

## THE ABSOLUTE STEREOSTRUCTURE OF PANAXYTRIOL, A BIOLOGICALLY ACTIVE DIACETYLENIC ACETOGENIN, FROM GINSENG RADIX RUBRA

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The absolute stereostructure of panaxytriol (**1**), a diacetylenic constituent of Ginseng Radix Rubra, was determined by applying the modified Mosher method and the CD exciton chirality method to be expressed as (3*R*, 9*R*, 10*R*)-heptadec-1-ene-4,6-diyne-3,9,10-triol.

**KEY WORDS** Panaxytriol; Ginseng Radix Rubra; Mosher's method modified; CD exciton chirality method

Panaxytriol (**1**) was first isolated in 1983 as a characteristic diacetylenic constituent of Ginseng Radix Rubra (red ginseng, processed ginseng root) and the plain structure was elucidated.<sup>2)</sup> Since then, the biological activity of **1** has been extensively investigated and recently it has been received attention as a potential new type of antitumor agent.<sup>3)</sup> As a continuation of our chemical studies on crude drug processing, *i.e.*, on the characteristic constituents of Ginseng Radix Rubra,<sup>2,4)</sup> we have investigated the absolute stereostructure of panaxytriol (**1**), which is essential from the biological activity viewpoint.

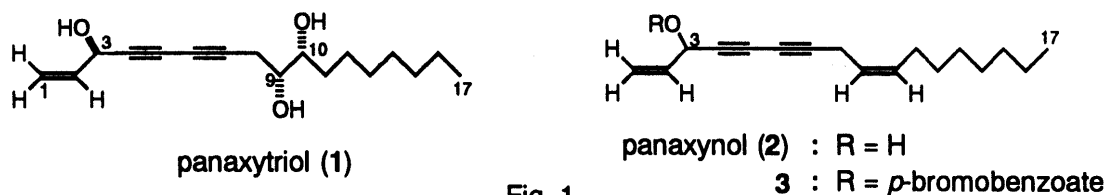
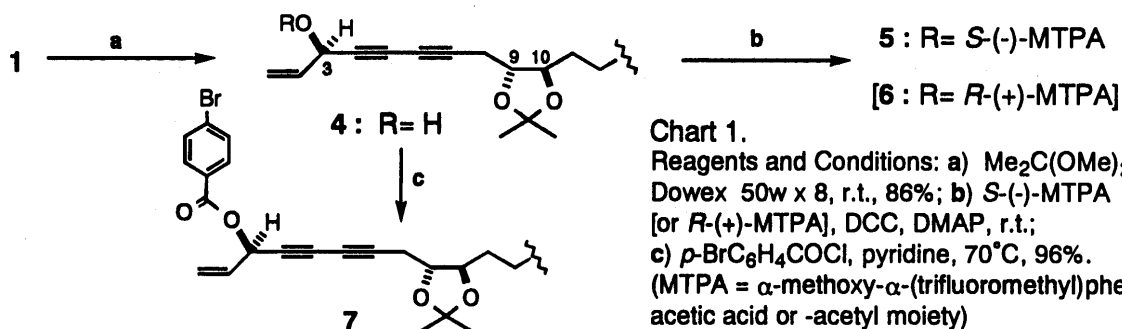


Fig. 1

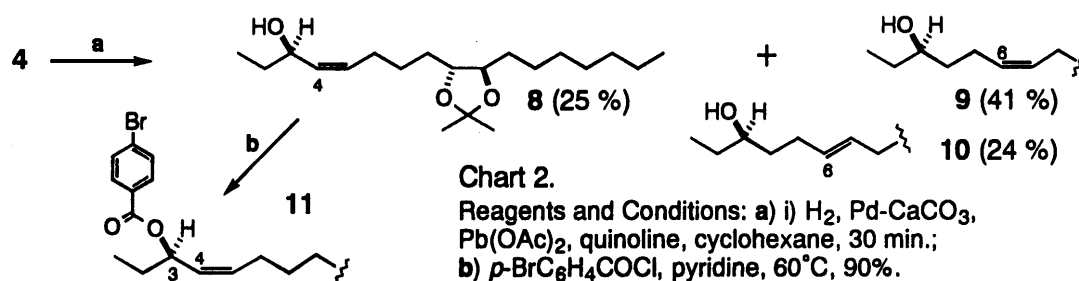
In regard to the absolute configuration at C-3 of panaxynol (**2**), another diacetylenic constituent of white ginseng (Fig. 1), Shim *et al.* applied the CD exciton chirality method to the *p*-bromobenzoate **3** and concluded that panaxynol (**2**) possessed a 3*S* configuration.<sup>5)</sup> On the other hand, by means of the modified Mosher method, Bernard *et al.*<sup>6)</sup> recently defined the 3*S* configuration for (+)-farcarinol, which is a known enantiomer of panaxynol (**2**), and found that the  $[\alpha]_D$  value of (+)-farcarinol as well as the CD spectrum of its *p*-bromobenzoate showed opposite signs to those of panaxynol (**2**) and its *p*-bromobenzoate **3**. Therefore Bernard *et al.* claimed that panaxynol (**2**) must possess a 3*R* configuration and that the CD exciton chirality method applied to secondary allylic alcohols was not applicable to secondary alcohols flanked by two unsaturated chromophores as seen in **2**.

Bearing in mind the panaxynol problem, in order to determine the absolute configuration at C-3 of panaxytriol (**1**), which showed levorotatory ( $[\alpha]_D - 19.0^\circ$ ,  $c = 1.0$ ,  $\text{CHCl}_3$ ), both the *R*- and *S*-MTPA esters (**5** and **6**) of **1** were first prepared after prior acetonide protection of the 9,10-diol moiety in **1**.<sup>7)</sup> Examination of the proton NMR signals of **5** and **6**, of which the  $\Delta\delta$  values ( $\delta_S - \delta_R$ ) are illustrated in Fig. 2, has led us to assign a 3*R* configuration to **5** and **6**. For comparison purposes, the *p*-bromobenzoate **7** of **1** was next prepared and was found to show a negative CD maximum [249 nm ( $\Delta\epsilon = -7.9$ )], which was similar to that of **3**.

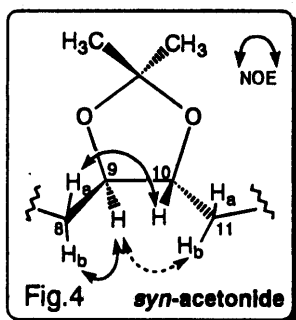
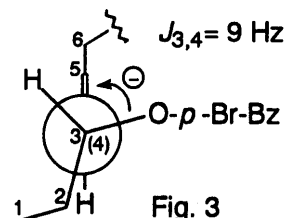
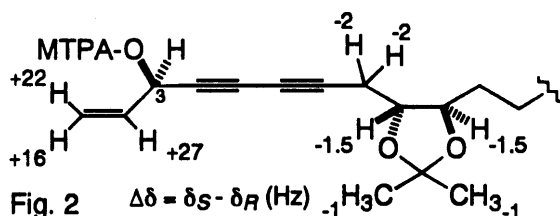
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In order to confirm our results further and to shed light on the above conflicting reports on the C-3 configuration of panaxynol (2) as well,<sup>5,6</sup> we then prepared the simple *p*-bromobenzoate derivative 11,<sup>8</sup> to which the CD exciton chirality method is unequivocally applicable. Thus, partial hydrogenation of 4 using Lindlar catalyst<sup>9</sup> furnished three products, 8, 9, and 10, among which 8 was further converted to *p*-bromobenzoate 11.



The CD spectrum of 11 showed a negative maximum at 245 nm ( $\Delta\epsilon = -9.1$ ), and thus the absolute configuration of C-3 in panaxytriol (1) has been reconfirmed to be *R*<sup>10</sup> (Fig. 3).



Next, we investigated the absolute stereochemistry of the vicinal glycol moiety at C-9 and C-10 of panaxytriol (1). In the relative configuration, the *syn* structure was defined by a NOESY experiment of acetonide 4. Thus, the NOE correlations in 4 were observed between 8- $\text{H}_b$  and 9-H; 8- $\text{H}_a$  and 10-H; and 9-H and 11- $\text{H}_b$ , as illustrated in Fig. 4. Furthermore, the coupling constant (8 Hz) between 9-H and 10-H as well as the isopropylidene methyl proton signals observed at  $\delta$  1.40 (6H, s) supported the *syn*-acetonide structure in 4.<sup>11, 12)</sup>

The absolute configurations of C-9 and C-10 were then defined as based on the CD analysis of the di-*p*-bromobenzoate 12,<sup>13</sup> which showed a negative exciton split [255 nm ( $\Delta\epsilon = -6.5$ ) and 239 nm ( $\Delta\epsilon = +10.6$ )] to indicate 9*R*, 10*R* stereochemistry.<sup>14)</sup>

In order to eliminate the effect of the 4,6-diyne chromophore, we further prepared a saturated di-*p*-bromobenzoate derivative 14. Here again, the CD spectrum of 14 showed a clear exciton split with similar amplitude [first Cotton at 255 nm ( $\Delta\epsilon = -6.5$ ); second Cotton at 239 nm ( $\Delta\epsilon = +7.1$ )], and thus the 9*R* and 10*R* configurations were confirmed unambiguously.

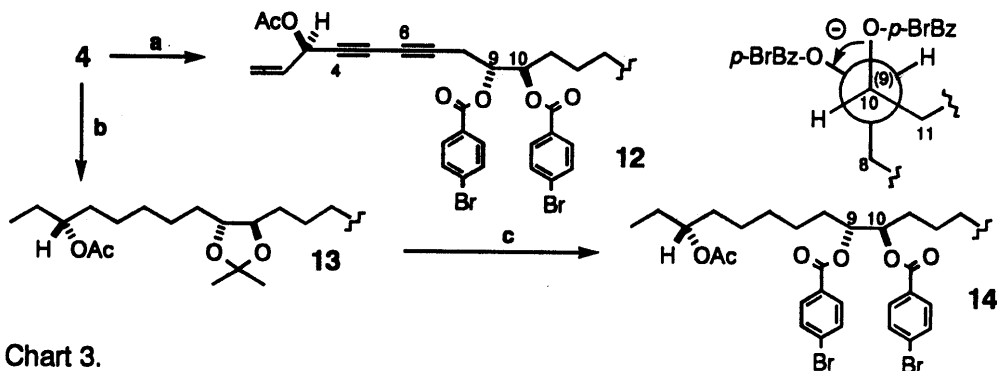


Chart 3.

Reagents and Conditions: a) i)  $\text{Ac}_2\text{O}$ , pyridine, r.t., ii) 80% aq.  $\text{AcOH}$ ,  $60^\circ\text{C}$ , iii)  $p\text{-BrC}_6\text{H}_4\text{COCl}$ , pyridine,  $60^\circ\text{C}$ , 3 steps 60%; b) i)  $\text{H}_2$ ,  $\text{Pd-CaCO}_3$ ,  $\text{Pb}(\text{OAc})_2$ , cyclohexane, 90%, ii)  $\text{Ac}_2\text{O}$ , pyridine, r.t., 85%; c) i) 80% aq.  $\text{AcOH}$ ,  $60^\circ\text{C}$ , ii)  $p\text{-BrC}_6\text{H}_4\text{COCl}$ , pyridine,  $60^\circ\text{C}$ , 2 steps 72%.

From the above-mentioned evidence, the absolute stereostructure of panaxytriol has been determined to be (3*R*, 9*R*, 10*R*)-heptadec-1-ene-4,6-diyne-3,9,10-triol (1).

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- 7) 4:  $[\alpha]_D -22.5^\circ$  ( $c = 1.2$ , acetone,  $25^\circ\text{C}$ ). FAB-MS  $m/z$ : 341 ( $\text{M}+\text{Na}$ )<sup>+</sup>,  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.94 (ddd,  $J=17, 10, 5$  Hz, 2-H), 5.47 (d,  $J=17$ , 1- $\text{H}_b$ ), 5.25 (d,  $J=10$ , 1- $\text{H}_a$ ), 4.92 (dd,  $J=7, 5$ , 3-H), 3.80 (td,  $J=8, 4, 10$ -H), 3.73 (dt,  $J=8, 5$ , 9-H), 2.63 (dd,  $J=17, 5$ , 8- $\text{H}_b$ ), 2.59 (dd,  $J=17, 5$ , 8- $\text{H}_a$ ), 1.87 (d,  $J=7$ , 3-OH), 1.58 (m, 11- $\text{H}_2$ ), 1.40 (s, 19- $\text{H}_3$  and 20- $\text{H}_3$ ), 0.89 (t,  $J=7$ , 17- $\text{H}_3$ ).
- 8) 11: FAB-MS  $m/z$ : 531 ( $\text{M}+\text{Na}$ )<sup>+</sup>,  $^1\text{H-NMR}$  (270 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.69 (dt,  $J=9, 7$  Hz, 3-H), 5.64 (dt,  $J=11, 7, 5$ -H), 5.42 (dd,  $J=9, 11$ , 4-H), 2.24 (m, 6- $\text{H}_2$ ), 1.79 (m, 2- $\text{H}_b$ ), 1.69 (m, 2- $\text{H}_a$ ), 0.95 (t,  $J=7, 1$ - $\text{H}_3$ ), 0.87 (t,  $J=7, 17$ - $\text{H}_3$ ).
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- 13) 12: FAB-MS  $m/z$ : 707 ( $\text{M}+\text{Na}$ )<sup>+</sup>,  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.87 (d,  $J=6$  Hz, 3-H), 5.84 (ddd,  $J=16, 10, 6$ , 2-H), 5.49 (d,  $J=16$ , 1- $\text{H}_b$ ), 5.49 (m, 10-H), 5.38 (m, 9-H), 5.33 (d,  $J=10$ , 1- $\text{H}_a$ ), 2.83 (dd,  $J=18, 6$ , 8- $\text{H}_b$ ), 2.76 (dd,  $J=18, 6$ , 8- $\text{H}_a$ ), 2.10 (s, 3- $\text{OCOCH}_3$ ), 1.74 (m, 11- $\text{H}_2$ ), 0.84 (t,  $J=3$ , 17- $\text{H}_3$ ).
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