over silica gel (CH_2Cl_2–EtOAc, 10:1) furnished **8** (0.213 g, 89% over 2 steps) as a colorless oil. Characterization matched perfectly with literature values.[3]

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