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First Total Synthesis of Optically Active Oplopandiol Acetate, a Potent Antimycobacterial Polyyne Isolated from *Oplopanax horridus*

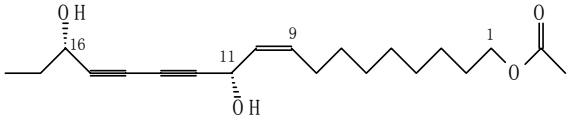
Liang XU, Xi Han WU, Guang Rong ZHENG, Jun Chao CAI*

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

Abstract: The first stereoselective total synthesis of oplopandiol acetate **1**, a potent antimycobacterial polyyne isolated from *Oplopanax horridus*, is presented. And its absolute configuration is confirmed to be (11S,16S).

Keywords: Total synthesis, oplopandiol acetate.

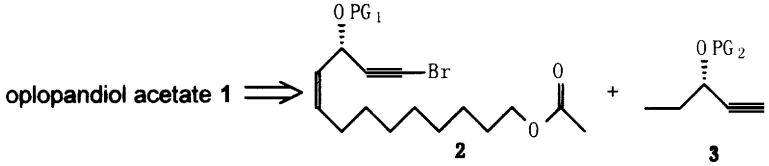
Oplopanax horridus, commonly known as devil担 club, is a well-known shrub of western North American forests. The inner bark and roots can be used for a variety of ailments such as diabetes, rheumatism, tuberculosis, headache, and lung hemorrhage. Oplopandiol acetate **1**, a bioactive polyyne with significant anti-*candida*, antibacterial, and anti- mycobacterial activity, was isolated from *O. horridus* by Kobaisy in 1997. And its absolute configuration was determined to be (11S,16S) by the Mosher method[1].



(11S,16S)-oplopandiol acetate **1**

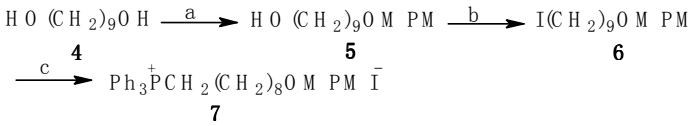
In this communication, the first total synthesis of the optically pure oplopandiol acetate **1** is described, and its absolute configuration is confirmed to be (11S, 16S). According to our previous procedure for synthesis of polyacetylene[2-4], a retrosynthetic analysis of **1** involves the dissection of C13-C14 bond to afford two fragments **2** and **3**, which are respectively prepared from L-(+)-tartaric acid and D-gluconolactone(**scheme 1**).

Scheme 1



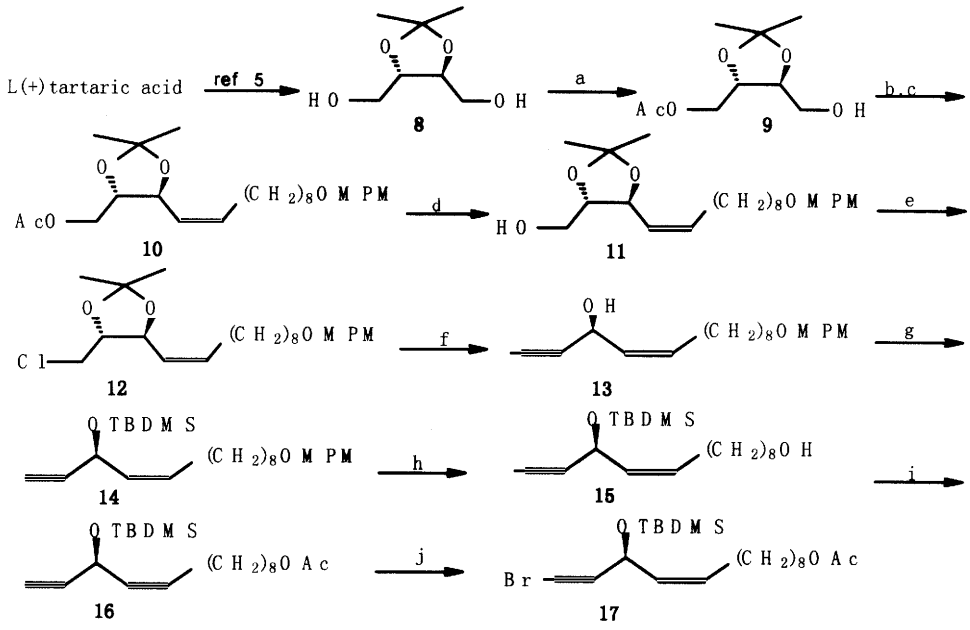
1,9-Nonanediol **4** was monosubstituted by *p*-methoxybenzyl chloride (MPMCl) to give the alcohol **5** which was subsequently converted to iodide **6** as depicted in **scheme 2**. Refluxing the iodide **6** and Ph_3P in toluene for 20 hours afforded the phosphonium salt **7** in high yield.

Scheme 2



a) MPMCl / NaH, DMF-THF, 68%. b) Ph_3P, imidazole, I_2, ether, r.t. 30min, 89%. c) Ph_3P, toluene, reflux 20 h, 82%.

Scheme 3



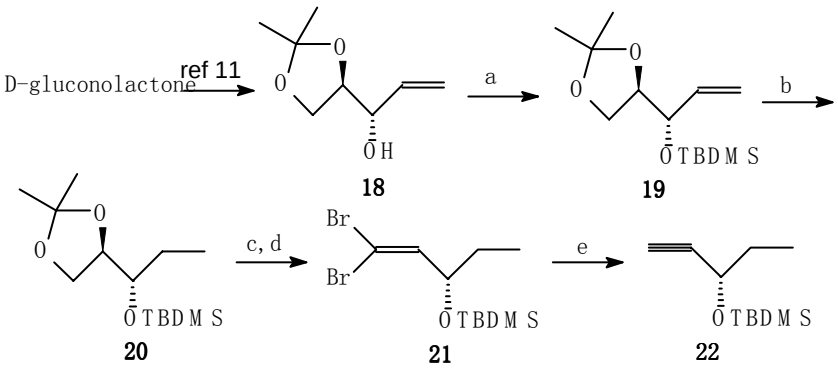
a) AcCl / pyridine, CH_2Cl_2, 0 ℃, 68%. b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ℃. c) $Ph_3P^+(CH_2)_9OMPMI^-$, t-BuOK, THF, r.t. 30min then -78 ℃, 65% in two steps. d) K_2CO_3 / MeOH, rt 45min, 95%. e) Ph_3P / CCl_4, reflux 24 h, 89%. f) LDA, THF, -78 ℃, 65%. g) TBDMSCl, imidazole, DMF, 88%. h) DDQ, CH_2Cl_2-H_2O, r.t. 2h, 86%. i) Ac_2O / pyridine, r.t. 20h, 96%. j) NBS, $AgNO_3$, acetone, r.t. 6h, 75%.

The fragment **2** was synthesized by using L-(+)-tartaric acid as a chiral template, which was transformed into **8** by the published method[5](**scheme 3**). Monoacetylation of **8** provided the monoprotected alcohol **9**, followed by Swern-Oxidation of **9** to generate the corresponding aldehyde. The aldehyde was used directly for the Wittig reaction with phosphorus ylide which was prepared from the phosphonium salt **7**. Deacetylation of **10**,

and then chlorination of the resulting alcohol **11** with Ph_3P/CCl_4 yielded chloride **12**. Treatment **12** with LDA in THF[6] afforded terminal alkyne **13**. The hydroxy group in **13** was protected by using tertbutyldimethylsilyl chloride(TBDMSCl), and the resulted ether **14** was treated with DDQ/CH_2Cl_2-H_2O[7] to remove the protective group (MPM) successfully. Very interestingly, when we utilized methoxymethyl(MOM) as the protective group, the desired deprotected alcohol cannot be obtained by commonly known procedures[8-10] for removal of MOM group. Acetylation of alcohol **15** with Ac_2O / pyridine furnished acetate **16,** which upon reaction with NBS in the presence of $AgNO_3$ gave the bromoacetylene **17**.

On the other hand, the synthesis of fragment **3** started with D-gluconolactone which was converted to alcohol **18** by the known procedure[11](**scheme 4**). Protection of the alcohol **18** as its TBDMS ether followed by catalytic hydrogenation of the ether **19** with H_2/10%Pd-C in ethanol resulted in the exclusive formation of ether **20**, which was subsequently dehomologated with H_5IO_6 in EtOAc[12] to generate an aldehyde. The resulting aldehyde was used directly for the Wittig reaction with Ph_3P, CBr_4 and Et_3N at -78℃[13] to give dibromoalkene **21**. Treatment of **21** with 2eqv of LDA in THF at -78℃, and then with 2eqv of n-BuLi afforded the desired alkyne **22**.

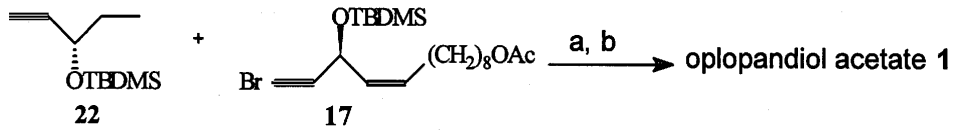
Scheme 4



a) TBDMSCl, imidazole, DMF, r.t 12h, 85%. b) H_2/10%Pd-C, r.t 4h, 100%. c) H_5IO_6, EtOAc, r.t 1h. d) CBr_4, Ph_3P, Et_3N, -78℃, 63% in two steps. e) 2eqLDA, THF, -78℃, 45min, then 2eq n-BuLi, -78℃ 3hr, 85%.

Coupling alkyne **22** with bromoacetylene **17** *via* Cadiot-Chodkiewcz reaction under nitrogen (**scheme 5**), followed by deprotection of silyl groups with tetrabutyl ammonium fluoride(TBAF) in THF-H_2O at 0℃ completed the total synthesis of the target molecule **1**.

Scheme 5



a) CuCl, $NH_2OH \bullet HCl$, 65%$EtNH_2$, MeOH, 0℃20min. b) TBAF, THF-H_2O, 0℃6h, 52% in two steps.

The spectral data of the synthetic **1** are virtually identical with the reported data of the natural product. The optical rotation of the synthetic **1**: $[\alpha]_D$ +194 (c=1.67, $CHCl_3$) and the natural product: $[\alpha]_D$ +164.5 (c=5.7, $CHCl_3$). Consequently, the absolute configuration of oplopandiol acetate is confirmed to be (11S, 16S). The anti-tumor activity of the synthetic **1** is under evaluation.

Acknowledgment

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References and notes

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14. Data of **1:** $[\alpha]_D$ +194 (c=1.67, $CHCl_3$), IR (film) 3407, 2920, 1716, 1610, 1510, 1367, 1247, 1035cm^{-1}, ^{1}HNMR ($CDCl_3$, 400MHz) δ_H 0.99 (3H, t, J=7.4Hz), 1.25 (10H, m), 1.6 (2H, m), 1.71 (2H, m), 2.02 (3H, s), 2.12 (2H, dq, J=7.3, 1.5Hz), 4.05 (2H, t, J=6.8Hz), 4.35 (1H, t, J=6.5Hz), 5.18 (1H, d, J=8.3Hz), 5.5 (1H, dt, J=10.8, 8.0Hz), 5.6 (1H, dt, J=10.8, 7.3Hz)ppm. ^{13}CNMR (400MHz, $CDCl_3$) δ_C 9.3 (C-18), 21.0 (CH_3 of Ac), 25.8 (C-2), 27.5 (C-8), 28.5 (C-6), 28.9 (C-4 and C-5), 29.1 (C-3), 29.2 (C-7), 30.6 (C-17), 58.5 (C-11), 63.9 (C-16), 64.7 (C-1), 68.8 (C-13 and C-14), 79.1(C-12), 80.8 (C-15), 127.9 (C-9), 134.3 (C-10), 171.4 (C=O) ppm. EIMS (*m/z*): 334 (M^+), 316, 301, 173, 131, 117. HREIMS (*m/z*): 334.2187 (calcd for $C_{20}H_{30}O_4$, 334.2144). 316.2041(calcd for $C_{20}H_{28}O_3$, M^+-H_2O, 316.2038).

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