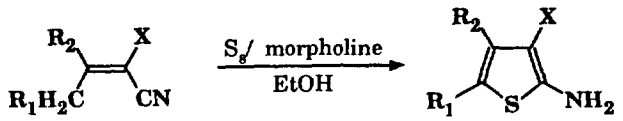


**Figure 1.**

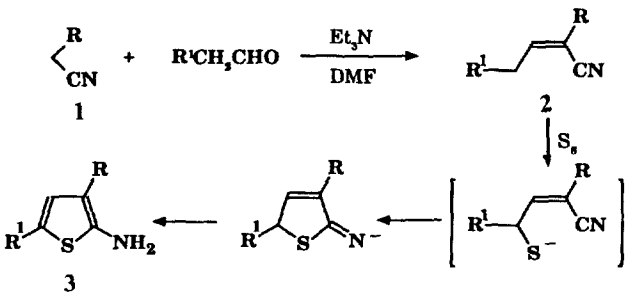


**Figure 2.**

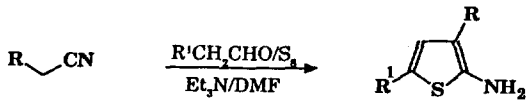
logically active lead compound we needed various functionalized thiophenes. In the literature, numerous methods are available for the construction of thiophene ring systems[2]; such as oxidative cyclization of 1,3-diene-1-thiol[3], cyclization of 3-methylenethio-1-oxopropyl derivatives[4], addition of thioglycolic esters to 1,3-diketones[5], Dieckmann cyclization of 3-thiaadipic acid derivatives[6] and ring closure of unsaturated nitriles with sulfur (Gewald Synthesis).[7]

Most of the exisisting methods except those of Gewald, however, possess severe limitation due to either harsh reaction condition or difficulties to obtain staring material. So, further research to develope better synthetic methodologies are certainly warranted. In this context Gewald's method deserves some mention. He treated α,β-unsaturated nitriles, which are available by condensation of activated cyanomethylene derivatives, with elemental sulfur in ethanol containing a base to produce the corresponding 3-substituted 2-amino thiophenes (Figure 1).

After careful thought, however, it was envisioned that the aforementioned compounds may be obtained simply by condensing active methylene compounds, *e.g.*, α-cyano ethylacetate, with aldehyde in the presence of sulfur without isolating the α,β-unsaturated nitriles as an intermediate in a single one-pot process. Indeed it turned out to be successful efforts and its synthetic scheme, and the results are shown in Figure 2 and Table 1, respectively. However, it should be noted that the attempts to prepare 2-*hydroxy* thiophenes starting from either diethyl malonate or diethyl carboethoxymethyl phosphonate were not fruitful. Although the compounds **3** were known in prior art as mentioned above,[8] each compound was fully identified by $^1$H NMR and mass spectroscopy.

**The preparation of entry 1 is a typified procedure.** To a solution of ethyl cyanoacetate (5 g, 44.2 mmol), n-butylaldehyde (3.9 m*l*, 44.2 mmol) were added triethylamine (6.2 m*l*, 44.2 mmol) and DMF (6.8 m*l*, 88.4 mmol). After stirring 30 min sulfur powder (1.4 g, 44.2 mmol) was added. The resulting suspension was stirred at r.t. overnight. Water (100 m*l*) was added and the reaction mixture was extracted with ether (50 m*l* × 3). The combined ether extracts were washed with brine (100 m*l* × 1), dried over $MgSO_4$ and passed through short path of silica gel. Concentration of the filtrates *in vacuo* gives practically pure product (6.5 g, 73% yield) as yellow solid. mp. 59-62℃; $^1$H-NMR (80 MHz) δ 1.25(t, 3H), 1.30(t, 3H), 2.57(q, 2H), 4.25(q, 2H), 5.20(−$NH_2$), 6.60(s, 1H); M/S 200.

**Table 1.** Preparation of 2-Aminothiophenes (**3**) from Cyano Derivatives (**1**) and Varione Aldehydes



| Entry | R | $R^1$ | Yield[a] (%) |
|---|---|---|---|
| 1 | $CO_2Et$ | Et | 73 |
| 2 | $CO_2Et$ | *i*Pr | 92 |
| 3 | $CO_2Et$ | Ph | 43 |
| 4 | $P(O)(OEt)_2$ | Et | 51 |
| 5 | $P(O)(OEt)_2$ | Me | 52 |
| 6 | $P(O)(OEt)_2$ | Ph | 37 |

[a] Not optimized, but purified and isolated yield.

With these 2-amino-5-substituted thiazoles in hand we are now actively involved in designing biologically active compounds containing thiophene moiety. The resulting progress will be reported in due course.

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## Absolute Configuration of Panaxydol


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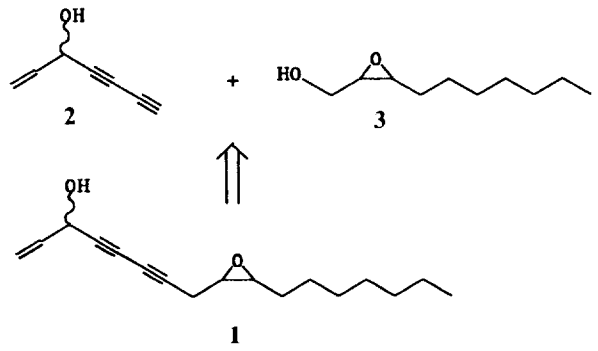
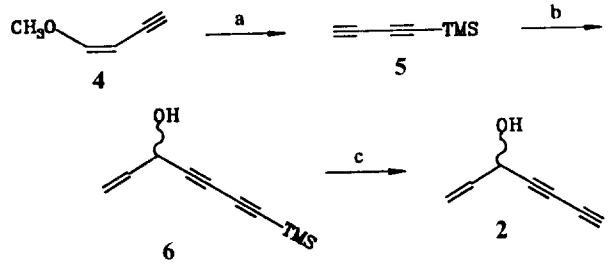
*Panax ginseng* C. A. Meyer (Araliaceae) has been known



**Scheme 1.** Retrosynthesis of panaxydol.

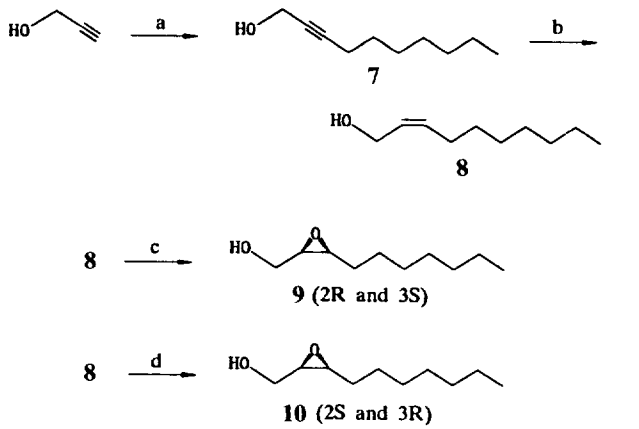


**Scheme 2.** (a) 1) *n*-BuLi, $(CH_3)_3SiCl$, THF, −78℃ (b) 2*n*-BuLi, $CH_2$=CH-CHO, THF, −40℃ (c) 1 N NaOH/MeOH (60%)

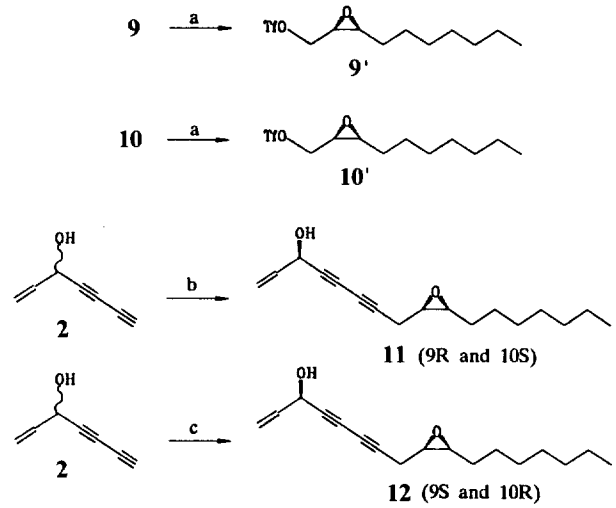
for many years to be the most valuable of all the herbal medicines in Korea, China, and Japan. A polyacetylene compound, panaxynol, from ginseng roots was first obtained by Takahashi *et al.*, as a yellowish viscous liquid of the ether soluble neutral portion.[1,2] The structure turned out to be identical with falcarinol isolated from *Falcaria vulgaris B.*[3] and carotatoxin isolated from *Daucus carota L.*[4] Wrobel *et al.* isolated another $C_{17}$ polyacetylene compound, panaxydol, from dried Korean ginseng roots[5] and the chemical structure turned out to be heptadeca-1-en-4,6-diyn-9,10-epoxy-3-ol (**1**). According to recent reports,[6-9] panaxydol extracted from fresh Korean ginseng roots has been shown to have cytotoxic activity against human carcinoma cells such as L1210, Sarcoma 180 cell *etc.*, and the active site for the cytotoxicity is the epoxy group of the compound. Although absolute configuration of panaxynol was determined as 3R through total synthesis,[10] the stereochemistry of three chiral centers at C-3, C-9, and C-10 in panaxydol has not been established. We, therefore, determined the absolute stereochemistry of panaxydol by total synthesis and comparison with the authentic sample.

The retrosynthetic analysis of panaxydol is shown in Scheme 1. The synthesis of the $C_1$-$C_7$ moiety (**2**) was accomplished as shown in Scheme 2. Trimethylsilylbutadiyne (**5**) was prepared by treating (Z)-1-methoxybut-1-en-3-yne (**4**) with trimethylchlorosilane and 2 eq. of *n*-buthyllithium in tetrahydrofuran.[11] 4-Lithio-1-(trimethylsilyl)-butadiyne was generated from the reaction of trimethylsilylbutadiyne (**5**) with *n*-buthyllithium and added acrolein to the anion generated to afford the compound (**6**), which yielded the $C_1$-$C_7$ moiety (**2**) in 60% yield on base treatment.

The synthesis of $C_8$-$C_{17}$ moiety (**3**) is outlined in Scheme 3. Propargyl alcohol was treated with two molecular proportions of lithium amide in liquid ammonia to form dilithio



**Scheme 3.** (a) Li, $NH_3$, $Fe(NO_3)_3 \cdot 9H_2O$, $CH_3(CH_2)_5CH_2Br$ (75%), (b) $Pd/BaSO_4$, $H_2$, Quinoline, MeOH (90%) (c) Ti(O-*i*-Pr)$_4$, (−)-DIPT, *t*-BuOOH, 4 Å molecular sieves, −20℃, 3 days (92%, 84% *e.e.*) (d) Ti(O-*i*-Pr)$_4$, (+)-DIPT, *t*-BuOOH, 4 Å molecular sieves, −20℃, 29 h (74%, 86% *e.e.*)



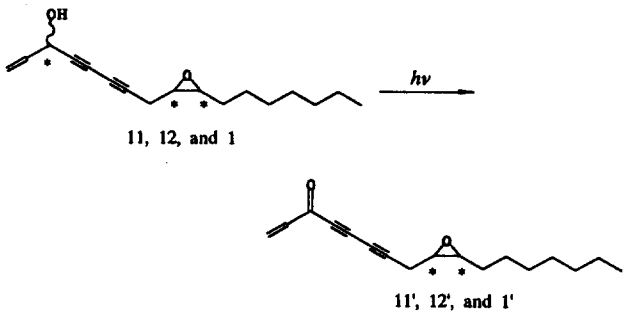
**Scheme 4.** (a) $(CF_3SO_2)_2O$, $2Et_3N$, −78℃ (b) $(CF_3SO_2)_2O$, $2Et_3N$, −78℃ (c) HMPA, 2*n*-BuLi, THF, 9′, −78℃ (77%) (d) HMPA, 2*n*-BuLi, THF, 10′, −78℃ (76%)

complex. Subsequent addition of 1-bromoheptane into the dilithio complex gave the C-alkylation product, dec-2-yn-1-ol (**7**). Lindlar's catalytic hydrogenation of the compound (**7**) gave the *cis*-olefin (**8**) exclusively. Sharpless epoxidation[12] of (Z)-alcohol (**8**) produced 3-heptyloxiranemethanols (**9** and **10**), respectively. When diisopropyl D-tartrate was used, the absolute configuration of the epoxy alcohol is 2R and 3S (**9**), while 2S and 3R (**10**) when diisopropyl L-tartrate was used. Each epoxy alcohol was immediately treated with trifluoromethane sulfonic anhydride in dichloromethane to yield triflate (**9′** and **10′**). The triflate was treated with the dianion of diacetylenic alcohol (**2**) to obtain heptadeca-1-en-4,6-diyn-9,10-epoxy-3-ol [**11** (9R, 10S) and **12** (9S, 10R) in Scheme 4].

Two polyacetylene compounds **11** and **12** show the typical polyacetylenic vibrational fine structure in the UV spectra.[13] The infrared spectra of **11** and **12** show hydroxyl stretching frequency 3400 $cm^{-1}$ and $\nu_{C\equiv C}$ of conjugated two triple bonds

at 2260 $cm^{-1}$. The $^1$H-NMR spectral data[13] of **11** and **12** show a complex spin system of terminal vinyl group at 5.25, 5.47, and 5.95 ppm, methylene protons of straight aliphatic hydrocarbon chain at 1.29-1.57 ppm, and terminal methyl proton signals at 0.82 ppm. Protons at 2.91 and 3.09 ppm indicate the presence of an epoxy group and pairs of doublets at 2.71 and 2.39 ppm are attributed to a geminal coupling of epoxy protons with a characteristic large coupling constant of 17.7 Hz. The molecular skeleton of polyacetylene compounds can be easily recognized by use of $^{13}$C-NMR. The $^{13}$C-NMR spectral data[13] of **11** and **12** show the typical aliphatic methylene carbons at 22.6, 27.5, 26.4 (27.4), 31.7, 29.1 and 29.4 ppm, a terminal methyl carbon at 14.0 (14.1) ppm, terminal vinyl carbons at 117.1 and 136.0 ppm, allylic carbon to the terminal vinyl group at 64.4 (63.4) ppm, conjugated two triple bond carbons at 76.7, 70.8 66.3, and 74.9 ppm, and epoxy group carbons at 54.3 and 55.0 (57.0) ppm. The mass spectra determined by electron impact method showed a molecular ion peak at m/z 260.

It was impossible to distinguish the compounds **11** and **12** from the spectral analyses since their UV, IR, MS, and NMR spectral data were exactly same. The optical rotation values, $[\alpha]_D^{25}$, were measured for the synthetic polyacetylene compounds (**11** and **12**), panaxydol (**1**), and their photooxidation products (**11'**, **12'**, and **1'**). Heptadeca-l-en-4,6-diyn-9,10-epoxy-3-ol was photooxidized to obtain heptadeca-1-en-4,6-diyn-9,10-epoxy-3-one on irradiation of the aerated solution with 300 nm UV light as shown below.[14] The photooxidized compounds **11'**, **12'**, and **1'** lost $C_3$ chiral center and optical rotation values are solely due to the chiral centers in the epoxy group and the comparison of the optical rotation values of these compounds will establish the absolute configuration of chiral centers. The specific rotation of **12** (9S, 10R) was +24.5° (*c* 0.118 in $CHCl_3$) but those of **11** (9R, 10S) and **1** are negative values of −23.7° (*c* 0.127 in $CHCl_3$) and −29.7° (*c* 0.094 in $CHCl_3$), respectively. The specific rotation values of photooxidation products (**11'**, **12'**, and **1'**) were −2.5° (*c* 0.097 in $CHCl_3$) +2.6° (*c* 0.087 in $CHCl_3$), and −2.9° (*c* 0.069 in $CHCl_3$) indicating that the absolute configuration of the epoxy ring in compounds **11'** and **1'** is identical. After photooxidation, the chiral centers of **11**, **12**, and **1** are reduced to two carbons in epoxy ring. Therefore, specific rotations of photooxidation products are not related to $C_3$ carbon.




From these results, the absolute configuration of epoxy group in panaxydol is determined to be 9R and 10S.

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13. (**11**) $\lambda_{max}$ (MeOH) 254, 240, 228, and 217 nm; $\nu_{max}$ (NaCl) 3381, 2930, 2857, 2257, 1668, 1430, 1282, 1116, 986, and 932 $cm^{-1}$; $\delta_H$ (300 MHz; $CDCl_3$) 5.25(1H, *dm*), 5.47(1H, *dm*), 5.95(1H, *ddd*), 4.92(1H, *m*), 2.71(1H, *dd*), 2.39(1H, *d*), 3.15(1H, *m*), 2.98(1H, *m*), 1.29-1.54(12H, *m*), and 0.89 (3H, *t*); $\delta_C$ (75 MHz; $CDCl_3$) 117.1, 136.0, 64.4, 76.7, 70.8, 66.3, 74.9, 19.4, 54.3, 55.0, 27.4, 26.4, 29.4, 29.1, 31.7, 22.6, and 14.0; *m/z* 260 $[M]^+$, 119 $[C_8H_7O]^+$ (**12**) $\lambda_{max}$ (MeOH) 254, 240, 228, and 217 nm; $\nu_{max}$ (NaCl) 3389, 2930, 2856, 2257, 1657, 1442, 1281, 1118, 986, and 932 nm; $\delta_H$ (300 MHz; $CDCl_3$) 5.25(1H, *dm*), 5.47(1H, *dm*), 5.95(1H, *ddd*), 4.87(1H, *m*), 2.71 (1H, *dd*), 2.39(1H, *dd*), 3.15(1H, *m*), 2.97 (1H, *m*), 1.29-1.57(12H, *m*), and 0.89(3H, *t*); $\delta_C$ (75 MHz; $CDCl_3$) 117.1, 136.0, 64.4, 76.7, 70.8, 66.3, 74.9, 19.4, 54.3, 57.0, 27.4, 26.4, 29.4 29.1, 31.7, 22.6, and 14.1; *m/z* 260 $[M]^+$, 119$[C_8H_7)]^+$ (**1**) $\lambda_{max}$ (MeOH) 254, 240, 228, and 217 nm; $\delta_H$ (300 MHz; $CDCl_3$) 5.18(1H, *dm*), 5.40(1H, *dm*), 5.87(1H, *ddd*), 4.85(1H, *m*), 2.65(1H, *dd*), 2.32(1H, *dd*), 3.09(1H, *m*), 291(1H, *m*), 1.15-1.50(12H, *m*), and 0.82 (3H, *t*); $\delta_C$ (75 MHz; $CDCl_3$) 117.6, 136.8, 64.4, 77.7, 71.4, 67.0, 75.8, 20.1, 55.0, 57.6, 28.1, 27.1, 30.0, 29.8, 32.4, 23.2, and 14.7; *m/z* 260 $[M]^+$, 119 $[C_8H_7O]^+$.
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