APPLICATION OF FURAN OXIDATIONS IN SYNTHESIS: TOTAL SYNTHESIS OF (±)-CORIOLIC ACID

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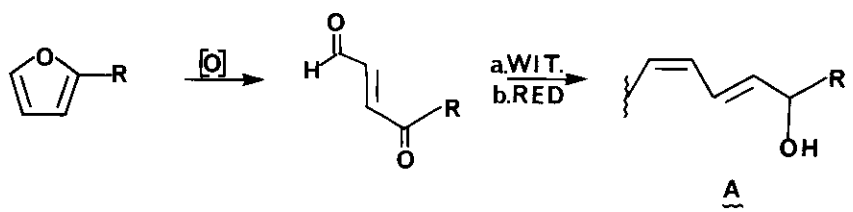
Abstract - As a general synthetic approach to compounds containing the cis-trans allylhydroxy functionality (subunit **A**), an appropriately substituted furan nucleus is oxidatively cleaved to provide an unsaturated 1,4-dicarbonyl moiety suitably disposed for further elaboration. The total synthesis of (±)- coriolic acid demonstrates the utility of the approach.

A number of different groups of oxygenated unsaturated long chain fatty acids[1] have as a common structural feature the cis-trans allylhydroxy functionality as depicted in **A**. Coriolic acid[2] **1** is one such C18 unsaturated acid. It exhibits an interesting calcium specific ionophore activity[3] and also has been isolated from the resistant cultivation of the rice plant (Oryza Sativa L.) which has been demonstrated to operate as a self-defense substance against rice blast disease.[4] A recent report by Rama Rao[5] and co-workers delineating a rather elaborate approach to coriolic acid, prompts us to disclose a facile synthesis of this compound based upon a strategy developed in our laboratories designed specifically for the efficient construction of the subunit **A**.

Our approach to the problem is depicted in Scheme I. We envisioned that the latent 1,4-dicarbonyl nature of the furan nucleus could be successfully exploited to our advantage. Thus, an oxidative ring opening of a suitably substituted furan nucleus would provide a differentiated 1,4-dicarbonyl compound. The resulting keto-aldehyde would then be amenable to further elaboration via a cis-selective Wittig olefination. Finally, a reduction of the ketone carbonyl would provide subunit A.

SCHEME I

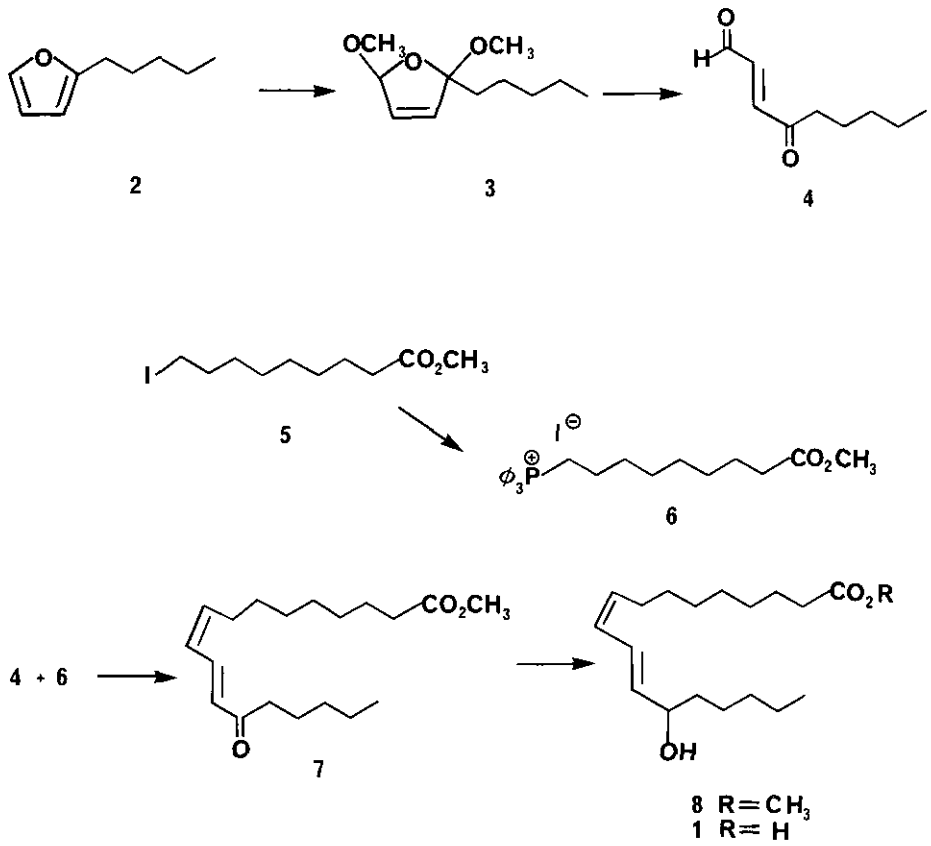


A

Our synthetic strategy is outlined in Scheme II. Our approach involved the synthesis of two convergent pieces obtained from dissecting **1** between the C9 and C10 cis olefinic bond. The synthesis began with the alkylation[6] of furan with 1-iodopentane to afford 2-pentylfuran **2** in 70% yield. Treatment of **2** with bromine in methanol[7] smoothly gave a 2:1 cis/trans mixture[8] of the dimethoxy compound **3** in 86% isolated yield. Treatment of **3** with a crystal of p-toluenesulfonic acid in 1:1 acetonitrile/water smoothly afforded the cis ene-dione which was isomerized directly to the trans compound **4** by exposure to iodine in ether in 93% yield over two steps.[9]

The preparation of the phosphonium salt **6** was accomplished in a very straightforward manner from commercially available 9-bromononanoic acid.[10] Esterification with diazomethane followed by halogen exchange with sodium iodide in refluxing acetone gave iodide **5** in 90% yield. The phosphonium salt **6** was prepared by refluxing one equivalent of **5** with 1.1 equivalents of triphenylphosphine in acetonitrile for 36 h in essentially quantitative yield.

SCHEME II



The stage was now set for the olefination reaction. In the event, a THF solution of 1.0 equivalents of ene-dione **4** was added to a preformed THF solution of the potassium t-butoxide generated ylide derived from 1.0 equivalents of phosphonium salt **6** at 0°C to give the unsaturated ketone **7** in 45% yield. Reduction of **7** with sodium borohydride in methanol gave **8** in 70% yield. Treatment of **8** with aqueous lithium hydroxide quantitatively gave (±)-coriolic acid **1** (9 steps, 16% overall yield).

The advantages of this strategy for synthesis of compounds containing subunit **A** are four-fold: 1) the approach is flexible and generality is realized simply by appending the appropriate side chain to the furan starting material; 2) the procedure is operationally simple and easily amenable to scale-up; 3) the synthesis is convergent; 4) there are several options available to effect the furan oxidation.[11] The scope of this methodology is under active investigation and several applications in the field of eicosanoid natural products will be forthcoming.[12,13]

EXPERIMENTAL

IR spectra were taken with a Perkin-Elmer 283B infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a General Electric QE-300 NMR apparatus at 300 and 75.48 MHz, respectively, using TMS as an internal standard. Mass spectra were recorded with an HP5985A spectrometer and high resolution mass spectra were obtained on a Kratos MS50 instrument. Merck TLC plates were used for analytical TLC and Merck Kieselgel 60 was used for column chromatography. A 20% ether in pentane chromatography eluting system refers to 20 ml of ether diluted to a 100 ml total volume with pentane.

2-Pentylfuran **2**. A dry round bottom flask under N_2 was charged with THF (50 ml) and furan (15.64 g, 0.23 mol) and cooled to -25°C. To the magnetically stirred solution was added n-butyllithium (15 g (2.5 M in pentane), 0.23 mol) dropwise over 15 min. The resulting yellow suspension was stirred for 1.5 h at -15°C and then allowed to warm to -5°C whereupon a pentane (30 mL) solution of 1-iodopentane (30 mL, 0.23 mol) was added dropwise over 10 min. After allowing to warm to room temperature and stirring for 6 h, the reaction was quenched with sat. NH_4Cl and extracted with pentane (3x100 ml). After drying over $MgSO_4$, distillation at atmospheric pressure afforded 2-pentylfuran **2**, 22.0 g (70%), bp_{760} 152-155°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29 (m, 1H), 6.28 (m, 1H),5.97 (m, 1H), 2.61 (t, J=7.2 Hz, 2H), 1.69-1.58 (m, 2H), 1.4-1.2 (m, 4H), 0.85 (t, J=7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75.48 MHz): δ 156.63, 140.60, 109.99, 104.48, 31.38,

27.94, 27.72, 22.41, 13.99. IR ($CDCl_3$, cm^{-1}): 2955, 2925, 1595, 1505, 1145, 1010. MS: m/e 138; 81 (100), 53 (33).

2-n-Pentyl-2,5-dimethoxy-2,5-dihydrofuran **3.** To a methanol (25 ml) solution of **2** (2.0 g, 14.5 mmol) containing sodium carbonate (6.14 g, 58 mmol) cooled to -15°C was added a methanol (10 ml) solution of bromine (2.3 g, 14.5 mmol) dropwise over 10 min. The bromine color was discharged immediately. After addition of the bromine was complete, the reaction mixture was diluted with water (50 ml) and extracted with ether (3x50 ml). After drying over $MgSO_4$ and concentration in vacuo, chromatography of the residue on silica gel eluting with 20% ether in pentane afforded 2.5 g (86%) of a 2:1 cis/trans mixture of the dimethoxy compound **3.** ^1H NMR ($CDCl_3$, 300 MHz) major isomer: δ 6.05-6.00 (m, 1H), 5.93-5.87 (m, 1H), 5.46 (m, 1H), 3.52 (s, 3H), 3.21 (s, 3H), 1.84-1.72 (m, 2H), 1.35-1.23 (m, 6H), 0.88 (t, J=7 Hz, 3H); minor isomer: δ 6.05-6.00 (m, 1H), 5.93-5.87 (m, 1H), 5.75 (m, 1H), 3.46 (s, 3H), 3.13 (s, 3H), 1.84-1.72 (m, 2H), 1.35-1.23 (m, 6H), 0.88 (t, J=7 Hz, 3H). IR ($CDCl_3$, cm^{-1}): 2955, 2925, 1465, 1370, 1110, 1015. MS: m/e (m-OCH_3) 169, 129 (100), 101 (45), 55 (30). High resolution MS: m/e-OCH_3 169.1233 (calcd for $C_{10}H_{17}O_2$, 169.1228).

Trans-2-nonene-1-al-4-one **4.** To a 1:1 water/acetonitrile (10 ml) solution of **3** (500 mg, 2.5 mmol) under nitrogen at room temperature was added a few crystals of p-toluenesulfonic acid monohydrate. The progress of the reaction was monitored by TLC (30% ether/pentane). After 1.5 h, the yellow solution was extracted with ether (3x50 ml) and the combined organic layers were washed sequentially with sat. sodium bicarbonate (25 ml) and water (25 ml). After drying over $MgSO_4$, the ether solution was concentrated in vacuo to approximately 10-15 ml. A few crystals of iodine were added and the solution was allowed to stand at room temperature for 1 h to effect complete isomerization of the cis-enedione to the trans compound. After washing with sat. sodium thiosulfate (25 ml) and water (25 ml), the ether layer was dried over $MgSO_4$ and concentrated in vacuo. Chromatography on silica gel eluting with 30% ether in pentane afforded 358 mg (93% over two steps) of a yellow low melting solid. This material is unstable at ambient temperature but stores well for months in a -10°C freezer. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.79 (d, J=7 Hz, 1H), 6.88 (d, J=16 Hz, 1H), 6.78 (dd, J=7,16 Hz, 1H), 2.70 (t, J=7 Hz, 2H), 1.68 (quint., J=7 Hz, 2H), 1.40-1.25 (m, 4H), 0.92 (t, J=7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.48 MHz): δ 199.75, 193.07, 144.58, 136.89, 40.81, 30.84, 22.95, 22.01, 13.49. IR ($CDCl_3$, cm^{-1}): 2955, 2925, 2715, 1690, 1620, 980. MS: m/e 154; 125 (25), 98 (23), 83 (30), 70 (32), 55 (100). High resolution MS: m/e 154.1004 (calcd for $C_9H_{14}O_2$, 154.0994).

Methyl-9-iodononanoate **5.** An ether (15 ml) solution of commercially available 9-bromononanoic acid (1.0 g, 4.22 mmol) was esterified with excess diazomethane at 0°C. The crude ester was then refluxed for 1 h in acetone (20 ml) containing sodium iodide (693 mg, 4.64 mmol). After cooling, the acetone was removed in vacuo, the crude product was taken up in water (20 ml) and extracted with ether (2x50 ml) and dried over $MgSO_4$. Chromatography on silica gel eluting with 5% ether in pentane afforded 1.13 g (90% over two steps) of iodide **5.** ^1H NMR ($CDCl_3$, 300 MHz): δ 3.67 (s, 3H), 3.19 (t, J=7 Hz, 2H), 2.31 (t, J=7 Hz, 2H), 1.83 (quint., J=7 Hz, 2H), 1.67-1.55 (m, 2H), 1.45-1.25 (m, 8H). ^{13}C NMR ($CDCl_3$, 75.48 MHz): δ 174.13, 51.40, 33.98, 33.42, 30.34, 28.94, 28.26, 24.81, 7.15 (only 9 peaks observed). IR ($CDCl_3$, cm^{-1}): 2935, 2860, 1735, 1440. MS: m/e 298; 267, 183, 171, 155, 139. High resolution MS: m/e ($m-OCH_3$) 267.0248 (calcd for $C_9H_{16}IO$, 267.0246).

(8-Carboxyoctyl)-triphenylphosphonium iodide, methyl ester **6.** An acetonitrile (20 ml) solution of iodide **5** (1.0 g, 3.36 mmol) and triphenylphosphine (967 mg, 3.69 mmol) were refluxed under nitrogen for 36 h. After cooling, the acetonitrile was removed in vacuo and the product was dissolved in dichloromethane (20 ml) and precipitated by dilution with ether (100 ml) to obtain 1.9 g (97%) of **6** as a clear syrup. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.88-7.78 (m, 9H), 7.77-7.69 (m, 6H), 3.70-3.45 (m, 2H), 3.65 (s, 3H), 2.26 (t, J=7 Hz, 2H), 1.70-1.50 (m, 6H), 1.35-1.20 (m, 6H). MS (FAB+): m/e 433.

Methyl (9Z, 11E)-13-oxo-coriolate **7.** To a THF (10 ml) solution of phosphonium salt **6** (560 mg, 1.0 mmol) at 0°C under N_2 was added potassium t-butoxide (112 mg, 1.0 mmol). The bright orange solution was stirred for 10 min and then a THF (5 ml) solution of ene-dione **4** (154 mg, 1.0 mmol) was added rapidly. The reaction mixture was stirred an additional 5 min and then quenched with sat. ammonium chloride (25 ml). Extraction with ether (2x50 ml), drying over $MgSO_4$ and concentration in vacuo gave a crude product which was chromatographed on silica gel eluting with 20% ether in pentane to afford 139 mg of enone **7** (45%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.49 (ddd, J=1.5, 11, 16 Hz, 1H), 6.21-6.05 (m, 1H), 6.17 (d, J=16 Hz, 1H), 5.95-5.84 (m, 1H), 3.66 (s, 3H), 2.55 (t, J=7 Hz, 2H), 2.35-2.25 (m, 2H), 2.30 (t, J=7 Hz, 2H), 1.68-1.55 (m, 4H), 1.35-1.25 (m, 12H), 0.90 (t, J=7 Hz, 3H). IR ($CDCl_3$, cm^{-1}) 2925, 2865, 1725, 1685, 1590, 1430. ^{13}C ($CDCl_3$, 75.48 MHz): δ 201.09, 174.23, 142.39, 136.89, 129.40, 126.96, 51.43, 41.08, 34.04, 31.49, 29.27, 29.10, 29.02, 28.99, 28.32, 24.87, 24.07, 22.48, 13.93. High resolution MS: m/e 308.2355 (calcd for $C_{19}H_{32}O_3$, 308.2351).

Methyl coriolate **8.** To a methanol (10 ml) solution of enone **7** (50 mg, 0.16 mmol) at 0°C under N_2 was added sodium borohydride (12 mg, 0.32 mmol) in one portion. After 5 min, the reaction was quenched with sat. ammonium chloride and extracted with ether (3x25 ml). After drying and concentration in vacuo, the residue was chromatographed on silica gel eluting with 30% ether in pentane to afford 35 mg of **8** (70%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.49 (dd, J=10, 15 Hz, 1H), 5.98 (bt, J=10 Hz, 1H), 5.67 (dd, J=6, 15 Hz,1H), 5.49-5.38 (m, 1H), 4.17 (bq, J=7 Hz, 1H), 3.67 (s, 3H), 2.31 (t, J=7 Hz, 2H), 2.18 (bq, J=7 Hz, 2H), 1.70-1.50 (m, 6H), 1.45-1.20 (m, 12H), 0.90 (t, J=7 Hz, 3H). IR ($CDCl_3$, cm^{-1}): 3600, 2930, 2855, 1730, 1435. ^{13}C NMR ($CDCl_3$, 75.48 MHz): δ 174.31, 135.91, 132.79, 127.79, 125.72, 72.89, 51.44, 37.31, 34.06, 31.78, 29.46, 29.04(2), 28.93, 27.67, 25.11, 24.89, 22.60, 14.03. High resolution MS: m/e (m-H_2O)=292.2406 (calcd for $C_{19}H_{32}O_2$, 292.2402).

(±)-Coriolic acid **1.** The ester 8 (35 mg, 0.11 mmol) was taken up in a 2:1 isopropanol/water solution (10 ml) and lithium hydroxide (23 mg, 0.55 mmol) was added. After 1.5 h at room temperature, the reaction mixture was acidifed to pH 3 with 88% formic acid. Extraction with ether (3x20 ml), drying over $MgSO_4$ and concentration in vacuo afforded 30 mg (ca. 100%) of coriolic acid **1.**

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