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On the Identity of a Neo-lignan from the Fruits of *Virola Sebifera*.

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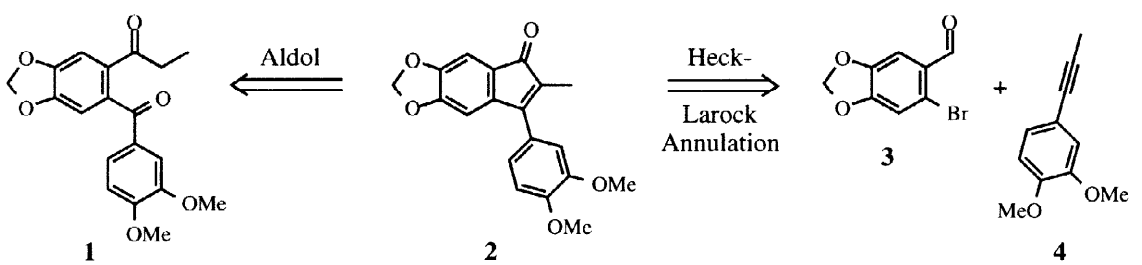
Abstract: 7-(3,4-Dimethoxyphenyl)-6-methylindeno[5,6-d][1,3]dioxol-5-one **2** has been reported as a neo-lignan isolated from the fruits of *Virola sebifera*. However, physical and spectroscopic data obtained from two synthetic samples of **2** do not match those quoted in the isolation paper. Data obtained from an isomer, 3-(benzo[1,3]dioxol-5-yl)-5,6-dimethoxy-2-methylinden-1-one **10**, are in closer agreement but the ^{13}C NMR spectrum reveals many inconsistencies.

Keywords: Natural products, Annulation, Transmetallation, Heck reactions, Indenes, Aldol Reactions.

Of the compounds isolated from the fruits of *Virola sebifera*, indenone **2** has attracted greatest interest.[1] As the only 3-arylindenone to have been isolated from natural sources it appears to represent a new class of lignans, prompting speculation as to its origin and biosynthesis.[2] Our interest in lignan total synthesis,[3] together with recent reports that 3-arylindenones display anti-tumour[4] and post coital contraceptive activity,[5,6] led us to target this natural product. The *Letter* that follows details two syntheses of **2** and outlines our reasons for believing that the original structural assignment is in error.



Scheme 1

Two syntheses of indenone **2** were envisioned (Scheme 1). The first was based on a classical, intramolecular aldol condensation and began with the elaboration of piperonal **5** to bromoalcohol **6**. Simultaneous deprotonation and transmetallation of **6** to **7** with *n*-butyllithium then facilitated union with 3,4-dimethoxybenzaldehyde **8**. Oxidation of the resulting diols **9** next gave **1** which cyclised to **2** on exposure to tosic acid in refluxing toluene (Scheme 2).[7] Unexpectedly, the spectral and physical characteristics displayed by our synthetic sample differed markedly from those reported for the natural product. Though UV, IR and mass spectral data were consistent, the melting point, ^1H NMR and ^{13}C NMR spectra revealed several discrepancies (Table 1). Most notably, our synthetic sample had a melting point of 142-145°C (MeOH) compared to 214-216°C (MeOH) for the natural product.

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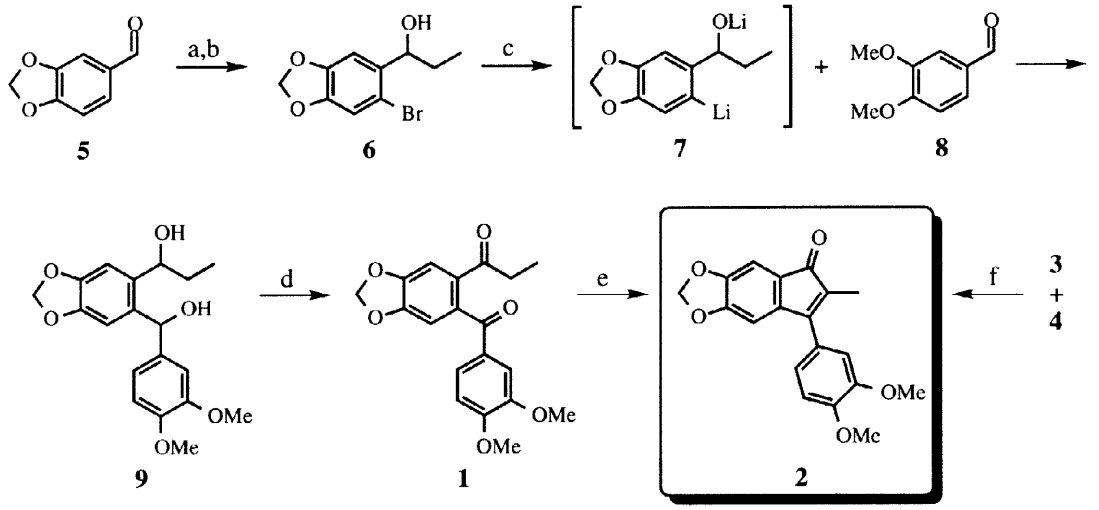
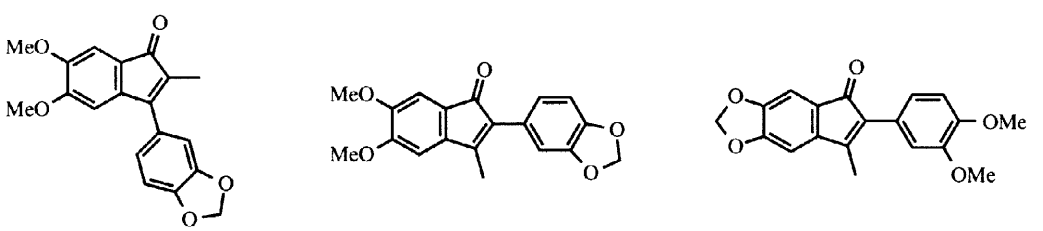
While we were confident that our synthesis had proceeded without incident we thought it wise to secure an independent route to **2** in order to dispel any lingering doubts. The approach adopted utilised a new annulation procedure developed in the laboratories of Heck and Larock.[8,9] Thus, warming a toluene solution of 6-bromopiperonal **3**,[10] arylpropyne **4**,[11] and sodium hydrogen carbonate with 25 mol% palladium chloride and 50 mol% triphenylphosphine gave indenone **2** directly. As expected, the physical and spectral characteristics exhibited by our synthetic samples were identical and the mixed melting point showed no depression.



Reagents and Conditions: **a.** Br_2, AcOH, r.t., 20h, 82%;[10] **b.** EtMgBr, THF, 0°C, 1h; 2M HCl, 76%; **c.** *n*-BuLi, THF, -78°C, 1h; **8**, -78°C to r.t. over 1h; aq. NH_4Cl, 81% (1:1); **d.** $BaMnO_4$, CH_2Cl_2, 48h, 82%; **e.** *p*-TsOH, PhMe, 110°C, 6h, 54%;[7] **f.** 25 mol% $PdCl_2$, 50 mol% PPh_3, PhMe, $NaHCO_3$, 100°C, 16h, 38%.

Scheme 2

At this juncture we reassessed the published data and concluded that the most likely structure for the natural product was 3-arylindenone **10**. Our reasons for favouring **10** over the isomeric 2-arylindenones **11** and **12** were i. the UV/visible spectra obtained for **2** agreed with data reported in the isolation paper suggesting the presence of a similar chromophore; ii. the chemical shift of the allylic methyl group in **2** and virola indenone were both δ_H 1.89 suggesting an attachment at C-2; and iii. the biosynthesis of virola indenone proposed by Whiting was equally valid for **10**.[2]



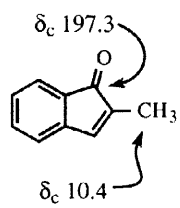
10 **11** **12**

A sample of **10** was prepared using the method outlined in Scheme 2 but with the arenes **5** and **8** interchanged. Gratifyingly, the appearance, m.p., UV and mass spectral data displayed by our synthetic sample were identical to those reported for the natural product. IR and ^1H NMR data were also consistent except that those signals above δ_H 6.0 ppm were 0.05 ppm lower than expected. These facts suggested that the structure of virola indenone should be revised to **10**.

Table 1 Physical and Spectral Characteristics of **2**, **10** and Virola Indenone.

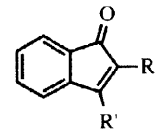
Characteristics	**2**	Natural Product	**10**
Appearance	red solid	red solid	red solid
m.p. (MeOH)	142-145°C	214-216°C	213-215°C
m/e	MH^+ (APCI) 325	M^+ (EI) 324	MH^+ (APCI) 325
IR	Bio-Rad FTS on solid 1692, 1601, 1590, 1515	KBr 1692, 1600, 1484-1440	CH_2Cl_2 solution 1699, 1589, 1491, 1447
UV (MeOH)	465 (700) 343 (8100) 271 (32000)	 340 (7600) 265 (32400)	465 (500) 343 (7400) 270 (32000)
^1H NMR ($CDCl_3$)	300 MHz	60 MHz	300 MHz
ArH	6.95 (1H, obscured s)	7.17 (1H, s)	7.12 (1H, s)
3 x ArH	7.1-6.9 (3H, m)	7 (3H, m)	7.0-6.9 (3H, m)
ArH	6.62 (1H, s)	6.69 (1H, s)	6.64 (1H, s)
OCH_2O	5.97 (2H, s)	6.10 (2H, s)	6.05 (2H, s)
OMe	3.95 (3H, s)	3.89 (3H, s)	3.89 (3H, s)
OMe	3.92 (3H, s)	3.86 (3H, s)	3.87 (3H, s)
CMe	1.89 (3H, s)	1.89 (3H, s)	1.89 (3H, s)
^{13}C NMR ($CDCl_3$)	75.5 MHz	20 MHz	75.5 MHz
CH_3	56.2, 56.1, 8.9	55.8, 55.7, 18.0	56.5, 56.5, 8.9
CH_2	102.1	103.5	101.6
CH	121.2, 111.3, 111.1, 105.1, 103.6	120.8, 111.7, 108.5, 108.0, 105.9	122.3, 108.9, 108.4, 107.6, 105.6
C	197.0, 152.9, 151.2, 149.9, 149.1, 147.0, 142.4, 129.3, 125.4, 125.3	208.0, 168.6, 159.9, 151.7, 149.3, 148.2, 147.7, 132.4, 128.9, 127.9	197.9, 153.0, 152.5, 148.4, 148.4, 148.2, 140.2, 129.5, 126.8, 123.6

However, a ^{13}C NMR analysis of **10** showed numerous inconsistencies. In particular, values for δ_C *C*=O (198 ppm for **10** with 208 ppm reported for the natural product) and δ_C CCH_3 (9 ppm for **10** with 18 ppm reported for the natural product) were out of line (Table 1). Recently published ^{13}C NMR data for indanones (Figure[12] and Table 2) show good agreement with our observations.



Figure

Table 2 δ_C C=O for a variety of Indenones



R	R'	δ_C C=O	Reference
nPr	nPr	198.5	9
$C(OH)Me_2$	Ph	199.6	9
Br	Ph	189.7	9
$SiMe_3$	Ph	201.6	9
Me	H	197.3	12
Et	Ph	198.2	13
Et	Me	194.8	14
H	Me	197.8	14

In conclusion, two syntheses of **2** have been secured. The first, a classical approach using an acid catalysed intramolecular aldol condensation, is notable for the ease with which simultaneous deprotonation and transmetallation of **6** to **7** was achieved. A noteworthy feature of the second synthesis, which used a Heck-Larock annulation reaction to elaborate the indenone, was the high degree of regioselectivity observed in the key step.[9] Importantly, our work has shown that the structure **2** assigned to a natural product isolated from the fruits of *Virola sebifera* is in error: discrepancies in the melting point and ^{1}H NMR data providing compelling evidence.[1] The isomeric 3-arylindenone **10** has also been synthesised and, with the exception of ^{13}C NMR data, displays physical and spectral characteristics consistent with those reported in the isolation paper. Our attempts to reveal the identity of virola indenone continue with programmes directed towards the synthesis of **11** and **12**.

Acknowledgements

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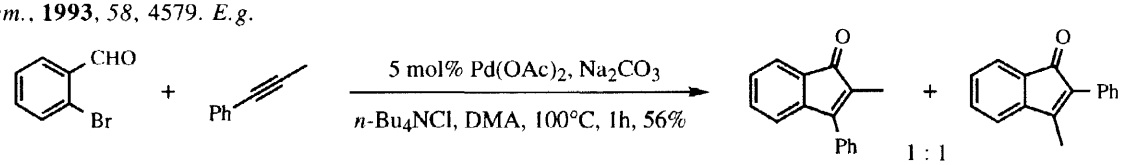

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