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

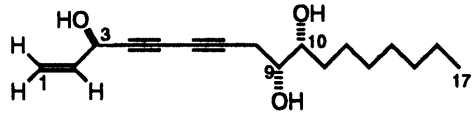
Motomasa KOBAYASHI,* Taifo MAHMUD, Takashi UMEZOME, and Isao KITAGAWA*,[1)]

Faculty of Pharmaceutical Sciences, Osaka University, Yamada-oka 1-6, Suita, Osaka 565, Japan

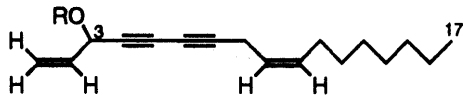
The absolute stereostructure of panaxytriol (**1**), a diacetylenic constituent of Ginseng Radix Rubra, was determined by applying the modified Mosher method and the CD exciton chirality method to be expressed as (3*R*, 9*R*, 10*R*)-heptadec-1-ene-4,6-diyne-3,9,10-triol.

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.[2)] 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.[3)] As a continuation of our chemical studies on crude drug processing, *i.e.*, on the characteristic constituents of Ginseng Radix Rubra,[2,4)] we have investigated the absolute stereostructure of panaxytriol (**1**), which is essential from the biological activity viewpoint.



panaxytriol (**1**)



panaxynol (**2**) : R = H

3 : R = *p*-bromobenzoate

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.[5)] On the other hand, by means of the modified Mosher method, Bernard *et al.*[6)] 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 °, *c*= 1.0, $CHCl_3$), 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**.[7)] Examination of the proton NMR signals of **5** and **6**, of which the $\Delta\delta$ values (δS-δR) 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 ($\Delta\varepsilon$ = - 7.9)], which was similar to that of **3**.

* To whom correspondence should be addressed.

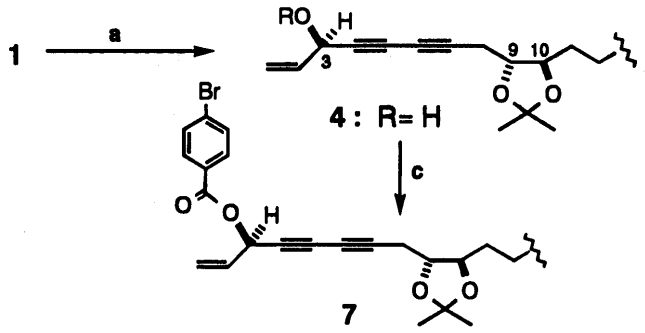


Chart 1.
Reagents and Conditions: a) $Me_2C(OMe)_2$, Dowex 50w x 8, r.t., 86%; b) *S*-(-)-MTPA [or *R*-(+)-MTPA], DCC, DMAP, r.t.; c) *p*-BrC_6H_4COCl, pyridine, 70°C, 96%. (MTPA = α-methoxy-α-(trifluoromethyl)phenylacetic acid or -acetyl moiety)

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,[5,6] we then prepared the simple *p*-bromobenzoate derivative **11**,[8] to which the CD exciton chirality method is unequivocally applicable. Thus, partial hydrogenation of **4** using Lindlar catalyst[9] furnished three products, **8**, **9**, and **10**, among which **8** was further converted to *p*-bromobenzoate **11**.

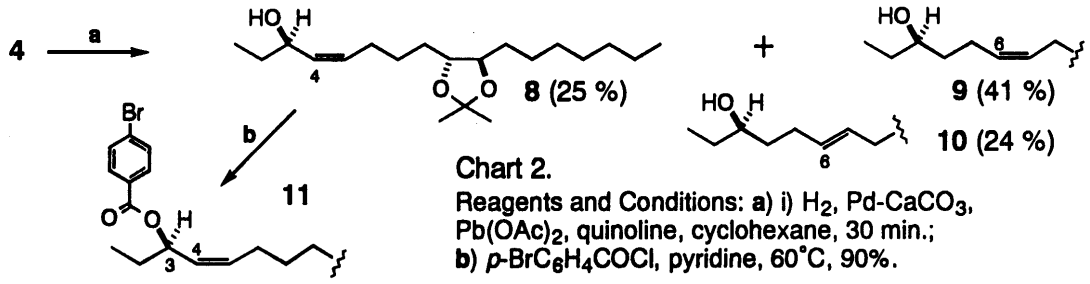


Chart 2.
Reagents and Conditions: a) i) H_2, Pd-$CaCO_3$, $Pb(OAc)_2$, quinoline, cyclohexane, 30 min.; b) *p*-BrC_6H_4COCl, pyridine, 60°C, 90%.

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

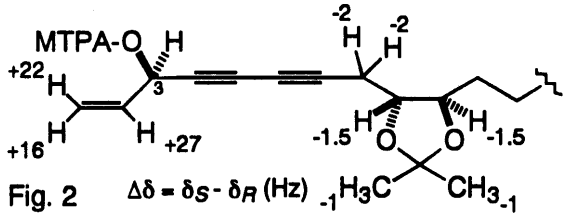


Fig. 2 $\Delta\delta = \delta_S - \delta_R$ (Hz)

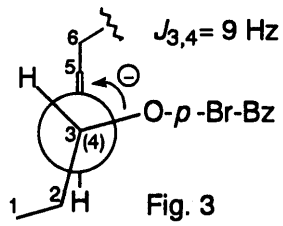


Fig. 3

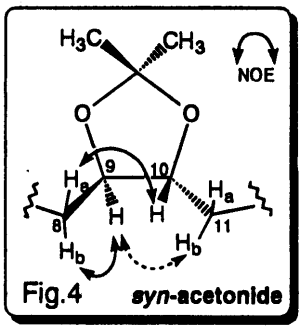


Fig.4 *syn*-acetonide

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-H_b and 9-H; 8-H_a and 10-H; and 9-H and 11-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 δ 1.40 (6H, s) supported the *syn*-acetonide structure in **4**.[11,12]

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

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 ($\Delta\varepsilon$ = - 6.5); second Cotton at 239 nm ($\Delta\varepsilon$ = + 7.1)], and thus the 9*R* and 10*R* configurations were confirmed unambiguously.

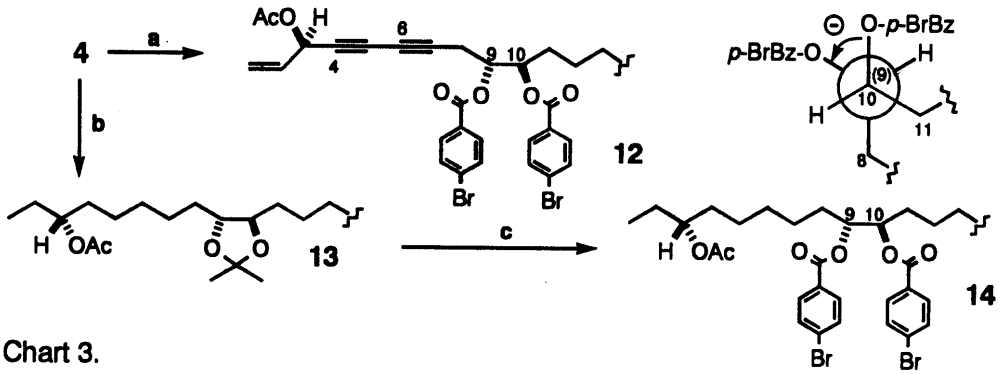


Chart 3.

Reagents and Conditions: a) i) Ac_2O, pyridine, r.t., ii) 80% aq. AcOH, 60°C, iii) *p*-BrC_6H_4COCl, pyridine, 60°C, 3 steps 60%; b) i) H_2, Pd-$CaCO_3$, $Pb(OAc)_2$, cyclohexane, 90%, ii) Ac_2O, pyridine, r.t., 85%; c) i) 80% aq. AcOH, 60°C, ii) *p*-BrC_6H_4COCl, pyridine, 60°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**).

REFERENCES AND NOTES

1) Present address: *Faculty of Pharmaceutical Sciences, Kinki University, Kowakae 3-4-1, Higashiosaka, Osaka 577, Japan.*

2) Kitagawa I., Yoshikawa M., Yoshihara M., Hayashi T., Taniyama T., *Yakugaku Zasshi*, **103**, 612-622 (1983).

3) For examples: a) Sata T., Matsunaga H., Yamamoto H., Nagumo F., Fujito H., Mori M., Katano M., *Biol. Pharm. Bull.*, **17**, 798-802 (1994); b) Matsunaga H., Katano M., Yamamoto H., Mori M., Takata K., *Chem. Pharm. Bull.*, **37**, 1279-1281 (1989).

4) a) Kitagawa I., Taniyama T., Yoshikawa M., Ikenishi Y., Nakagawa Y., *Chem. Pharm. Bull.*, **37**, 2961-2970 (1989); b) Kitagawa I., Taniyama T., Shibuya H., Noda T., Yoshikawa M., *Yakugaku Zasshi*, **107**, 495-505 (1987); c) Kitagawa I., Taniyama T., Hayashi T., Yoshikawa M., *Chem. Pharm. Bull.*, **31**, 3353-3356 (1983).

5) Shim S. C., Koh H. Y., Chang S-K., *Tetrahedron Lett.*, **26**, 5775-5776 (1985).

6) Bernard M. W., Hallock Y. F., Cardellina II J. H., Boyd M. R., *Tetrahedron Lett.*, **35**, 993-994 (1994).

7) **4**: $[\alpha]_D$ - 22.5 ° (*c*= 1.2, acetone, 25°C). FAB-MS *m/z*: 341 $(M+Na)^+$, ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.94 (ddd, *J*=17, 10, 5 Hz, 2-H), 5.47 (d, *J*=17, 1-H_b), 5.25 (d, *J*=10, 1-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-H_b), 2.59 (dd, *J*=17, 5, 8-H_a), 1.87 (d, *J*=7, 3-OH), 1.58 (m, 11-H_2), 1.40 (s, 19-H_3 and 20-H_3), 0.89 (t, *J*=7, 17-H_3).

8) **11**: FAB-MS *m/z*: 531 $[M+Na]^+$, ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 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-H_2), 1.79 (m, 2-H_b), 1.69 (m, 2-H_a), 0.95 (t, *J*=7, 1-H_3), 0.87 (t, *J*=7, 17-H_3).

9) Marvell E. N., Tashiro J., *J. Org. Chem.*, **30**, 3991-3993 (1965).

10) Gonnella N. C., Nakanishi K., *J. Am. Chem. Soc.*, **104**, 3775-3776 (1982).

11) Chuche J., Dana G., Monot M-R., *Bull. Soc. Chim. France*, **9**, 3300-3307 (1967).

12) Oikawa H., Matsuda I., Kagawa T., Ichihara A., Kohmoto K., *Tetrahedron*, **50**, 13347-13368 (1994).

13) **12**: FAB-MS *m/z*: 707 $[M+Na]^+$, ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.87 (d, *J*=6 Hz, 3-H), 5.84 (ddd, *J*=16, 10, 6, 2-H), 5.49 (d, *J*=16, 1-H_b), 5.49 (m, 10-H), 5.38 (m, 9-H), 5.33 (d, *J*=10, 1-H_a), 2.83 (dd, *J*=18, 6, 8-H_b), 2.76 (dd, *J*=18, 6, 8-H_a), 2.10 (s, 3-OCOCH_3), 1.74 (m, 11-H_2), 0.84 (t, *J*=3, 17-H_3).

14) a) Harada N., Nakanishi K., *J. Am. Chem. Soc.*, **91**, 3989-3991 (1969); b) Harada N., Saito A., Ono H., Uda H., Gawronski J., Gawronska K., Symposium Papers, 33rd Symposium on the Chemistry of Natural Products, Osaka, Japan, Oct. 1991, pp. 464-471.

(Received June 13, 1995; accepted July 15, 1995)