Synthetic Studies on Naturally Occurring Coumarins. I. A Convenient Synthesis of 5,8-Dimethoxy- and 7,8-Dimethoxycoumarins

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The coumarin isolated from *Artemisia carvifolia* WALL was proved synthetically to be 7,8-dimethoxycoumarin and not 5,8-dimethoxycoumarin as previously proposed. 3,4-Dimethoxy- and 3,6-dimethoxysalicylaldehydes gave the corresponding coumarins in good yield by the method using phosphorane reagent in *N,N*-diethylaniline under reflux.

Keywords coumarin synthesis; 5,8-dimethoxycoumarin; 7,8-dimethoxycoumarin; structure revision; *Artemisia carvifolia*; dimethoxysalicylaldehyde; Wittig reagent

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 of the lack of generality of the available methods.[3] We have recently reported a new synthetic method for simple coumarins using the Wittig reaction of salicylaldehyde with carbethoxymethylenetriphenylphosphorane in *N,N*-diethylaniline under reflux.[4] In order to examine the generality of the method, we planned to apply the method to synthesis of a natural coumarin, 5,8-dimethoxycoumarin (**1**), isolated by one of authors (W. Döpke) and his colleagues from *Artemisia carvifolia* WALL.[5] This compound is very interesting structurally because 5,8-dioxygenated coumarins are unusual.[6] There are several publications[7] concerning synthesis of **1**, in which it is reported that its melting point was 138 °C,[7a] 138—140 °C,[7b] and 133—135 °C,[7c] being in conflict with mp 118—120 °C reported for the natural coumarin.[5] Thus, for the purpose of structural confirmation by synthesizing **1**, we designed the retrosynthetic strategy shown in Chart 1, involving two new methods developed by us, *i.e.*, coumarin synthesis by the Wittig reaction of salicylaldehyde[4] and salicylaldehyde synthesis *via* CsF-mediated Claisen rearrangement of an aryl propargyl ether, followed by oxidative cleavage of a benzofuran[8] (see Chart 2). The latter would be suitable for synthesizing aromatic compounds having four successive substituents such as salicylaldehyde (**2**).

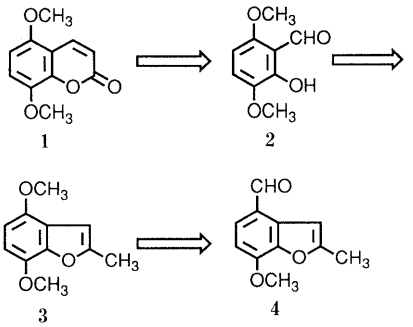

Chart 1

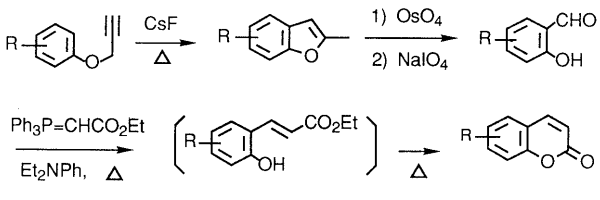

Chart 2

Our approach started with Baeyer-Villiger oxidation of 4-formyl-7-methoxy-2-methylbenzofuran (**4**),[9] which was used an intermediate for synthesis of chelerythrine.[10] Thus, Baeyer-Villiger oxidation[11] of **4** with 30% hydrogen peroxide and selenium dioxide in methylene chloride, followed by alkaline hydrolysis afforded the phenol (**5**) in 73.8% yield. Methylation of **5** with dimethyl sulfate and potassium carbonate in dimethylformamide (DMF) gave the methyl ether (**3**) in 91.9% yield. Then, an attempt was made to prepare **2** from **3** by oxidative cleavage of the furan ring.[8] Successive treatment of **3** with osmium tetroxide in pyridine and sodium hydrogen sulfite solution provided the diol (**6**) in 69.4% yield. Compound **6** appears to exist as a keto-phenol form (**6A**) in a chloroform solution, because **6** showed the absorption band due to the ketone group at 1722 cm^{-1} in its infrared (IR) spectrum and the signal due to the methyl ketone group at δ 2.08 in its proton-nuclear magnetic resonance (^{1}H-NMR) spectrum. Reaction of **6** with sodium metaperiodate and hydrolysis with ethanolic 1% sodium hydrogen carbonate solution gave **2**[12,13] in 61.5% yield. Finally, coumarin ring formation of **2** with carbethoxymethylenetriphenylphosphorane in *N,N*-diethylaniline under gentle reflux[4] for 30 min afforded a synthetic coumarin (**1**), mp 141.5—142.5 °C, in 90.5% yield. However, the synthetic coumarin (**1**) was not identical with the natural coumarin, mp 118—120 °C, on the basis of a comparison of their melting points, IR spectra, and ^{1}H-NMR spectra. The synthetic coumarin (**1**) showed in its ^{1}H-NMR spec-

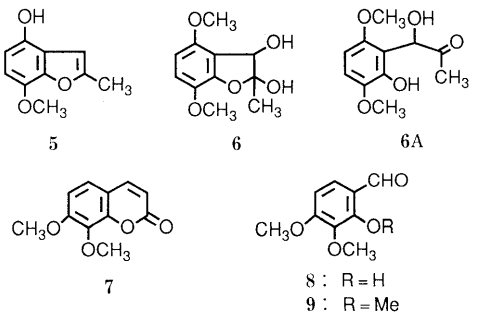

Chart 3

trum (500 MHz) the signal due to C_4-H at δ 8.06 (d, J= 9.8 Hz), whereas the natural coumarin showed the signal due to C_4-H at δ 7.62 (d, J=9.4 Hz). Since it is known that C_4-H usually appears in the δ 7.58 to δ 7.70 region when there is no methoxy group at C_5,[14] it can be concluded that the structure of the natural coumarin should be 7,8-dimethoxycoumarin (**7**) by taking into account the ^{1}H-NMR signals due to two aromatic protons with *ortho* coupling [δ 6.84 and 7.16 (each d, J=8.7 Hz)].[5]

Compound **7** has been synthesized by methylation of daphnetin (7,8-dihydroxycoumarin) or its derivatives.[15] So we attempted to synthesize directly **7** from 2-hydroxy-3,4-dimethoxybenzaldehyde (**8**)[16] by our method using the Wittig reaction in diethylaniline. Compound **8** was prepared from 2,3,4-trimethoxybenzaldehyde (**9**) by selective demethylation with boron trichloride in methylene chloride in 86.8% yield.[17] Reaction of **8** with Wittig reagent in *N*,*N*-diethylaniline for 1.25 h under gentle reflux[4] gave **7**, mp 119.5—120.5 °C, in 91.0% yield, which was identical with the natural coumarin isolated from *Artemisia carvifolia* on the basis of IR and ^{1}H-NMR spectral comparison.

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 Hitachi 215 spectrometer, and ^{1}H-NMR spectra in deuteriochloroform on Hitachi R-24B (60 MHz) and/or JEOL GSX-500A (500 MHz) spectrometers, unless otherwise noted. The NMR data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0) and coupling constants in hertz. Mass spectra (MS) were taken on a JEOL JMS-HX110A instrument (direct inlet) at 70 eV. Column chromatography was carried out on silica gel (Merck, Silica gel 60, No. 7734) or Florisil (Nacalai Tesque Inc., 100—200 mesh). In general, the extract was dried over anhydrous magnesium sulfate, then filtered, and the filtrate was evaporated to dryness under reduced pressure.

4-Hydroxy-7-methoxy-2-methylbenzo[*b*]furan (5) 4-Formyl-7-methoxy-2-methylbenzo[*b*]furan (**4**, 4.003 g, 21.03 mmol) was dissolved in CH_2Cl_2, and selenium dioxide (256.7 mg, 2.31 mmol) and 30% H_2O_2 (7.10 ml, 69.41 mmol) were added under ice-cooling. The mixture was stirred vigorously at room temperature for 4 d. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The extracts were washed with aqueous 10% $NaHSO_3$ solution, aqueous 5% $NaHCO_3$ solution and brine. The residue was dissolved in MeOH (50 ml) and a solution of KOH (1.2 g, 21.45 mmol) in MeOH (50 ml) was added. The mixture was stirred for 5 min under an argon atmosphere and concentrated to dryness under reduced pressure. The residue was diluted with water and made acidic with 5% HCl, then extracted with CH_2Cl_2. The residue in benzene was chromatographed on Florisil (30 g). Elution with the same solvent gave **5** (2.767 g, 73.8% yield), mp 98.5—100.5 °C (colorless needles from ether–hexane). IR: 3250 cm^{-1}. ^{1}H-NMR (60 MHz): 2.44 (3H, s, CH_3), 3.94 (3H, s, OCH_3), 5.20 (1H, br s, O<u>H</u>, disappeared on addition of D_2O), 6.40 (1H, br s, C_3-H), 6.50 (2H, s, arom. protons). *Anal.* Calcd for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.29; H, 5.62.

4,7-Dimethoxy-2-methylbenzo[*b*]furan (3) A mixture of **4** (1.350 g, 7.58 mmol) and K_2CO_3 (6.285 g, 45.48 mmol) in DMF (48.4 ml) was stirred at room temperature for 10 min and dimethyl sulfate (1.08 ml, 11.41 mmol) was added, then stirring was continued for 30 min under an argon atmosphere. The reaction mixture was diluted with water and extracted with hexane. The extract was washed with aqueous 5% NH_4OH solution and brine. The residue in $CHCl_3$–hexane (1 : 4) was chromatographed on silica gel (30 g). Elution with the same solvent afforded **3** (1.338 g, 91.9% yield), mp 57.5—58.5 °C, (colorless needles from hexane). IR: 1600 cm^{-1}. ^{1}H-NMR (60 MHz): 2.46 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.43 (1H, d, J=8 Hz, arom. proton), 6.46 (1H, s, C_3-H), 6.68 (1H, d, J=8 Hz, arom. proton). *Anal.* Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.85; H, 6.10.

2,3-Dihydro-2,3-dihydroxy-4,7-dimethoxy-2-methylbenzo[*b*]furan (6) A solution of **3** (630 mg, 3.28 mmol) and osmium tetroxide (1 g, 3.93 mmol) in pyridine (12 ml) was stirred at room temperature for 1 h. A solution of $NaHSO_3$ (1.54 g, 8.66 mmol, calculated as 58% $NaHSO_3$) in H_2O (23 ml) and pyridine (16 ml) was added to the reaction mixture and the whole was stirred at room temperature for 1 h, then diluted with water and extracted with AcOEt. The extract was thoroughly washed with saturated $CuSO_4$ solution and brine. The residue in AcOEt–benzene (1 : 4) was chromatographed on silica gel (15 g). Elution with the same solvent gave **6** (514.2 mg, 69.4% yield). IR ($CHCl_3$): 3530, 1722 cm^{-1}. ^{1}H-NMR (500 MHz): 2.08 (3H, s, $OCOCH_3$), 3.76 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.11 (1H, d, J=5.9 Hz, CH–O<u>H</u>, disappeared on addition of D_2O), 5.56 (1H, d, J=5.9 Hz, C<u>H</u>–OH, changed to singlet on addition of D_2O), 6.10 (1H, s, Ar-O<u>H</u>, disappeared by adding D_2O), 6.37 (1H, d, J=8.9 Hz, arom. proton), 6.79 (1H, d, J=8.9 Hz, arom. proton). MS m/z: 226 (M^+).

2-Hydroxy-3,6-dimethoxybenzaldehyde (2) Sodium metaperiodate (1.46 g, 6.82 mmol) was added to a solution of **6** (514.2 mg, 2.27 mmol) in methanol (15 ml) and H_2O (5 ml). The reaction mixture was stirred at room temperature for 1 h, then diluted with water and extracted with CH_2Cl_2. Aqueous 1% $NaHCO_3$ solution (27.4 ml) was added to a solution of the residue in EtOH (68 ml) and the mixture was heated for 16 h under reflux. The reaction mixture was diluted with water and made acidic with concentrated HCl and then extracted with CH_2Cl_2. The residue in $CHCl_3$–benzene (1 : 4) was chromatographed on silica gel (15 g). Elution with the same solvent gave **2** (254.8 mg, 61.5% yield), mp 70—71 °C (lit.[12] mp 68—69 °C), (yellow plates from ether–hexane). IR: 1658, 1640, 1603 cm^{-1}. ^{1}H-NMR (60 MHz): 3.85 (6H, s, 2 × OCH_3), 6.29 (1H, d, J=9 Hz, arom. proton), 7.06 (1H, d, J=9 Hz, arom. proton), 10.28 (1H, s, CHO), 12.14 (1H, s, Ar-O<u>H</u>). *Anal.* Calcd for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.18; H, 5.42.

5,8-Dimethoxycoumarin (1) A solution of **2** (0.3 g, 1.65 mmol) and carbethoxymethylenetriphenylphosphorane (0.69 g, 1.98 mmol) in *N*,*N*-diethylaniline (12 ml) was heated at 215 °C for 30 min under an argon atmosphere. The reaction mixture was diluted with water and extracted with ether. The extract was thoroughly washed with aqueous 5% HCl solution and brine. The residue in benzene–AcOEt (15 : 1) was subjected to chromatography on silica gel (30 g). Elution with the same solvent gave **1** (0.307 g, 90.5% yield), mp 141.5—142.5 °C (lit. mp 138 °C,[7a] 138—140 °C,[7b] 133—135 °C,[7c]), (yellow prisms from AcOEt). IR (KBr): 1760 (sh), 1730, 1603 cm^{-1}. ^{1}H-NMR (500 MHz): 3.88 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 6.35 (1H, d, J=9.8 Hz, C_3-H), 6.61 (1H, d, J=8.8 Hz, arom. proton), 7.01 (1H, d, J=8.8 Hz, arom. proton), 8.06 (1H, d, J=9.8 Hz, C_4-H). *Anal.* Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.14; H, 4.71.

2-Hydroxy-3,4-dimethoxybenzaldehyde (8) Boron trichloride (2.9 ml, 33.9 mmol) was added to a stirred solution of 2,3,4-trimethoxybenzaldehyde (**9**) (2.2 g, 11.2 mmol) in absolute CH_2Cl_2 (75 ml) at −78 °C. After 4 h, additional boron reagent (1 ml, 11.7 mmol) was added at −30 °C, and the mixture was stirred at the same temperature for a further 1 h. The reaction mixture was carefully poured into ice-water with stirring, and then extracted with CH_2Cl_2. The organic layer was extracted with aqueous 5% NaOH solution. The alkaline layer was made acidic with 10% HCl and extracted with ether. The residue in benzene–AcOEt (8 : 1) was chromatographed on silica gel (40 g). Elution with the same solvent afforded **8** (1.771 g, 86.8% yield), mp 73—74 °C (lit.[16] mp 70—72 °C) (pale yellow needles from hexane–ether). IR: 1650 cm^{-1}. ^{1}H-NMR (60 MHz): 3.92 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 6.62 (1H, d, J=9 Hz, arom. proton), 7.31 (1H, d, J=9 Hz, arom. proton), 9.79 (1H, s, CHO), 11.12 (1H, s, Ar-O<u>H</u>, disappeared upon addition of D_2O). *Anal.* Calcd for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.50; H, 5.56.

7,8-Dimethoxycoumarin (7) A solution of **8** (0.3 g, 1.65 mmol) and carbethoxymethylenetriphenylphosphorane (0.69 g, 1.98 mmol) in *N*,*N*-diethylaniline (12 ml) was heated at 215 °C for 1.25 h under an argon atmosphere. The reaction mixture was diluted with water and extracted with ether. The extract was thoroughly washed with aqueous 5% HCl solution and brine. The residue in benzene–AcOEt (2 : 1) was chromatographed on silica gel (30 g). Elution with the same solvent afforded **7** (0.31 g, 91.0% yield), mp 119.5—120.5 °C (lit. mp 117—119 °C,[15a] 118—119 °C,[15b,c]), (colorless plates from AcOEt). IR (KBr): 1730, 1608 cm^{-1}. ^{1}H-NMR (500 MHz): 3.96 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 6.26 (1H, d, J=9.5 Hz, C_3-H), 6.87 (1H, d, J=8.8 Hz, arom. proton), 7.17 (1H, d, J=8.8 Hz, arom. proton), 7.62 (1H, d, J=9.5 Hz, C_4-H). *Anal.* Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.97; H, 4.94.

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References and Notes

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