Total Synthesis of Coriandrin

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Abstract
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.

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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.

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 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 ester using dimethyl carbonate and base. Fortunately, using the cyanoformaldehyde 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 of 2 using 2 equiv of lithium disopropylamide (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 benzoyl 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 isocoumarin, and (3) oxidation of the phenolate anion to a hydroquinone.

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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This synthesis made available compounds commercial suppliers and were used without purification. h. The reaction mixture was neutralized with 2 N HCl, Hz, 1 H), 2.97 (dd, J = 208.98 mmol of methyl cyanoforate was added. The solution was stirred for 10 min. After the addition of 100 mL of H2O, the solution was extracted with ether (3 × 40 mL), dried over Na2SO4, and concentrated in vacuo, and sgc purification with 7:1 H:EA gave 1.70 g (82% yield) of 6.

5: NMR (CDCl3) 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), 2.65 (m, 1 H), 2.63 (dd, J = 17.1, 9.6 Hz, 2 H), 1.24 (d, J = 6.9 Hz, 3 H); IR (CDCl3) 2934, 1743, 1682, 1201 cm⁻¹; MS m/e 208, 176, 145, 118, 89, 63; TLC (5:1 H:EA) Rf = 0.47.

Methyl 4-Hydroxy-6-methylbenzofuran-5-carboxylate (2). To 1.25 g (6.01 mmol) of 8 in 50 mL of CCl4 were added 1.60 g (9.01 mmol) of NBS and 0.026 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 (CDCl3) 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 (CDCl3) 1652, 1442, 1379 cm⁻¹; MS m/e 206, 174, 145, 118, 89, 63; TLC (5:1 H:EA) Rf = 0.33.

Methyl 4-Acetoxy-6-(bromomethyl)benzofuran-5-carboxylate (6). To 0.750 g (5.06 mmol) of 2 in 20 mL of Ac2O 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 washed with Na2SO4, concentrated in vacuo, and purified by sgc with 10:1 H:EA to give 1.24 g (100% yield) of the acetoate of 2 (NMR (CDCl3) 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 (CDCl3) 1773, 1727, 1286 cm⁻¹; TLC (5:1 H:EA) Rf = 0.51).

To 0.55 g (2.217 mmol) of the above acetate in 25 mL of CCl4 were added 0.011 g (0.04 mmol) of benzoyl peroxide and 0.434 g (2.44 mmol) of activated zinc powder. The reaction was stirred at 120 °C for 16 h, filtered, and concentrated in vacuo to give a quantitative yield of 6.

8: NMR (CDCl3) 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), 2.77 (s, 3 H); IR (CDCl3) 1778, 1260, 1020 cm⁻¹; TLC (5:1 H:EA) Rf = 0.83.

3-Methyl-5,9-dihydroxyfuroisoumarin (7). To 0.66 g (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 washed with 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 (CDCl3) 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 (CDCl3) 3746, 1777, 1186 cm⁻¹; MS m/e 161, 178, 190, 207, 232; TLC (5:1 H:EA) Rf = 0.21.

Methyl 4-Acetoxy-6-allylbenzofuran-5-carboxylate (8). To 0.97 g (2.96 mmol) of 7 in 2 mL of HMFA were added 0.0157 g (0.021 mmol of PhCHOCH2Pd(PPh3)2Cl) and 1.061 g (3.34 mmol) of tributylinylstannane and a catalytic amount of a palladium(I1) salt afforded an 87% yield of ester Hy-

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.

-5-tetrahydrobenzofuran-4-one (4). To 0.85 g (6.74 mmol) of 3 in 10 mL of H2O at 0 °C were added 0.47 g (8.425 mmol) of KOH in 10 mL of H2O 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 CI2CHO. The ice bath was removed and the reaction was stirred for rt for 12 h. The reaction mixture was neutralized with 2 N HCl, extracted with CH2Cl2 (3 × 60 mL), dried over Na2SO4, and concentrated in vacuo. Sgc purification with 5:1 H:EA afforded an 87% yield of ester 8. Hy-
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9: NMR (CDCl₃) 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 (CDCl₃) 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) Rₚ = 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 Na₂CO₃ and 0.142 g (0.548 mmol) of Pd(CH₃-CN)₂Cl₂. The solution was stirred at rt for 4 h, 20 mL of H₂O was added, and the solution was extracted with ether (3 × 20 mL) and dried over Na₂SO₄. After the ether was removed in vacuo, purification by sgc with 8:1 H:EA afforded 0.08 g (69%) of 10.

10: NMR (CDCl₃) 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 (CDCl₃) 1684, 1194, 908 cm⁻¹; MS m/e 216, 174, 145, 89, 43; ¹³C NMR (CDCl₃) 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) Rₚ = 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 Ph₃P. The solution was allowed to slowly reach rt with stirring for 6 h. The reaction was then diluted with 30% H₂O₂ (2 mL) and 20 mL of ether. The ether/H₂O₂ solution was washed with 20% NaHSO₃ (3 × 5 mL), 2 N NaOH (3 × 5 mL), and brine (1 × 10 mL), dried over Na₂SO₄, concentrated in vacuo, and purified by sgc with 3:1 H:EA to give 0.019 g (89% yield) of 1.

1: NMR (CDCl₃) 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 (CDCl₃) 1723, 1380, 1118 cm⁻¹; MS m/e 230, 201, 159, 129, 43; ¹³C NMR (CDCl₃) 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) Rₚ = 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.