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FURAN RING AS MASKED 3-ACYLACRYLATE MOIETY. PRACTICAL SYNTHESIS OF RACEMIC (E)4,4(ETHYLENEDIOXY)-7-HYDROXY 2-OCTENOIC ACID, THE C-8 SUBUNIT OF PYRENOPHORIN.

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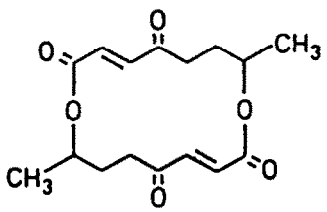
Abstract: Furfural and acetone are the starting materials for a new practical synthesis of racemic (E)4,4(ethylenedioxy)-7-hydroxy-2-octenoic acid, the protected C-8 subunit of Pyrenophorin. Furan ring has been used as masked 3-acylacrylate moiety.

Undiminished efforts are currently devoted to search a convenient reagent for the 3-acylacrylate synthon since a large number of biologically active natural products possess this moiety as a structural feature.[1-6] Among them pyrenophorin[1] (1) is a macrocyclic 16-membered dilactide with fungicidal and cytostatic activity produced by the plant pathogenic fungus **Pyrenophora avenae** and by **Stemphylium radicinum**. The synthesis of pyrenophorin (1) has been achieved by several routes[7-2]



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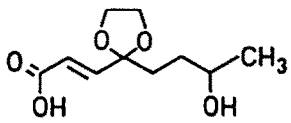

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including the "dimerizing cyclization" of ketal protected hydroxyacid 2.[8,12,13,17,19,21,25] We wish to report here a practical synthesis of racemic (E)4,4(ethylenedioxy)-7-hydroxy-2-octenoic acid (2), the protected building block of the C-8 subunit of pyrenophorin (1). Scheme 1 summarizes our procedure. The more relevant features of our strategy are the choise of the furan ring as latent 3-acylacrylate moiety and 2-furfural (3) and acetone (4) as cheap starting materials.

4-(2-Furyl)-3-buten-2-one (5), prepared from furfural and acetone by treatment with sodium hydroxide according to a well known procedure,[26] was reduced with lithium aluminium hydride in tetrahydrofuran to give 4-(2-furyl)-butan-2-ol (6) in 60% yield. Reaction with acetic anhydride

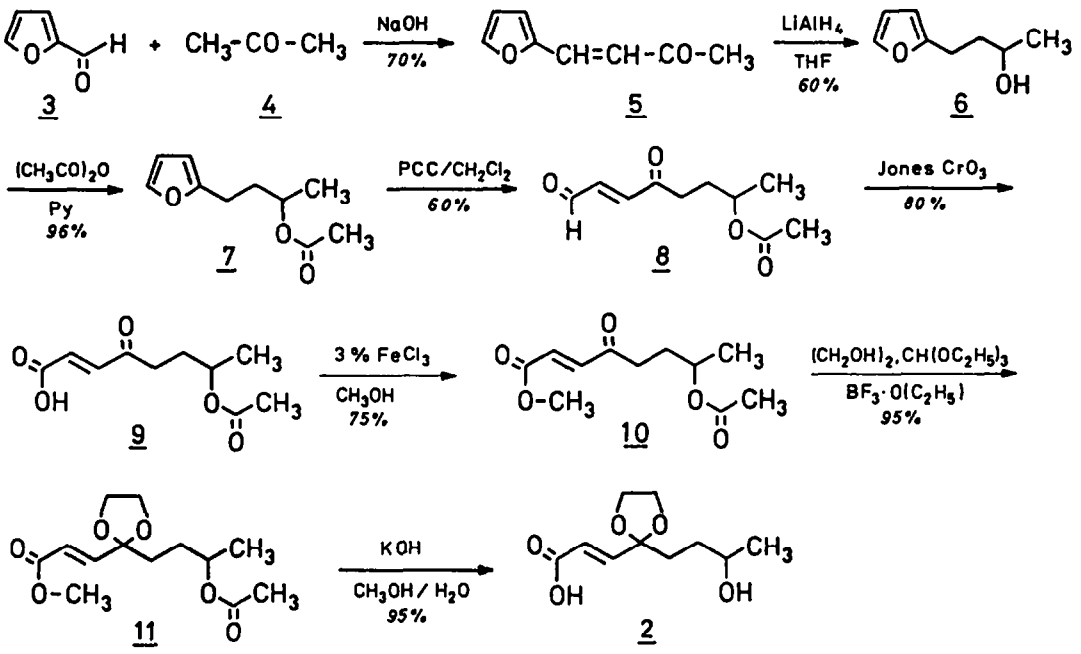

FIG. I

and pyridine at room temperature afforded 7 in an almost quantitative yield. The 2-substituted furan 7 contained the structural elements of the monomeric unit from which the diolide system 1 was derived, with the 3-acylacrylate moiety conveniently masked as furan ring. The crucial point in our sequence was the regioselective oxidative ring cleavage of 2-substituted furan 7. To our knowledge several procedures have been used to perform such a reaction,[27-28] however we have found that pyridinium chlorochromate (PCC) oxidation[29] of compound 7 and subsequent Jones CrO_3 oxidation of enedicarbonyl compound 8 was the more convenient method to achieve the preparation of racemic (E)-7-acetoxy-4-oxo-2-octenoic acid 9. Successive steps to have the protected unit 2 were accomplished readily. In fact, compound 9 was treated with a 3% methanol solution of anhydrous ferric chloride at room temperature to give diester 10 in a 75% yield. The latter underwent ketalization by a standard procedure to produce 11. Finally, the protected pyrenophorin subunit 2 was obtained by treatment with potassium hydroxide in aqueous methanol.

This eight steps procedure provides racemic (E)4,4(ethylenedioxy)-7-hydroxy-2- octenoic acid (2) in a 13% overall yield based on starting furfural (3) and acetone (4). Since the Mitsunobu reaction[30] allows the conversion of 2 into pyrenophorin by a dimerizing cyclization procedure [8,12,13] our route constitutes a formal synthesis of this macrodiolide.

EXPERIMENTAL

Proton NMR spectra were recorded at 90 MHz on a Varian EM390 instrument. ^1H shifts are given in parts per million from Me_4Si in $CDCl_3$ solvent. IR spectra were recorded with a Perkin Elmer 257 spectrophotometer. Microanalyses were performed by using C, H, N Analyser model 185 from Hewlett Packard Co.. Vapor phase chromatographic analyses were performed on a Carlo Erba Fractovap 4160 HRCG instrument using capillary column of duran glass (0.3÷0.32 mmx25 mt), stationary phase OV1 (film thickness 0.4÷0.45 μm). Furfuraldeyde, and acetic anhydride were distilled before use.

4-(2-Furyl)-3-buten-2-one (5).[26] A 500 ml three necked flask equipped with mechanical stirrer, a reflux condenser and dropping funnel was charged with 16.6 ml (19.25 g, 0.2 mol) of 2-furylaldehyde (3), 150 ml of water and 31.57 ml (25.0 g, 0.43 mol) of acetone (4). The mixture was stirred and cooled to 10°C and 33% aqueous NaOH solution (3.75 ml) was slowly added. The solution was then stirred 4 h at room temperature, then 10% aqueous H_2SO_4 solution was added until pH=5. The two layers which have formed were separated and the upper aqueous layer was extracted with ether (3x60 ml). The organic extracts and the lower phase were combined, dried ($MgSO_4$) and distilled to give 19.5 g (70% yield) of compound 5; bp 114-116°C/10 mmHg, mp 37-39°C; lit[24]: mp 37-39°C. IR (KBr) ν: 1680 (C=O); 1615 (C=C) cm^{-1}. ^1H NMR δ: 7.64-7.20 (m,2H); 6.81-6.43 (m,3H); 2.31 (s,3H). Anal. Calcd for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.41; H, 5.76.

4-(2-Furyl)-butan-2-ol (6). In a 250 ml three necked flask equipped with mechanical stirrer, reflux condenser, dropping funnel and nitrogen flush, a suspension of $LiAlH_4$ (0.7 g, 18 mmol) in dry THF (50 ml) was cooled at 0°C and compound 5 (5.0 g, 36 mmol) dissolved in dry THF (25 ml) was slowly added. The mixture was stirred at room temperature during 1 h and the reaction progress was monitored by vapor phase chromatographic analysis. Water (50 ml) was added and the solution was acidified with 2N HCl until pH=5. The organic layer was then separated and the aqueous phase was washed with ether (3x50 ml). The extracts were combined and dried ($MgSO_4$). Distillation of solvent at normal pressure gave an oil which distilled: bp 71-72°C/2 mmHg: 3.0 g (60% yield). IR (neat) : 3360 (OH) cm^{-1}. ^1H NMR δ: 7.38-7.25 (m,1H); 6.33-6.20 (m,1H); 6.09-5.92 (m,1H); 3.98-3.60 (m, 1H); 2.85-2.61 (m,2H); 2.32 (s,1H, disappeared by treatment with D_2O); 1.89-1.62 (m,2H); 1.16 (d,3H,J=6.5 Hz). Anal. Calcd for $C_8H_{12}O_2$: C, 68.57; H, 8.63. Found: C, 68.66; H, 8.51.

(±)4-(2-Furyl)-butan-2-ol Acetate (7). A 50 ml flask equipped with magnetical stirring and $CaCl_2$ dry tube was charged with alcohol 6 (8.0 g, 56 mmol) acetic anhydride (5.84 g, 56 mmol) freshly distilled and dry pyridine (5.40 g, 68 mmol). The mixture was stirred during 1.5 h at room temperature and then extracted with ether (2x100 ml). The ethereal solution was washed with 10% aqueous Na_2CO_3 solution (3x30 ml), 2N HCl (3x30 ml), water and finally dried ($MgSO_4$). The solvent was evaporated at reduced pressure and the residue distilled to afford 7 (10.0 g, 96% yield): bp 98-100°C/2 mmHg. IR (neat) ν: 1735 (C=O) cm^{-1}. ^1H NMR : 7.55-7.53 (m,1H); 6.71-6.50 (m,1H); 6.38-6.20 (m,1H); 5.28-4.87 (m,1H); 2.89-2.57 (m,2H); 2.01 (s,3H); 2.16-1.73 (m,2H); 1.23 (d,3H,J=6.5 Hz). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.05; H, 7.90.

(±)(E)7-Acetoxy-4-oxo-2-octenal (8). In a 1 lt two necked flask equipped with mechanical stirring and reflux condenser, compound 7 (3.6 g, 19.7 mmol) was dissolved in dichloromethan (400 ml). The solution was stirred and PCC (22.5 g, 104 mmol) was added. The stirring was continued at room temperature during 12 h and then was refluxed 36 h (reaction progress was monitored by vapor phase chromatographic analysis). After cooling the mixture was diluted with ether (400 ml) and decanted. The residue was washed several times with ether. The organic phases were combined and filtered through Fluorisil. Removing of the solvent under reduced pressure afforded 2.34 g (60% yield) of compound 8 (96% pure by vpc). IR (neat) ν: 1730 (C=O esther); 1690 (C=O); 1620 (C=C) cm^{-1}. ^1H NMR δ: 10.18-10.08 (m,1H); 7.16-7.00 (m,2H); 5.36-4.85 (m,1H); 3.14-2.75 (m,2H); 2.01 (s,3H) 2.20-1.73 (m,2H); 1.24 (d,3H,J=6.5 Hz). ^1H N.M.R. (C_6D_6) δ: 9.27 (d,1H,H_x), 6.40 (dd,1H,H_A); 6.21 (d,1H,H_B) J_{AX} = 6.40 Hz; J_{AB} = 16.27 Hz; $|J_{BX}| \leq 1.0$ Hz for the ABX system $CH_B = CH_A-CH_X O$.[29,31] Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.42; H, 7.25.

(±)(E)7-Acetoxy-4-oxo-2-octenoic Acid (9). In a 100 ml flask equipped with a dropping funnel and magnetic stirring, compound 8 (2.0 g, 10 mmol) was dissolved in acetone (80 ml). The solution was cooled (0°C) and 4 ml of Jones reagent (26.72 g of CrO_3 in 23 ml of concentrated sulfuric acid then water until a volume of 100 ml) were added. The mixture was stirred at 0°C during 2 h (reaction progress was monitored by vpc analysis) the acetone was removed at reduced pressure and water (80 ml) was added. The mixture was extracted with ether (4x30 ml) and the ethereal solution washed with 10% aqueous Na_2CO_3. The basic solution was acidified with 2N HCl then extracted with ether (4x20 ml). Removing the solvent under reduced pressure afforded 1.7 g (80% yield) of compound 9 (98% pure by vpc): mp 6667°C; lit[15] 66-66.5°C. IR (KBr) ν: 3600-2400 (COOH); 1730 (C=O); 1695 (C=O); 1670 (C=O); 1625 (C=C) cm^{-1}. ^1H NMR δ: 10.06 (s,broad,1H); 7.04 (d,1H,J=16 Hz); 6.60 (d,1H,J=16 Hz); 5.03-4.61 (m,1H); 2.90-2.45 (m,2H); 2.01 (s,3H); 2.04-1.59 (m,2H); 1.17 (d,3H,J=6.5 Hz). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.21; H, 6.72.

Methyl(±)(E)7-Acetoxy-4-oxo-2-octenoate (10). Acid 9 (1.3 g, 6 mmol) was dissolved with a 3% methanolic solution of anhydrous ferric chloride (20 ml). After 72 h methanol was evaporated under reduced pressure, the residue was dissolved in ether (150 ml), washed with water, saturated aqueous $NaHCO_3$ solution and dried ($MgSO_4$). The solvent was evaporated at reduced pressure to give 1.05 g (75% yield) of the corresponding esther 10 (95% pure by vpc). IR (neat) ν: 1740 (C=O); 1695 (C=O); 1635 (C=C) cm^{-1}. ^1H NMR δ: 7.08 (d,1H,J=16 Hz); 6.68 (d,1H,J=16 Hz); 5.20-4.72 (m,1H); 3.81 (s,3H); 2.88-2.55 (m,2H); 2.02 (s,3H); 2.08-1.68 (m,2H); 1.24 (d,3H,J=6.5 Hz). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.70; H, 7.21.

Methyl(±)(E)7-Acetoxy-4,4-(ethylendioxy)-2-octenoate (11). Compound **10** (1.14 g, 5 mmol) was dissolved in dry benzene (35 ml) and ethylene glycol (0.28 ml, 8.0 mmol), triethylorthoformate (0.90 ml, 5.4 mmol) and 0.2 ml of $BF_3.Et_2O$. This mixture was refluxed during 24 h. Then mixture was washed with saturated aqueous $NaHCO_3$, dried and evaporated at reduced pressure to give compound **11** (1.2 g, 94% yield) as an oil. IR (neat) ν: 1730 (C=O), 1665 (C=O). ^1H NMR δ : 6.75 (d,1H, J=16 Hz); 6.08 (d,1H,J=16 Hz); 5.20-4.80 (m,1H); 3.85 (s,3H); 2.90-2.65 (m,2H); 2.02 (s,3H); 2.10-1.70 (m,2H); 1.24 (d,3H,J=6.0 Hz). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.31; H, 7.36.

(±)(E)4,4-(Ethylenedioxy)-7-hydroxy-2-octenoic Acid (2). To a solution of compound **11** (1.0 g, 3.6 mmol) in methanol (25 ml) was added 2N aqueous KOH solution (10 ml) and allowed to stand at room temperature during 7 h. Then the reaction mixture was cooled (0-5°C), 2N H_2SO_4 added until pH=3.5, and extracted with dichloromethane (3x30 ml). The organic extracts were collected, washed with brine and dried ($MgSO_4$). The evaporation of the solvent at reduced pressure afforded compound **2** (0.70 g, 95%) as an oil: IR (neat): ν =3600-2350 (COOH), 1720, 1690 (C=O), 1625 (C=C) cm^{-1}. ^1H NMR δ: 6.80 (d,1H,J=16Hz); 6.05 (d,1H,J=16Hz); 5.6 (br s,2H); 4.05 (s,4H); 3.80 (m,1H); 2.25-1.45 (m,4H); 1.2 (d,3H,J=6.5 Hz). Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.61; H, 7.38. Our sample showed the same spectroscopic characteristics described in the literature.[17,25]

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