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A NEW VERSATILE SYNTHESIS OF CERULENIN

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Optically active cerulenin was synthesized by connecting the epoxy aldehyde **4** with the lithiated diene generated from **5**. The way of carbon labeling at C-5 was also investigated.

KEYWORDS——cerulenin synthesis; antibiotic; Cephalosporium caerulens; fatty acid synthetase

Cerulenin (**1**), an antibiotic isolated from Cephalosporium caerulens, strongly inhibits β-ketoacyl thioester synthetase (condensing enzyme) in fatty acid biosynthesis.[1] The inhibition mechanism is assumed to be an S-C bond formation between the C-2 of **1** and cysteine-SH located at the condensation center.[2] To investigate the inhibition mechanism of **1** in detail, radioisotope-labeled cerulenin and cerulenin analogues will be useful probes. Though several syntheses of cerulenin have been reported,[3,4] natural cerulenin has only been derived from D-glucose.[4] The synthetic procedure reported here was designed to introduce ^{14}C at C-5 with $Na^{14}CN$.

In a retro-synthetic analysis, the target molecule (**1**) was divided into two parts, 'head cation' (from C-1 to C-4) and 'tail anion' (from C-5 to C-12). Six

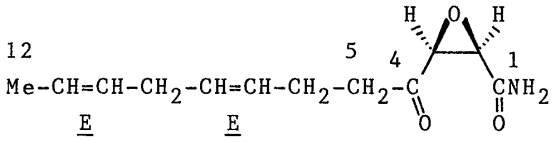
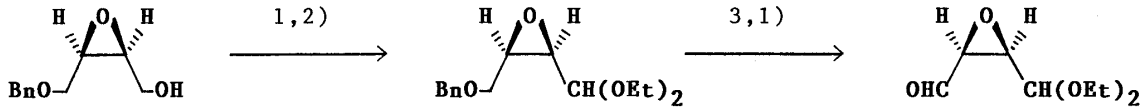
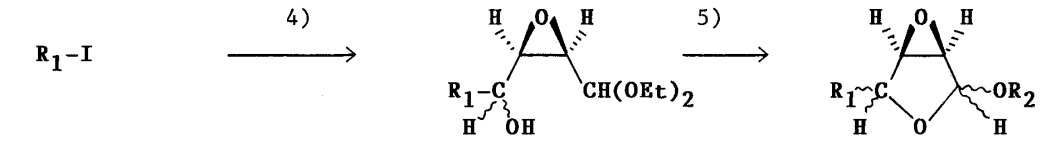


Fig. 1. Structure of Cerulenin (1)



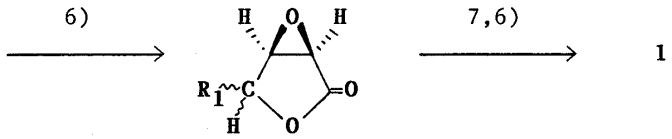
2:(2S,3R)-(-)-isomer **3** **4**

Chart 1



5:R_1= MeCH=CHCH$_2$CH=CHCH$_2$CH$_2$ (E, E) **6a**:(4R)-(+)-isomer **6b**:(4S)-(-)-isomer

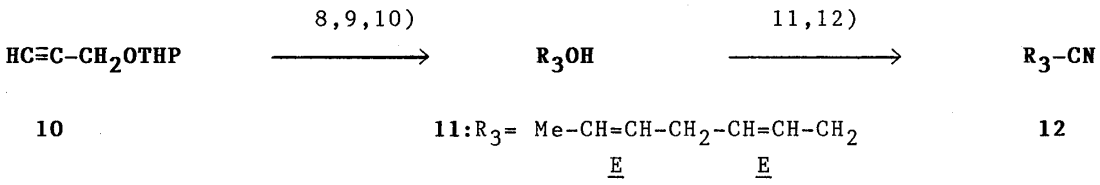
7a:R_2= Et,(1SorR,4R)-isomer
7b:R_2= Et,(1S&R,4S)-isomers
8a:R_2= H,(1S&R,4R)-isomers
8b:R_2= H,(1S&R,4S)-isomers



1

9a:(4R)-(+)-isomer
9b:(4S)-(+)-isomer

Chart 2



10 **12**

13 **14** **5**

Chart 3

Reagents in the Charts 1, 2 & 3
1) DMSO/$(COCl)_2$/CH_2Cl_2,TEA; 2) $HC(OEt)_3$/Amberlyst 15; 3) Na/NH_3; 4) t-BuLi in pentane, **4** in THF; 5) H_2SO_4(1%) in H_2O-acetone; 6) CrO_3/pyridine/CH_2Cl_2; 7) NH_4OH/MeOH; 8) EtMgBr/Et_2O-THF, CuCl/MeCH=$CHCH_2$Br(mainly trans)/Et_2O-THF; 9) MeOH/Amberlyst 15; 10) LAH/Et_2O; 11) MsCl/TEA/CH_2Cl_2; 12) NaCN/Aliquat 336/CH_2Cl_2-H_2O; 13) HCl(25%)-MeOH, H_2O; 14) NaI/Aliquat 336/CH_2Cl_2-H_2O

head synthones were considered according to the oxidation states of C-1 and C-4 of the chiral epoxides, i.e. CH_2OR, $CH(OR)_2$ or COR for C-1, and CHO or COX for C-4 functionality. In this report, we describe the synthesis using the chiral epoxide **4** as the head part.

The synthesis of **4** started with the Sharpless' epoxide **2**,[5] $[\alpha]_D$ = -23.9°(c=2.04,$CHCl_3$). Swern oxidation[6] of **2** followed by acetalization[7] gave **3** in 76% yield.[8] The benzyl group of **3** was difficult to cleave off with H_2/Pd-C even at 50 atm. Deprotection was attained by treatment with Na/NH_3.[9] Swern oxidation of the resulting alcohol gave the chiral epoxy aldehyde **4** in 65% yield from **3** (**Chart 1**).

The head epoxide **4** and the lithio derivative of (E,E)-3,6-octadienyl iodide[3c] (**5**) was connected to give a pair of isomers, **6a** and **6b** from **5** in 63% and 16% yields, respectively. The stereochemistry of these isomers was assigned at the stage of lactones, **9a** and **9b**, by their spectral comparisons with the reported data.[3b,3e] The acetal **6a** was hydrolyzed with H_2SO_4 in aqueous acetone at 55°C for 20 h to give a mixture of **7a** and **8a**. The cyclic acetal **7a** was separated and hydrolyzed under the same conditions to obtain **8a** (total 62% yield from **6a**). The cyclic hemiacetal **8b** was obtained from **6b** in 20% yield by a single treatment with H_2SO_4 in aqueous acetone.

Collins oxidation[10] of **8a** gave **9a** in 66% yield, and the oxidation of **8b** under the same conditions gave **9b**[11] in 71% yield. Ammonolysis of **9a** followed by Collins oxidation gave **1** as a white powder in 45% yield with 94% ee.[12] The recrystallization of the product from benzene gave colorless prisms, mp 93°C (lit.[4] 93°C), which were used for $[\alpha]_D$ measurements.[12] The ^{1}H-NMR, EI-MS and IR data of the synthetic **1** were identical with those of natural cerulenin (**Chart 2**).

In the tail part synthesis, a preliminary experiment for the introduction of C_1 unit at C-5 with NaCN was examined. The (E,E)-dienol **11**,[13] prepared from **10** in 50% yield after purification with $AgNO_3$-impregnated silica gel column chromatography, was mesylated[14] and treated with NaCN in the presence of phase transfer catalyst, aliquat 336[15] in CH_2Cl_2-H_2O to give **12** in 70% yield. The nitrile **12** was treated successively with HCl(25%)-MeOH and ice-water[16] at 0°C to give the corresponding methyl ester **13** in 77% yield.[17] The methyl ester **13** was reduced with LAH to give the alcohol **14**[3c] which was converted into iodide **5** in 74% yield from **14** via the mesylate of **14**. The iodide **5** was obtained in 38% yield from the alcohol **11** (**Chart 3**).

The synthesis method described is applicable for preparations of optically active analogues with a variety of tail-chains, and labeled **1**. Experimental details and further studies will be described elsewhere.

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11) Because of a shortage of the sample, **9b** was not converted to **1**.
12) Optical purity was calculated from $[\alpha]_D$ values of **9a**, $[\alpha]_D$=+53.1°(c=0.51, $CHCl_3$), and the reported one, $[\alpha]_D$=+56.5° (c=0.8,$CHCl_3$).[4a] Synthetic **1** showed $[\alpha]_D$=-6.5°(c=0.09, $CHCl_3$). The difference between the value and the reported one, $[\alpha]_D$=-12°(c=1,$CHCl_3$),[1a] is the result of the facile equilibration between **1** and its diastereomeric hydroxy lactams.[3e]
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17) L.M. du Plessis and J.A.D.Erasmus, S.Afr.J.Chem.,31,75(1978).
18) [Selected ^{1}H-NMR data(δ,$CDCl_3$)] **1**: 1.66(3H,m,C$\underline{H}_3$), 2.31(2H,'q',J=7 Hz,H-6), 2.63(1H,dt,J=17.4,7.2 Hz,H-5), 2.65(2H,m's,H-9), 2.69(1H,dt,J=17.4,7.5 Hz,H-5), 3.73(1H,d,J=5.4 Hz,H-2), 3.87(1H,d,J=5.4 Hz,H-3), 5.32-5.51(5H,m's,C$\underline{H}$=C$\underline{H}$ X 2 & N$\underline{H}$), 6.3(1H,bs,N$\underline{H}$); **4**: 1.20,1.24(3H X 2,t X 2,J=7.0 Hz,C$\underline{H}_3$ X 2), 3.38(1H,dd,J=4.4,4.5 Hz,H-2), 3.42(1H,dd,J=3.2,4.5 Hz,H-3), 3.57,3.58,3.70,3.70(1H X 4,dq X 4,J=9.4,7.0 Hz,C$\underline{H}_2$ X 2), 4.77(1H,d,J=3.2 Hz,H-4), 9.50(1H,d,J=4.4 Hz,H-1); **5**: 1.66(3H,d,J=6.4 Hz,C$\underline{H}_3$CH=CH), 2.56(2H,dt,J=7.2, 7.2 Hz,H=CHC$\underline{H}_2$CH$_2$I), 2.68(2H,'bt',J=6 Hz,CH=CHC$\underline{H}_2$CH=CH), 3.15(2H,t,J=7.2 Hz,C$\underline{H}_2$I), 5.3-5.6(4H,m's,C$\underline{H}$=C$\underline{H}$ X 2); **6a**: 1.24,1.27(3H X 2,t X 2,J=7.0 Hz,OCH$_2$C$\underline{H}_3$ X 2), 1.65(3H,m,C$\underline{H}_3$-CH=CH), 1.74(2H,m's,H-5), 2.10-2.28(2H,m's,H-6), 2.67(2H,m's,H-9), 2.7(1H,bd,J=2 Hz,O$\underline{H}$), 2.91(1H,dd,J=4.1,8.1 Hz,H-3), 3.14(1H,dd,J=4.1,5.9 Hz,H-2), 3.49(1H,'q',J=8 Hz,H-4), 3.55-3.83(4H,dq X 4,OC$\underline{H}_2$CH$_3$ X 2), 4.52(1H,d,J=5.9 Hz,H-1), 5.36-5.52(4H,m's,C$\underline{H}$=C$\underline{H}$ X 2); **6b**: 1.22,1.26(3H X 2,t X 2,J=7 Hz,OCH$_2$C$\underline{H}_3$ X 2), 1.65(5H,m's,H-5 and C$\underline{H}_3$-CH=CH), 2.0(1H,bd,J=4 Hz,O$\underline{H}$), 2.08-2.28(2H,m's,H-6), 2.67(2H,m's,H-9), 2.99(1H,dd,J=4.3,7.4 Hz,H-3), 3.19(1H,dd,J=4.3,6.4 Hz,H-2), 3.53(1H,dq,J=9.3,7.0 Hz,OC$\underline{H}_2$CH$_3$), 3.6-3.8(3H,dq X 3,OC$\underline{H}_2$CH$_3$), 3.62(1H,m,H-4), 4.41(1H,d,J=6.4 Hz,H-1), 5.36-5.52(4H,m's,C$\underline{H}$=C$\underline{H}$ X 2); **9a**: 1.66(3H,m,C$\underline{H}_3$), 1.76(2H,m's,H-5), 2.20(2H,m's,H-6), 2.68(2H,m's,H-9), 3.77(1H,d,J=2.2 Hz,H-2), 3.96(1H,d,J=2.2 Hz,H-3), 4.59(1H,dd,J=6.3,6.8 Hz,H-4), 5.34-5.55(4H,m's,C$\underline{H}$=C$\underline{H}$ X 2); **9b**: 1.66(3H,m,C$\underline{H}_3$), 1.84,1.93(1H X 2,m X 2,H-5), 2.21(2H,m's,H-6), 2.68(2H,m's,H-9), 3.77(1H,d,J=2.5 Hz,H-2), 4.06(1H,d,J=1.3,2.5 Hz,H-3), 4.47(1H,ddd,J=1.3,6.3,7.4 Hz,H-4), 5.36-5.56(4H,m's,C$\underline{H}$=C$\underline{H}$ X 2).

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