Facile Synthesis of Ginsenoside Ro

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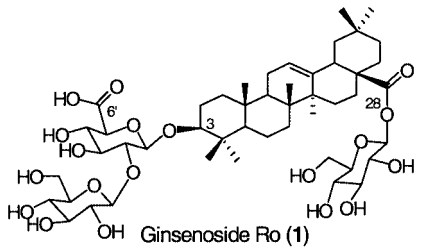
Abstract: Two concise synthetic routes, being different in the glycosylation sequence, toward ginsenoside Ro (**1**) are developed. These syntheses feature the elaboration of the glucuronide residue at a later stage via the TEMPO-mediated selective oxidation and the installation of AZMB as a benzoylic neighboring participating group capable of being selectively removed afterward.

Key words: ginsenoside Ro, triterpene saponin, synthesis, glycosylation, oxidation

Ginsenoside Ro (**1**) (Figure 1), namely 28-*O*-β-D-glucopyranosyl oleanate 3-*O*-β-D-glucopyranosyl-(1→2)-β-D-glucuronopyranoside, since its first isolation from *Panax japonicus*,[1] has been found wide occurrence in *Panax* species[2] as well as many other plants.[3] In ginseng (*Panax ginseng* C. A. Meyer), the most famous Oriental herb being rich in dammarane saponins, ginsenoside Ro emerges as the unique oleanane saponin.[2,4] Structurally, ginsenoside Ro represents a typical saponin of the family termed glucuronide oleanane-type triterpene carboxylic acid 3,28-*O*-bisdesmoside (GOTCAB).[5] Such a structure shows no hemolytic nor cytotoxic activities;[6,7] but is an effective solubilizer for hydrophobic compounds in water.[8] Moreover, ginsenoside Ro demonstrates significant antithrombic, anti-inflammatory, and anti-hepatitis activities in experimental models.[9–11]

However, synthetic approach toward ginsenoside Ro or any other GOTCAB saponin has not been developed.[12] Here we report the first such synthesis.



Ginsenoside Ro (**1**)

Figure 1

Adopting the most common tactics for introduction of uronate residues in the synthesis of complex oligosaccharides and glycoconjugates,[13] we scheduled to elaborate the 6′-carboxyl function via oxidation of the primary 6′-OH at a later stage after assembly of the trisaccharide. The 3-*O*-disaccharide bearing a 1→2 linkage, which is common in GOTCAB, precludes the use of a disaccharide donor with a neighboring participating group to ensure a stereospecific glycosylation at the 3-OH; thus sequential assembly of the two monosaccharide residues is planed. Strategically, the sequence for assembly of the 3- and 28-glycosyl residues determines two different routes toward the synthesis of ginsenoside Ro (**1**).

The first synthetic route toward ginsenoside Ro (**1**) was depicted in Scheme 1. We have employed trityl, TMS, TES, TBDMS, and allyl groups to temporarily protect the 28-COOH of the oleanolic acid; and found allyl protection difficult to remove while others labile toward glycosylation.[12f,g] Therefore, TBDPS, the most robust among silyl groups, was chosen to protect the 28-COOH. Treatment of oleanolic acid with TBDPSCl in the presence of imidazole in DMF provided the TBDPS ester **5** selectively in 92% yield (Scheme 1). For construction of the 1,2-*trans*-glycosidic bond at the 3-OH of triterpenoids and steroids, the glycosylation conditions have been optimized,[14] where glycosyl trichloroacetimidate (or trifluoroacetimidate)[12g,15] donors with a benzoyl group at 2-OH and TMSOTf as catalyst are required. Thus, 4,6-di-*O*-Ac-2-*O*-AZMB-3-*O*-Piv-D-glucopyranosyl trifluoroacetimidate (**4**) was designed. The benzoylic 2-*O*-2-(azidomethyl)benzoyl(AZMB) group, a newly evolved protecting group,[16] was expected to ensure a high yielding 1,2-*trans*-glycosylation and afterwards a selective removal in the presence of other acyl groups. And the 4,6-*O*-Ac groups could be removed selectively, in the presence of benzoyl and pivaloyl groups,[17] at a later stage for selective elaboration of the 6′-carboxyl function. Trifluoroacetimidate **4** was prepared from the readily available phenyl 4,6-*O*-benzylidene-3-*O*-pivaloyl-1-thio-β-D-glucopyranoside (**2**)[18] in six easy steps. Three steps, i.e., protection of the 2-OH with AZMB (87%), cleavage of the 4,6-benzylidene, and acetylation of the resulting 4,6-OHs were used to convert **2** to **3**; then thioglycoside **3** was subjected to conversion into bromide, hydrolysis into 1-OH, and addition with *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (80% yield for three steps). Expectedly, glycosylation of **5** with **4** in the presence of a catalytic amount of TMSOTf

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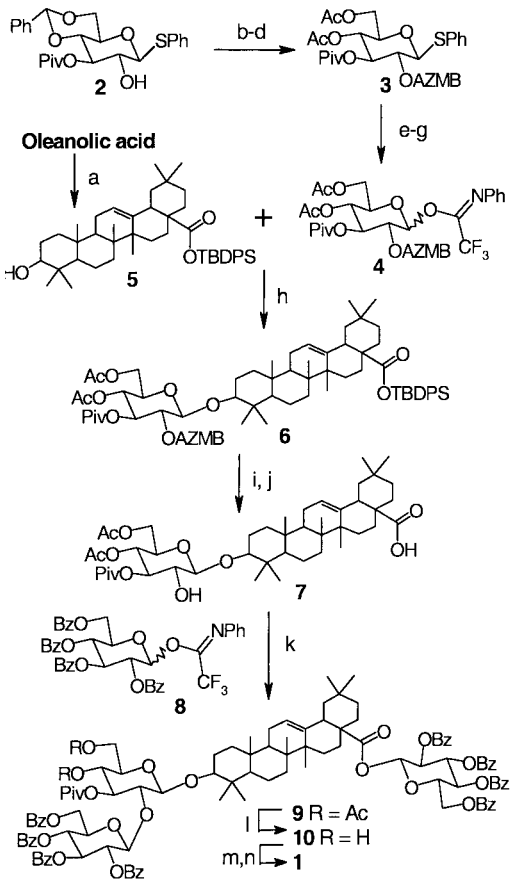
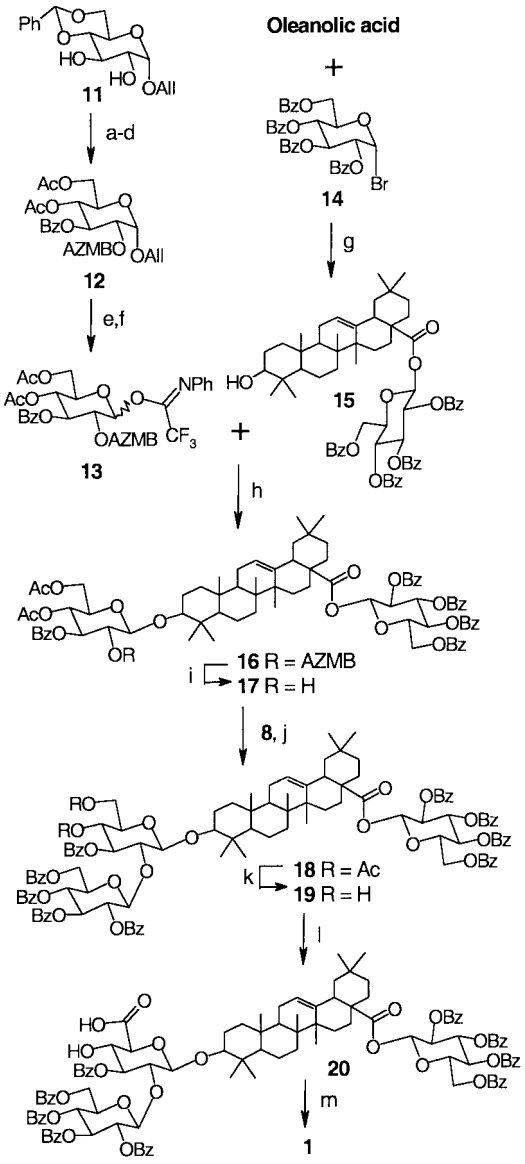


Scheme 1 First synthetic route to ginsenoside Ro (**1**). *Reagents and conditions*: (a) TBDPSCl, imidazol, DMF, 80 °C, 92%; (b) AZMBCl, DMAP, CH_2Cl_2, r.t., 87%; (c) 80% HOAc, r.t.; (d) Acetic anhydride, pyridine, r.t., 91% (two steps); (e) Br_2, CH_2Cl_2, r.t.; (f) Ag_2CO_3, acetone–H_2O, r.t.; (g) PhN=CClCF$_3$, K_2CO_3, acetone, r.t., 80% (three steps); (h) TMSOTf (0.05 equiv), CH_2Cl_2, 4 Å MS, r.t., 87%; (i) TBAF, THF, r.t., 92%; (j) Bu_3P, THF–H_2O, r.t., 76%; (k) TMSOTf (0.1 equiv), CH_2Cl_2, 4 Å MS, r.t., 74%; (l) 1% acetyl chloride, MeOH, r.t., 84%; (m) TEMPO, $Ca(ClO)_2$, KBr, Bu_4NBr, $CHCl_3$–H_2O, 0 °C; (n) NaOH, THF–H_2O, 43% (two steps).



Scheme 2 Second synthetic route to ginsenoside Ro (**1**). *Reagents and conditions*: (a) AZMBCl, pyridine–CH_2Cl_2, 0 °C, 78%; (b) BzCl, DMAP, CH_2Cl_2, r,t., 89%; (c) *p*-TsOH, MeOH–CH_2Cl_2, reflux, 97%; (d) Acetic anhydride, pyridine–CH_2Cl_2, r.t., 98%; (e) $PdCl_2$ (0.5 equiv.), MeOH–CH_2Cl_2, r.t., 80%; (f) PhN=CClCF$_3$, K_2CO_3, acetone, r.t., 90%; (g) K_2CO_3, Bu_4NBr, CH_2Cl_2–H_2O, reflux, 90%; (h) TBSOTf (0.1 equiv), CH_2Cl_2, 4 Å MS, r.t., 91%; (i) Bu_3P, THF–H_2O, r.t., 75%; (j) **8** (3.0 equiv), TBSOTf (0.4 equiv), CH_2Cl_2, 4 Å MS, r.t., 79%; (k) 1% Acetyl chloride, MeOH–CH_2Cl_2, 0 °C–r.t., 89%; (l) TEMPO, $Ca(ClO)_2$, KBr, Bu_4NBr, $CHCl_3$–H_2O, 0 °C, 89%; (m) NaOMe, MeOH–CH_2Cl_2, r.t., 72%.

afforded the β-glycoside **6** in a satisfactory yield (87%). Attempts of selective removal of the 2′-*O*-AZMB group on **6** with PBu_3 resulted in partial cleavage of the 28-TBDPS ester. Therefore, the 28-TBDPS ester was cleaved first with TBAF (92%), and then 2′-*O*-AZMB was removed with PBu_3 to give **7** (76%). Treatment of the 2′-OH-28-COOH derivative **7** with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl trifluoroacetimidate (**8**)[15] in the presence of TMSOTf (0.1 equiv) afforded the 2′,28-bis-β-glycosylated trisaccharide **9** in 74% yield. Selective removal of the 4′,6′-*O*-acetate on **9** was achieved with 1% HCl in MeOH,[17] providing 4′,6′-diol **10** in 84% yield. Diol **10** was then subjected to selective oxidation with TEMPO–KBr–$Ca(ClO)_2$ under phase-transfer aqueous conditions.[19] The resulting 6′-COOH derivative was directly treated with NaOH in H_2O–THF to afford the target ginsenoside Ro (**1**), after C18 reverse phase column chromatography, in 43% yield.

Alternatively, the 28-glycosyl ester could be assembled first in the synthetic route toward ginsenoside Ro (Scheme 2). Treatment of oleanolic acid with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**14**) under the modified literature conditions (K_2CO_3, Bu_4NBr, CH_2Cl_2–H_2O, reflux)[12c] provided the desired 28-glucosyl ester **15** in 90% yield. 4,6-Di-*O*-acetyl-2-*O*-AZMB-3-*O*-benzoyl-D-glucopyranosyl trifluoroacetimidate (**13**), the desired donor for glycosylation of the 3-OH of **15**, was prepared employing an improved route compared to the previous

one for donor **4**. The replacement of the 3-*O*-pivaloyl group (in **4**) with a 3-*O*-benzoyl group (in **13**) would facilitate the final removal under alkaline conditions. Thus, trifluoroacetimidate donor **13** was obtained in six convenient steps and in 48% yield from the ready available allyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**11**) (Scheme 2). Expectedly, glycosylation of **15** with **13** in the presence of a catalytic amount of TBSOTf afforded the 3-*O*-β-glucoside **16** in a satisfactory 91% yield. Here, the use of TBSOTf as the catalysis in place of TMSOTf improved the glycosylation yield by avoiding the production of the corresponding 3-*O*-TMS ether. Then selective removal of the 2′-*O*-AZMB group with PBu_3 in the presence of acetyl and benzoyl groups was achieved, providing **17** in 75% yield. Glycosylation of the 2′-OH of **17** with trifluoroacetimidate **8** in the presence of TBSOTf (0.4 equiv) afforded the β-glycosylated trisaccharide **18** in 79% yield. Selective removal of the 4′,6′-*O*-acetate on **18** succeeded with 1% HCl in MeOH, providing 4′,6′-diol **19** in 89% yield. Diol **19** was then subjected to selective oxidation with TEMPO–KBr–$Ca(ClO)_2$ under phase-transfer aqueous conditions. The resulting 6′-carboxylic acid derivative **20** was isolated in 89% yield. Finally, removal of the benzoyl groups with NaOMe in MeOH–CH_2Cl_2 afforded the target ginsenoside Ro (**1**) in 72% yield. All the analytical data of **1** are in good agreement with those reported in the literature.[1,2,20]

In summary, two synthetic routes toward ginsenoside Ro (**1**) are developed. The first route starts with temporary protection of the 28-COOH of oleanolic acid and finishes with a linear eight steps and 14% overall yield. The second route starts with selective glycosylation of the 28-COOH of oleanolic acid and achieves a linear seven steps and 28% overall yield. These syntheses feature the elaboration of the glucuronide residue at a later stage via the TEMPO-mediated selective oxidation of the primary 6′-OH and the installation of AZMB as a benzoylic neighboring participating group capable of being selective removed afterwards. The present synthetic routes should be adaptable to the synthesis of other GOTCABs.

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(20) All compounds involved in the synthesis have been well characterized. Selected data for **18**–**20** and **1** are herewith listed. **18**: $[\alpha]_D$ = 43.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 7.7 Hz, 4 H), 7.99 (d, *J* = 7.1 Hz, 2 H), 7.92–7.80 (m, 7 H), 7.72 (t, *J* = 8.8 Hz, 4 H), 7.66–7.18 (m, 28 H), 6.00 (t, *J* = 9.6 Hz, 1 H), 5.96 (d, *J* = 8.2 Hz, 1 H), 5.78 (dd, *J* = 9.6, 8.4 Hz, 1 H), 5.71 (t, *J* = 9.6 Hz, 1 H), 5.66 (t, *J* = 9.3 Hz, 1 H), 5.58 (t, *J* = 9.4 Hz, 1 H), 5.41 (dd, *J* = 9.3, 9.1 Hz, 1 H), 5.39 (t, *J* = 9.1 Hz, 1 H), 5.26 (s, 1 H), 5.12 (t, *J* = 9.6 Hz, 1 H), 5.02 (d, *J* = 7.7 Hz, 1 H), 4.67 (dd, *J* = 12.1, 3.6 Hz, 1 H), 4.61–4.53 (m, 2 H), 4.52–4.43 (m, 2 H), 4.30–4.19 (m, 2 H), 4.13–4.01 (m, 3 H), 3.68 (m, 1 H), 3.08 (dd, *J* = 4.5, 3.1 Hz, 1 H), 2.79 (m, 1 H), 2.05, 1.76, 1.09, 0.97, 0.86, 0.84, 0.76, 0.69, 0.43 (9 × s, 3 H each). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 170.6, 169.5, 166.2, 165.7, 165.1, 164.8, 143.1, 133.6, 133.5, 133.3, 133.2, 133.0, 129.8, 129.6, 129.2, 128.9, 128.7, 128.3, 122.7, 103.3, 100.6, 91.9, 90.9, 75.3, 72.9, 72.0, 71.1, 70.4, 70.1, 69.4, 68.9, 63.4, 62.8, 62.4, 55.4, 47.4, 46.8, 45.7, 41.5, 41.0, 39.1, 38.9, 38.4, 36.5, 33.7, 33.0, 31.7, 30.5, 29.7, 27.8, 25.8, 25.5, 23.5, 23.3, 22.6, 20.7, 20.4, 18.0, 16.4, 16.3, 15.2. HRESI–MS: *m*/*z* [M + Na]$^+$ calcd for $C_{115}H_{118}O_{29}Na$: 1985.7651; found: 1985.7643. **19**: $[\alpha]_D$ = 51.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05–7.82 (m, 13 H), 7.76–7.71 (m, 4 H), 7.64–7.16 (m, 28 H), 6.01 (t, *J* = 9.6 Hz, 1 H), 5.96 (d, *J* = 8.0 Hz, 1 H), 5.76 (dd, *J* = 9.6, 8.4 Hz, 1 H), 5.71 (t, *J* = 9.6 Hz, 1 H), 5.67–5.61 (m, 2 H), 5.53 (t, *J* = 8.7 Hz, 1 H), 5.27 (s, 1 H), 5.18 (t, *J* = 9.2 Hz, 1 H), 5.13 (d, *J* = 7.7 Hz, 1 H), 4.68 (dd, *J* = 11.8, 3.7 Hz, 1 H), 4.61–4.45 (m, 4 H), 4.27 (m, 1 H), 4.11 (m, 1 H), 4.04 (t, *J* = 8.1 Hz, 1 H), 3.88 (m, 1 H), 3.75–3.65 (m, 2 H), 3.38 (m, 1 H), 3.10 (m, 1 H), 2.80 (m, 1 H), 1.11, 0.97, 0.87, 0.84, 0.78, 0.70, 0.43 (7 × s, 3 H each). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 167.0, 166.15, 166.07, 165.6, 165.2, 165.1, 164.7, 143.0, 133.9, 133.4, 133.2, 133.0, 129.8, 129.6, 129.0, 128.7, 128.3, 128.2, 122.7, 103.3, 100.8, 91.9, 90.7, 79.4, 75.1, 72.9, 72.0, 70.3, 70.1, 69.4, 63.4, 62.7, 62.4, 55.4, 47.4, 46.8, 45.7, 41.5, 40.9, 39.1, 38.9, 38.4, 36.5, 33.7, 32.9, 31.7, 30.5, 29.6, 27.8, 26.1, 25.4, 23.4, 23.3, 22.6, 18.0, 16.4, 16.3, 15.1. HRESI–MS: *m*/*z* [M + Na]$^+$ calcd for $C_{111}H_{114}O_{27}Na$: 1901.7440; found: 1901.7436. **20**: $[\alpha]_D$ = 44.4 (*c* 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02–7.80 (m, 13 H), 7.78–7.71 (m, 4 H), 7.64–7.19 (m, 28 H), 6.00 (t, *J* = 9.6 Hz, 1 H), 5.96 (d, *J* = 7.7 Hz, 1 H), 5.78–5.68 (m, 3 H), 5.64 (t, *J* = 9.5 Hz, 1 H), 5.44 (t, *J* = 8.4 Hz, 1 H), 5.27 (s, 1 H), 5.25–5.11 (m, 2 H), 4.75–4.62 (m, 2 H), 4.60–4.44 (m, 3 H), 4.28 (m, 1 H), 4.18–3.95 (m, 4 H), 3.58–2.92 (br s, 1 H), 3.12 (m, 1 H), 2.79 (m, 1 H), 1.26, 1.00, 0.86, 0.84, 0.71, 0.68, 0.42 (7 × s, 3 H each). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.6, 166.1, 165.6, 165.2, 165.1, 164.7, 142.9, 133.4, 133.0, 129.8, 129.6, 128.6, 128.3, 128.2, 122.7, 102.9, 100.5, 91.9, 91.0, 72.9, 72.0, 70.3, 69.9, 69.3, 63.4, 62.7, 55.3, 47.3, 46.8, 45.7, 41.5, 40.9, 38.9, 38.8, 38.3, 36.4, 33.7, 32.9, 31.7, 30.5, 29.6, 27.8, 25.4, 23.4, 22.6, 18.0, 16.4, 16.2, 15.1. HRESI–MS: *m*/*z* [M + Na]$^+$ calcd for $C_{111}H_{112}O_{28}Na$: 1915.7232; found: 1915.7197. **1**: $[\alpha]_D$ = 3 (*c* 0.35, MeOH) {lit.[1]: $[\alpha]_D$ = 2.85 (MeOH)}. ^{13}C NMR (100 MHz, C_5D_5N): δ = 177.9, 144.9, 126.0, 105.6, 105.4, 96.3, 90.7, 81.8, 78.9, 78.5, 78.3, 78.1, 77.0, 74.4, 73.9, 72.3, 71.6, 63.4, 62.7, 56.6, 48.7, 47.9, 47.0, 42.8, 42.4, 40.6, 40.3, 39.5, 37.6, 34.7, 33.9, 33.2, 31.5, 30.6, 28.9, 28.8, 26.8, 24.4, 19.2, 18.2, 17.4, 16.2. HRESI–MS: *m*/*z* [M+ Na]$^+$ calcd for $C_{48}H_{76}O_{19}Na$: 979.4873; found: 979.4907.