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(9) The thioacetic acid used in this study was obtained commercially from Aldrich Chemical Company or Matheson, Coleman and Bell. The acid was distilled twice before using and stored in a stoppered flask at −20 °C. The content of acetic acid in the purified compound was estimated to be less than 0.5%.
(10) The chemical shifts of the –SH protons were not resolved for the individual isomers in dry acetone-d_6 as solvent. However, in the presence of a trace amount of water, the broad absorption for these protons changed into a sharp peak at δ 5.90 and a broad, overlapping peak. The chemical shifts observed for the acidic proton in thioacetic acid show that the isomers are *E*-**1** and *Z*-**1**, rather than the –OH tautomers, which should absorb at much lower field.
(11) Hydrogen-bonding solvents such as acetone are known to suppress exchange in alcohols and amines. For example, see (a) J. G. Traynham and G. A. Knesel, *J. Am. Chem. Soc.*, **87**, 4220 (1965), and references cited therein; (b) G. A. Yousif and J. D. Roberts, *ibid.*, **90**, 6428 (1968).
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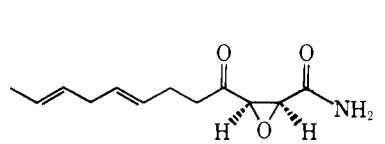
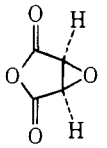
A Total Synthesis of *dl*-Cerulenin: a Novel Fatty Acid Antibiotic and Lipid Synthesis Inhibitor

Sir:

Cerulenin (**1**) was isolated from *Cephalosporium caerulens*, and shown to possess antibiotic[1] as well as lipid synthesis inhibitory properties.[2] The novel structure, **1**, has been assigned on the basis of IR, NMR, and chemical degradative data.[3,4] We have undertaken the total synthesis of cerulenin described herein in hopes of confirming the structural assignment as well as providing a route to the labeled antibiotic for biological studies of current interest[5] and to structural analogues of this novel class of substances.

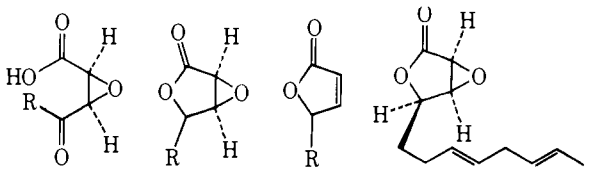


1



2

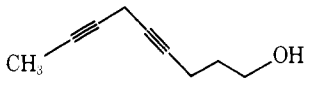
We considered initially, that cerulenin might be readily derived from interaction of anhydride **2**[6] already possessing the requisite acyl epoxy acrylate system, and suitably constituted organometallic reagents. However, a variety of reagents under a range of reaction conditions failed to lead to the desired epoxy acrylic acid derivatives, **3**. We turned instead to the preparation of epoxy lactones, **4**, from which cerulenin might be readily derived. The straightforward routes to the class of substances, **4**, such as epoxidation of unsaturated lactones such as **5**, proved unfeasible.[7] Consequently, we investigated indirect methods of production of the key intermediate, lactone **6**.



3 4 5 6

Treatment of 4-pentyn-1-ol tetrahydropyranyl ether successively with ethyl magnesium bromide in tetrahydrofuran (THF), cuprous chloride, and 1-bromo-2-butyne afforded, after removal of the protecting group, the air sensitive 1,4 diynol, **7**, as high boiling liquid (bp 70–75 °C (0.08 mm); 67%).[8] Reduction of **7** with lithium (6 equiv) in liquid ammonia, in the presence of *tert*-butyl alcohol (1 equiv) and solid ammonium sulfate (10 equiv) to prevent undesired base catalyzed isomerization and overreduction, produced the trans,trans dienol **8** in quantitative yield. Although few metal–ammonia reductions of 1,4 diynes have been recorded, the foregoing conditions seem generally applicable to the synthesis of trans,trans 1,4-dienes. Oxidation of **8** to the aldehyde **9** (bp 45 °C (0.5 mm) with pyridinium chlorochromate[9] (1.5 equiv) proceeded smoothly (65% yield) and this intermediate was readily purified by distillation.

Treatment of **9** with lithio propargyl alcohol tetrahydropyranyl ether at −78 °C in THF[10] provided the addition product which was hydrolyzed (wet methanol; *p*-toluenesulfonic acid; 20 °C, 4 h), partially reduced (palladium/barium sulfate, quinoline),[11] and selectively epoxidized utilizing vanadyl acetylacetonate/*tert*-butyl hydroperoxide.[12] After purification by chromatography (silica gel) the epoxy diol **10** was obtained in ~50–60% overall yield.[13]



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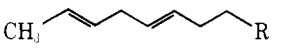
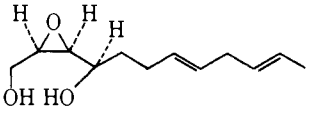


8, R = CH_2OH
9, R = CHO



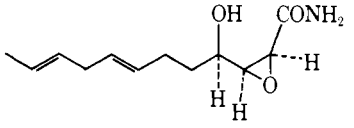
10

Epoxydiol **10** was then converted to epoxy lactone **6** (bp 120 °C at 0.5 mm); NMR ($CDCl_3$): δ 2.8 (m, 2 H), 3.76 (d, 1 H), 4.1 (m, 1 H), 4.5 (m, 1 H), 5.5 (m, 4 H) utilizing silver carbonate on celite (15 equiv) in refluxing benzene for 2 h (50%).

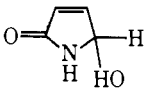
Aminolysis of lactone **6** (NH_4OH/ether; room temperature) proceeded cleanly to give the amido alcohol **11** in nearly quantitative yield. The final conversion of amido alcohol **11** to cerulenin **1** was effected by treatment with pyridinium chlorochromate (3 equiv in CH_2Cl_2; 25 °C; 2 h).[15] Isolation and purification by successive chromatography (fluorosil; silica gel) provided *dl*-cerulenin (mp 40–42 °C) identical with an authentic sample[16] by comparison of spectral properties (IR–NMR–mass spectra) and thin layer mobility in several solvent systems.

The route seems amenable to the production of optically active cerulenin by resolution of the alcohol derived from **9** and efforts toward this end as well as the synthesis of analogues are under investigation currently.

It is of interest to note that cerulenin (**1**), somewhat surprisingly, seems to exist both in the crystal and in solution primarily, if not exclusively, in the open form (two carbonyl absorbtions in the infrared), whereas related substances derived from the photooxygenation of pyrrole appear to prefer the closed aminol structure **12**.[17] This is presumably due to the greater stability of hemiacetals relative to hemiketals.



11



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(16) We wish to thank Professor Konrad Bloch of Harvard University for a generous gift of natural cerulenin for comparison.
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(18) Fellow of the Alfred P. Sloan Foundation (1976–1978).

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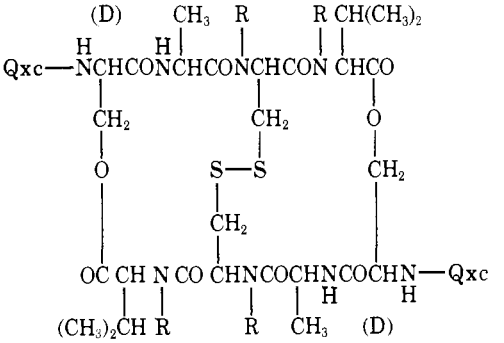
Synthesis of Des-*N*-tetramethyltriostin A, a Bicyclic Octadepsipeptide Related to the Quinoxaline Antibiotics

Sir:

The quinoxaline antibiotics are a group of bicyclic octadepsipeptides.[1] These antibiotics show activity against gram-positive bacteria[2] and certain animal tumors,[1c,3] and are potent inhibitors of RNA synthesis.[4] Their mechanism of action apparently occurs by binding to DNA in which they function as bifunctional intercalating agents.[5] Few reports[6,7] have appeared relating to synthetic studies on these substances. We report herein the first total synthesis of a close analogue of the quinoxaline antibiotics, namely, des-*N*-tetramethyltriostin A (**1**).

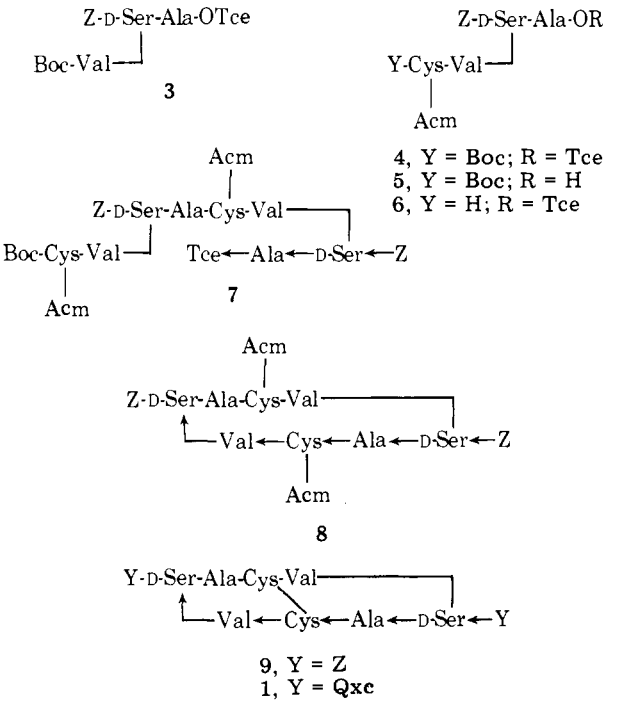
The title compound differs from the natural antibiotic, triostin A (**2**),[1d,e] by lack of *N*-methyl groups on the L-cysteine and L-valine residues. The synthesis of **1** proceeded as follows.[8] Coupling of *Z*-D-Ser-OH with the trichloroethyl ester[9] of L-alanine by use of *N,N'*-dicyclohexylcarbodiimide (DCC) in methylene chloride gave (71%) *Z*-D-Ser-Ala-OTce, which was converted in 76% yield to tridepsipeptide **3** by ester bond formation using DCC in pyridine.[6] Deprotection of **3** with trifluoroacetic acid (TFA), followed by neutralization and coupling to Boc-Cys(Acm)OH[10] using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide[11]:hydroxybenztriazole[12] gave tetradepsipeptide **4** in 69% yield.



1, R = H
2, R = Me

Qxc = quinoxaline-2-carbonyl

Removal of the Tce ester function in **4** by use[9] of zinc in acetic acid yielded (87%) **5**, while removal of the Boc group in **4** gave (88%) **6**. Fragment coupling of **5** and **6** was effected by either the mixed anhydride[13] (from isobutyl chloroformate) (78%) or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide[11]: hydroxybenztriazole[12] (93%) methods to furnish the linear octadepsipeptide **7**. A sequence of deprotection (Zn in AcOH, then TFA), neutralization, and cyclization (*N*-hydroxysuccinimide:DCC,[14] high dilution of compound **7** at concentration of 2.6×10^{-3} M in THF:DMF (190:15), 4 days at room temperature) provided, following chromatography on a silica gel column and recrystallization, the cyclic depsipeptide **8** in 43% yield from **7**. Treatment of **8** with iodine in methanol[15] effected conversion (89%) to the disulfide **9**, which upon acidolysis of the benzyloxycarbonyl group (HBr in acetic acid)



4, Y = Boc; R = Tce
5, Y = Boc; R = H
6, Y = H; R = Tce

7

8

9, Y = Z
1, Y = Qxc