Structure Revision of Polypodoside A. Major Sweet Principle of *Polypodium glycyrrhiza*

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The aglycone stereochemistry of an intensely sweet saponin, polypodoside A isolated from the fern *Polypodium glycyrrhiza*, was revised from 22S, 25R, 26S to 22R, 25S, 26R based on a direct chemical correlation with a related sweet saponin, osladin.

The major sweet tasting principle of the North American fern, *Polypodium glycyrrhiza*, was characterized and named polypodoside A. The structure 1 was proposed by spectral study in comparison to a related saponin, osladin (2) which is the sweet principle of *P. vulgare*.2 6 When we synthesized compound 2, the initially reported wrong structure for osladin, we found it was not sweet at all. The revised structure 4 with 22R, 25S, 26R stereochemistry was then definitely established by single crystal X-ray diffraction study.7 Thus, the structure of polypodoside A requires reinvestigation. We wish to present herein the revised structure 3 for polypodoside A on the basis of a direct chemical correlation with an intermediate of the total synthesis of real osladin (4).8

![Chemical structures](image-url)
When $^{13}$C NMR chemical shifts of anomic carbons (C 1', 1'', 1'''', and 26) of polyposode A were compared with those of synthetic 2 (the wrong structure of osladin) and natural real osladin 4, polyposode A was found to have close similarity with 4 at the 1'' and 26 positions but not with 2. Thus, the structure 3 rather than 1 is much more likely for polyposode A.

Table 1. $^{13}$C NMR chemical shifts (ppm) and coupling constants ($J_{C1-H1\text{H}}$; Hz) of anomic carbons

<table>
<thead>
<tr>
<th>Carbon</th>
<th>2</th>
<th>4</th>
<th>Polyposode A $^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1'</td>
<td>100.3 (157)</td>
<td>99.6 (155)</td>
<td>99.5 (158)</td>
</tr>
<tr>
<td>1''</td>
<td>102.1 (173)</td>
<td>102.1 (173)</td>
<td>102.2 (176)</td>
</tr>
<tr>
<td>1'''</td>
<td>97.3 (169)</td>
<td>101.8 (166)</td>
<td>102.0 (165)</td>
</tr>
<tr>
<td>26</td>
<td>102.6 (154)</td>
<td>107.3 (157)</td>
<td>107.3 (159)</td>
</tr>
</tbody>
</table>

We first examined the catalytic hydrogenation of polyposode A nonacacetate (3a). Although the reduction proceeded with complete stereoselectivity, the single product obtained was not identical with osladin nonacacetate (4a). Structure 5a was assigned for this reduction product based on a spectral study. This compound should reinforce to take the boat form conformation in its B-ring. Birch reduction (Li/NH$_3$) also provided the same product. Interestingly, the deprotected compound 5, showed a moderate sweet taste. Therefore we planned the following partial synthesis of polyposode A aglycone from a key intermediate of the total synthesis of real osladin (4).$^8$

The lactone 6 was methylated by treatment with LDA and then with methyl iodide to give a mixture of C-25 stereoisomers. Catalytic amount of triflic acid efficiently accelerated the solvolysis of the three-membered ring to give 7 in 73% yield from 6. Hemiacetals prepared by DIBAH reduction of 7 were treated with MeONa in methanol leading to 8 in 89% yield as a 76:24 mixture of C-26 stereoisomers. The stereochemistry of C-25 of 8 was controlled to the desired $S$ (equatorial) configuration exclusively.$^8$ Silylation of 8 gave 9 as a sole product which was then converted to ketone 10 by hydroboration followed by oxidation in 50% yield. The enolate derived from ketone 10 with LDA was quenched with TMSCl to give the corresponding vinyl silyl ether, which upon palladium acetate-catalyzed dehydroisilylation in the presence of $p$-benzoquinone in benzene-acetonitrile, provided $\alpha$, $\beta$-unsaturated ketone 11 in 17% yield. Although the deprotection of 11 was unsuccessful, the same enone 11 was obtained from the aglycone of polyposide A$^1$ by the successive treatment with $n$-BuLi, Et$_3$N, and TBSOTf in THF in 20% yield. These two enones were identified by means of $^1$H as well as $^{13}$C NMR spectra. Thus the stereochemistry of polyposide A is confirmed to be 22R and 25S. The remaining 26 position of 3 was assigned to be R by $^1$H NMR ($\delta$ 4.45, 1H, d, $J =$ 8 Hz)$^1$ reflecting the trans relationship between the 25 and 26 positions.

During the isolation experiment of osladin (4) from Polyodium vulgare, we found this fern also contains polyposide A (3).$^7$ Although these two saponins showed quite similar behavior during a variety of chromatography, pure osladin was easily obtained by recrystallization. Isolation of polyposide A was not so simple. The mother liquor of the crystallization of osladin was concentrated and then acetylated. The mixture was subjected to HPLC (YMC D-Sil-5 20 x 250 nm column, and hexane/ethyl acetate (3:2) as eluant, flow rate
a) LDA/THF/HMPA then MeI, -78.0 °C.  b) TFOH (0.005 equiv)/dioxane-H$_2$O (9:1), reflux, 2 h.
c) DIBAH/THF, -55 °C, 7 h.  d) MeONa/MeOH, reflux, 2 h.  e) TBSOTf/Et$_3$N/CH$_2$Cl$_2$, 0°C, 10 min.
f) BH$_3$/THF, rt, 2 h then H$_2$O$_2$/NaOH, 45-55 °C, 1 h.  g) PDC/CH$_2$Cl$_2$, rt, 12 h.  h) LDA/THF then TMSCI, -78 °C.  i) Pd(OAc)$_2$/p-benzoquinone/PhH/CH$_2$CN, 50 °C, 10 h.
30 mL/min) to give polyodolide A nonaacetate (3a). Hydrolysis of 3a with MeONa in methanol provided 3 which was identified with the material obtained from P. glycyrrhiza by every spectral feature.

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References
9) Spectral data: 9: \([\alpha]_d^{27} +2.7^\circ (c 1.3, \text{CHCl}_3); \text{FT IR (film)} 2934, 2857, 1462, 1385, 1232, 1171, 1094, 1060, 833, 777 \text{ cm}^{-1}; \text{H NMR (200 MHz in CDCl}_3) 0.05 \text{ (6H, s), 0.09 (3H, s), 0.10 (3H, s), 0.70 (3H, s), 0.87 (3H, d, J = 6.8 Hz), 0.89 (9H, s), 0.90 (9H, s), 0.96 (3H, d, J = 6.8 Hz), 1.00 (3H, s), 3.33 (1H, m), 3.47 (1H, m), 4.23 (1H, d, J = 7.9 Hz), 5.31 (1H, d, J = 5.1 Hz); \text{C NMR (50 MHz in CDCl}_3) -4.9q, -4.6q (\times 2), -3.6q, 11.9q, 13.6q, 16.8q, 18.2s, 18.3s, 19.5q, 21.3t, 23.8t, 24.4t, 25.9q (\times 3), 26.8q (\times 3), 27.7q, 31.3t, 32.0t (\times 2), 32.1d, 36.6s, 37.4t, 38.1d, 39.8t, 40.2d, 42.6s, 42.8t, 50.3d, 52.7d, 56.6d, 72.7d, 78.2d, 102.5d, 121.1d, 141.6s; \text{HRMS(EI) m/z} \text{ calcd for C}_{16}H_{25}O_{10}Si, 644.5076 \text{ (M}), \text{ found 644.5048. 10: [\alpha]_d^{22} +7.8^\circ (c 1.1, \text{CHCl}_3); \text{FT IR (film)} 2953, 2862, 1709, 1462, 1387, 1252, 1173, 1094, 1070, 837, 779 \text{ cm}^{-1}; \text{H NMR (200 MHz in CDCl}_3) 0.03 \text{ (6H, s), 0.08 (3H, s), 0.10 (3H, s), 0.68 (3H, s), 0.74 (3H, s), 0.86 (3H, d, J = 6.8 Hz), 0.87 (9H, s), 0.90 (9H, s), 0.96 (3H, d, J = 6.8 Hz), 2.03 (1H, br d, J = 12.5 Hz), 2.16 (1H, dd, J = 12.8, 2.6 Hz), 2.19 (1H, dd, J = 12.3, 3.7 Hz), 3.33 (1H, m), 5.52 (1H, m), 4.24 (1H, d, J = 7.9 Hz); \text{C NMR (50 MHz in CDCl}_3) -4.9q, -4.6q (\times 2), -3.6q, 11.9q, 13.2q, 13.6q, 16.6q, 18.2q (\times 2), 21.5t, 23.8t, 24.1t, 25.9q (\times 6), 27.6t, 30.3t, 31.2t, 31.4t, 37.0t, 38.0d, 38.1d, 39.6t, 40.2d, 41.0s, 43.2s, 46.8t, 52.7d, 54.1d, 56.6d, 57.0d, 71.5d, 78.1d, 102.4d, 211.1s; \text{MS(EI) m/z} \text{ 659 (M^-1), 603 (M^-C, H}_2, \text{MS(Cl) m/z} \text{ 661 (M^-1), 659 (M^-1), 603 (M^-C, H}_2, \text{MS(Cl) m/z} \text{ OTBS), 11: [\alpha]_d^{22} +11.2^\circ (c 0.7, \text{CHCl}_3); \text{FT IR (film) 2928, 2857, 1667, 1462, 1385, 1252, 1173, 1096, 1065, 837, 777 \text{ cm}^{-1}; \text{H NMR (200 MHz in CDCl}_3) 0.05 \text{ (3H, s), 0.06 (3H, s), 0.09 (3H, s), 0.10 (3H, s), 0.62 (3H, s), 0.88 (3H, d, J = 6.8 Hz), 0.88 (9H, s), 0.90 (9H, s), 0.98 (3H, d, J = 6.8 Hz), 1.24 (3H, s), 3.34 (1H, m), 3.56 (1H, m), 4.24 (1H, d, J = 7.8 Hz), 7.35 (1H, s); \text{C NMR (50 MHz in CDCl}_3) -5.0q, -4.7q, -4.6q, -3.6q, 12.2q, 13.3q, 13.8q, 16.8q (\times 2), 21.8t, 22.7t, 23.8t, 25.9q (\times 6), 27.2t, 29.7t, 30.5t, 31.2t, 37.1t, 38.1d, 38.3s, 38.9t, 40.4d, 44.7s, 50.2d, 52.8d, 53.5d, 55.3d, 71.5d, 77.9d, 102.4d, 123.2d, 163.3s, 200.0s; \text{MS(Cl) m/z} \text{ 659 (M^-1).}

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