REVISION OF STRUCTURE OF A NEW COUMARIN ISOLATED FROM *Artemisia carviforia* Wall

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Four coumarins (**1-4**) were synthesized by routes shown in Charts 2-5, respectively. A proposed structure for a new coumarin isolated from *Artemisia carviforia* was incorrect, and the structure of coumarin should be represented by formula (**3**).

KEYWORDS Claisen rearrangement; aryl propargyl ether; salicylaldehyde; Wittig reaction; coumarin synthesis; structure revision

In 1990, W. Döpke *et al.* isolated a new coumarin (mp 108-110°C, $C_{15}H_{16}O_4$) from *Artemisia carvifolia* Wall[1] and proposed a formula (**1**) having one methoxy- and one prenoxy group as the structure of coumarin on the basis of spectral data (all of the reported ^{1}H-NMR and ^{13}C-NMR spectral data are listed in Table I). It is generally known that simple 5-alkoxy-coumarins show the C_4-H signal between δ 7.9 and δ 8.2 in ^{1}H-NMR spectra.[2] However, since the signal at δ 7.69 (d, J=9.5 Hz) is assigned to C_4-H, the structure (**1**) proposed for the new coumarin appears doubtful. For the purpose of structural confirmation, we planned to synthesize **1** by using two new synthetic methods developed by us, *i.e.*, salicyl-aldehyde synthesis *via* CsF-mediated Claisen rearrangement of an aryl propargyl ether, followed by oxidative cleavage of a benzofuran[3] and coumarin synthesis by the Wittig reaction of salicylaldehyde in diethylaniline under reflux[4](see Chart 1).

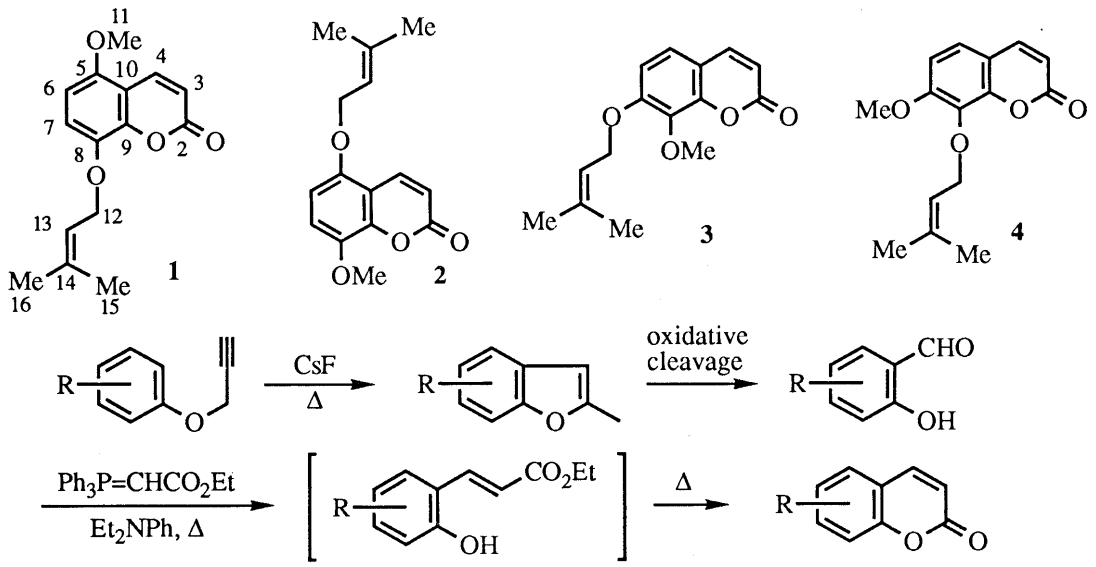

Chart 1

Synthesis of **1** from 2-hydroxy-4-methoxybenzaldehyde (**5**) was illustrated in Chart 2. Thus, the CsF-mediated Claisen rearrangement of propargyl ether acetal of **5** gave **6**, which was converted to the phenol (**7**) by the Baeyer-Villiger oxidation with SeO_2-H_2O_2.[5] Protection of **7** with methoxymethylchloride (MOMCl) followed by ozonolysis afforded the salicylaldehyde (**9**). The Wittig reaction of **9** gave **10**, from which **1** was derived *via* hydrolysis and prenylation.

As can be seen from melting points and NMR data indicated in Table I, the data of synthetic **1** were not identical with those of natural coumarin, indicating that the proposed structure (**1**) for the new coumarin is incorrect. We considered three formulas (**2**, **3**, and **4**) as other possible structures for the Döpke's new coumarin[6] and examined synthesis of these compounds.

Compound (**2**) was prepared from 4-hydroxy-7-methoxybenzo[*b*]furan (**11**)[4b] in six steps as shown in Chart 3. Thus, methoxymethylation of **11** followed by ozonolysis and hydrolysis afforded the salicylaldehyde (**13**), which was converted into **2** *via* the Wittig reaction, demethoxymethylation and prenylation.

The compound (**3**) was easily synthesized from 2,4-dihydroxy-3-methoxybenzaldehyde (**15**)[8] using the Wittig reaction and prenylation (Chart 4).

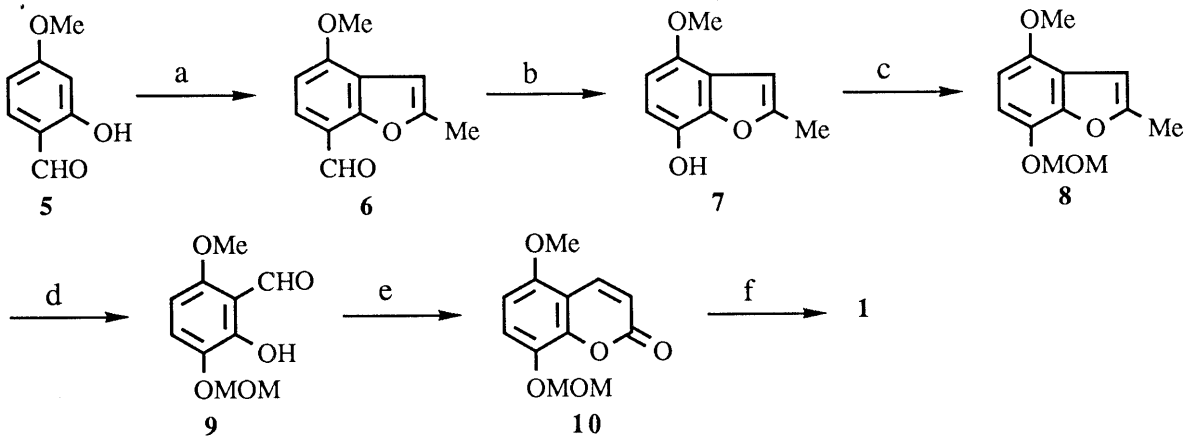

Chart 2. Reagents and Conditions ; (a) i) $HC{\equiv}CCH_2Br$; ii) $HC(OEt)_3$; iii) CsF, $PhNEt_2$, reflux, 55%. (b) SeO_2, 30% H_2O_2, 75%. (c) MOMCl, NaH, 95%. (d) i) O_3, Me_2S; ii) $NaHCO_3$, 47%. (e) $Ph_3P{=}CHCO_2Et$, $PhNEt_2$, reflux for 1.5 h, 88%. (f) i) conc. HCl; ii) $Me_2C{=}CHCH_2Br$, K_2CO_3, 81%.

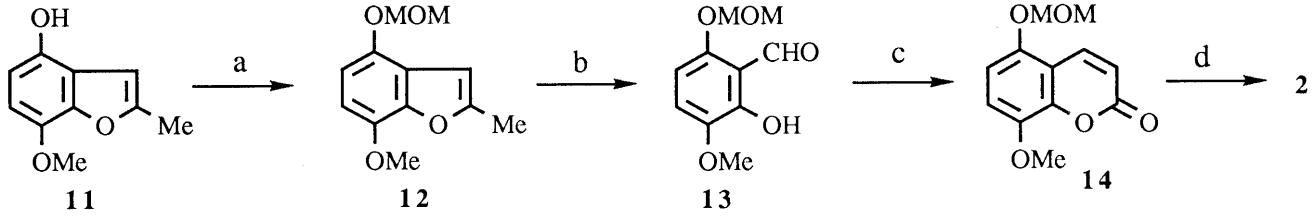

Chart 3. Reagents and Conditions ; (a) MOMCl, NaH, 98%. (b) i) O_3, Me_2S; ii) $NaHCO_3$, 51%. (c) $Ph_3P{=}CHCO_2Et$, $PhNEt_2$, reflux for 1.2 h, 79%. (d) i) conc. HCl; ii) $Me_2C{=}CHCH_2Br$, K_2CO_3, 84%.

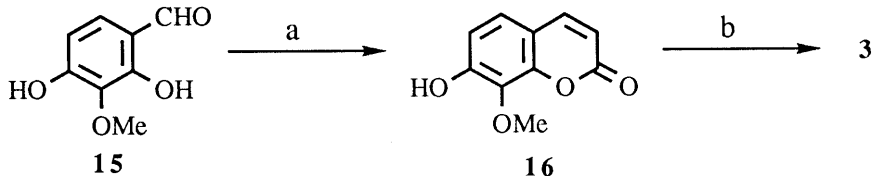

Chart 4. Reagents and Conditions ; (a) $Ph_3P{=}CHCO_2Et$, $PhNEt_2$, reflux for 15 min, 74%. (b) $Me_2C{=}CHCH_2Br$, K_2CO_3, 97%.

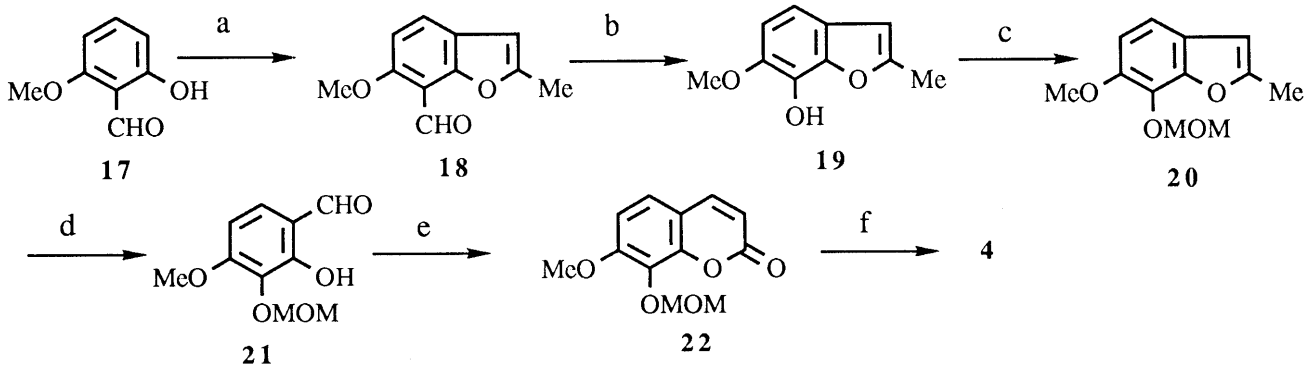

Chart 5. Reagents and Conditions ; (a) i) $HC{\equiv}CCH_2Br$; ii) $HC(OEt)_3$; iii) CsF, $PhNEt_2$, reflux, 25%. (b) SeO_2, 30% H_2O_2, 69%. (c) MOMCl, NaH, 98%. (d) i) O_3, Me_2S; ii) NaOH, 54%. (e) $Ph_3P{=}CHCO_2Et$, $PhNEt_2$, reflux for 1.5 h, 60%. (f) i) conc. HCl; ii) $Me_2C{=}CHCH_2Br$, K_2CO_3, 92%.

Compound (**4**) was prepared from 2-hydroxy-6-methoxybenzaldehyde (**17**)[9] as shown in Chart 5. Thus, the CsF-mediated Claisen rearrangement of propargyl ether acetal of **17** provided benzofuran (**18**), which was converted to salicylaldehyde (**21**) by Baeyer-Villiger oxidation, methoxymethylation and ozonolysis. The Wittig reaction of **21** afforded coumarin (**22**), which was deprotected and prenylated to produce **4**.

Melting points and NMR spectral data of the synthesized compounds (**1-4**) and natural coumarin are listed in Table I, and the data of **3** are identical with those reported for the natural coumarin. Therefore, we propose formula (**3**) as a revised structure for Döpke's coumarin, although direct comparison of our samples with the natural sample and/or its spectral data could not be made due to their non-availability.

Table I. Melting Points and NMR Data[a] of the Coumarins

		Döpke's coumarin[b]	**1**	**2**	**3**	**4**
mp (°C)		108-110	62-63	121.5-123	104-106	71.5-72
^{1}H	C_3-H	6.16 d (9.5)	6.34 d (9.8)	6.34 d (9.8)	6.25 d (9.5)	6.24 d (9.4)
	C_4-H	7.69 d (9.5)	8.05 d (9.8)	8.09 d (9.8)	7.63 d (9.5)	7.69 d (9.4)
^{13}C	C_2		160.2	160.2	160.6	160.5
	C_3		114.7	114.7	113.3	113.3
	C_4		138.7	139.0	143.6	143.6
	C_5		149.8	148.9	122.6	122.7
	C_6		104.1	105.4	110.0	108.3
	C_7		117.5	114.7	154.9	156.0
	C_8		140.2	141.1	136.5	134.9
	C_9	154.5 *	145.3	144.6	148.6	148.4
	C_{10}	113.2	110.4	110.7	113.6	113.6
	C_{11}	60.7	55.9	56.8	61.3	56.3
	C_{12}	65.7	67.1	65.8	66.1	69.9
	C_{13}	118.7	119.7	119.1	119.0	119.9
	C_{14}	138.1	138.2	138.5	138.6	139.2
	C_{15}	25.2 **	18.1	18.2	18.2	17.9
	C_{16}	17.7 **	25.7	25.7	25.7	25.7

a) ^{1}H-(500MHz) and ^{13}C-NMR(125MHz) spectra were measured in $CDCl_3$ solution. Chemical shifts are given in δ (ppm) and the values in parentheses in ^{1}H-NMR data are coupling constants in Hz. ^{13}C-NMR assignments are based on NOE, ^{1}H-^{13}C COSY, and ^{1}H-^{13}C long range COSY experiments.
b) The data were those of the ^{1}H-(400MHz) and ^{13}C-NMR (100MHz) spectra in $CDCl_3$ solution (see reference 1).
* This signal should be assigned to C_7.
** These assignments should be exchanged.

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6) Formula (**2**) corresponds to a regio-isomer of **1**. We postulated two formulas (**3** and **4**) having vicinal hydrogens on benzene ring as other candidates, because Döpke et al. proposed formula (**1**) having vicinal hydrogens although there is no report of ^{1}H-NMR data for vicinal hydrogens in the literature.[1] Although **3** and **4** were known,[7] we planned to synthesize **3** and **4**, expecting a direct comparison of synthetic samples with natural sample.
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