Chinese Chemical Letters Vol. 10, No. 4, pp. 275–276, 1999

The Synthesis of Podophyllotoxin Derivatives with Macrocyclic Dilactone

Min YANG[1], Ning CHEN[1], Xin Fu PAN[1,*], Bing Chang QIN[2]

[1]Department of Chemistry, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, 730000
[2]Department of chemistry, Anyang Teachers College, Anyang 455002

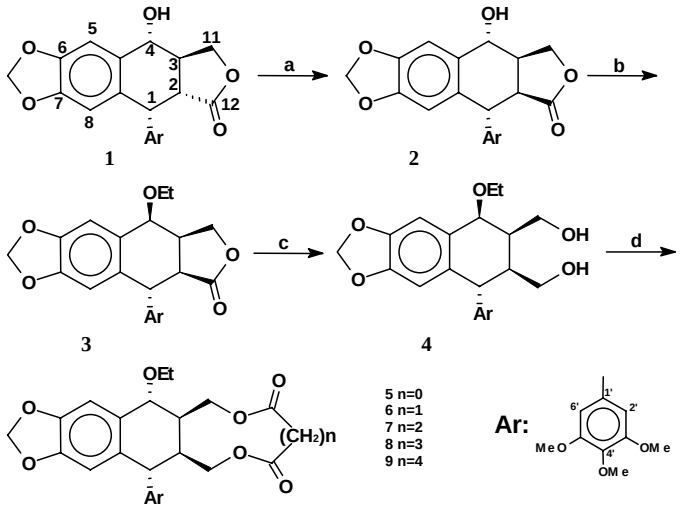
Abstract: Starting from podophyllotoxin, five new derivatives with macrocyclic dilactone 5～9 have been synthesized,and their structures were confirmed by IR, MS, ^{1}H NMR as well as HRMS. The key step is cyclization by high dilution method.

Keywords: Podophyllotoxin, derivatives, macrocyclic dilactone, synthesis.

Podophyllotoxin **1** and many of its derivatives, including C-2 epimer, picropodophyllin **2**, are antimitotic agents[1]. The semi-synthetic derivatives of **1** etoposide (VP-16-213) and teniposide (VM-26) are in clinical use as anti-cancer agents[2]. Some analogues of **1** with a modified lactone ring have been synthesized and found to be still antimitotic[3], thereby indicating that the lactone ring is not required for antimitotic activity in **1**. Anjanamurthy *et al*[4]. have synthesized a derivative by enlarging the five-membered lactone ring in **1** to a six-membered one. Since then, however, no study on the effect of enlarging the five-membered lactone ring of **1** to a larger one than six-membered ring on its biological activity has been made. Neither has study on the effect of altering the position of carbonyl group on its biological activity. Hence synthesis of new analogues of **1** with macrocyclic dilactone **5~9** was undertaken.

The reaction sequence leading to the formation of compounds **5** ~ **9** is shown in **Scheme**, Podophyllotoxin **1** was epimerized to **2** by the method of Gensler and then treated with H_2SO_4 in ethanol at reflux temperature for 15 min. Reduction of **3** by $LiAlH_4$ at 0℃ for 4h afforded the diol 4-O-Ethylepipicropodophyllol **4. The** diol **4** reacts with five kinds of diacid chloride at 45~50℃ for 7 days to obtain compounds **5**~**9**.

Scheme



a. EtOH, NaOAc, H_2O, reflux, 20h, (yield 75%); b. EtOH, H_2SO_4, reflux, 15min, (yield 84%); c. $LiAlH_4$, THF, 0℃, 4h, (yield 92%); d. Oxalyl chloride (Malonyl dichloride, Succinyl chloride, Glutaryl chloride, or Adipoyl chloride),THF,45～50℃, 7d, (yield 36～42%).

It deserves to discuss the configuration of the C-4 substituent. We initially anticipated that during the course of synthesis, there could be epimerization of the C-4 substituent from 4 β side to 4 α side by acid (HCl gas emitted from reaction system) in S_N1 mechanism, *i.e.*, one C-4 benzyl cation was first formed in acidic condition. However, because of the hindrance of the C-3 substituent, it is more covenient for HOEt to reattack the benzyl cation from less hindered 4 α -side than from 4 β -side. Indeed, this was confirmed by ^{1}H NMR (400M) spectra of compounds **5**~**9**. If the C-4 substituent is in β side (see compounds **3** and **4**), $J_{3,4(cis)}$ = 4Hz; If it is in α side, in the presence of lactone, $J_{3,4(trans)}$ >9.5Hz[5]. On the other hand, if the lactone is opened, the substituent at the C-3 position is able to rotate freely, so that the substituents of C-2 and C-3 will be in gauche conformation rather than in eclipsed one. Therefore, the angle between the H_3 and H_4 is approximately 90. According to the regulation of Karplus, $J_{3,4}$ = 0. Actually, ^{1}H NMR spectrum of **5**~**9** shows clearly that there is a only singlet not doublet at δ = 4.7 ppm (H_4), which confirms that C_4-OC_2H_5 is in the α -side.

The biological activity of the five new compounds described herein will be reported elsewhere.

Acknowledgments

We thank the National Natural Science Foundation of China (No:29572049) for financial support.

References and notes

1. M. G. Kelly, J. L. Hartwell, *J. Natl. Cancer inst.* , **1954**, *14*, 969.
2. C. MA, S. R. LUO. , *Chinese Traditional and Herbal Drugs*, **1992**, *23 (5)*, 271.
3. W. J. Gensler , C. A. Murthy, M. H. Trammel, *J. Med. Chem.* ,**1977**, *20*:635.
4. C. Anjanamurthy, R. K. M. Lokanatha, *Indian. J. Chem.* , **1985**, *24B*, 502.
5. K. H. Lee, Y. Imakura, M. Haruna *et al. J. Nat. Prod.* , **1989**, *52 (3)*, 606.
6. 4-O-Ethylpicropodophyllyl oxalate **5**: MS (EI): m/z 500 (M^+,100); HRMS (EI): Calcd for $C_{26}H_{28}O_{10}$ 500. 1683, found : m/z 500. 1781; ^{1}H NMR: δ 6. 73 (s,1H,C_5-H), 6. 50 (s,1H,C_8-H),6. 20 (s,2H,$C_{2',6'}$-H), 5. 97,5. 91 (2d,2H,-OCH_2O-), 4. 76 (s,1H,C_4-H),4. 32 (q,2H,4-OCH_2), 4. 26-4. 09 (m,3H,C_1-H, 2×C_{11}-H), 3. 84 (s,3H,$C_{4'}$-OCH_3), 3. 78 (s,6H,$C_{3',5'}$-OCH_3), 3. 75 (d,2H, J = 9. 14Hz, 2×C_{12}-H), 2. 72 (m, 1H, C_2-H), 2. 54 (m,1H,C_3-H), 1. 36 (t, J=7. 3Hz, 3H, CH_3); IR υ /cm^{-1} :1743 (C=O),1589, 1507, 1484 (Ar); [α]$_D^{18}$ -19. 8 (c 0. 51, $CHCl_3$).
7. 4-O-Ethylpicropodophyllylmalondiate **6**: MS (EI): m/z 514 (M^+,100); HRMS (EI): Calcd for $C_{27}H_{30}O_{10}$ 514. 1839, found: m/z 514. 1935; ^{1}H NMR: δ 6. 72 (s,1H,C_5-H), 6. 50 (s,IH,C_8-H), 6. 21 (s,2H,$C_{2',6'}$-H), 5. 97,5. 91 (2d,2H,-OCH_2O-), 4. 70 (s,1H,C_4-H), 4. 19-3. 96 (m,5H,C_1-H,2×C_{11}-H,4-OCH_2), 3. 84 (s,3H,$C_{4'}$-OCH_3), 3. 78 (s,6H,$C_{3',5'}$-OCH_3), 3. 76 (d,2H,J=8. 91Hz,2×C_{12}-H), 3. 33 (s, 2H, O=C-CH_2-C=O), 2. 64 (m, 1H, C_2-H), 2. 50 (m, 1H, C_3-H), 1. 25 (t, J= 6. 7Hz, 3H, CH_3); IR υ /cm^{-1}: 1731 (C=O), 1588, 1505, 1481(Ar); [α]$_D^{18}$-21. 3 (c 0. 40, $CHCl_3$).
8. 4-O-Ethylpicropodophyllyl succindiate **7**: MS (EI): m/z 528 (M^+,100);HRMS (EI) : Calcd for $C_{28}H_{32}O_{10}$ 528. 1995, found: m/z 528. 2061 ; ^{1}H NMR: δ 6. 73 (s,1H,C_5-H),6. 50 (s,IH,C_8-H),6. 21 (s,2H,$C_{2',6'}$-H), 5. 97,5. 91 (2d,2H,-OCH_2O-), 4. 70 (s,1H,C_4-H), 4. 15-3. 93 (m,5H, C_1-H,2×C_{11}-H,4-OCH_2), 3. 84 (s,3H,$C_{4'}$-OCH_3), 3. 78 (s,6H,$C_{3',5'}$-OCH_3), 3. 73 (d,2H,J=8. 74Hz,2× C_{12}-H), 2. 61 (m,1H, -C_2-H), 2. 57 (s,4H,O=C-CH_2CH_2-C=O), 2. 49 (m,1H,C_3-H),1. 25 (t, J=7. 3Hz, 3H,CH_3); IR, υ /cm^{-1}: 1731 (C=O), 1589, 1502,1480(Ar); [α]$_D^{18}$ +36. 1 (c 0. 69, $CHCl_3$).
9. 4-O-Ethylpicropodophyllyl glutardiate **8**: MS (EI): m/z 542 (M^+,100); HRMS (EI): Calcd for $C_{29}H_{34}O_{10}$ 542. 2152, found: m/z 528. 2213; ^{1}H-NMR: δ 6. 73 (s,1H,C_5-H), 6. 50 (s,IH, C_8-H), 6. 21 (s,2H,$C_{2',6'}$-H), 5. 97,5. 91 (2d,2H,-OCH_2O-), 4. 70 (s,1H,C_4-H), 4. 14-3. 89 (m,5H,C_1-H,2×C_{11}-H, 4-OCH_2), 3. 84 (s,3H,$C_{4'}$-OCH_3), 3. 78 (s,6H,$C_{3',5'}$-OCH_3), 3. 73 (d,2H,J=8. 89Hz,2×C_{12}-H), 2. 61 (m,1H,C_2-H), 2. 50 (m,1H,C_3-H), 2. 31 (t,4H,-CH_2CCH_2-), 1. 83 (q,2H, CCH_2C),1. 25 (t, J= 7. 3Hz, 3H, CH_3); IR, υ /cm^{-1}: 1729 (C=O), 1587, 1505,1482 (Ar); [α]$_D^{18}$ -210. 1 (c 1. 28, $CHCl_3$).
10. 4-O-Ethylpicropodophyllyl adipodiate **9**: MS (EI): m/z 556 (M^+,100); HRMS (EI): Calcd for $C_{30}H_{36}O_{10}$ 556. 2309, found: m/z 556. 2363; ^{1}H-NMR: δ 6. 73 (s,1H,C_5-H), 6. 50 (s,IH,C_8-H), 6. 21 (s,2H,$C_{2',6'}$-H), 5. 97,5. 91 (2d,2H,-OCH_2O-), 4. 70 (s,1H,C_4-H), 4. 14~3. 89 (m,5H,C_1-H,2×C_{11}-H,4-OCH_2), 3. 84 (s,3H,$C_{4'}$-OCH_3), 3. 78 (s,6H,$C_{3',5'}$-OCH_3), 3. 73 (d,2H,J=8. 89Hz,2×C_{12}-H), 2. 61 (m,1H, C_2-H), 2. 50 (m, 1H,C_3-H), 2. 31 (t,4H,-CH_2CCH_2-), 1. 83 (q,2H, CCH_2C), 1. 25 (t, J=6. 9Hz, 3H, CH_3);
IR, υ /cm^{-1}: 1730 (C=O),1587, 1503, 1483 (Ar); [α]$_D^{18}$ -191. 6 (c 0. 60, $CHCl_3$).

Received 30 November 1998