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

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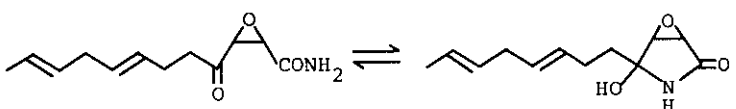
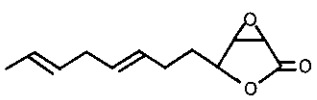
Abstract——Antibiotic (±)-cerulenin and (±)-tetrahydrocerulenin have been synthesized from furfuryl alcohol. The developed procedure involves chemoselective alkylation of furfuryl alcohol and epoxidation of 4-methoxybutenolide.

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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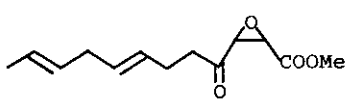

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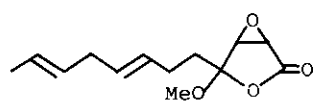

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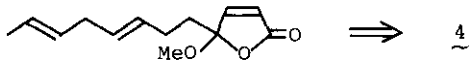
cis-epoxyester 3 and 4-methoxy-2,3-epoxylactone 4 were the convergent products which gave cerulenin (1) merely by their ammonolysis.

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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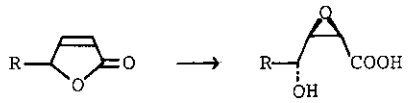
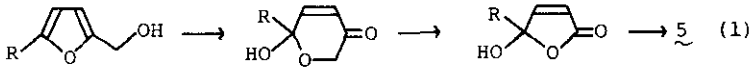


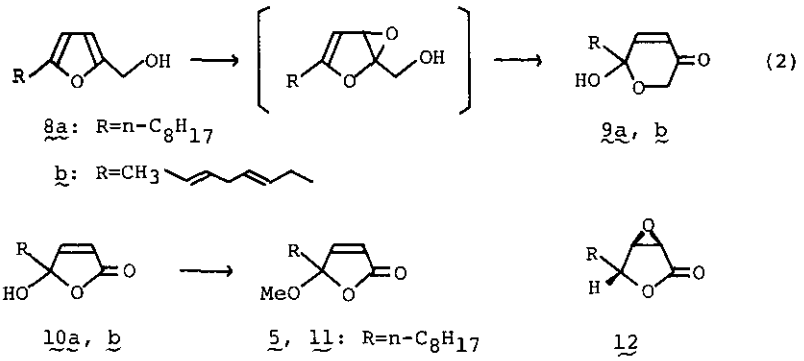
6 7



5 (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_8H_{17}
b: R=CH_3

9a, b

10a, b

5, 11: R=n-C_8H_{17}

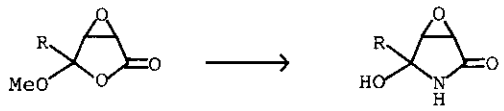
12

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, ν 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; ^1H 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}; ^1H 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) υ 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) υ 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) υ 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) υ 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) υ 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) υ 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) υ 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) υ 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) υ 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) υ 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 ($CHCl_3$) υ 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.

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REFERENCES

1. A. Kawaguchi, H. Tomoda, S. Nozoe, S. Omura, and S. Okuda, J. Biochem., 1982, 92, 7, and references cited therein.
2. S. Omura, Bacteriol. Reviews, 1976, 40, 681; M. Sunagawa, T. Ohta, and S. Nozoe, J. Antibiot., 1983, 36, 25.
3. M. J. Schlesinger and C. Malfer, J. Biol. Chem., 1982, 257, 9887.
4. H. Funabashi, S. Iwasaki, S. Okuda, and S. Omura, Tetrahedron Lett.,1983, 24, 2673.
5. A. A. Jakubowski, F. S. Guziec, Jr., and M. Tishler, Tetrahedron Lett., 1977, 2399; M. Pietraszkiewicz, and P. Sinay, Tetrahedron Lett., 1979, 4741; R. K. Boeckman, Jr., and E. W. Thomas, J. Amer. Chem. Soc., 1979, 101, 987.
6. E. J. Corey, and D. R. Williams, Tetrahedron Lett., 1977, 3847.
7. G. Buchi, and H. Wuest, J. Org. Chem., 1966, 31, 977.
8. H. Kikuchi, Y. Tsukitani, H. Nakanishi, I. Shimizu, S. Saito, K. Iguchi, and Y.Yamada, Chem. Lett., 1982, 233.
9. cf. T. Shono and Y. Matsumura, Tetrahedron Lett., 1976, 1363.

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