Pergamon

Tetrahedron Letters 39 (1998) 9521–9522

TETRAHEDRON LETTERS

First Total Synthesis of Optically Active Panaxydol, a Potential Antitumor Agent Isolated from *Panax Ginseng*

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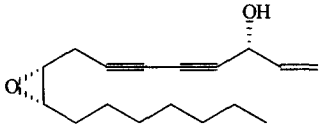
Received 24 August 1998; revised 13 October 1998; accepted 19 October 1998

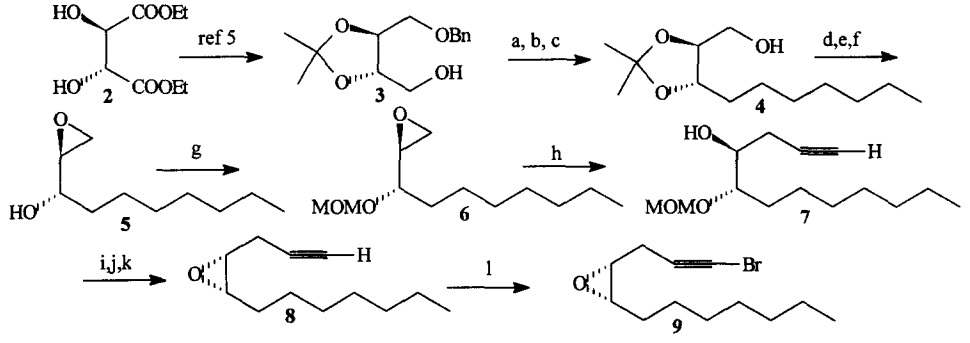
Abstract: The first total synthesis of panaxydol **1** is described, starting from L-(+)-diethyl tartrate **2**.

Panax ginseng C. A. Meyer is one of the most important oriental medicinal plants.[1] The biologically active constituents of ginseng have been pursued extensively, and recently many polyacetylenic compounds, including panaxydol **1**, were isolated.[2] These polyacetylenic compounds have received attention as a possible new type of antitumor agent.[3]



Panaxydol **1**

The absolute configuration[4] of panaxydol **1** was determined to be (3*R*, 9*R*, 10*S*)-9,10-epoxy-heptadec-1-ene-4,6-diyn-3-ol. Herein, the first total synthesis of optically active panaxydol **1** is described.



Scheme **1**: a) Swern oxid. b) *n*-$C_6H_{13}P^+Ph_3Br^-$, *n*-BuLi, THF, -78 - 0°C., 75% in two steps c) 10%Pd/C, 95%EtOH, 72hr, 85%. d) *p*-TsCl, Py. 96%. e) *p*-TsOH, MeOH. f) K_2CO_3, MeOH, 90% in two steps. g) MOMCl, i-Pr_2NEt, CH_2Cl_2, 0°C - rt, 82%. h) $HCCLi{\cdot}NH_2(CH_2)_2NH_2$, THF-HMPA, -20°C, 78%. i) MsCl, Et_3N, Py. j) MeOH, HCl(cat.). k) K_2CO_3, MeOH, 77% in three steps. l) NBS, $AgNO_3$, acetone, 82%.

The absolute configurations of C9 and C10 in panaxydol **1** were established using L-(+)-diethyl tartrate **2** as a chiral template (Scheme **1**). Accordingly, **2** was transformed into the monobenzyl ether **3** according to the known procedure.[5] Swern oxidation of **3**, subsequent Wittig reaction with n-$C_5H_{11}CH{=}PPh_3$ and catalytic hydrogenation afforded the primary alcohol **4**, which on successive treatment with *p*-TsCl in

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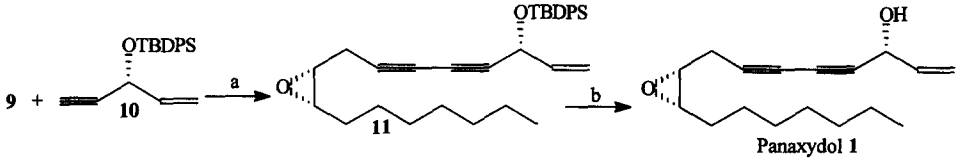
PII: S0040-4039(98)02212-6

pyridine, acidic methanol and excess K_2CO_3 in methanol gave the epoxy alcohol **5**. The secondary hydroxyl group of **5** was protected as the methoxymethyl (MOM) ether to yield **6**, which was allowed to react with lithium acetylide to give the coupling product **7**. By treatment with methylsulfonyl chloride, methanolic HCl and K_2CO_3 in methanol, **7** was converted into the epoxide **8**, which was reacted with NBS and $AgNO_3$[6] to afford the (9*R*, 10*S*) C6-C17 fragment **9** of panaxydol **1**.

Using the Cadiot-Chodkiczwicz reaction,[8] fragment **9** was then coupled with (3*R*)-(t-butyldiphenylsilyoxy)-pent-1-en-4-yne **10**[7] After deprotection of the TBDPS group, panaxydol **1** was obtained[9](Scheme 2).



Scheme 2: a) CuCl, $NH_2OH{\cdot}HCl$, $EtNH_2$, MeOH, 0°C, 69%. b) TBAF, THF, rt, 66.5%.

In conclusion, panaxydol **1** was obtained in **14** steps in 10.1% overall yield, starting from the monobenzyl ether **3** which was prepared from L-(+)-diethyl tartrate **2**.

References and notes:

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9. Data for **1**: $[\alpha]_D$ - 96.1 (c = 1.30, $CHCl_3$); IR(film) 3410 cm^{-1}; ^{1}HNMR(300MHz, $CDCl_3$) δ_H 0.88 (3H, t, J=6.7Hz), 1.29 (10H, m), 1.50 (2H, m), 2.39 (1H, dd, J=7.1, 17.7Hz), 2.70 (1H, dd, J=5.5, 17.8Hz), 2.94 (1H, m), 3.13 (1H, m), 4.92 (1H, d, J=5.2Hz), 5.27 (1H, dt, J=1.2, 10.2Hz), 5.49 (1H, dt, J=1.4, 17.0Hz), 5.95 (1H, ddd, J=5.4, 10.1, 17.0Hz) ppm; ^{13}CNMR(300MHz, $CDCl_3$) δ_C136.1, 117.1, 76.7, 75.0, 70.8, 66.3, 63.4, 57.0, 54.3, 31.7, 29.4, 29.1, 27.5, 26.2, 22.6, 19.4, 14.0; HREIMS(m/z) M^+-H calcd for $C_{17}H_{23}O_2$: 259.1698, found: 259.1704.