133. Reassignment of the Configuration of Several Keto-cyclolignans Prepared from Podophyllotoxin

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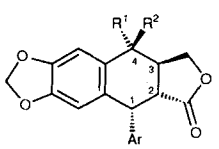
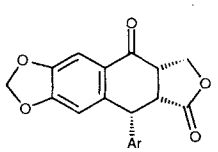
The configuration of several keto-cyclolignans related to podophyllotoxin has been reviewed. Under basic catalysis, the configuration at the C-atom in α-position to the lactone carbonyl group in podophyllotoxone is inverted instead of the C-atom in α-position to the ketone group, as it has been reported.

Last year, in a paper published in this Journal, *Höfert* and *Matusch* reported a 'novel rearrangement of podophyllotoxone' [1]. They described the epimerization of podophyllotoxone (**1**) at C(3) α to the C(4)=O, and the formation of isopicropodophyllone (**2**), in equilibrium with **1**, when treating the former substance with BuLi in refluxing Et_2O. Subsequently, preparation of the unsaturated keto-acid **3** and several other derivatives were reported.



1 R^1, R^2=O
4 R^1=OH, R^2=H



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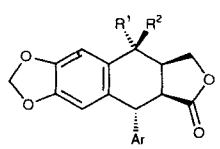
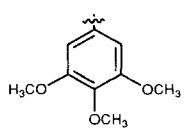
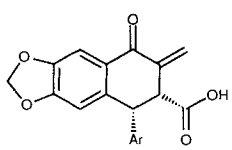


6 R^1, R^2=O
7 R^1=OH, R^2=H

Ar =





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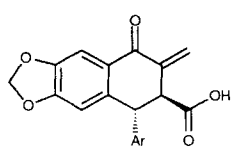

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It is well known that the *trans*-fused lactone podophyllotoxin (**4**) and its derivatives readily epimerize at C(2), leading to the more stable *cis*-fused picro analogues, in basic or even neutral media [2]. However, those authors assigned the structure of **2** to the epimerization product, based on the speculative assumption that the greater acidic character of H at C(3) as compared to H at C(2) is sufficient to favor the transformation of **1** into **2**. They did not provide any experimental proof or calculations supporting that assumption.

We believe that *Höfert* and *Matusch* did not realize that the spectral properties they observed for compounds **2** and **3** almost perfectly matched those published by us for

picropodophyllone (**6**) and thuriferic acid (**5**), respectively [3], because no reference to our paper, reporting the structure assignment of **5** and related compounds, was mentioned in [1].

The aim of this communication is to correct the structures proposed by *Höfert* and *Matusch* for most of the compounds reported in [1].

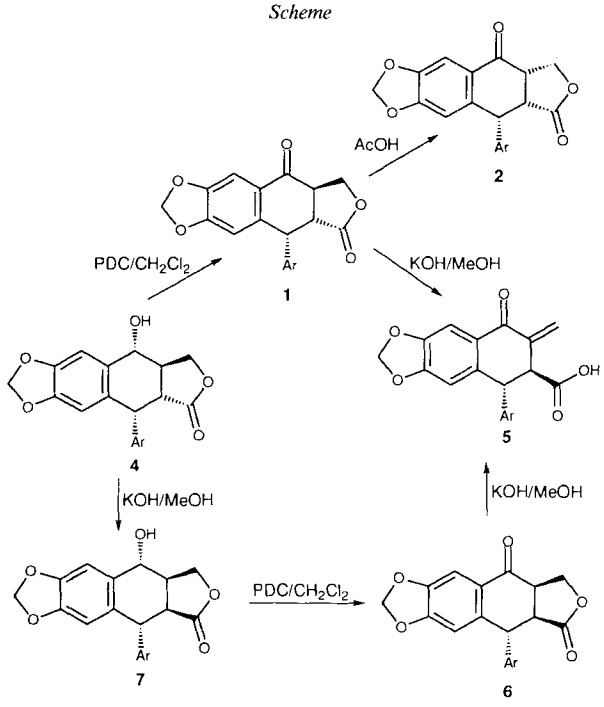
Thus, podophyllotoxone (**1**), prepared by oxidation of podophyllotoxin (**4**) [4], was equilibrated in refluxing AcOH to obtain a mixture containing the C(3)-epimer, isopicropodophyllone (**2**; *Scheme*). Further, picropodophyllin (**7**), prepared by epimerization of podophyllotoxin (**4**), was transformed into picropodophyllone (**6**) through PDC oxidation [5]. NMR Data for the keto derivatives are shown in *Tables 1* and *2*.

Spectral data of **2** coincide with those reported in [6] for isopicropodophyllone, whereas data for compound **6** is in agreement with those reported by *Höfert* and *Matusch* [1] for the assigned structure of isopicropodophyllone (named isopodophyllotoxone in [1]).

Finally, the treatment of either **1** and **6** with 1% KOH in MeOH afforded thuriferic acid (**5**) as the only product in a fair yield, demonstrating that epimerization at C(2) occurred preferentially with respect to C(3) under basic treatment of podophyllotoxone.

It seems obvious that the arguments presented by *Höfert* and *Matusch* failed to justify the structure of the product of the reaction of podophyllotoxone with BuLi. It is evident from calculations[1]) (*Fig.*) that H–C(3), α to the keto group, is more acidic than H–C(2),

Scheme



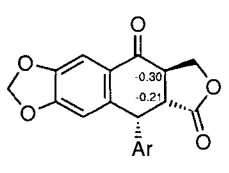
[1]) Atomic charges have been calculated from the lowest-energy conformer using *Stewart*'s Hamiltonian in MOPAC [7].

Table 1. *^{1}H-NMR Data* ($CDCl_3$) *for Keto-cyclolignans* **1**, **2**, *and* **6**

H-Atom	**1**	**2**	**6**
H–C(1)	4.85 (*d*, *J* = 4.2)	4.57 (*d*, *J* = 5.2)	4.70 (*s*)
H–C(2)	3.33 (*dd*, *J* = 15.5, 4.2)	3.60–3.63 (*m*)	3.29 (*m*)
H–C(3)	3.52 (*ddd*, *J* = 15.2, 9.6, 7.3)	3.60–3.63 (*m*)	3.29 (*m*)
H–C(3a)	4.35 (*t*, *J* = 9.6);	3.87 (*m*);	4.36 (*dd*, *J* = 9.3, 3.9);
	4.55 (*dd*, *J* = 9.6, 7.3)	4.48 (*m*)	4.77 (*d*, *J* = 9.3)
H–C(5)	7.52 (*s*)	7.38 (*s*)	7.50 (*s*)
H–C(8)	6.71 (*s*)	6.66 (*s*)	6.70 (*s*)
H–C(2′)	6.34 (*s*)	6.28 (*s*)	6.21 (*s*)
H–C(6′)	6.34 (*s*)	6.28 (*s*)	6.21 (*s*)
OCH_2O	6.07 (*d*, *J* = 1.5);	6.05 (*d*, *J* = 1.5);	6.00 (*s*)
	6.10 (*d*, *J* = 1.5)	6.10 (*d*, *J* = 1.5)	
MeO–C(3′)	3.75 (*s*)	3.72 (*s*)	3.75 (*s*)
MeO–C(4′)	3.81 (*s*)	3.79 (*s*)	3.81 (*s*)
MeO–C(5′)	3.75 (*s*)	3.72 (*s*)	3.75 (*s*)

Table 2. *^{13}C-NMR Data* ($CDCl_3$) *for Keto-cyclolignans* **1**, **2**, *and* **6**

C-Atom	**1**	**2**	**6**	C-Atom	**1**	**2**	**6**
C(1)	44.8	44.8	43.3	C(10)	128.3	128.8	127.1
C(2)	46.7	45.1	46.3	C(1′)	132.2	133.9	137.3
C(2a)	173.5	175.2	175.3	C(2′)	108.0	107.0	104.8
C(3)	43.6	44.3	43.1	C(3′)	153.2	153.4	153.6
C(3a)	67.0	69.4	70.2	C(4′)	138.0	138.9	137.9
C(4)	192.4	194.1	193.3	C(5′)	153.2	153.4	153.6
C(5)	106.3	106.1	105.8	C(6′)	108.0	107.0	104.8
C(6)	148.2	148.4	148.2	OCH_2O	102.4	102.2	102.0
C(7)	153.2	153.4	153.6	*Me*O–C(3′)	56.6	56.2	56.0
C(8)	109.7	108.6	109.2	*Me*O–C(4′)	60.8	60.8	40.5
C(9)	141.6	139.1	139.4	*Me*O–C(5′)	56.6	56.2	56.0



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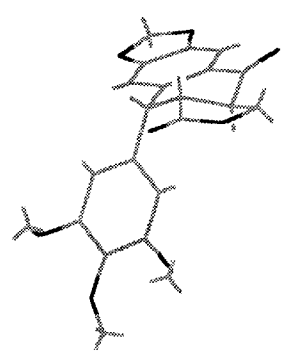

Figure. *Comparative electronic and stereochemical aspects for podophyllotoxone* (**1**). Calculated with semiempirical MOPAC 6.0.

α to the lactone C=O. Moreover, from the stereochemical point of view, the access of bases to H at C(3) is hindered due to the presence of the trimethoxyphenyl group at C(1), which is pseudoaxially disposed.

In conclusion, practically all the structures proposed for those compounds reported in [1] by *Höfert* and *Matusch* should be corrected in the configurations at C(2) and C(3).

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Experimental Part

General. Column chromatography: performed over silica gel (0.063–0.2 mm). Flash chromatographies (FC): with 3–85 ml/min flow rates, over silica gel (0.040–0.063 mm). TLC was performed on precoated silica-gel polyester plates (0.25-mm thickness) with fluorescent indicator UV_{254}. Solns. of 10% phosphomolybdic acid in EtOH or 10% H_2SO_4 in EtOH were used for visualization, after heating at 110°. PLC was developed on silica gel F_{254} plates. M.p.: determined in silicone bath; uncorrected. IR Spectra: in $CHCl_3$ soln. NMR Spectra: recorded at 200/50 MHz ($^1H/^{13}C$) in $CDCl_3$ soln., chemical shifts (δ) in ppm, referred to internal TMS, and coupling constants (J) in Hz. Mass spectra (EI): recorded under ionization energy of 70 eV.

Picropodophyllin (**7**). Compound **4** (150 mg) in 10 ml of 1% KOH in MeOH was stirred for 30 min at r.t. After neutralization and extraction with AcOEt, 140 mg (93%) of **7** were obtained.

Podophyllotoxone (**1**). Compound **4** (500 mg) in 15 ml of dry CH_2Cl_2 was treated with 600 mg of PDC. The suspension was stirred for 3 h at r.t. Usual workup afforded after FC (CH_2Cl_2/AcOEt 1:1) 416 mg (84%) of **1**.

Picropodophyllone (**6**). By the same method described for **1**, 200 mg of **6** were obtained from the treatment of 220 mg of **7** with 280 mg of PDC.

Isopicropodophyllone (**2**). Compound **1** (100 mg) in 7 ml of AcOH was refluxed for 1 h. After addition of H_2O and extraction with AcOEt, the resulting material was chromatographed (Cl_2CH_2/AcOEt 95:5) yielding 70 mg (70%) of **1** and 22 mg of **2**.

Thuriferic Acid (**5**). Compound **1** (110 mg) was treated with 5 ml of 1% KOH/MeOH. The mixture was left 30 min at r.t., yielding, after usual workup and FC, 90 mg of **5**. M.p. 92–96° (Et_2O). Spectroscopic and physical data are identical to those reported in [3].

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