Articles

Total Synthesis of Coriandrin

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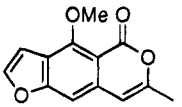
Coriandrin, an antiviral agent, has been synthesized in nine steps from diketone **3**. The key steps in the synthesis include an efficient aromatization reaction using *N*-bromosuccinimide and a palladium-mediated coupling of a benzylic bromide with a vinyl stannane.

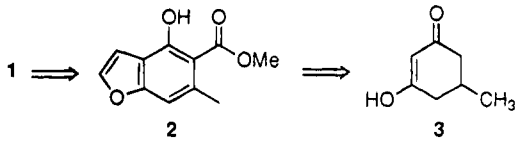
Coriandrin (**1**) is a novel furoisocoumarin isolated from *Coriandrum sativum L.* in 1988.[1] It is structurally related to the psoralens, some members of which are therapeutically useful in the treatment of skin diseases.



1

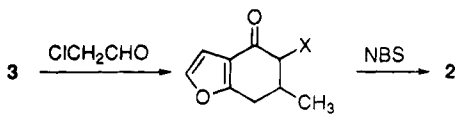
Recently, Hudson and co-workers reported that **1** exhibits UVA-dependent antiviral activity against a variety of enveloped viruses. Notably, it showed in vitro activity against HIV-1.[2] In the context of our continuing interest in the synthesis of novel antiviral agents, we report herein the first synthesis of coriandrin.

A retrosynthetic analysis is depicted below. The key intermediate in our synthesis was ester **2**. We felt that



2 **3**

the lactone ring might be appended by use of standard carbanion chemistry. The synthesis of **2** was straightforward and commenced with a furan synthesis reported by Hammond.[3] Commercially available diketone **3** was treated with chloroacetaldehyde to produce furan **4** in 86% yield. Ketone **4** could not be converted into a β-keto

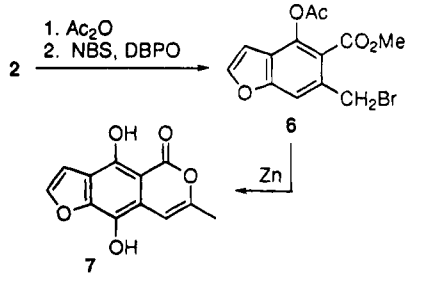


4: X = H
5: X = CO_2Me

ester using dimethyl carbonate and base. Fortunately, using the cyanoformate methodology developed by Mander,[4] we were able to produce keto ester **5** in 82% isolated yield. The resulting tetrahydrobenzofuran could be conveniently aromatized in 68% yield using NBS in hot carbon tetrachloride, a procedure that we had previously employed for a synthesis of pachybasin.[5]

With gram quantities of ester **2** in hand, the construction of the lactone ring was investigated. Unexpectedly, the attempted generation of the dianion[6] of **2** using 2 equiv of lithium diisopropylamide (LDA) in either THF or THF/HMPA followed by reaction with acetaldehyde or acetic anhydride failed to produce the desired adducts. When the reaction was conducted at −78 or −40 °C, only starting ester **2** was recovered. When the reaction was performed at 0 °C, the main product appeared to be derived from deprotonation of the furan subunit.

We next synthesized benzylic bromide **6** in quantitative yield from **2** by acetylation of the phenol with acetic anhydride followed by benzylic bromination with NBS and dibenzoyl peroxide. Initially, we had anticipated that a Reformatsky reaction with acetaldehyde would provide a useful intermediate. After several unsuccessful experiments, we concluded that the phenolic acetate in **6** might be an appropriate electrophile. The reaction of **6** with activated zinc generated a new compound in low yield. However, it was not the desired keto ester. On the basis of NMR, IR, and mass spectrometry, it appeared to be hydroquinone **7**. This compound might have been produced by a sequence involving (1) an intermolecular Reformatsky reaction, (2) cyclization to afford the isocumarin, and (3) oxidation of the phenolate anion to a hydroquinone.



6 **7**

Although substitution of the benzylic bromide using an acyl carbanion equivalent had good literature precedent, the reaction of bromide **6** with either 2-lithio-1,3-

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(1) Ceska, O.; Chaudary, S. K.; Warrington, P.; Ashwood-Smith, M. J.; Bushnell, G. W.; Poulton, G. A. *Photochem. Photobiol.* **1988**, *27*, 2083.

(2) Hudson, J. B.; Graham, E. A.; Harris, L.; Ashwood-Smith, M. J. *Photochem. Photobiol.* **1993**, *57*, 491.

(3) Zambias, R. A.; Caldwell, C. G.; Kopka, I. E.; Hammond, M. L. *J. Org. Chem.* **1988**, *53*, 4135.

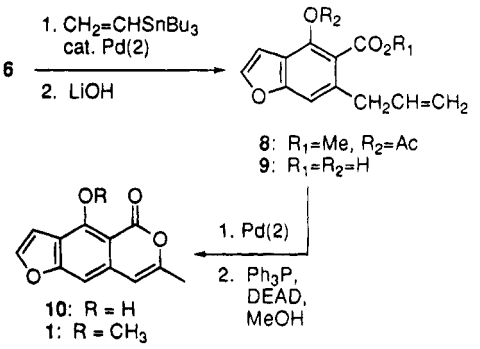
(4) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

(5) Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh S. *J. Org. Chem.* **1983**, *48*, 3439.

(6) Evans, G. E.; Leeper, F. J.; Murphy, J. A.; Staunton, J. *J. Chem. Soc., Chem. Commun.* **1979**, 205.

0022-3263/94/1959-4735$04.50/0

dithiane or the cuprate dervied from lithiated ethyl vinyl ether[7] returned recovered **6**. However, a palladium-mediated coupling procedure developed by Stille using tributylvinylstannane and a catalytic amount of a palladium(II) salt afforded an 87% yield of ester **8**.[8] Hydrolysis of **8** using 20 equiv of LiOH in aqueous THF furnished carboxylic acid **9** in 75% yield. Cyclization of the olefinic acid **9** with palladium chloride–bis(acetonitrile) complex using the method of Hegedus provided **10** in 69% yield.[9] Phenol **10** was resistant to standard methylation conditions using NaH and methyl iodide in DMF. However, a Mitsunobu procedure[10] using triphenylphosphine, diethyl azodicarboxylate (DEAD), and methanol cleanly produced coriandrin (**1**) in 89% yield. The NMR and IR spectra of the compound produced by our synthetic route were identical to the spectrum of coriandrin reported in the literature.[1]



Coriandrin (**1**) has been synthesized in nine steps from diketone **3**. Our synthesis provides a flexible and reasonably direct route to the furoisocoumarin skeleton. In addition to providing quantities of **1** for antiviral testing, this synthesis makes available compounds **7** and **10** which may also be novel antiviral agents.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes:ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (sgc). The purity of all title compounds was determined to be >95% by 300-MHz proton NMR.

6-Methyl-4,5,6,7-tetrahydrobenzofuran-4-one (4). To 0.85 g (6.74 mmol) of **3** in 10 mL of H_2O at 0 °C were added 0.47 g (8.425 mmol) of KOH in 10 mL of H_2O at a rate in which the solution temperature remained below 10 °C. After KOH addition, 0.22 g (1.35 mmol) of KI was added followed by the dropwise addition of 2.22 g (14.15 mmol) of $ClCH_2CHO$. The ice bath was removed and the reaction was stirred at rt for 12 h. The reaction mixture was neutralized with 2 N HCl, extracted with $CHCl_3$ (3 × 60 mL), dried over Na_2SO_4, and concentrated in vacuo. Sgc purification with 5:1 H:EA afforded 0.87 g (86% yield) of pure **4**.

4: NMR ($CDCl_3$) δ 7.32 (d, J = 1.8 Hz, 1 H), 6.60 (d, J = 1.8 Hz, 1 H), 2.97 (dd, J = 4.5, 16.5 Hz, 2 H), 2.59–2.20 (m, 3 H), 1.18 (d, J = 6.3 Hz, 3 H); IR ($CDCl_3$) 2959, 1680, 753 cm^{-1}; MS m/e 150, 108, 80, 52, 39; TLC (5:1 H:EA) R_f = 0.37.

Methyl 4-Oxo-6-methyl-4,5,6,7-tetrahydrobenzofuran-5-carboxylate (5). To a solution of LDA (11.9 mmol) in 20 mL of dry THF at −78 °C was added 1.5 g (9.99 mmol) of **4** in 20 mL of dry THF. The solution was stirred for 1 h at 0 °C and then recooled to −78 °C; 3.43 g (20.18 mmol) of HMPA was added and stirring was continued for 45 min. Then 1.78 g (20.98 mmol) of methyl cyanoformate was added. The solution was stirred for 10 min. After the addition of 100 mL of H_2O, the solution was extracted with ether (3 × 40 mL), dried over Na_2SO_4, and concentrated in vacuo, and sgc purification wtih 7:1 H:EA gave 1.70 g (82% yield) of **5**.

5: NMR ($CDCl_3$) δ 7.33 (d, J = 1.5 Hz, 1 H), 6.67 (d, J = 1.8 Hz, 1 H), 3.80 (s, 3 H), 3.26 (d, J = 10.5 Hz, 1 H), 2.85 (m, 1 H), 2.63 (dd, J = 17.1, 9.6 Hz, 2 H), 1.24 (d, J = 6.9 Hz, 3 H); IR ($CDCl_3$) 2934, 1743, 1682, 1201 cm^{-1}; MS m/e 208, 176, 148, 108, 80, 52; TLC (5:1 H:EA) R_f = 0.47.

Methyl 4-Hydroxy-6-methylbenzofuran-5-carboxylate (2). To 1.25 g (6.01 mmol) of **5** in 50 mL of CCl_4 were added 1.60 g (9.01 mmol) of NBS and 0.029 g (0.12 mmol) of dibenzoyl peroxide. The mixture was stirred at 120 °C for 20 h, cooled to rt, filtered, and concentrated in vacuo. Purification by sgc with 10:1 H:EA afforded 0.84 g (68% yield) of pure **2**.

2: NMR ($CDCl_3$) δ 7.49 (d, J = 2.1 Hz, 1 H), 6.91 (d, J = 1.8 Hz, 1 H), 6.89 (s, 1 H), 3.98 (s, 3 H), 2.63 (s, 3 H); IR ($CDCl_3$) 1662, 1442, 1379 cm^{-1}; MS m/e 206, 174, 145, 118, 89, 63; TLC (5:1 H:EA) R_f = 0.33.

Methyl 4-Acetoxy-6-(bromomethyl)benzofuran-5-carboxylate (6). To 0.750 g (5.06 mmol) of **2** in 20 mL of Ac_2O was added 0.55 g (5.57 mmol) of KOAc. The mixture was stirred at 120 °C for 12 h, cooled to rt, diluted with 50 mL of 2 N NaOH, and extracted with ether (3 × 60 mL). The organic layer was dried over Na_2SO_4, concentrated in vacuo, and purified by sgc with 10:1 H:EA to give 1.24 g (100% yield) of the acetate of **2** (NMR ($CDCl_3$) δ 7.56 (d, J = 2.1 Hz, 1 H), 6.62 (s, 3 H), 3.90 (s, 3 H), 2.50 (s, 3 H), 2.35 (s, 3 H); IR ($CDCl_3$) 1778, 1727, 1266 cm^{-1}; TLC (5:1 H:EA) R_f = 0.51).

To 0.55 g (2.217 mmol) of the above acetate in 25 mL of CCl_4 were added 0.011 g (0.04 mmol) of benzoyl peroxide and 0.434 g (2.44 mmol) of NBS. The mixture was stirred at 120 °C for 16 h, filtered, and concentrated in vacuo to give a quantitative yield of **6**.

6: NMR ($CDCl_3$) δ 7.67 (d, J = 2.1 Hz, 1 H), 7.49 (s, 1 H), 6.70 (d, J = 1.8 Hz, 1 H), 4.81 (s, 2 H), 3.96 (s, 3 H), 2.37 (s, 3 H); IR ($CDCl_3$) 1778, 1260, 1020 cm^{-1}; TLC (5:1 H:EA) R_f = 0.63.

3-Methyl-5,9-dihydroxyfuroisocumarin (7). To 0.66g (2.02 mmol) of **6** in 20 mL of dry THF was added 0.165 g (2.52 mmol) of activated zinc powder. The reaction was heated to reflux for 6 h. The reaction was cooled, diluted with 10 mL of saturated ammonium chloride, and extracted three times with ether. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by sgc with 6:1 H:EA to afford 0.120 g (32% yield) of hydroquinone **7**.

7: NMR ($CDCl_3$) δ 7.43 (d, J = 0.6 Hz, 1 H), 6.88 (d, J = 0.9 Hz, 1 H), 5.36 (s, 1 H), 2.50 (s, 3 H); IR ($CDCl_3$) 3746, 1777, 1186 cm^{-1}; MS m/e 161, 178, 190, 207, 232; TLC (5:1 H:EA) R_f = 0.21.

Methyl 4-Acetoxy-6-allylbenzofuran-5-carboxylate (8). To 0.97 g (2.96 mmol) of **6** in 2 mL of HMPA were added 0.0157 g (0.021 mmol) of $PhCH_2Pd(PPh_3)_2Cl$ and 1.061 g (3.34 mmol) of tributylvinylstannane in a sealed tube in an air atmosphere. The mixture was stirred at 65 °C for 6 h, diluted with H_2O, and extracted with ether (3 × 20 mL). The combined organic layers were washed with H_2O and dried over Na_2SO_4. Ether was removed in vacuo, and the product was diluted with CH_3CN (25 mL) and washed with hexanes (3 × 10 mL). CH_3CN was removed in vacuo, affording 0.75 g (92% yield) of **8**. This material was sufficiently pure for the next step. Further purification by sgc resulted in an isolated yield of 87%.

8: NMR ($CDCl_3$) δ 7.60 (d, J = 2.1 Hz, 1 H), 7.31 (s, 1 H), 6.64 (d, J = 1.8 Hz, 1 H), 5.96 (m, 1 H), 5.11 (dd, J = 1.5, 7.8 Hz, 2 H), 3.89 (s, 3 H), 3.60 (d, J = 6.6 Hz, 2 H), 2.35 (s, 3 H); TLC (5:1 H:EA) R_f = 0.73.

4-Hydroxy-6-allylbenzofuran-5-carboxylic Acid (9). To 0.48 g (1.75 mmol) of **8** in 4.5 mL of THF, 4.5 mL MeOH, and 2.25 mL of H_2O was added 1.47 g (35.04 mmol) of $LiOH·H_2O$. The mixture was stirred at 70 °C for 40 h. The solution was acidified with 2 N HCl, extracted with ether (3 × 20 mL), and dried over Na_2SO_4. Ether was removed in vacuo to give 0.29 g (75% yield) of **9**.

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(8) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992.
(9) Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329.
(10) Mitsunobu, O. *Synthesis* **1981**, 1.

9: NMR ($CDCl_3$) δ 9.75 (bs, 1 H), 7.52 (d, J = 1.8 Hz, 1 H), 6.98 (s, 1 H), 6.94 (d, J = 1.8 Hz, 1 H), 6.09 (m, 1 H), 5.07 (dd, J = 5.4, 4.2 Hz, 2 H), 3.88 (d, J = 6.3 Hz, 2 H); IR ($CDCl_3$) 2979, 1651, 907 cm^{-1}; MS m/e 218, 200, 174, 115, 89; ^{13}C NMR ($CDCl_3$) δ 175.9, 159.7, 158.9, 143.9, 140.9, 137.7, 115.8, 115.7, 107.2, 106.7, 104.9, 40.6; TLC (5:1 H:EA) R_f = 0.43.

3-Methyl-9-hydroxyfuroisocoumarin (10). To 0.12 g (0.547 mmol) of **9** in 6 mL of dry THF were added 0.084 g (0.793 mmol) of Na_2CO_3 and 0.142 g (0.548 mmol) of $Pd(CH_3CN)_2Cl_2$. The solution was stirred at rt for 4 h, 20 mL of H_2O was added, and the solution was extracted with ether (3 × 20 mL) and dried over Na_2SO_4. After the ether was removed in vacuo, purification by sgc with 8:1 H:EA afforded 0.08 g (69%) of **10**.

10: NMR ($CDCl_3$) δ 7.58 (d, J = 1.8 Hz, 1 H), 7.00 (d, J = 1.8 Hz, 1 H), 6.93 (s, 1 H), 6.31 (s, 1 H), 2.28 (s, 3 H); IR ($CDCl_3$) 1684, 1194, 908 cm^{-1}; MS m/e 216, 174, 145, 89, 43; ^{13}C NMR ($CDCl_3$) δ 167.5, 157.3, 152.3, 146.2, 146.0, 143.4, 134.2, 106.0, 103.6, 99.6, 97.8, 20.1; TLC (5:1 H:EA) R_f = 0.67.

Coriandrin (1). To 0.02 g (0.093 mmol) of **10** in 1 mL of dry THF at 0 °C were added 0.0045 g (0.14 mmol) of MeOH, 0.02 g (0.11 mmol) of DEAD, and 0.29 g (1.11 mmol) of Ph_3P. The solution was allowed to slowly reach rt with stirring for 6 h. The reaction was then diluted with 30% H_2O_2 (2 mL) and 20 mL of ether. The ether/H_2O_2 solution was washed with 20% $NaHSO_3$ (3 × 5 mL), 2 N NaOH (3 × 5 mL), and brine (1 × 10 mL), dried over Na_2SO_4, concentrated in vacuo, and purified by sgc with 3:1 H:EA to give 0.019 g (89% yield) of **1**.

1: NMR ($CDCl_3$) δ 7.60 (d, J = 2.1 Hz, 1 H), 7.10 (s, 1 H), 7.06 (d, J = 1.5 Hz, 1 H), 6.22 (s, 1 H), 4.23 (s, 3 H), 2.50 (s, 3 H); IR ($CDCl_3$) 1723, 1380, 1118 cm^{-1}; MS m/e 230, 201, 159, 129, 43; ^{13}C NMR ($CDCl_3$) δ 157.0, 145.2, 144.0, 136.3, 105.9, 105.7, 105.0, 103.6, 103.1, 101.5, 100.7, 65.9, 14.4; TLC (5:1 H:EA) R_f = 0.28.

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Supplementary Material Available: Copies of ^1H NMR spectra of **1**, **2**, **4–6**, and **8–10** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.