The Reaction of 2-(Trialkylsiloxy)furans with Lead(IV) Acetate. The Synthesis of *dl*-Pyrenophorin

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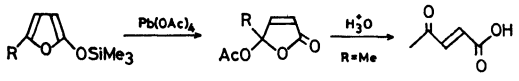
(Received September 25, 1979)

The reaction of 2-(trimethylsiloxy)furans with lead(IV) acetate afforded the corresponding α,β-unsaturated γ-acetoxy-γ-lactones in good yields. The lactones were easily converted into the corresponding 3-acylacrylic acids. Utilizing this reaction, *dl*-pyrenophorin was synthesized.

Several macrolide antibiotics incorporate a γ-oxo α,β-unsaturated lactone moiety.[1] A variety of methods are available for the synthesis of 3-acylacrylic acids, but the methods applicable to the macrolide synthesis are not so simple and efficient.[2] Previously, we reported the synthesis of 2-(trialkylsiloxy)furans from unsaturated lactones and their reactions with dienophiles and some electrophiles.[3,4] In this paper we will describe the conversion of 2-(trialkylsiloxy)furans into 3-acylacrylic acids.

Results and Discussion

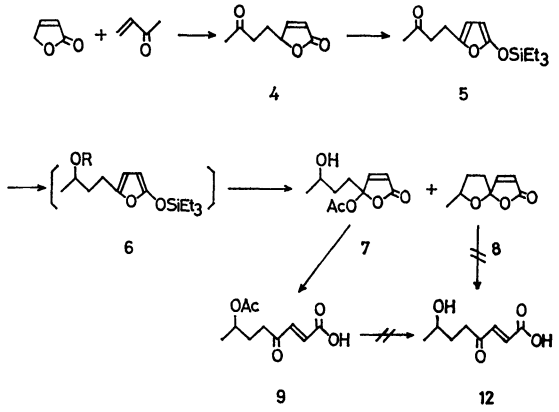
The treatment of 2-(trimethylsiloxy)furan (**1a**) and 5-methyl-2-(trimethylsiloxy)furan (**1b**) with lead(IV) acetate gave 4-acetoxy-2-buten-4-olide (**2a**) and 4-acetoxy-2-penten-4-olide (**2b**) in 87 and 76% yields respectively. The conversion of the latter product to 4-oxo-2-pentenoic acid (**3**) in an 86% yield was easily performed by acid hydrolysis.



1a R=H 2a R=H 3
1b R=Me 2b R=Me

Scheme 1.

This three-step synthesis of 3-acylacrylic acid starting from unsaturated γ-lactones (formation of siloxyfurans, oxidation with Pb(IV) acetate, and acid hydrolysis) seems to be widely applicable, since a variety of methods of synthesizing unsaturated γ-lactones[5] are available and each step can be carried out in a high yield. Thus, the application of this strategy to the synthesis of pyrenophorin, a 16-membered dilactone isolated as a metabolite of plant pathogenic fungi,[1a] was examined. The starting material, 7-oxo-2-octen-4-olide (**4**), was easily obtained by the Michael addition of 2-buten-4-olide to 3-buten-2-one or the reaction of 2-(trimethylsiloxy)furan with 3-buten-2-one in the presence of Lewis acid. The silylation of **4** using triethylchlorosilane and triethylamine afforded the corresponding siloxyfuran derivative, **5**, in an 88% yield. First, the reduction of the carbonyl group, followed by the oxidation of siloxyfuran with lead(IV) acetate, was examined. The reduction of the carbonyl group proceeded smoothly by lithium aluminium hydride, but the oxidation of **6** (R=Li or Al) with lead(IV) acetate afforded the expected compound, **7**, in only a 16% yield, the major product was found to be the spiro compound (**8**, 51%; about a 1 : 1 mixture of the stereoisomers).[6] Though the yield of **7** was improved to 45% when **6** (R=H) was treated with lead(IV) acetate, the formation of **8** (35%) could not be avoided. When the siloxyfuran (**6**, R=Li or Al) was oxidized with copper(II) chloride, the spiro compound was obtained in a 60% yield. The 3-acylacryric acid derivative, **9**, was obtained in an almost quantitative yield by heating **7** in xylene in the presence of a small amount of 2-pyridinethiol. However, all attempts to prepare the hydroxy acid, **12**, from **9** or **7** failed. The hydrolysis of **9** as well as **7** under various reaction conditions afforded mainly the spiro compound, **8**.

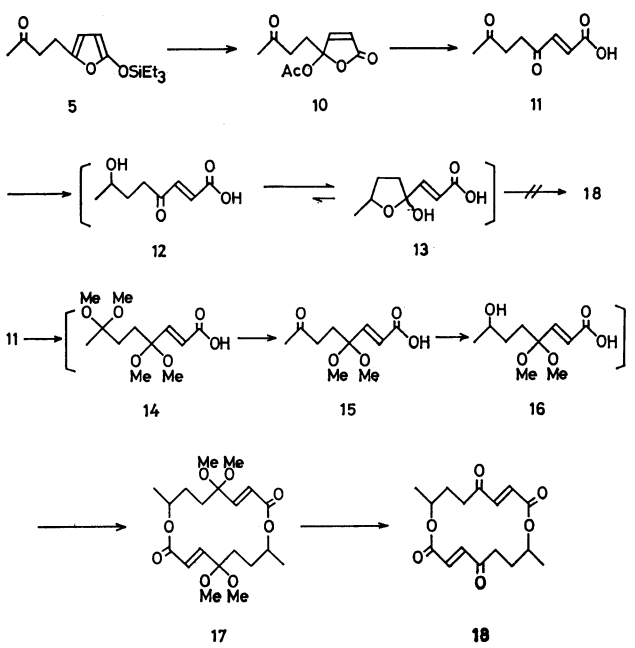


4 5 6 7 8 9 12

Scheme 2.

Then, the oxidation of **5** with lead(IV) acetate, followed by the reduction of carbonyl group, was examined. The oxidation of **5** with lead(IV) acetate gave 7-oxo-4-acetoxy-2-octen-4-olide (**10**) in an 83% yield. The acid hydrolysis of **10** yielded the desired 4,7-dioxo-2-octenoic acid (**11**) in a 75% yield. First, the selective reduction of **11**, followed by the dimerization cyclization, was examined. The selective reduction of **11** was achieved with sodium borohydride at −78 °C. However, the cyclization of the reduction product to pyrenophorin failed, probably because of the predominance of the hemiacetal structure, **13**. Then, the protection of the carbonyl groups of **11** was examined. The acetalization of two carbonyl groups was carried out using trimethyl orthoformate and methanol in the presence of an acid catalyst. The selective hydrolysis of **14** to **15** proceeded smoothly in THF–water. Sodium borohydride reduction of **15** at −30 °C afforded the hydroxy acid, **16**. All three of these compounds (**14**, **15**, and **16**) were relatively unstable oils and could not be

obtained in pure forms by silica-gel chromatography. However, the crude **16** was almost homogenious on TLC; thus, the crude **16** was used for the next lactonization step. The dimerization lactonization was carried out according to the method of Mitsunobu *et al.*,[7] using triphenylphosphine and diethyl azodicarboxylate; a mixture of *dl*- and *meso*-pyrenophorin bis(dimethyl acetal)s (**17**) was thus obtained in a 17% over-all yield from **11**. The acid hydrolysis of the diacetals with acetic acid–water proceeded quantitatively to give *dl*- and *meso*-pyrenophorin[8] (**18**), which could be separated by TLC. The structures of both were comfirmed by their elemental analyses and spectral data.



Scheme 3.

Experimental

4-Acetoxy-2-buten-4-olide (2a). To a suspension of lead(IV) acetate (1.17 g, 2.64 mmol) in dry dichloromethane (10 ml), 2-(trimethylsiloxy)furan (**1a**, 375 mg, 2.4 mmol)[3] was added, drop by drop, at −21 °C. The reaction temperature was gradually raised to room temperature over a period of 1 h. After the addition of ether (30 ml), the precipitate was filtered off. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel to give **2a** (297 mg, 87%), using hexane–ether as the eluent. IR(NaCl): 1820—1740 cm^{-1} (C=O), 1612 cm^{-1} (C=C), NMR ($CDCl_3$): δ 2.13 (3H, s), 6.26 (1H, d), 6.92 (1H, s), 7.35 (1H, d). Found: C, 50.57; H, 4.23%. Calcd for $C_6H_6O_4$: C, 50.71; H, 4.26%.

4-Acetoxy-2-penten-4-olide (2b). The reaction of 5-methyl-2-(trimethylsiloxy)furan (**1b**, 1.74 g, 10.2 mmol)[3] with lead(IV) acetate (6.6 g, 15 mmol) was carried out in dry benzene (40 ml) at 4 °C—room temperature for 3 h. Purification by short silica-gel column chromatography, followed by bulb-to-bulb distillation, afforded **2b** in a 76% yield (1.21 g); bp 150—155 °C/23—24 mmHg (bath temp.). NMR($CDCl_3$): δ=1.80 (3H, s), 2.05 (3H, s), 6.15 (1H, d), 7.59 (1H, d). IR(NaCl): 1770—1790, 1750 cm^{-1} (C=O), 1611 cm^{-1} (C=C). Found: C, 53.57; H, 5.14%. Calcd for $C_7H_8O_4$: C, 53.84; H, 5.16%.

4-Oxo-2-pentenoic Acid (3). A mixture of 4-acetoxy-2-penten-4-olide (**2b**, 1.21 g, 7.78 mmol) in 1 M hydrochloric acid (20 ml) was stirred for 3 d at room temperature. After the subsequent removal of the hydrochloric acid under reduced pressure, the residue was dissolved in benzene, which contained a catalytic amount (*ca.* 1 mg) of 2-pyridinethiol,[9] and heated to reflux. Upon cooling, **3** was precipitated as colorless crystals. After filtration, the filtrate was concentrated under reduced pressure. The residue was treated with 2-pyridinethiol in hot benzene as has been described above, and then these operations were repeated to give 760 mg (86%) of **3**; mp 126 °C. IR(KBr): 1670—1730 cm^{-1} (C=O), 1623 cm^{-1} (C=C). NMR($CDCl_3$): δ=2.36 (3H, s), 6.61 (1H, d), 7.06 (1H, d), 9.1—9.8 (1H, m). Found: C, 52.92; H, 5.36% Calcd for $C_5H_6O_3$: C, 52.63; H, 5.30%.

7-Oxo-2-octen-4-olide (4). A mixture of 2-buten-4-olide (176 mg, 2.1 mmol) and 3-buten-2-one (147 mg, 2.1 mmol) was cooled to −50 °C, and then 1 drop of 0.1 M potassium hydroxide was added to the mixture, After it had then been warmed to room temperature, the mixture was neutralized with Amberlite IRC-50. The crude product was purified by TLC to give **4** in a 75% yield; bp 144—146 °C/4.5 mmHg. IR(NaCl): 1720, 1760—1780 cm^{-1} (C=O), 1600 cm^{-1} (C=C), NMR ($CDCl_3$): δ=2.00 (2H, dt), 2.16 (3H, s), 2.68 (2H, t), 5.00—5.30 (1H, m), 6.12 (1H, dd), 7.52 (1H, dd). Found: C, 61.85; H, 6.57%. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54%. This compound was also synthesized according to the following procedure. 2-(Trimethylsiloxy)furan (**1a**, 37.5 g, 0.24 mol) and 3-buten-2-one (17.6 g, 0.25 mol) dissolved in dry dichloromethane (50 ml) were cooled to −78 °C. After the addition of tin(IV) chloride (500 mg), the reaction mixture was warmed to room temperature over a period of 12 h. After the addition of water, the product was extracted with dichloromethane. Purification by silica gel column chromatography (hexane–ether) afforded **4** (19 g, 52%).

5-(3-Oxobutyl)-2-(triethylsiloxy)furan (5). A mixture of triethylchlorosilane (4.98 g, 33 mmol) and triethylamine (3.34 g, 33 mmol) was added to 7-oxo-2-octen-4-olide (**4**, 4.62 g, 30 mmol) under an argon atmosphere. After three days, dry benzene was added and the precipitated ammonium salt was filtered off under an argon atmosphere. The subsequent distillation of the filtrate gave **5** in an 88% yield; bp 105—106 °C/0.06 mmHg. IR(NaCl): 1720 cm^{-1} (C=O). NMR($CDCl_3$): δ=0.43—1.22 (15H, m), 2.18 (3H, s), 2.78 (4H, s), 5.04 (1H, d), 5.86 (1H, d).

4-Acetoxy-7-hydroxy-2-octen-4-olide (7) and 7-Methyl-1,6-dioxaspiro[4,4]non-3-enone (8). After the addition of lithium aluminium hydride (280 mg) to a solution of **5** (2.58 g, 10 mmol) in dry tetrahydrofuran (20 ml), the mixture was stirred at room temperature for 0.5 h and then cooled to −10 °C. Lead (IV) acetate (5.0 g) was added in one portion, after which the reaction mixture was allowed to warm to room temperature over a period of 2 h. After the removal of metal salts by short silica gel column chromatography, the concentrated eluate was put on a silica-gel column and eluted with hexane–ether to give **7** (338 mg, 16%) and **8** (791 mg, 51%).

7: IR (NaCl): 3400 cm^{-1} (OH, broad), 1750—1800 cm^{-1} (C=O), 1615 cm^{-1} (C=C). NMR ($CDCl_3$): δ=1.22 (3H, d), 1.36—1.82 (2H, m), 2.10 (3H, s), 2.00—2.48 (2H, m), 3.60—4.10 (1H, m), 6.28 (1H, d), 7.68 (1H, d). Found: C, 56.05; H, 6.59%. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59%.

8: IR(NaCl): 1760—1770 cm^{-1} (C=O), 1615 cm^{-1} (C=C). NMR ($CDCl_3$): δ=1.28 (1.5H, d), 1.40 (1.5H, d), 2.04—2.48 (4H, m), 4.20—4.70 (1H, m), 6.10 (1H, d), 7.15 (1H, d). Found: C, 62.16; H, 6.54%. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54%.

A mixture of **5** (546 mg, 2.03 mmol) and lithium aluminium hydride (30 mg, 0.75 mmol) in tetrahydrofuran (10 ml) was stirred for 1 h at room temperature. The reaction mixture was then filtered through cellite and silica gel under an argon atmosphere and evaporated. The residue was dissolved in dry dichloromethane (5 ml) and added to a precooled suspension of lead(IV) acetate (910 mg, 2.04 mmol) in dry dichloromethane at −10 °C. The reaction mixture was then allowed to warm to room temperature for 2 h. The subsequent separation of the products by TLC gave **7** (45%) and **8** (35%).

The spiro compound, **8**, was also obtained by the following procedure. A mixture of **5** (536 mg, 2 mmol) and lithium aluminium hydride (38 mg, 1 mmol) dissolved in tetrahydrofuran (5 ml) was stirred at room temperature for 0.5 h. Anhydrous copper(II) chloride (540 mg, 4 mmol) was then added to the stirred solution at −40 °C, and the reaction mixture was warmed to room temperature. After the removal of the metal salts by short silica gel column chromatography, the purification of the product by TLC (hexane–ether) afforded **8** (186 mg, 60%).

7-Acetoxy-4-oxo-2-octenoic Acid (9). A solution of **7** (178 mg) and 2-pyridinethiol (1 mg) in xylene (3 ml) was refluxed for 1.5 h. The subsequent removal of the solvent under reduced pressure gave almost pure **9**; mp 66.0—66.5 °C (from cyclohexane–benzene). IR(KBr): 2350—3600 cm^{-1} (COOH, broad), 1675, 1695, 1735 cm^{-1} (C=O). NMR ($CDCl_3$): δ=1.26 (3H, d), 2.04 (3H, s), 2.02 (2H, t), 2.76 (2H, t), 6.64 (1H, d), 7.14 (1H, d), 9.56 (1H, s). Found: C, 56.28; H, 6.40%. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59%.

4-Acetoxy-7-oxo-2-octen-4-olide (10). To a suspension of lead(IV) acetate (980 mg, 2.2 mmol) in dry benzene, **5** (482 mg, 1.8 mmol) dissolved in dry benzene (4 ml), was added, drop by drop, at 4 °C. The mixture was put in a short silica gel column and eluted with ether. The eluate was evaporated under reduced pressure, and the residue was separated by TLC to give **10** in an 83% yield (316 mg). An analytical sample was obtained by bulb-to-bulb distillation; bp 115—120 °C/0.02 mmHg (bath temp). IR (NaCl): 1750—1805 cm^{-1} (C=O), 1720 cm^{-1} (C=C). NMR ($CDCl_3$): δ=2.05 (3H, s), 2.17 (3H, s), 2.2—2.5 (2H, m), 2.5—2.8 (2H, m), 6.17 (1H, d), 7.18 (1H, d). Found: C, 55.91; H, 5.66%. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70%.

4,7-Dioxo-2-octenoic Acid (11). Hydrochloric acid (1M, 40 ml) was added to **10** (2.8 g), and the heterogeneous mixture was stirred for 4 d. The resulting homogenious solution was extracted several times with ethyl acetate. After the removal of the ethyl acetate, the residue was treated with a catalytic amount of 2-pyridinethiol in benzene as described before (see the synthesis of **3**) to give **11** (1.69 g, 75%); mp 112—113.5 °C. IR (KBr): 1705, 1680 cm^{-1} (C=O), 1627 cm^{-1} (C=C). NMR ($CDCl_3$): δ=2.21 (3H, s), 2.86 (4H, s), 6.70 (1H, d), 7.10 (1H, d). Found: C, 56.47; H, 5.83%. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92%.

meso- *and* dl-*Pyrenophorin Bis(dimethyl acetal)s (17).* 4,7-Dioxo-2-octenoic acid (**11**, 200 mg, 1.18 mmol), trimethyl orthoformate (1 ml), amberlyst 15 (50 mg), and methanol (4 ml) were stirred for 1.5 h at room temperature. After filtration through the celite, the trimethyl orthoformate and the methanol were removed. Tetrahydrofuran (6 ml) and water (2 ml) were then added to the residue, and the mixture was stirred for 1 h at 45 °C and then cooled to room temperature. Sodium hydrogencarbonate (118 mg, 1.4 mmol) was then added, and most of the tetrahydrofuran was removed under reduced pressure. After the addition of methanol (8 ml), sodium borohydride (60 mg, 1.58 mmol) was added at −38 °C. One hour later, acetone (2 ml) was added, and the mixture was warmed to room temperature. The solution was passed through an acidic resin column, and the solvent was evaporated under reduced pressure. In order to remove the boric acid, the addition and evaporation of methanol was repeated. The residue was almost homogeneous on TLC. The crude 7-hydroxy-4,4-dimethoxy-2-octenoic acid (**16**) [IR (NaCl): 3400 cm^{-1} (OH, broad), 2820 cm^{-1} (OMe), 1700 cm^{-1} (COOH); NMR ($CDCl_3$): δ=1.2 (3H, d), 1.2—2.25 (4H, m), 3.15 (6H, s), 3.5—4.1 (1H, m), 6.2 (1H, d), 6.7 (1H, d)] was used for the next step without further purification. Dry toluene (200 ml) and triphenylphosphine (800 mg, 3.05 mmol) were added to **16**, and the resulting mixture was cooled to −25 °C. After the addition of diethyl azodicarboxylate (540 mg, 3.10 mmol) dissolved in dry toluene, the reaction temperature was gradually raised to room temperature for 3 d. A mixture of *meso* and *dl* pyrenophorin bis(dimethyl acetal)s (40 mg, 17%) was obtained by using TLC; mp 143—144 °C. IR (KBr): 1715 cm^{-1} (C=O), 1650 cm^{-1} (C=C). NMR ($CDCl_3$): δ=1.22 (6H, d), 1.3—2.1 (8H, m), 3.10 (6H, s), 3.19 (6H, s), 4.8—5.3 (2H, m), 6.09 (2H, dd), 6.45 (2H, d). MS: *m/e* 400 (M^+). Found: C, 60.17; H, 7.99%. Calcd for $C_{20}H_{32}O_8$: C, 59.98; H, 8.05%.

dl- *and* meso-*Pyrenophorin (18).* Pyrenophorin bis(dimethyl acetal)s (13 mg) was dissolved in tetrahydrofuran/acetic acid/water 1:3:1 (2 ml) and warmed for 2 h at 40 °C. After the removal of the solvent, isolation with TLC gave *dl*-pyrenophorin (4 mg) and *meso*-pyrenophorin (6 mg). *dl*-Pyrenophorin; mp 139—140 °C (lit,[8b] 139—140 °C). IR (KBr): 1717, 1694 cm^{-1} (C=O), 1631 cm^{-1} (C=C), NMR ($CDCl_3$): δ=1.30 (6H, d), 1.9—2.3 (4H, m), 2.4—2.8 (4H, m), 4.8—5.3 (2H, m), 6.60 (2H, d), 6.89 (2H, d). MS: *m/e* 308 (M^+). Found: C, 62.30; H, 6.37%. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54%. *meso*-Pyrenophorin: mp 128—128.5 °C; (lit,[8b] 126—127.5 °C). IR (KBr): 1717, 1694 cm^{-1} (C=O), 1631 cm^{-1} (C=C); NMR ($CDCl_3$): δ=1.31 (6H, d), 1.9—2.4 (4H, m), 2.4—2.7 (4H, m), 4.8—5.3 (2H, m), 6.51 (2H, d), 6.85 (2H, d), MS: *m/e* 308 (M^+). Found: C, 62.25; H, 6.37%. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54%.

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9) This compound was found to be effective for the isomerization of a contaminated *cis* isomer to a *trans* isomer.