The Production of a Novel Podophyllotoxin Derivative

Andrew Pelter, Robert S. Ward, and Li Qianrong

J. Nat. Prod., **1993**, 56 (12), 2204-2206• DOI:
10.1021/np50102a030 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 56, No. 12, pp. 2204-2206, December 1993

THE PRODUCTION OF A NOVEL PODOPHYLLOTOXIN DERIVATIVE

ANDREW PELTER, ROBERT S. WARD,*

Chemistry Department, University of Swansea, Singleton Park, Swansea SA2 8PP, UK

and LI QIANRONG

Structure Research Laboratory, University of Science and Technology of China, Hefei 230 026, People's Republic of China

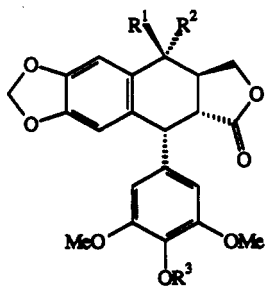
ABSTRACT.—Oxidation of 4′-demethylepipodophyllotoxin [**2**] using either phenyliodonium diacetate in MeOH or DDQ in MeOH affords a new class of podophyllotoxin derivatives containing a cyclohexadienone group.

Podophyllotoxin [**1**] is a well known natural product because of its long history of use in folk medicine and the biological activity of its many derivatives (1–3). In particular, derivatives of 4′-demethylepipodophyllotoxin [**2**] are used in cancer chemotherapy (4–6). As a result, there is much interest in devising new approaches to the synthesis of podophyllotoxin derivatives (7) and in studying their chemical modification (8–14).

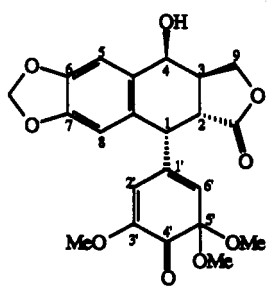
We have previously shown that reaction of phenolic compounds, including lignans, with phenyliodonium diacetate (PIDA) leads to cyclohexa-2,5-dienones (15) and to oxidative coupling reactions (16). We have also shown that treatment of lignans with DDQ leads to oxidative coupling and to rearrangement reactions (17,18). We have now investigated the reaction of PIDA with 4′-demethylepipodophyllotoxin [**2**] in MeOH and have obtained as a major product a crystalline compound, mp 189–191°, having $[M]^+$ 430 and showing two carbonyl carbon atoms at 175.33 and 190.37 ppm in its ^{13}C-nmr spectrum. We also find that the same product is obtained in comparable yield when **2** is treated with DDQ in MeOH.

Structure **3** is assigned to this product on the basis of a comparison of its ^{1}H- and ^{13}C-nmr spectra with those of the starting material. Thus, the presence of a new quaternary carbon atom at 93.07 ppm and a carbonyl carbon atom at 190.37 ppm confirms the presence of a quinone-monoketal moiety. Furthermore, the observation of clear signals for H-2′ and H-6′ and C-2′ and C-6′ in the ^{1}H- and ^{13}C-nmr spectra confirms the lack of symmetry introduced into the pendant aryl ring, thus ruling out the alternative 4-methoxycyclohexa-2,5-dienone. A possible mechanism accounting for the formation of **3** is shown in Scheme 1.

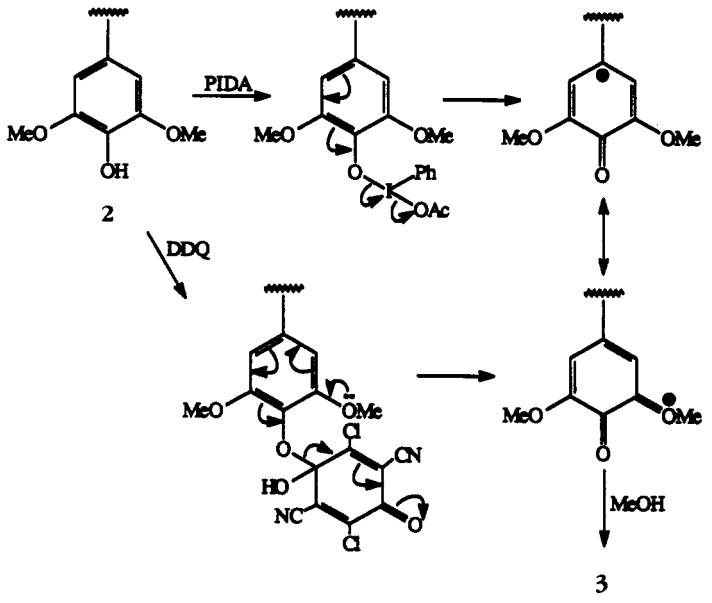
The reaction is noteworthy for two reasons: the product **3** represents a completely novel modification of podophyllo-



1 R^1=H, R^2=OH, R^3=Me
2 R^1=OH, R^2=R^3=H



3



SCHEME 1

toxin, and the oxidation proceeds to give substitution ortho to the phenolic group rather than para, which we had previously observed. However, a very recent paper gives some precedent for this (19). We are currently attempting to exploit these oxidative reactions to provide a series of novel podophyllotoxin derivatives.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H- and ^{13}C-nmr spectra were recorded on a Bruker 250 MHz instrument. Mass spectra were recorded on a VG12-253 quadrupole instrument and on a double focussing VG ZAB-E instrument. 4′-Demethylepipodophyllotoxin was obtained from the Shanghai Institute of Pharmaceutical Industry.

REACTION OF **2** WITH PIDA.—To a solution of **2** (0.20 g, 0.50 mmol) in dry MeOH (10 ml) was added PIDA (0.16 g, 0.50 mmol), and the mixture was stirred at room temperature for 1 h. Solid $NaHCO_3$ was added to neutralize the acid liberated, and the solvent was removed to give a yellow gum, which was dissolved in EtOAc (40 ml) and filtered. Evaporation in vacuo gave a yellow residue (225 mg) which from $CHCl_3$/MeOH gave yellow crystals of **3** (128 mg, 60%): mp 189–191°; *m/z* $[M]^+$ 430 (5%), 400 (100), 246 (18), 229 (7), 183 (14), 167 (13), 154 (24). Found $[M]^+$ 430.1264 ($C_{22}H_{22}O_9$ requires $[M]^+$ 430.1264). ^{1}H nmr δ ($CDCl_3$) 2.85 m (H-3), 2.40 br (OH), 3.17 s, 3.26 s, 3.71 s (OMe), 3.29 dd (J_1=5.30, J_2=14.10, H-2), 4.17 d (J=5.20, H-1), 4.82 d (J=3.20, H-4), 4.43 dd (J_1=5.65, H_a-9), 4.49 dd (J_1=3.49, H_b-9), 5.08 t (J=1.40, H-6′), 6.30 d (J=1.65, H-2′), 6.60 s, 6.84 s (H-5 and H-8), 5.99 ABq (J=1.20, OCH_2O); ^{13}C nmr δ ($CDCl_3$) 38.35, 39.29, 43.99 (C-1, C-2, and C-3), 50.14, 50.34, 55.73 ()Me), 66.23 (C-4), 68.02 (C-9), 93.07 (C-5′), 101.71 (OCH_2O), 109.22, 109.86 (C-5 and C-8), 113.54, 127.71 (C-2′ and C-6′), 129.92, 132.09, 137.50 (C-1′, C-4a, C-8a), 147.80, 148.59, 149.18 (C-6, C-7, C-3′), 175.33 (lactone CO), 190.37 (C-4′); ν max (KBr) 3410 (OH), 1755 (lactone CO), 1670 (CO) cm^{-1}.

REACTION OF **2** WITH DDQ.—To a mixture of **2** (0.40 g, 1 mmol) and DDQ (0.25 g, 1.1 mmol) was added MeOH (20 ml), and the mixture was stirred for 24 h at room temperature. The reaction mixture was poured onto crushed ice (50 g) and extracted with EtOAc (3×40 ml). The organic layer was washed with aqueous $NaHSO_3$ (3×30 ml), H_2O (3×30 ml), aqueous $NaHCO_3$ (3×30 ml), and brine (3×30 ml), and dried ($MgSO_4$). Removal of the solvent gave a yellow residue (0.37 g) that was crystallized from MeOH to give **3** as yellow crystals (210 mg, 49%), mp 193–194°.

ACKNOWLEDGMENTS

We are grateful to the British Council for support for this project under the Academic Links with China Scheme.

LITERATURE CITED

1. D.C. Ayres and J.D. Loike, "Lignans: Chemical, Biological and Clinical Properties," Cambridge University Press, 1990, pp. 85–137.
2. S.G. Weiss, M. Tin-Wa, R.E. Perdue, and N.R. Farnsworth, *J. Pharm. Sci.*, **64**, 95 (1975).
3. I. Jardine, in: "Anticancer Agents based on Natural Product Models." Ed. by J.M. Cassady and J.D. Douros, Academic Press, 1980, pp. 319–351.
4. J.L. Hartwell, *Cancer Treat. Rep.*, **60**, 1031 (1976).
5. A.H. Barclay and R.E. Perdue, *Cancer Treat. Rep.*, **60**, 1081 (1976).
6. B.F. Issell, A.R. Rudolph, A.C. Louie, and T.W. Doyle, in: "Etoposide (VP-16): Current Status and New Developments." Ed. by B.F. Issell, F.M. Muggia, and S.K. Carter, Academic Press, 1984, Chapters 1 and 2.
7. R.S. Ward, *Synthesis*, 719 (1992).
8. D.C. Ayres and T.J. Ritchie, *J. Chem. Soc., Perkin Trans. 1*, 2573 (1988).
9. Z.G. Wang, W.Y. Ma, B.S. Li, and C.N. Zhang, *Acta Pharm. Sin.*, **27**, 656 (1992).
10. Z.G. Wang, W. Zhuang, S.F. Yin, W.Y. Ma, B.S. Lee, and C.N. Zhang, *Acta Pharm. Sin.*, **27**, 345 (1992).
11. L.S. Thurston, H. Irie, S. Tani, F.S. Han, Z.C. Liu, Y.C. Cheng, and K.H. Lee, *J. Med. Chem.*, **29**, 1547 (1986).
12. S.A. Beers, Y. Imakura, H.J. Dai, D.H. Li, Y.C. Cheng, and K.H. Lee, *J. Nat. Prod.*, **51**, 901 (1988).
13. J.F. Kadow, D..M. Vyas, and T.W. Boyle, *Tetrahedron Lett.*, **30**, 3299 (1989).
14. M.B. Glinski, J.C. Freed, and T. Durst, *J. Org. Chem.*, **52**, 2749 (1987).
15. A. Pelter and S. Elgendy, *Tetrahedron Lett.*, **29**, 677 (1988).
16. A. Pelter, R.S. Ward, and A. Abd-El-Ghani, *J. Chem. Soc., Perkin Trans. 1*, 2249 (1992).
17. R.S. Ward, A. Pelter, I.R. Jack, P. Satyanarayana, B.V. Gopala Rao, and P. Subrahmanyam, *Tetrahedron Lett.*, 4111 (1981).
18. A. Pelter, R.S. Ward, R. Venkateswarlu, and C. Kamakshi, *Tetrahedron*, **47**, 1275 (1991).
19. A.S. Mitchell and R.A. Russell, *Tetrahedron Lett.*, **34**, 545 (1993).

Received 27 May 1993