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# TOTAL SYNTHESIS OF (±)-CERULENIN AND (±)-TETRAHYDROCERULENIN

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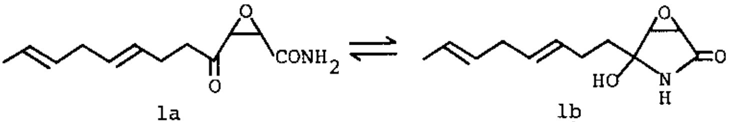
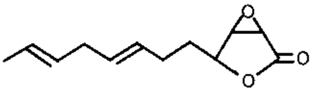
Abstract——Antibiotic (±)-cerulenin and (±)-tetrahydrocerulenin have been synthesized from furfuryl alcohol. The developed procedure involves chemoselective alkylation of furfuryl alcohol and epoxidation of 4-methoxybutenolide.

Antifungal antibiotic cerulenin (1) shows a potent inhibition on the biosynthesis of fatty acids and polyketides.[1] This unique biological activity of cerulenin has contributed to the biosynthetic study in which acyl condensation was involved.[2] Recent study by Schlesinger et al. demonstrated that cerulenin prohibits acylation of glycoprotein in a virus.[3] In addition to the consequence of structural feature including 7,10-diene system, 2,3-epoxide ring has been assumed to be the active site.[4] Cerulenin (1) has been synthesized by several routes, in which epoxy-γ-lactone 2 has been the mutual intermediate[5] with the exception of the case by Corey and Williams.[6]

They used epoxysuccinic anhydride as a $C_4$ synthon in their synthesis. 4-Keto-



1a 1b



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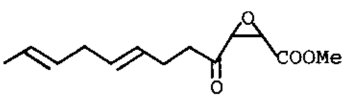

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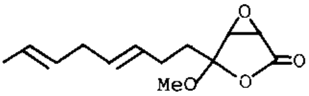

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*cis*-epoxyester 3 and 4-methoxy-2,3-epoxylactone 4 were the convergent products which gave cerulenin (1) merely by their ammonolysis.

We were interested in the synthetic utility of the latter lactone 4 as an intermediate. Lactone 4 was supposed to be prepared from 4-methoxy-2-buten-4-olide 5. The point may be that the epoxidation of 5 should accompany no solvolysis, unlike the case of NaClO-pyridine treatment of a butenolide (6) which gives epoxy acid 7. 4-Methoxylactone 5 could be synthesized from alkyl halide and furfuryl alcohol, which is an inexpensive resource, as shown in equation 1. Lactone 5 was transformed to (±)-cerulenin (1) with the aid of a newly developed epoxidation procedure.

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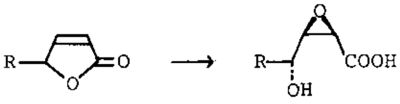

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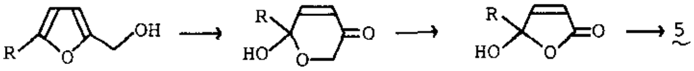
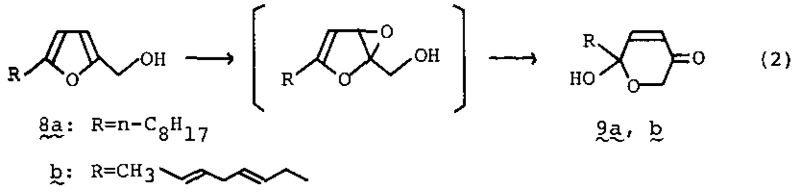


(1)

1-Iodooctane was used on our initial experiment and derivatives having saturated side chain were effective for model studies in further steps.

Furfuryl alcohol was lithiated with two equivalents of n-butyl lithium at -15 °C and the resulting dilithiated intermediate was treated with one equivalent of 1-iodooctane. Essentially negligible alkyl ether was obtained on this reaction. The yield (56%) of the coupling product (8a), which is comparably lower than the case of ordinary 2-lithiofuran[7], was increased to 80% (based on the halide) when the amount of 1-iodooctane was reduced to one-half. 5-(3,6-Octadienyl)furfuryl alcohol (8b) was obtained in 37.9% yield by a similar procedure. Substituted furfuryl alcohol (8b) was oxidized on Sharpless' condition because of the fact that $Br_2$/MeOH and m-chloroperbenzoic acid oxidation showed less chemoselectivity. Treatment of 8b with 1/50 equivalent of $VO(acac)_2$ and t-butyl hydroperoxide (TBHP) for a short time (15 min) afforded the hemiketal (9b) in 79% yield. Apparently the first step of this reaction should be the epoxidation of the furan ring (eq. 2). Although hemiketals, 9a and 9b, are somewhat unstable to acids, smooth



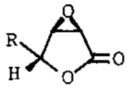
8a: R=n-C$_8$H$_{17}$

b: R=CH$_3$

9a, b

10a, b

5, 11: R=n-C$_8$H$_{17}$



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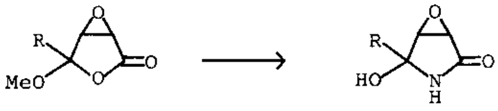
oxidation took place with $H_5IO_6$ in THF giving lactol 10a in 76% and 10b in 68.5% yield, respectively.

Despite the fact that tautomeric equilibrium is known with lactols such as 10,[8] 4-methoxybutenolide was obtained in good yield (11 in 78.7%, 5 in 82.5%) on treatment of the corresponding lactol (10a or 10b) with trimethyl orthoformate and tin(IV) chloride at -20 ~ 0 °C.[9] Cyclic structures of 11 and 5 were confirmed mainly on the basis of those ir spectra, $\nu$ 1815 and 1770 $cm^{-1}$ (2-buten-4-olide). No methyl ester was detected in this reaction.

Methyl ether 11 was unexpectedly resistant to epoxidation with NaClO-pyridine. It remained essentially unreacted at 0 °C for 1 h, and prolonged treatment at 0 °C or at a higher temperature gave complex hydrolyzate. NaClO epoxidation of ordinary butenolide 6 is known to proceed via hydroxy acid 7 which is easily dehydrated to afford epoxylactone 12.[5] A high stereoselectivity of this reaction indicates that a butenolide is epoxidized prior to hydrolysis. Considering that a steric hindrance of C-4 substituents regulates the epoxidation of 4-methoxybutenolide 11, we chose DMF which is known to solvate metal cations, as an alternative medium. The reactivity of NaClO was dramatically accelerated to yield the epoxylactone (13, 67.4%; 4, 59%).

Finally, epoxylactones 13 and 4 were transformed to (±)-tetrahydrocerulenin (14) and (±)-cerulenin (1), respectively, by treatment with methanolic ammonia. In both cases, most of the amide existed as a cyclic form (1b or 14) after evaporation of ammonia and methanol. Crystals of lactam 14 were obtained as a single tautomer from methanol. On the other hand, crystallization of cerulenin from benzene-methanol gave a mixture of two cyclic tautomers which showed ir absorption



4, 13:R=n-$C_8H_{17}$ 1b, 14:R=n-$C_8H_{17}$

at ν 1725 and 1710 cm$^{-1}$. Open form of cerulenin (1a) was obtained by passing through a silica gel column.

The synthetic procedure thus developed may be useful for preparation of analogues having a various side chain.

## EXPERIMENTAL

Melting points were obtained on a Yanagimoto micro melting point apparatus and are uncorrected. Mass spectra were recorded on a Hitachi M-52G mass spectrometer or a JEOL JMS-01SG-2 instrument interfaced with a JMA-2000 data system; ir spectra on a JASCO A-100S spectrophotometer; $^1$H nmr spectra on a JEOL PMX60 or a JEOL FX-100 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard, except where noted otherwise.

5-Substituted furfuryl alcohol (8). To a cooled solution of furfuryl alcohol (172 μl, 2 mmol) in dry THF (10 ml) was added 15% n-BuLi in n-hexane (2.6 ml, 4 mmol) dropwise at -40 °C. The mixture was stirred at -15 °C for 3∼4 h. Alkyl iodide (1 mmol) was added dropwise to the lithiate solution at -15 °C. Stirring was continued at -15∼-10 °C for 3 h and at -10∼0 °C overnight. The reaction mixture was diluted with 20 ml of $Et_2O$, washed with cold water several times and sat NaCl aq, dried and evaporated. The residue was chromatographed on silica gel, and elution with 25% $Et_2O$ in hexane gave 5-alkylfurfuryl alcohol as an oil.

5-Octylfurfuryl alcohol (8a). 168 mg (80%) of 8a was obtained from 1-iodooctane (172 μl, 1 mmol). 8a: ms m/z 210 ($M^+$); ir (neat) ν 3320, 3100, 1560, 1010 cm$^{-1}$; $^1$H nmr δ 0.89 (3H, m), 2.55 (2H, dd, J=7,7 Hz), 4.42 (2H, s), 5.82 (1H, d, J=3 Hz), 6.07 (1H, d, J=3 Hz).

5-[(3E,6E)-3,6-Octadienyl]furfuryl alcohol (8b). 8-Iodo-2,5-octadiene[6] (650 mg, 2.75 mmol) gave 215 mg (37.9%) of 8b: ms m/z 206 ($M^+$); ir (neat) ν 3320, 3100, 1560, 1010, 965 $cm^{-1}$; $^1H$ nmr δ 1.65 (3H, m), 2~2.8 (4H, m), 4.50 (2H, s), 5.40 (4H, m), 5.87 (1H, d, J=3.5 Hz), 6.11 (1H, d, J=3.5 Hz).

Sharpless oxidation of 5-octylfurfuryl alcohol (8a). 70% t-BuOOH (0.25 ml, 1.9 mmol) was added to the alcohol (8a) (135 mg, 0.64 mmol) and $VO(acac)_2$ (2.5 mg, 0.01 mmol) in $CH_2Cl_2$ (6 ml) and the mixture was stirred at 25°C for 15 min. The reaction mixture was diluted with $CH_2Cl_2$ (10 ml) and washed with water, 5% $NaHCO_3$ aq, water, and sat NaCl aq, dried and concentrated to ca. 3 ml. The concentrate was subjected to silica gel chromatography. Elution with 25% $Et_2O$ in n-hexane afforded 113 mg (77.8%) of 6-hydroxy-6-octyl-2H-pyran-3-one 9a: ms(FD) m/z 227 $[(M+1)^+]$; ir (neat) ν 3380, 1695, 1650, 1090 $cm^{-1}$; $^1H$ nmr δ 0.89 (3H, m), 4.02 (1H, d, J=16.5 Hz), 4.55 (1H, d, J=16.5 Hz), 6.02 (1H, d, J=10 Hz), 6.80 (1H, d, J=10 Hz).

6-Hydroxy-6-[(3E,6E)-3,6-octadienyl]-2H-pyran-3-one (9b). Alcohol 8b (170 mg, 0.82 mmol) in $CH_2Cl_2$ (8 ml) was oxidized with 70% t-BuOOH (0.32 ml, 2.5 mmol) and $VO(acac)_2$ (6 mg, 22 mmol) as above to give 145 mg (79%) of hemiketal 9b: ms(FD) m/z 223 $[(M+1)^+]$; ir (neat) ν 3400, 1690, 1630, 965 $cm^{-1}$; $^1H$ nmr δ 1.66 (3H, m), 2.69 (2H, m), 4.04 (1H, d, J=16.5 Hz), 4.57 (1H, d, J=16.5 Hz), 5.44 (4H, m), 6.03 (1H, d, J=10 Hz), 6.81 (1H, d, J=10 Hz).

4-Hydroxy-4-octyl-2-buten-4-olide (10a). To hemiketal 9a (266 mg, 1.18 mmol) in THF (15 ml) was added $H_5IO_6$ (283 mg, 1.24 mmol) in THF (15 ml) at 0 °C. After stirring for 2 h at rt, the reaction mixture was diluted with 15 ml of n-hexane, filtered, and the filtrate was extracted with 1N $NH_4OH$. $NH_4OH$ layer was washed once with $Et_2O$, acidified and extracted with $Et_2O$. $Et_2O$ layer was washed with water and sat NaCl aq, dried and evaporated. The residue was purified by silica gel chromatography (10% $Et_2O/CH_2Cl_2$ elution) to give 190 mg (76%) of lactol 10a which was crystallized from n-hexane. 10a: mp 57-58 °C; ms(FD) m/z 213$[(M+1)^+]$; ir (KBr) ν 3350, 1740, 1725 $cm^{-1}$; $^1H$ nmr δ 0.87 (3H, m), 6.00 (1H, d, J=6 Hz), 7.15 (1H, d, J=6 Hz).

4-Hydroxy-4-[(3E,6E)-3,6-octadienyl]-2-buten-4-olide (10b). 145 mg (0.65 mmol) of hemiketal was oxidized with 157 mg of $H_5IO_6$ (0.69 mmol) to yield 93 mg (68.5%) of lactol 10b: ms(FD) m/z 209 $[(M+1)^+]$; ir (neat) ν 3350, 1750, 965 $cm^{-1}$; $^1H$ nmr δ 1.66 (3H, m), 2.12 (4H, m), 2.68 (2H, m), 5.45 (4H, m), 6.10 (1H, d, J=6 Hz), 7.18 (1H, d, J=6 Hz).

4-Methoxy-4-octyl-2-buten-4-olide (11). 1M $SnCl_4$ in $CH_2Cl_2$ solution (120 μl) was added to lactol 10a (130 mg, 0.6 mmol) in $CH(OMe)_3$ (2.5 ml) at -20 °C and the mixture was left at -5∿0 °C for 20 h. The reaction mixture was diluted with n-hexane 15 ml, washed with cold $NaHCO_3$ aq, water, and sat NaCl aq, dried and evaporated. Silica gel chromatography (5% $Et_2O$/n-hexane elution) afforded 109 mg (78.7%) of 4-methoxy butenolide 11: ms m/z 211 [$(M-15)^+$]; ir (neat) ν 2840, 1815, 1770, 1610 $cm^{-1}$; $^1H$ nmr δ 0.87 (3H, m), 3.20 (3H, s), 6.19 (1H, d, J=5.9 Hz), 7.11 (1H, d, J=5.9 Hz).

4-Methoxy-4-[(3E,6E)-3,6-octadienyl]-2-buten-4-olide (5). Lactol 10b (75 mg, 0.36 mmol) was treated with $CH(OMe)_3$ (1.5 ml) and 1M $SnCl_4$ in $CH_2Cl_2$ solution (70 μl) as above to obtain 66 mg (82.5%) of 4-O-methyl ether 5: ms(FD) m/z 223 [$(M+1)^+$]; ir (neat) ν 1815, 1770, 965 $cm^{-1}$; $^1H$ nmr δ 1.66 (3H, m), 2.05 (4H, m), 2.67 (2H, m), 3.22 (3H, s), 5.42 (4H, m), 6.19 (1H, d, J=5.9 Hz), 7.13 (1H, d, J=5.9 Hz).

2,3-Epoxy-4-methoxy-4-octylbutan-4-olide (13). 10% NaClO (0.2 ml, ca. 0.27 mmol) was added dropwise to the stirred solution of 11 (30 mg, 0.13 mmol) in DMF-$Et_2O$ (1:1, 6 ml) at 0 °C. After stirring for 1 h at 0 °C, the mixture was diluted with $Et_2O$ (20 ml), washed with 10% $NaHSO_3$ aq, 5% $NaHCO_3$ aq, water, and sat NaCl aq, dried and evaporated. Chromatography (on $SiO_2$; 5% $Et_2O$/n-hexane elution) gave 13 mg (40.5%) of epoxide 13 and 12 mg of 11 (40%). 13: ms m/z 243 [$(M+1)^+$] (Found 243.1593, Calcd 243.1595 for $C_{13}H_{23}O_4$); ir (neat) ν 1790, 880 $cm^{-1}$; $^1H$ nmr δ 0.88 (3H, m), 3.39 (3H, m), 3.78 (1H, d, J=3 Hz), 3.94 (1H, d, J=3 Hz).

2,3-Epoxy-4-methoxy-4-[(3E,6E)-3,6-octadienyl]butan-4-olide (4). Treatment of butenolide 5 (35 mg, 0.15 mmol) in DMF-$Et_2O$ (1:1, 12 ml) with 10% NaClO (0.22 ml, ca. 0.3 mmol) at 0 °C for 1 h and chromatography as above afforded 14 mg (37%) of epoxide 4 and 5 (13 mg, 37%). 4: ms m/z 238 ($M^+$) (Found 238.1170, Calcd 238.1204 for $C_{13}H_{18}O_4$); ir (neat) ν 1780, 960, 875 $cm^{-1}$; $^1H$ nmr δ 1.66 (3H, m), 2.66 (2H, m), 3.39 (3H, s), 3.78 (1H, d, J=3 Hz), 3.94 (1H, d, J=3 Hz), 5.43 (4H, m).

(±)-Tetrahydrocerulenin (14). To epoxy lactone 13 (11 mg) in MeOH (0.5 ml) was added 0.5 ml of ca. 16% $NH_3$/MeOH at 0 °C. The mixture was stirred at 0 °C for 1.5 h and evaporated to give 13 mg of colorless solid which was recrystallized from MeOH. 14: mp 90-94 °C; ms m/z 228 [$(M+1)^+$](Found 228.1614, Calcd 228.1598 for $C_{12}H_{22}NO_3$); ir (KBr) ν 3360, 3280, 1700, 1030 $cm^{-1}$; $^1H$ nmr δ 0.89 (3H, m), 2.83 (1H, m, OH), 3.61 (1H, m), 3.82 (1H, m), 5.90 (1H, m, NH).

(±)-Cerulenin (1). Epoxylactone 4 (22 mg) in MeOH (1 ml) was treated with ca. 16% $NH_3$/MeOH at 0 °C as above giving 21 mg of an oil. The product (19 mg) was chromatographed on RP-18 (8 mm id x 250 mm; 70% MeOH 1 ml/min) to obtain 15 mg

(80.4%) of (±)-cerulenin (**1b**) which was crystallized from benzene-MeOH. **1b**: mp; 64-66°C; ms m/z 223 ($M^+$) (Found 223.1201, Calcd 223.1207 for $C_{12}H_{17}NO_3$); ir (KBr) ν 3370, 3260, 1725, 1710, 960 $cm^{-1}$; $^1H$ nmr ($CDCl_3$ + $D_2O$) δ 1.64 (3H, m), 1.88 (2H, m), 2.22 (2H, m), 2.66 (2H, m), 3.58 (1H, d, J=3 Hz), 3.80 (1H, d, J=3 Hz), 5.42 (4H, m). Silica gel chromatography (10% $Et_2O$ in $CH_2Cl_2$ elution) of the equilibrium mixture of **1** gave 3 mg of **1a** as an oil. **1a**: ir ($CHCl_3$) ν 3500, 3370, 1725, 1695, 1580, 960 $cm^{-1}$; $^1H$ nmr ($CDCl_3$) δ 1.65 (3H, m), 2.36 (2H, m), 2.65 (4H, m), 3.72 (1H, d, J=5 Hz), 3.85 (1H, d, J=5 Hz), 5.39 (4H, m), 5.56 (1H, bs), 6.30 (1H, bs).

These spectral data are identical with those of natural cerulenin.

## ACKNOWLEDGEMENT

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