Synthesis of Lepiochlorin, a Chlorinated Antibiotic, by Use of Electrochemical Haloalkoxylation

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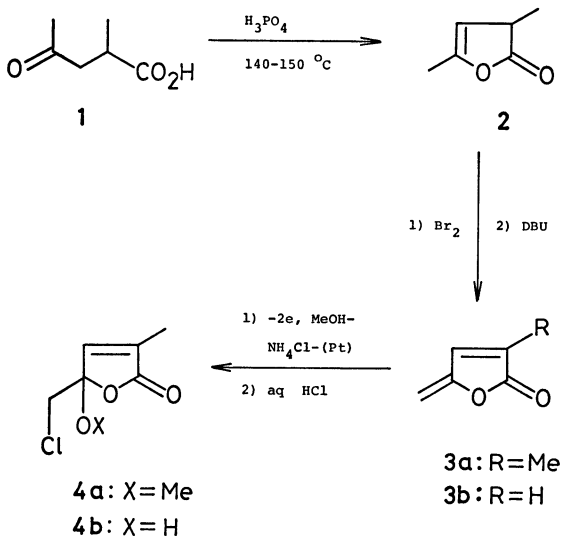
Synopsis. The fungal metabolite lepiochlorin was synthesized from 2-methyl-4-oxopentanoic acid by the electrochemical chloromethoxylation of 2-methyl-2,4-pentadien-4-olide in MeOH–NH_4Cl–(Pt–Pt) system followed by hydrolysis in a mixed solution of dioxane–H_2O–concd HCl (25/10/1 V/V/V) in 38% overall yield.

γ-Oxygenated butenolides appeared in naturally occurring products exhibit interesting biological activities.[1] Synthetic methodology for the butenolide has been well documented in a recent review.[2] As a new antibiotic butenolide, lepiochlorin (**4b**), a chlorinated metabolite of a fungus (a *Lepiota* species) cultivated by a leaf-cutting ants, has been isolated.[3] In the previous study,[4] we reported a convenient haloalkoxylation of enol ethers by the electrolysis in ROH–NH_4X (X=Cl, Br, I)–(Pt–Pt) system. This procedure is expected to be potentially useful for the preparation of chlorohydrin moiety of **4b**. We describe here a short-step synthesis of the butenolide **4b** by introducing the electrochemical chloromethoxylation of γ-methylenebutenolide **3a**.

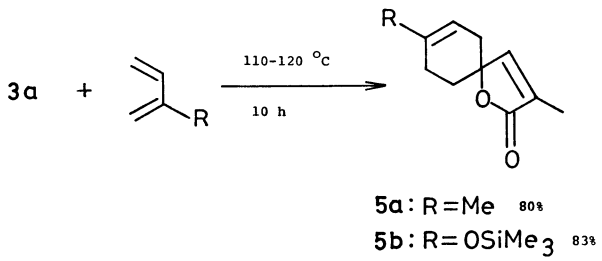
The target molecule **4b** has been synthesized recently by McMorris *et al.* in 18—20% overall yields in a laborious seven-step synthesis from α-phenylthiopropionic acid and allyl methoxyethoxymethyl ether.[5] In our route to **4b** we started with 2-methyl-3-penten-4-olide **2** which can be obtained from commercially available 2-methyl-4-oxopentanoic acid (**1**)[6] by the procedure of Helberger *et al.*[7] (Scheme 1).

Bromination of **2**, obtained by dehydration of **1** with phosphoric acid, with one equivalent of bromine and subsequent treatment with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) at −20 to 10 °C in benzene provided the key intermediate, γ-methylenebutenolide **3a**, in 51% yield (from **1**).[8]



Scheme 1.

It is interesting to note that the butenolide **3a** is stable to heat in contrast to unstable protoanemonine (**3b**) which lacks methyl group at C-2 position of **3a** and dimerizes spontaneously at room temperature.[7b,9] For example, Diels-Alder reaction of **3a** with 1,3-dienes, *i.e.*, isoprene and 2-trimethylsiloxy-1,3-butadiene, took place on heating at 110—120 °C for 10 h in toluene to give the corresponding diene adducts **5** in 80—83% yields (Scheme 2). In addition, the reaction of **3a** with appropriate nucleophiles has been explored to give the corresponding 1,6-adducts.[10]



Scheme 2.

Electrochemical halogenation of **3a** in a MeOH–NH_4Cl (1.5 equiv.)–(Pt–Pt) system was carried out under a current of 3.5—6.7 mA/cm² (applied voltage: 2.0 V, cell voltage: 0.8—1.0 V *vs.* Ag wire) in a beaker type undivided cell. The passage of 3.0 F/mol of electricity (10 h) at room temperature afforded the chlorinated acetal **4a** in 88% yield. On the other hand, attempts at the direct electrochemical chlorohydroxylation of **3a** employing a MeCN–H_2O (3/1 V/V)–NH_4Cl–(Pt–Pt) system resulted in the low yield of **4b** (10—20% yields). Hydrolysis of acetal group of **4a** by heating to reflux in a mixed solvent of dioxane–H_2O–concd HCl (25/10/1 V/V/V) afforded the desired **4b** in 86% yield.[11]

Experimental

Melting point is uncorrected and boiling points are indicated by an air-bath temperature without correction. IR spectra were determined with a JASCO IRA-1 grating spectrometer. NMR spectra were obtained with a Hitachi R-24 (60 MHz for proton) and/or a JEOL FX-100 (100 MHz for proton and 25.05 MHz for carbon-13) spectrometers. Samples were dissolved in $CDCl_3$ and the chemical shift values (δ) are expressed in parts per million downfield from an internal Me_4Si. Elemental analyses were performed in our laboratory.

2-Methyl-3-penten-4-olide (2). According to the procedure reported in the literature,[7b] **1** (5.0 g, 38.4 mmol) was heated with H_3PO_4 (0.25 g) at 140—150 °C for 4 h. The mixture was distilled at 140—150 °C/20 Torr and the distillate was chromatographed (SiO_2, hexane–AcOEt 8:1) to give 2.6 g of **2** (89% yield based on 1.06 g of unchanged

1). **2**: bp 77—78 °C/41 Torr (lit,[12] 53 °C/6 Torr).

*2-Methyl-2,4-pentadien-4-olide (**3a**).* To a solution of **2** (107.3 mg, 0.97 mmol) in CS_2 (2 ml) was added dropwise Br_2 (155 mg, 0.97 mmol) at −20 °C. After the solution had become colorless, the CS_2 was removed *in vacuo* with cooling in a water bath. The residue was dissolved in benzene (5 ml) containing a catalytic amount of 2,5-di-*t*-butylhydroquinone, and to this solution was added DBU (433 mg, 2.91 mmol) with immediate cooling to about −20 °C. The mixture was stirred for 30 min and warmed gradually to room temperature over about 5 h. Concentration and chromatography (SiO_2,[13] hexane–Et_2O 3:1) gave 62 mg (58%) of **3a**: bp 52—53 °C/2 Torr (lit,[14] 25 °C/0.05 Torr); MS, *m/e* (rel int.) 111 (M^++1, 8.2), 110 (M^+, 100), 82 (29.0), 68 (27.1), 54 (25.4). Spectroscopic properties were identical with those reported previously.[14]

*5-Chloro-4-methoxy-2-methyl-2-penten-4-olide (**4a**).* The electrochemical halogenation was carried out in an undivided cell fitted with two platinum foil (2.0×1.5 cm^2) electrodes.[4] A solution of **2a** (15 mg, 0.14 mmol) and NH_4Cl (11.3 mg, 0.21 mmol) in MeOH (4 ml) was electrolyzed under a constant applied voltage of 2.0 V (3.5—6.7 mA/cm^2). After 3.0 F/mol of electricity has been passed, the mixture was concentrated and the residue was taken up in ether. The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent followed by chromatography (SiO_2, hexane–AcOEt 3:1) gave 21.2 mg (88%) of **4a**: bp 88—89 °C/1.0 Torr; IR (neat) 3040, 1775 (lactone C=O), 1665 cm^{-1} (C=C); ^1H NMR (100 MHz) δ 1.99 (d, J=1.5 Hz, 3H, CH_3), 3.26 (s, 3H, OCH_3), 3.61 (d, J=12 Hz, 1H, CHCl), 3.85 (d, J=12 Hz, 1H, CHCl), 6.82 (q, J=1.5 Hz, 1H, HC=C); ^{13}C NMR δ 10.7 (q, C-2 Me), 48.5 (t, C-5), 51.7 (q, OMe), 106.7 (s, C-4), 135.8 (s, C-2), 143.5 (d, C-3), 170.4 (s, C-1); MS, *m/e* (rel int.) 179 (M^++2, 0.34), 177 (M^+, 0.94), 159 (0.51), 147 (6.9), 145 (21.6), 127 (100), 99 (35.3), 97 (18.3), 79 (17.0), 77 (48.4). Found: C, 47.56; H, 5.20. Calcd for $C_7H_9ClO_3$: C, 47.61; H, 5.13.

*5-Chloro-4-hydroxy-2-methyl-2-penten-4-olide (Lepiochlorin, **4b**).* A solution of **4a** (29 mg, 0.16 mmol) in a mixed solution of dioxane–H_2O–concd HCl (25/10/1 V/V/V, 2 ml) was heated to reflux for 6 h. The mixture was extracted with benzene–ether (1:1). The usual workup and chromatography (SiO_2,[13] hexane–AcOEt 3:1) gave 20 mg (86%) of **4b**: mp 69—70 °C (from petroleum ether) (lit,[3] 68—70 °C,[5] 74—74.5 °C); ^{13}C NMR δ 10.4 (q, C-2 Me), 46.7 (t, C-5), 103.8 (s, C-4), 134.1 (s, C-2), 145.0 (d, C-3), 172.0 (s, C-1). IR and ^1H NMR spectra were identical with those reported.[3]

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References

1) G. Pattenden, *Fortschr. Chem. Org. Naturst.*, **35**, 133 (1978).
2) Y. S. Rao, *Chem. Rev.*, **76**, 625 (1976).
3) M. S. R. Nair and A. Hervey, *Phytochemistry*, **18**, 326 (1979).
4) S. Torii, T. Inokuchi, S. Misima, and T. Kobayashi, *J. Org. Chem.*, **45**, 2731 (1980).
5) J. R. Donaubauer and T. C. McMorris, *Tetrahedron Lett.*, **21**, 2771 (1980).
6) Available from Aldrich Chemical Co., Milwaukee, WI.
7) a) J. H. Helberger, S. Ulubay, and H. Civelekoglu, *Ann.*, **561**, 215 (1949); b) C. Grundmann and E. Kober, *J. Am. Chem. Soc.*, **77**, 2332 (1955).
8) For the alternative methods of the preparation of γ-ylidenebutenolides: G. A. Kraus and H. Sugimoto, *J. Chem. Soc., Chem. Commun.*, **1978**, 30; T. Nakano and Y. Nagai, *ibid.*, **1981**, 815; M. Asaoka, N. Yanagida, K. Ishibashi, and H. Takei, *Tetrahedron Lett.*, **22**, 4269 (1981).
9) C. B. Chapleo, K. L. Svanholt, R. Martin, and A. S. Dreiding, *Helv. Chim. Acta*, **59**, 100 (1976); J. Cardellach, C. Estopa, J. Font, M. Moreno-Mañas, R. M. Ortuño, F. Sanchez-Ferrando, S. Valle, and L. Vilamajo, *Tetrahedron*, **38**, 2377 (1982).
10) H. Wyss, L. Révész, and R. Scheffold, *Helv. Chim. Acta*, **64**, 2272 (1981).
11) D. P. Marriott and J. R. Bantick, *Tetrahedron Lett.*, **22**, 3657 (1982).
12) J. A. Hirsch and A. J. Szur, *J. Heterocycl. Chem.*, **9**, 523 (1972).
13) SILICAR CC-7 SPECIAL silica gel purchased from Mallinckrodt, Inc. (Paris, Kentucky 40361) was used.
14) L.-C. Yu and P. Helquist, *J. Org. Chem.*, **46**, 4536 (1981).