Chinese Chemical Letters Vol. 10, No. 3, pp. 201–204, 1999

Synthesis of the (3R, 9S, 10S)- Diastereoisomer of Panaxytriol, a Potent Antitumor Polyacetylene from *Panax ginseng*

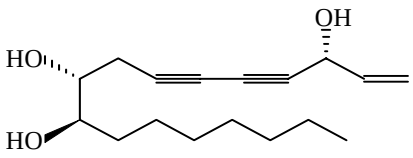
Wei LU, Guang Rong ZHENG, Jing Shan SHEN ,Jun Chao CAI*

Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 200031

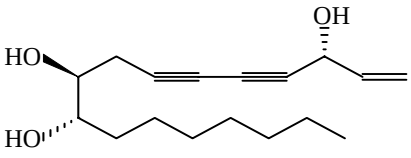
Abstract: (3R, 9S, 10S)-Heptadec-1-ene-4,6-diyne-3, 9, 10-triol **2**, a diastereoisomer of panaxytriol **1** was synthesized using L-(+)-diethyl tartrate **5** as a chiral template, through the Cadiot-Chodkiczwicz coupling of the terminal acetylene **3** with bromoacetylene **4**.

Keywords: Diastereoisomer; panaxytriol; Cadiot-Chodkiczwicz coupling.

In 1983, panaxytriol **1** was first isolated[1,2] as a diacetylenic constituent from *Panax ginseng*. Since then, the biological activity of **1** has been extensivly investigated and recently it has been received attention as a potential new type of antitumor agent[3,4]. The absolute configurations of **1** were confirmed to be (3R, 9R, 10R)-heptadec-1-ene-4,6-diyne-3,9,10-triol by the Mosher method and CD analysis[5,6]. But Fujimoto *et al*[7] asserted that the absolute configuration of **1** should be 3R, 9S, 10S through synthesis of a diastereomeric mixture at C-3 of panaxytriol. In the previous papers, we have reported the first total synthesis of **1** as a preliminary communication[8,9]. Herein, we describe the synthesis of a diastereoisomer of **1**, (3R, 9S, 10S)-heptadec-1-ene-4,6-diyne-3,9,10-triol **2**. We hope to determine the absolute configuration through comparing $[\alpha]_D$ values of two pure diastereoisomers.



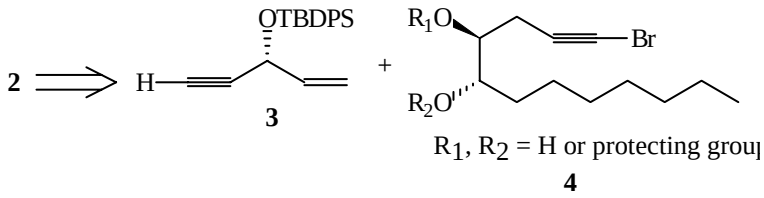
Panaxytriol **1**



(3R, 9S, 10S)-Panaxytriol **2**

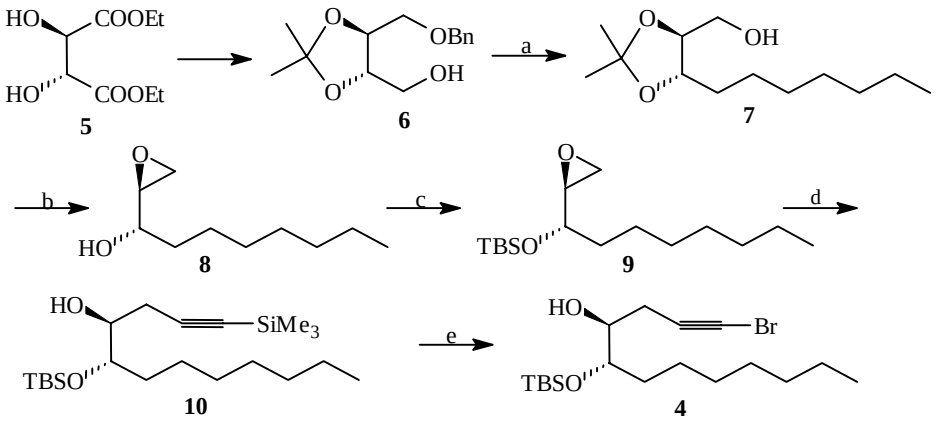
The general strategy for the synthesis of **2** is formulated, based on the retrosynthetic analysis as showed in **Scheme 1**. A Cadiot-Chodkiczwicz coupling[10] of the terminal acetylene **3**, (3R)-(t-butyldiphenylsilyoxy)-1-penten-4-yne, which we recently reported[8,9], with a bromoacetylene **4** should give the diacetylenic intermediate which on subsequent transformation would afford the desired product **2**.

Scheme 1



Accordingly an efficient approach for the synthesis of bromoacetylene **4** (R_1=H, R_2=TBS) was developed as depicted in **Scheme 2**. The absolute configuration of C9 and C10 in **2** were established using L-(+)-diethyl tartrate **5** as a chiral template. **5** was transformed to monobenzyl ether **6** according to known procedure[11,12]. Swern oxidation of **6**, subsequent Wittig reaction with n-$C_5H_{11}CH{=}PPh_3$ and catalytic hydrogenation afforded primary alcohol **7**, which on successive treatment with *p*-TsCl in pyridine, acidic methanol and excess K_2CO_3 in methanol led to epoxy alcohol **8**. The secondary hydroxy group of **8** was protected as a *tert*-butyldimethylsilyl(TBS) ether[13] to yield **9**, which was subjected to the coupling reaction with trimethylsilyl acetylene lithium in the presence of boron trifluoride etherate[14] to afford silylacetylene **10**. By treatment with NBS and $AgNO_3$[15], **10** was converted to the bromoacetylene **11** in one pot in high yield[16].

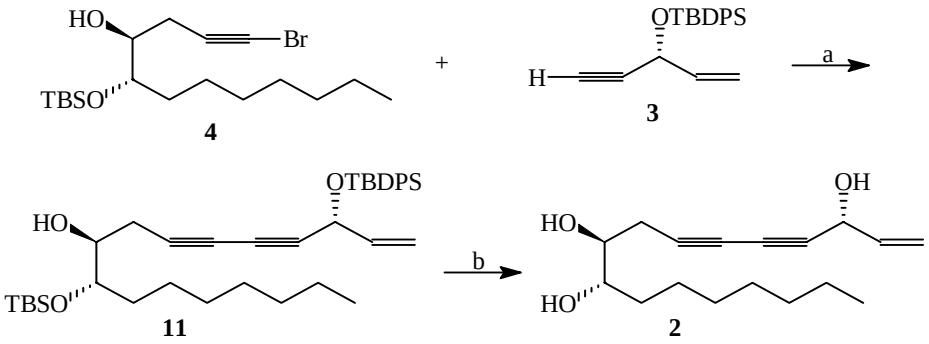
Scheme 2



Reagents and conditions: a) i Swern oxid.; ii *n*-$C_6H_{13}P^+Ph_3Br^-$, *n*-BuLi, THF, -78 - 0°C, 75% in two steps; iii 10%Pd/C, 95%EtOH, 72hr, 85%. b) i *p*-TsCl, Py. 96%; ii *p*-TsOH, MeOH; iii K_2CO_3, MeOH, 90% in two steps. c) TBSCl, THF, pyridine, $AgNO_3$, rt, 93%. d) Me_3SiCCH, *n*-BuLi, BF_3Et_2O,THF, -78¡ãC, 94%. e) NBS, $AgNO_3$, acetone, 86%.

Then, using the Cadiot-Chodkiczwicz reaction[10], bromoacetylene **4** was coupled with (3R)-(t-butyldiphenylsilyoxy)-1-penten-4-yne **3** to afford the diacetylenic product **11**, after deprotection of the silyl group, **2** was obtained[17] (**Scheme 3**).

Scheme 3



Reagents and conditions: a) CuCl, $NH_2OH{\cdot}HCl$, $EtNH_2$, MeOH, 0°C, 71%.
b) TBAF, THF, rt, 79%.

^1H and ^{13}CNMR spectra were similar with the reported data[5,6]. The $[\alpha]_D$ value of (3R, 9S, 10S)-panaxytriol **2** was -49.2 (c 0.90, $CHCl_3$), much different with the natural panaxytriol, -25.4 (c=1.54, $CHCl_3$),[6] -19.0 (c=1.0, $CHCl_3$).[5] Moreover, the $[\alpha]_D$ value of synthetic (3R, 9R, 10R)-panaxytriol **1**,[8] -21.2 (c=0.55, $CHCl_3$), was nearly identical to the natural product. Thus, the absolute configuration of panaxytriol was confirmed to be 3R, 9R, 10R.

Acknowledgment

We thank the State Key Laboratory of Drug Research for financial support.

References and Notes

1. I. Kitagawa, M. Yoshikawa, M. Yoshihara, T. Hayashi, and T. Taniyama, *Yakugaku Zasshi*, *103*, 612.
2. H. Matsunaga, M. Katano, H. Yamanoto, M. Mori, and K. Takata, *Chem. Pharm. Bull*., **1989**, *37*, 1279.
3. H. Matsunaga, M. Mori, K. Takata, and M. Nakamura, *Cancer Chemother. Pharmacol*., **1994**, *33*, 291.
4. S. Saita, H. Matsunaga, H. Yamamoto, F. Nagumo, H. Fujito, M. Mori, and M. Katano, *Biol. Pharm. Bull*., **1994**, *17*, 782.
5. I. Kitagawa, T. Umezome, T. Mahmud, and M. Kobayashi, *Chem. Pharm. Bull*., **1995**, *43*, 1595.
6. M. Kobayashi, T. Mahmud, T. Umezome, W. Q. Wang, N. Murakami, and I. Kitagawa, *Tetrahedron*, **1997**, *53*, 15691.
7. M. Satoh, N. Takeuchi, and Y. Fujimoto, *Chem. Pharm. Bull*., **1997**, *45*, 1114.
8. W. Lu, G. R. Zheng, and J. C. Cai, *Synlett*.,**1998**, 737.
9. W. Lu, G. R. Zheng, A. A. Haji, and J. C. Cai, *Chinese Chem. Lett*., (accepted)
10. W. Chodkiczwicz, "Chemistry of Acetylenes", H. G. Viehe, Ed. ; M. Deker, **1969**, p597.
11. P. W. Feit, *J. Med. Chem*., **1964**, *7*, 14.

12. B. Murrer, J. M. Brown, P. A. Chaloner, P. N. Nichiloson, and D. Parker, *Synthesis*, **1979**, 350.
13. G. H. Hakimelahi, Z. A. Proba, and K. K. Ogrlve, *Tetrahedron Lett*., **1981**, *22*, 4775.
14. M. Yamaquchi, and I. Hirao, *Tetrahedron Lett*., **1983**, *24*, 391.
15. T. Nishikawa, S. Shibuya, S. Hosokawa, and M. Isobe, *Synlett*., **1994**, 485.
16. Data of 4:
    $[\alpha]_D$ 15. 6 (c=0. 55, $CHCl_3$);
    IR (film): 3458, 1920, 2860, 2217, 1464, 1253, 1072, 837, 777 cm^{-1};
    ^{1}HNMR ($CDCl_3$, 300 MHz): δ_H 0. 09 (6H, s), 0. 88 (3H, t, J=6. 8Hz), 0. 90 (9H, s), 1. 20-1. 60 (12H, m), 2. 39 (2H, m), 3. 65 (1H, ddd, J=2. 3, 6. 3, 7. 5Hz), 3. 75 (1H, ddd, J=2. 3, 4. 9, 7. 4Hz) ppm;
    EIMS (m/z): 375(M^+-CH_3), 331(M^+-$C(CH_3)$), 319, 273, 257, 243(100), 229, 105, 75, 73;
    Anal. Calcd. for $C_{21}H_{44}O_2Si_2$: C, 55. 23; H, 9. 01;
    C, 55. 59; H, 9. 21.
17. Data of **2**:
    $[\alpha]_D$ -49. 2 (c=0. 90, $CHCl_3$);
    IR(film) 3332, 2920, 2860, 2256, 1643, 1466,, 1417, 1118, 1018, 958, 933 cm^{-1};
    ^{1}HNMR($CDCl_3$, 300MHz): δ_H 0. 88(3H, t, J=6. 8Hz), 0. 90(9H, s), 1. 20-1. 30(10H, m), 1. 50(2H, m), 2. 25(3H, br), 2. 57(2H, d, J=5. 6Hz), 3. 58(1H, m), 3. 63(1H, m), 4. 91(1H, d, J=5. 2Hz), 5. 24(1H, d, J=10. 1Hz), 5. 45(1H, d, J=17. 1Hz), 5. 95(1H, ddd, J=5. 4, 10. 1, 17. 0Hz) ppm;
    ^{13}CNMR($CDCl_3$, 75MHz): δ_C 136. 1(C-2), 117. 1(C-1), 78. 2(C-7), 74. 8(C-4), 73. 1(C-10), 72. 2(C-9), 70. 9(C-5), 66. 5(C-6), 63. 5(C-3), 33. 6(C-11), 31. 8(C-15), 29. 5(C-13), 29. 2(C-14), 25. 6(C-8), 25. 0(C-12), 22. 6(C-16), 14. 0(C-17);
    EIMS(m/z) 261(MH^+-H_2O), 243, 159, 145, 102(100);
    HREIMS(m/z) M^+-H_2O calcd for $C_{17}H_{24}O_2$: 260. 1776; found: 260. 1773.

Received 31 August 1998