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

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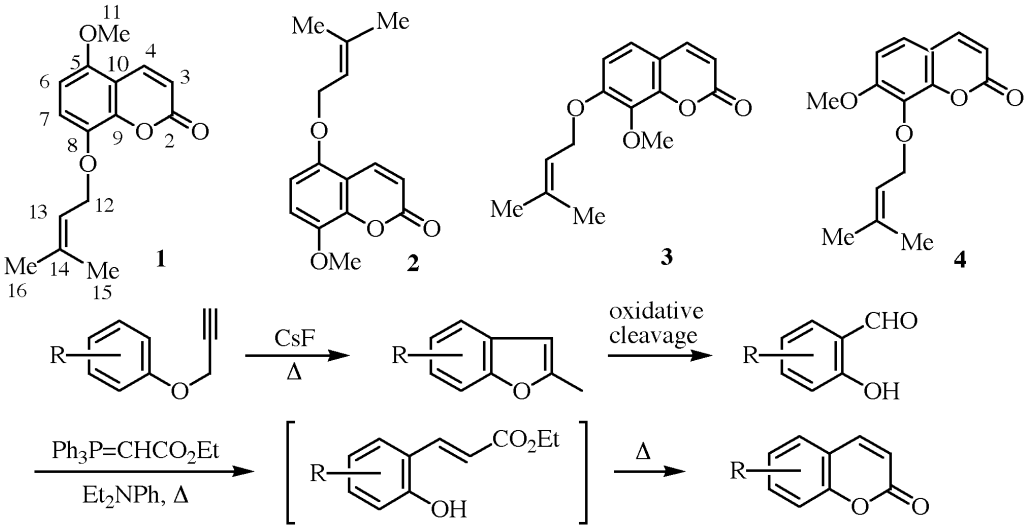
Abstract - Four coumarins (**1**-**4**) were synthesized by the routes shown in Schemes 2-5, respectively. The previously proposed structure for a new coumarin isolated from *Artemisia carviforia* was incorrect; the structure of the coumarin is represented by formula (**3**).

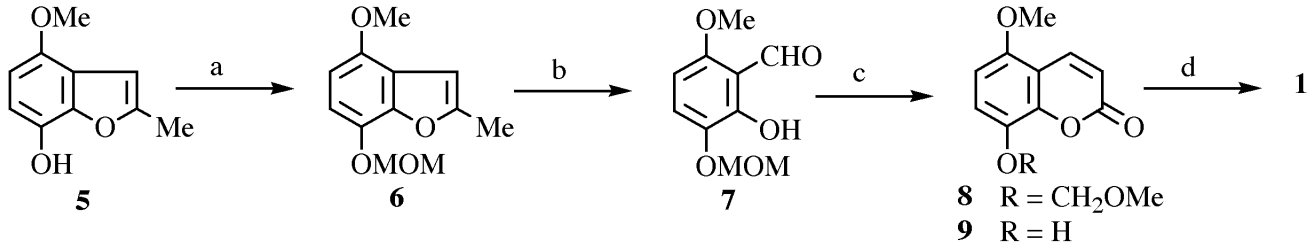
Coumarins are widely distributed in nature and exhibit useful biological activities.[1] Although many synthetic routes[2] to coumarins, especially simple (3,4-unsubstituted) coumarins, have been developed, including the Perkin, Knoevenagel, and Pechmann reactions, much effort is still being devoted to exploring new synthetic methods, because none of the available methods are comprehensive.[3] We have been studying the development of new synthetic methods for simple coumarins using i) salicylaldehyde synthesis by ozonolysis of 2-methylbenzofuran obtained from the cesium fluoride-mediated Claisen rearrangement of an aryl propargyl ether[4] and ii) coumarin synthesis by the Wittig reaction of salicylaldehyde in diethylaniline under reflux.[5]



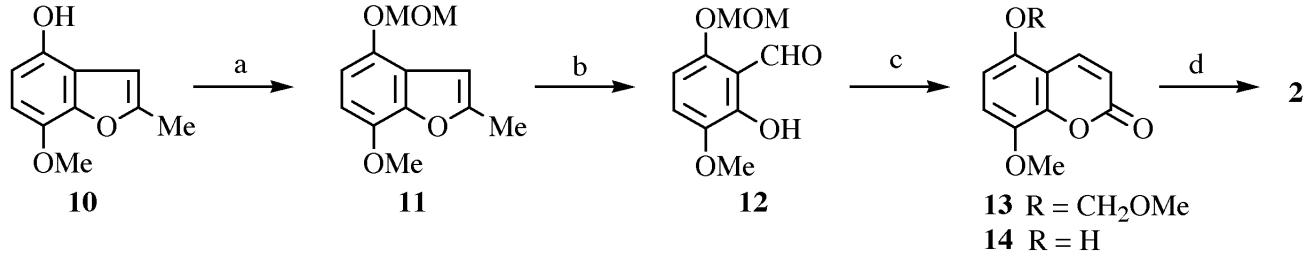
Scheme 1

† Dedicated to Professor Shô Itô for the celebration of his 77th birthday.

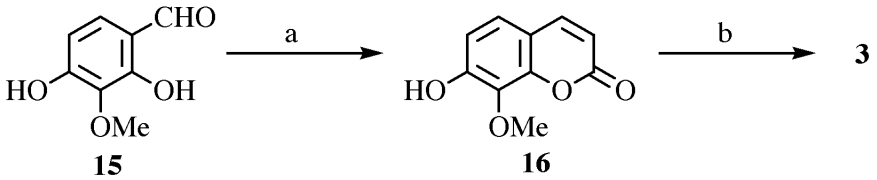
In 1990, W. Döpke *et al.* isolated a new coumarin (mp 108-110°C, $C_{15}H_{16}O_4$) from *Artemisia carvifolia* Wall[6] and proposed a formula (**1**) for a coumarin with one methoxy- and one prenoxy groups on the basis of spectral data (all of the reported ^{1}H-NMR and ^{13}C-NMR spectral data are listed in Table I). It is generally known that simple 5-alkoxycoumarins show a C_4-H signal between δ 7.9 and δ 8.2 in ^{1}H-NMR spectra.[7] 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 synthesized **1** using two new synthetic methods mentioned above (see Scheme 1).



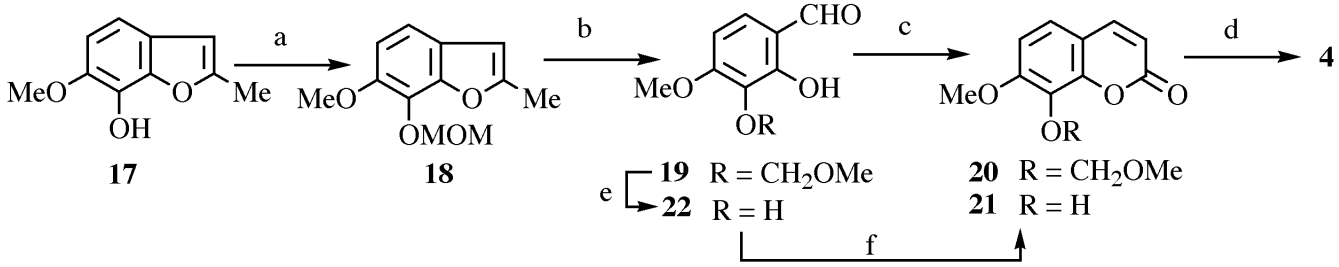
Scheme 2. Reagents and Conditions ;(a) MOMCl, NaH. (b) i) O_3, Me_2S; ii) $NaHCO_3$.
(c) i) $Ph_3P{=}CHCO_2Et$, $PhNEt_2$, reflux for 1.5 h; ii) conc. HCl. (d) $Me_2C{=}CHCH_2Br$, K_2CO_3.



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



Scheme4. Reagents and Conditions ; (a) $Ph_3P{=}CHCO_2Et$, $PhNEt_2$, reflux for 15 min.
(b) $Me_2C{=}CHCH_2Br$, K_2CO_3.



Schemet 5. Reagents and Conditions ; (a) MOMCl, NaH. (b) i) O_3, Me_2S; ii) NaOH.
(c) i) $Ph_3P{=}CHCO_2Et$, $PhNEt_2$, reflux for 1.5 h; ii) conc. HCl. (d) $Me_2C{=}CHCH_2Br$, K_2CO_3.
(e) conc. HCl. (f)$Ph_3P{=}CHCO_2Et$, $PhNEt_2$, reflux for 15 min.

The synthesis of **1** from 7-hydroxy-4-methoxy-2-methylbenzo[*b*]furan (**5**)[8] is illustrated in Scheme 2. Reaction of the phenol (**5**) with methoxymethyl chloride (MOMCl) gave the MOM ether (**6**) in 95% yield. This was converted to the salicylaldehyde (**7**) in 47% yield *via* ozonolysis and alkaline hydrolysis. Coumarin ring formation of **7** with the Wittig reagent (carbethoxymethylenetriphenylphosphorane) in diethylaniline under reflux proceeded smoothly to provide the MOM coumarin (**8**) and hydroxycoumarin (**9**) in 88 and 8% yields, respectively. The cleavage of the MOM group of **8** with acid gave **9** in 95% yield. This was prenylated to produce compound (**1**) in 85% yield.

As seen in Table I, the melting point and NMR data for synthetic **1** were not identical with those of natural coumarin, indicating that the proposed structure (**1**) for the new coumarin is incorrect. Therefore, we considered three other possible structures (**2**, **3**, and **4**) for Döpke's new coumarin. Formula (**2**) corresponds to a regio-isomer of **1** and formulas (**3**) and (**4**) contain vicinal hydrogens on their benzene rings. Formulas (**3**) and (**4**) were chosen because Döpke's proposed formula (**1**) includes vicinal hydrogens, though there are no reports of ^{1}H-NMR data for vicinal hydrogens in the literature.[6] Although **3** and **4** are known,[9] we attempted to synthesize **3** and **4** for direct comparison of the synthetic samples with the authentic sample.

Compound (**2**) was prepared from 4-hydroxy-7-methoxy-2-methylbenzo[*b*]furan (**10**)[10] in six steps as shown in Scheme 3. Thus, methoxymethylation of the phenol (**10**) provided the MOM ether (**11**) in an

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-(500 MHz) and ^{13}C-NMR(125 MHz) 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-(400 MHz) and ^{13}C-NMR (100 MHz) spectra in $CDCl_3$ solution (see reference 6).

* This signal should be assigned to C_7.

** These assignments should be exchanged.

excellent yield, and subsequent ozonolysis and hydrolysis of **11** afforded the salicylaldehyde (**12**) in 51% yield. Reaction of **12** with the Wittig reagent gave the MOM coumarin (**13**), which was treated with acid to afford the hydroxy coumarin (**14**) in 73% yield. Finally, prenylation of **16** gave the expected compound (**2**) in 90% yield.

Compound (**3**) was easily synthesized from 2,4-dihydroxy-3-methoxybenzaldehyde (**15**)[11] in two steps. Reaction of **15** with the Wittig reagent produced the hydroxy coumarin (**16**) in 74% yield, and reaction of **16** with prenyl bromide produced **3** in an excellent yield (Scheme 4).

Compound (**4**) was prepared from 7-hydroxy-6-methoxy-2-methylbenzo[*b*]furan (**17**)[8] as shown in Scheme 5. Reaction of **17** with MOMCl gave the MOM ether (**18**) in an excellent yield. Ozonolysis of **18** followed by alkaline hydrolysis afforded the salicylaldehyde (**19**) in 54% yield. The Wittig reaction of **19** afforded the MOM coumarin (**20**) and the hydroxy coumarin (**21**) in 60 and 3% yields, respectively. Cleavage of the MOM group on **20** with acid provided **21**, which was subsequently prenylated to produce **4** in an excellent yield. Another synthetic route to **21** was examined in order to improve the total yield from **19**. Treatment of **19** with acid gave compound (**22**) in 90% yield. This was converted to **21** by the Wittig reaction in 70% yield, resulting in a slight improvement in total yield.

The melting points and NMR spectral data of the synthesized compounds (**1**-**4**) and the coumarin isolated by Döpke *et al*. are listed in Table I. Since the spectral data of synthetic sample (**3**) were identical with those of authentic sample, which was kindly provided by Prof. P. T. Son,[6] the proposed structure for the coumarin isolated from *Artemisia carvifolia* should be revised to formula (**3**).

EXPERIMENTAL

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded in Nujol on a JASCO A-102 spectrophotometer and ^{1}H- and ^{13}C-NMR spectra in deuteriochloroform on a Hitachi R-1500 (60 MHz) or Varian VXR-500 (500 MHz) spectrometer unless otherwise stated. NMR data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0) and coupling constants are given in Hertz. Column chromatography was carried out on silica gel (Wako gel C-200 or Merck, silica gel 60, No. 9385). All experiments were carried out in an argon atmosphere and the extract was washed with brine, dried over anhydrous $MgSO_4$, then filtered, and the filtrate was evaporated to dryness under reduced pressure, unless otherwise noted.

General Procedure for the Synthesis of MOM Ethers (6, 11, and 18) by Methoxymethylation of the Phenol (5, 10, and 17)

To a suspension of freshly washed (n-hexane) NaH (1.11 g, 63% dispersion in oil, 29 mmol) in dry DMF (10 mL) were added a solution of the phenol (3.03 g, 17 mmol) in dry DMF (20 mL) and methoxymethyl-chloride (1.9 mL) with stirring under ice cooling. The reaction mixture was stirred at rt for 20 min. After excess hydride was decomposed with wet ether, the mixture was diluted with water and extracted with ether.

4-Methoxy-7-methoxymethoxy-2-methylbenzo[*b*]furan (6)

The residue dissolved in benzene was subjected to column chromatography. Elution with hexane : AcOEt (20 : 1) gave **6** (3.60 g, 95%) as colorless needles (from ether-hexane), mp 48-49°C. ^{1}H-NMR δ : 2.46 (3H, s, C_2-Me), 3.55 (3H, s, CH_2-OMe), 3.87 (3H, s, OMe), 5.29 (2H, s, OCH_2), 6.40-6.55 (2H, m, C_3-H and C_5-H or C_6-H), 6.89 (1H, d, *J*=9.0 Hz, C_5-H or C_6-H). *Anal*. Calcd for $C_{12}H_{14}O_4$: C, 64.84; H, 6.36. Found: C, 64.73; H, 6.36.

7-Methoxy-4-methoxymethoxy-2-methylbenzo[*b*]furan (11)

The residue dissolved in hexane : AcOEt (9 : 1) was subjected to column chromatography. Elution with hexane : AcOEt (19 : 1) gave **11** (3.68 g, 98%), as an oily compound. ^{1}H-NMR δ : 2.46 (3H, d, J=1.2 Hz, C_2-Me), 3.52 (3H, s, CH_2-OMe), 3.96 (3H, s, OMe), 5.21 (2H, s, OCH_2), 6.48 (1H, m, C_3-H), 6.58 (1H, d, J=8.4 Hz, C_5-H or C_6-H), 6.78 (1H, d, *J*=8.4 Hz, C_5-H or C_6-H). *Anal*. Calcd for $C_{12}H_{14}O_4$: C, 64.84; H, 6.36. Found: C, 64.73; H, 6.16.

6-Methoxy-7-methoxymethoxy-2-methylbenzo[*b*]furan (18)

The residue dissolved in AcOEt-benzene was subjected to column chromatography. Elution with hexane : AcOEt (15 : 1) gave **18** (3.68 g, 98%) as colorless needles (from hexane), mp 32-33°C. ^{1}H-NMR δ : 2.43 (3H, s, C_2-Me), 3.63 (3H, s, CH_2-OMe), 3.90 (3H, s, OMe), 5.35 (2H, s, OCH_2), 6.28 (1H, m, C_3-H), 6.84 (1H, d, *J*=8.2 Hz, C_4-H or C_5-H), 7.11 (1H, d, *J*=8.2 Hz, C_4-H or C_5-H). *Anal*. Calcd for $C_{12}H_{14}O_4$: C, 64.84; H, 6.36. Found: C, 64.72; H, 6.09.

General Procedure for the Synthesis of MOM Salicylaldehydes (7, 12, and 19) from MOM Ethers (6, 11, and 18)

MOM ether (9.46 g, 42 mmol) was dissolved in dry CH_2Cl_2 (100 mL) and cooled to -78°C. Ozone gas was bubbled through the solution for 30 min with stirring. The pale blue reaction mixture was stirred at the same temperature for a further 2 h. Excess ozone was removed by bubbling argon through the solution for about 10 min. Dimethyl sulfide (12.5 mL) was added and the reaction mixture was stirred at rt for 30 min and the mixture was then concentrated under reduced pressure. The residue was heated in EtOH (200 mL) and saturated aqueous $NaHCO_3$ solution (67 mL) under reflux. The reaction mixture was poured into water, acidified with 10% HCl solution and then extracted with ether.

2-Hydroxy-6-methoxy-3-methoxymethoxybenzaldehyde (7)

The residue dissolved in benzene was subjected to column chromatography. Elution with hexane : AcOEt (7 : 1) gave **7** (4.20 g, 47%), as colorless needles (from ether-hexane), mp 55-56°C. IR ν : 1635 cm^{-1}. ^{1}H-NMR δ : 3.53 (3H, s, CH_2-OMe), 3.86 (3H, s, OMe), 5.14 (2H, s, OCH_2), 6.28 (1H, d, *J*=9.0 Hz, C_4-H or C_5-H), 7.30 (1H, d, *J*=9.0 Hz, C_4-H or C_5-H), 10.33 (1H, s, CHO), 12.16 (1H, s, OH). *Anal*. Calcd for $C_{10}H_{12}O_5$: C, 56.59; H, 5.71. Found: C, 56.51; H, 5.77.

2-Hydroxy-3-methoxy-6-methoxymethoxybenzaldehyde (12)

The residue dissolved in benzene was subjected to column chromatography. Elution with hexane : AcOEt (9 : 1) gave **12** (4.60 g, 51%), as colorless needles (from ether-hexane), mp 47-48°C. IR ν : 1640 cm^{-1}. ^{1}H-NMR δ : 3.51 (3H, s, CH_2-OMe), 3.86 (3H, s, OMe), 5.23 (2H, s, OCH_2), 6.54 (1H, d, *J*=8.8 Hz, C_4-H or

C_5-H), 7.03 (1H, d, *J*=8.8 Hz, C_4-H or C_5-H), 10.37 (1H, s, CHO), 12.10 (1H, s, OH). *Anal*. Calcd for $C_{10}H_{12}O_5$: C, 56.59; H, 5.71. Found: C, 56.81; H, 5.68.

2-Hydroxy-4-methoxy-3-methoxymethoxybenzaldehyde (19)

The residue dissolved in AcOEt-benzene was subjected to column chromatography. Elution with hexane : AcOEt (4 : 1) gave **19** (4.88 g, 54%), as colorless needles (from ether-hexane), mp 53-54°C. IR ν : 1640 cm^{-1}. ^{1}H-NMR δ : 3.63 (3H, s, CH_2-OMe), 3.95 (3H, s, OMe), 5.19 (2H, s, OCH_2), 6.61 (1H, d, *J*=8.8 Hz, C_5-H or C_6-H), 7.32 (1H, d, *J*=8.8 Hz, C_5-H or C_6-H), 9.36 (1H, s, CHO), 11.26 (1H, s, OH). *Anal*. Calcd for $C_{10}H_{12}O_5$: C, 56.59; H, 5.71. Found: C, 56.73; H, 5.68.

General Procedure for the Synthesis of MOM Coumarins (8, 13, and 20) from MOM Salicylaldehydes (7, 12, and 19) by the Wittig reaction.

A solution of salicylaldehyde (0.30 g, 1.4 mmol) and carbethoxymethylenetriphenylphosphorane (0.59 g, 1.7 mmol) in diethylaniline (15 mL) was heated at 210-215°C for 1.5 h. After cooling, the reaction mixture was diluted with 5% HCl solution (400 mL) and extracted with ether. The residue was dissolved in benzene and the solution was subjected to column chromatography.

Products (8 and 9) from the Wittig reaction of 7 with carbethoxymethylenetriphenyl-phosphorane

Elution with hexane : AcOEt (7 : 1) gave 5-methoxy-8-methoxymethoxy-2*H*-1-benzopyran-2-one (**8**) (0.29 g, 88%) as colorless needles (from ether-hexane), mp 113-115°C. IR ν : 1730 cm^{-1}. ^{1}H-NMR δ : 3.56 (3H, s, CH_2-OMe), 3.88 (3H, s, OMe), 5.20 (2H, s, OCH_2), 6.34 (1H, d, *J*=10.0 Hz, C_3-H), 6.60 (1H, d, *J*=9.0 Hz, C_6-H or C_7-H), 7.27 (1H, d, *J*=9.0 Hz, C_6-H or C_7-H), 8.07 (1H, d, *J*=10.0 Hz, C_4-H). *Anal*. Calcd for $C_{12}H_{12}O_5$: C, 61.00; H, 5.13. Found: C, 60.87; H, 5.19. Successive elution with the same solvent gave 8-hydroxy-5-methoxy-2*H*-1-benzopyran-2-one (**9**) (22 mg, 8%), as yellow needles (from MeOH), mp 202-204°C. IR ν: 3200, 1690 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ : 3.90 (3H, s, OMe), 6.30 (1H, d, *J*=10.0 Hz, C_3-H), 6.74 (1H, d, *J*=9.0 Hz, C_6-H or C_7-H),7.05 (1H, d, *J*=9.0 Hz, C_6-H or C_7-H), 8.11 (1H, d, *J*=10.0 Hz, C_4-H), 8.29 (1H, s, OH). *Anal*. Calcd for $C_{10}H_8O_4$: C, 62.49; H, 4.20. Found: C, 62.17; H, 4.16.

8-Methoxy-5-methoxymethoxy-2*H*-1-benzopyran-2-one (13)

Elution with hexane : AcOEt (4 : 1) gave **13** (0.26 g, 79%), as pale yellow prisms (from benzene), mp 110-111°C. IR ν : 1730 cm^{-1}. ^{1}H-NMR δ : 3.51 (3H, s, CH_2-OMe), 3.92 (3H, s, OMe), 5.23 (2H, s, OCH_2), 6.38 (1H, d, *J*=10.0 Hz, C_3-H), 6.87 (1H, d, *J*=9.0 Hz, C_6-H or C_7-H), 7.04 (1H, d, *J*=9.0 Hz, C_6-H or C_7-H), 8.08 (1H, d, *J*=10.0 Hz, C_4-H). *Anal*. Calcd for $C_{12}H_{12}O_5$: C, 61.00; H, 5.13. Found: C, 61.14; H, 5.13.

Products (20 and 21) from the Wittig reaction of 19 with carbethoxymethylenetriphenyl-phosphorane

Elution with hexane : AcOEt (4 : 1) gave 7-methoxy-8-methoxymethoxy-2*H*-1-benzopyran-2-one (**20**), (0.20 g, 60%) as colorless needles (from ether-hexane), mp 96-97°C. IR ν: 1730 cm^{-1}. ^{1}H-NMR δ : 3.57 (3H, s, CH_2-OMe), 3.95 (3H, s, OMe), 5.24 (2H, s, OCH_2), 6.26 (1H, d, *J*=9.7 Hz, C_3-H), 6.87 (1H, d, *J*=8.8 Hz, C_5-H or C_6-H),7.04 (1H, d, *J*=8.8 Hz, C_5-H or C_6-H), 8.08 (1H, d, *J*=9.7 Hz, C_4-H). *Anal*. Calcd for $C_{12}H_{12}O_5$: C, 61.00; H, 5.13. Found: C, 61.17; H, 5.22. Successive elution with the same solvent

gave 8-hydroxy-7-methoxy-2*H*-1-benzopyran-2-one (**21**), (10 mg, 3%), as colorless needles (from CH_2Cl_2), mp 176-177°C (lit.,[12] mp 169-171°C; lit.,[13a] mp 155°C). IR ν: 3380, 1720 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ : 3.96 (3H, s, OMe), 6.20 (1H, d, *J*=10.0 Hz, C_3-H), 7.07 (2H, d, *J*=2.3 Hz, C_5-H and C_6-H), 7.85 (1H, d, *J*=10.0 Hz, C_4-H), 8.21 (1H, S, OH). *Anal*. Calcd for $C_{10}H_8O_4$: C, 62.49; H, 4.20. Found: C, 62.21; H, 4.45.

General Procedure for the Synthesis of Hydroxy Coumarins (16 and 21) from Salicylaldehydes (15 and 22) by the Wittig reaction

A solution of salicylaldehyde (0.30 g, 1.8 mmol) and carbethoxymethylenetriphenylphosphorane (0.75 g, 2.2 mmol) in diethylaniline (20 mL) was heated at 210-215°C for 15 min. The reaction mixture was diluted with 5% HCl solution (400 mL) and extracted with ether.

7-Hydroxy-8-methoxy-2*H*-1-benzopyran-2-one (16)

The residue dissolved in AcOEt was subjected to column chromatography. Elution with hexane : AcOEt (3 : 1) gave **16** (0.25 g, 74%), as colorless needles (from ether-hexane), mp 157-159°C (decomp)(lit.,[14] mp 185-186°C). IR ν: 3320, 1695 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ : 3.95 (3H, s, OMe), 6.18 (1H, d, *J*=10.0 Hz, C_3-H), 6.88 (1H, d, *J*=8.7 Hz, C_6-H), 7.28 (1H, d, *J*=8.7 Hz, C_5-H), 7.87 (1H, d, *J*=10.0 Hz, C_4-H), 8.89 (1H, s, OH). *Anal*. Calcd for $C_{10}H_8O_4$: C, 62.49; H, 4.20. Found: C, 62.30; H, 4.07.

8-Hydroxy-7-methoxy-2*H*-1-benzopyran-2-one (21)

The residue dissolved in benzene was subjected to column chromatography. Elution with hexane : AcOEt (2 : 1) gave **21** (0.22 g, 70%), as colorless needles (from ether-hexane), mp 156-159°C.

General Procedure for the Synthesis of Hydroxy Coumarins (9, 14, and 21) by Demethoxymethylation of MOM Coumarin (8, 13, and 20)

A solution of MOM-coumarin (0.30 g, 1.2 mmol) in MeOH (12 mL) and conc-HCl (0.7 mL) was stirred at 50°C for 20 min. The mixture was poured into ice water and extracted with AcOEt.

8-Hydroxy-5-methoxy-2*H*-1-benzopyran-2-one (9)

The residue was recrystallized from MeOH to give **9** (0.23 g, 95%), as yellow needles, mp 202-204°C, which was identical with the by-product (**9**) obtained from the Wittig reaction of **7**.

5-Hydroxy-8-methoxy-2*H*-1-benzopyran-2-one (14)

The residue dissolved in CH_2Cl_2-acetone was subjected to column chromatography. Elution with CH_2Cl_2 gave **14** (0.22 g, 93%), as yellow needles (from MeOH), mp 205-209°C. IR ν: 3250, 1690, 1680 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ : 3.81 (3H, s, OMe), 6.34 (1H, d, *J*=10.0 Hz, C_3-H), 6.66 (1H, d, *J*=9.4 Hz, C_6-H or C_7-H), 7.14 (1H, d, *J*=9.4 Hz, C_6-H or C_7-H), 8.01 (1H, s, OH), 8.08 (1H, d, *J*=10.0 Hz, C_4-H). *Anal*. Calcd for $C_{10}H_8O_4$: C, 62.49; H, 4.20. Found: C, 62.71; H, 4.22.

8-Hydroxy-7-methoxy-2*H*-1-benzopyran-2-one (21)

The residue was recrystallized from CH_2Cl_2 to give **21** (0.23 g, 95%), as colorless needles, mp 176-177°C.

General Procedure for the Prenylation of Hydroxy Coumarin (9, 14, 16, and 21)

A suspension of hydroxycoumarin (0.24 g, 1.2mmol), prenyl bromide (0.5 mL, 4.2 mmol) and K_2CO_3 (0.24 g, 1.7 mmol) in DMF (2 mL) was stirred at rt for 6.5 h. The reaction mixture was poured into water and extracted with ether. The extract was washed with 10% NaOH aqueous solution (10 mL).

5-Methoxy-8-[(3-methyl-2-butenyl)oxy]-2*H*-1-benzopyran-2-one (1)

The residue was recrystallized from ether-pentane to afford **1** (0.28 g, 85%) , as yellow needles, mp 62-63°C. IR ν: 1720 cm^{-1}. ^{1}H-NMR δ : 1.75 (6H, d, J=2.3 Hz, CMe_2), 3.87 (3H, s, OMe), 4.59 (2H, d, J=7.0 Hz, OCH_2), 5.30-5.70 (1H, m, CH), 6.34 (1H, d, *J*=10.0 Hz, C_3-H), 6.57 (1H, d, *J*=9.0 Hz, C_6-H), 7.03 (1H, d, *J*=9.0 Hz, C_7-H), 8.05 (1H, d, *J*=10.0 Hz, C_4-H). *Anal*. Calcd for $C_{15}H_{16}O_4$: C, 69.20; H, 6.20. Found: C, 69.04; H, 6.15.

8-Methoxy-5-[(3-methyl-2-butenyl)oxy]-2*H*-1-benzopyran-2-one (2)

The residue dissolved in CH_2Cl_2-benzene was subjected to column chromatography. Elution with hexane : AcOEt (5 : 1) gave **13** (0.29 g, 90%), as pale-yellow prisms (from benzene), mp 121.5-123°C. IR ν : 1730 cm^{-1}. ^{1}H-NMR δ : 1.76 (3H, s, Me), 1.80 (3H, s, Me), 3.91 (3H, s, OMe), 4.56 (2H, d, *J*=6.4 Hz, OCH_2), 5.30-5.70 (1H, m, CH), 6.33 (1H, d, *J*=10.0 Hz, C_3-H), 6.61 (1H, d, *J*=8.8 Hz, C_6-H), 7.01 (1H, d, *J*=8.8 Hz, C_7-H), 8.09 (1H, d, *J*=10.0 Hz, C_4-H). *Anal*. Calcd for $C_{15}H_{16}O_4$: C, 69.20; H, 6.20. Found: C, 69.13; H, 6.15.

8-Methoxy-5-[(3-methyl-2-butenyl)oxy]-2*H*-1-benzopyran-2-one (3)

The residue was recrystallized from ether-pentane to afford **3** (0.31 g, 97%) , as colorless prisms, mp 104-106°C (lit.,[9] mp 100-101°C, lit.,[15] mp 102-103°C). IR ν : 1730 cm-1. ^{1}H-NMR δ : 1.77 (6H, s, CMe_2), 3.98 (3H, s, OMe), 4.66 (2H, d, *J*=6.5 Hz, OCH_2), 5.30-5.70 (1H, m, CH), 6.24 (1H, d, *J*=9.4 Hz, C_3-H), 6.85 (1H, d, *J*=8.8 Hz, C_6-H), 7.16 (1H, d, *J*=8.8 Hz, C_5-H), 7.62 (1H, d, *J*=9.4 Hz, C_4-H). *Anal*. Calcd for $C_{15}H_{16}O_4$: C, 69.20; H, 6.20. Found: C, 68.85; H, 6.38.

7-Methoxy-8-[(3-methyl-2-butenyl)oxy]-2*H*-1-benzopyran-2-one (4)

The residue dissolved in benzene was subjected to column chromatography. Elution with hexane : AcOEt (6 : 1) gave **13** (0.31 g, 97%), as colorless needles (from ether), mp 71.5-72°C (lit.,[9, 13a] mp 94°C, lit.,[13b] mp 60-61°C). IR ν: 1710 cm^{-1}. ^{1}H-NMR δ : 1.71 (6H, s, 2xMe), 3.95 (3H, s, OMe), 4.66 (2H, d, *J*=7.0 Hz, OCH_2), 5.42-5.80 (1H, m, CH), 6.25 (1H, d, *J*=10.0 Hz, C_3-H), 6.85 (1H, d, *J*=8.8 Hz, C_6-H), 7.18 (1H, d, *J*=8.8 Hz, C_5-H), 7.63 (1H, d, *J*=10.0 Hz, C_4-H). *Anal*. Calcd for $C_{15}H_{16}O_4$: C, 69.20; H, 6.20. Found: C, 69.21; H, 6.16.

2,3-Dihydroxy-4-methoxybenzaldehyde (22)

A solution of **19** (0.60 g, 2.82 mmol) in MeOH (28 mL) and conc-HCl (1.7 mL) was stirred at rt for 40 min. The mixture was poured into ice water and extracted with AcOEt. The residue was recrystallized from ether to give **22** (0.43 g, 90%) as pale yellow prisms, mp 116-117°C (lit.,[16] 117-118°C), IR ν : 3400, 1635 cm^{-1}. ^{1}H-NMR δ : 3.98 (3H, s, OMe), 5.56 (1H, s, C_3-OH), 6.62 (1H, d, *J*=8.8 Hz, C_4-H or C_5-H), 7.15 (1H, d, *J*=8.8 Hz, C_4-H or C_5-H), 9.77 (1H, s, CHO), 11.12 (1H, s, OH). *Anal*. Calcd for $C_8H_8O_4$: C, 57.14; H, 4.84. Found: C, 56.86; H, 4.99

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