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A TOTAL SYNTHESIS OF dl-CERULENIN AND dl-TETRAHYDROCERULENIN

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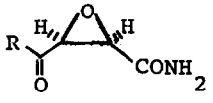
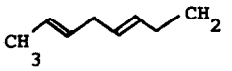
Cerulenin, an antibiotic active against a number of bacteria and fungi,[1] was first isolated from Cephalosporium caerulens in 1960 by Hata and coworkers.[2] It has attracted considerable attention because of its inhibitory action in the biosynthesis of lipids and steroids.[3,4,5] The structure of cerulenin was established as 2S,3R-epoxy-4-oxo-7,10-trans, trans-dodecadienoic acid amide 1b [6,7]

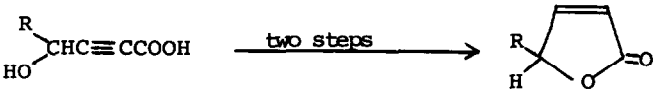


1a R=n-C_8H_{17}

1b R=C_8H_{13} = 

The synthesis of cerulenin and its derived, microbiologically active, tetrahydrocerulenin 1a were undertaken to confirm their structures and to provide routes for their preparation in sufficient quantity to carry out adequate pharmacological studies. Since the completion of our synthesis, however, the first report of a synthesis of dl-cerulenin has appeared.[8] Inasmuch as there are interesting differences between this synthesis by Boeckman and Thomas and ours, we feel it is appropriate to communicate our data at this time .

Our synthetic approach involved the 4-substituted-2-butenolides 3a and 3b as key intermediates. This ring system is particularly useful since it controls epoxide stereochemistry

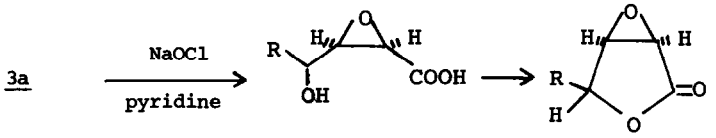


2a R=C_8H_{17}
2b R=C_8H_{13}

3a R=C_8H_{17}
3b R=C_8H_{13}

and provides a mild route to the very sensitive 4-keto-2,3-epoxy amide system in cerulenin.[9] Boeckman and Thomas indicated that they considered the direct epoxidation of an appropriate butenolide for the synthesis of cerulenin but were unsuccessful in their attempts to effect this transformation in model lactones.[8,10] In contrast to their lack of success, we found that both lactones 3a and 3b undergo epoxidation with great ease by treatment with sodium hypochlorite in pyridine[11] at 0°.

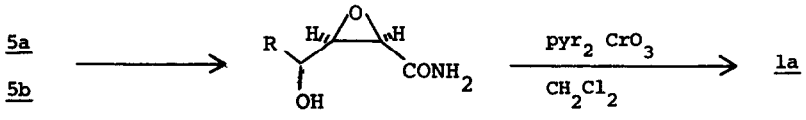
The butenolide 3a, required for the synthesis of tetrahydrocerulenin, was prepared by reaction of the Grignard dianion of propiolic acid with nonaldehyde affording 4-hydroxy-2-dodecynoic acid 2a, m.p. 68-69° (52%) which on hydrogenation with Lindlar catalyst cyclized into the butenolide 3a, b.p. 113° (1 mm), m.p. 24-26° in over 90% yield. The hypochlorite-pyridine treatment gave the hydroxy acid 4a which on warming to 65° closed to a single isomer*of the epoxy lactone 5a, b.p. 134° (1 mm), m.p. 29.5-31°. The overall yield of 5a from 3a was 97%.



4a R=C_8H_{17} 5a R=C_8H_{17}

4b R=C_8H_{13} 5b R=C_8H_{13}

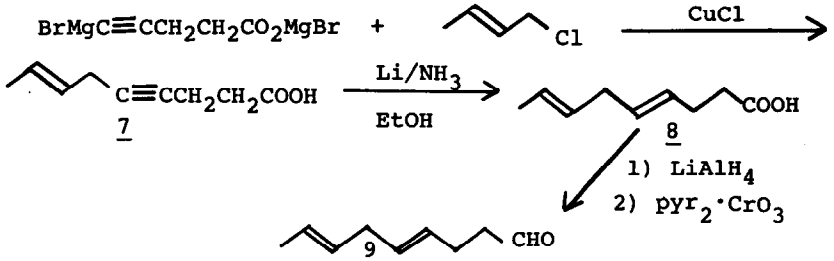
Ammonolysis of 5a with ammonium hydroxide in methanol led to the hydroxy-cis-epoxy amide 6a, m.p. 106-107° (CCl_4) in 85% yield which was converted into dl-tetrahydrocerulenin 1a, m.p. 79-80°(CCl_4) by oxidation with Collins reagent[12] in 92% yield.



6a R=C_8H_{17}

6b R=C_8H_{13}

dl-Cerulenin was similarly synthesized starting with 4-pentynoic acid[13] and trans-crotyl chloride. The Grignard dianion of the former was coupled with the chloride in the presence of Cu(I) and the resulting acetylenic acid 7, m.p. 57.5-58.5° (hexanes)(72%), was reduced by lithium-liquid ammonia-ethanol to trans,trans-4,7-nonadienoic acid 8, b.p. 106-108° (1 mm) (85%). Lithium aluminum hydride reduction of 8 followed by Collins oxidation produced trans, trans-4,7-nonadienal 9, b.p. 50° (1 mm) (82%).



Repetition of the sequence established for tetrahydrocerulenin beginning with the dienal 10 yielded 2b (52%); 3b, b.p. 105-107° (0.35 mm) (64%); 5b, b.p. 120-121° (0.4 mm) (84%); and dl-cerulenin 1b, m.p. 40-43° (75%).[14,15]

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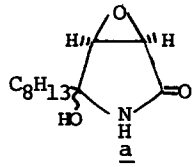
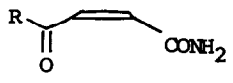
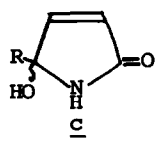
9. One interesting phenomena noted by Arison and Ōmura (unpublished) and also by us, but not observed by Boeckman and Thomas[8], is the cyclization of cerulenin in a variety of solvents into a mixture of diastereomeric hydroxylactams a. Although cerulenin tends to maintain its acyclic form in aprotic solvents, it has been established by nmr and two dimensional tlc in protic solvents such as CD_3OD that the equilibrium between cerulenin and its tautomeric hydroxylactams favors the cyclic form. In another synthetic scheme, to be reported at a later time, involving intermediates containing the 4-keto-cis-enoic acid amide system, we observed the hydroxylactams c with little or no acyclic forms b.



a



b



c

R=C_8H_{17} or R=C_8H_{13}

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11. Sodium hypochlorite and pyridine has been used previously only to epoxidize benzalacetophenone and 1,4-naphthoquinone. S. Marmor, J. Org. Chem., 28, 250 (1963).

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14. Yields in the cerulenin series have not been optimized.

15. Satisfactory spectral data have been obtained for all intermediates and products. Synthetic dl-cerulenin and dl-tetrahydrocerulenin compare favorably with natural cerulenin and its tetrahydro-derivative with respect to nmr, ir, mass spec and tlc. All compounds show M^+ (or in the case of amides, M+1) in the mass spectrum. Selected spectral characteristics are summarized here: 1a ir ($CHCl_3$) ν1730, 1685, 1580 cm^{-1}; nmr($CDCl_3$) δ0.7-1.8 (m,15H), 2.61 (t,2H), 3.82 (ABQ,2H)[J=5.5 Hz], 6.2 (bs,1H), 6.45 (bs,1H); 1b ir ($CHCl_3$) ν1720, 1690, 1585, 970 cm^{-1}; nmr ($CDCl_3$) δ 1.68 (m,3H), 2.17-2.87 (m,6H), 3.81 (ABQ, 2H)[J=5.5 Hz], 5.47 (m,4H), 6.1-6.6 (b,2H); 2a ir (CCl_4)ν2230, 1690 cm^{-1}; nmr ($CDCl_3$-D_2O) δ 0.70-2.0 (m,17H), 4.42 (t,1H); 2b ir (neat) ν2250, 1700, 965 cm^{-1}; nmr ($CDCl_3$-D_2O) δ1.68 (m,3H),1.75-2.50 (m,4H), 2.53-2.83 (m,2H), 4.57 (t,1H), 5.32-5.62 (m,4H); 3a ir (CCl_4) ν 1755, 1600 cm^{-1}; nmr (CCl_4)δ 0.7-2.0 (m,17H), 4.96 (m,1H), 6.00 (dd,1H) [$J_{\ }$=6 Hz, J_{13}=2 Hz], 7.50 (dd,1H)[J_{23}=1 Hz]; 3b ir (neat) ν 1750, 1600, 965 cm^{-1}; nmr ^{12}($CDCl_3$) ^{13} δ 1.68 (m,3H), 1.75-2.50 (m,4H), 2.52-2.79 (m,2H), 5.09 (m,1H), 5.31-5.63 (m,4H), 6.10 (dd,1H) [J_{12}=6 Hz][J_{23}=2 Hz], 7.51 (dd,1H)[J_{23}=1.5 Hz]; 5a ir ($CHCl_3$) ν1775, 1160, 855 cm^{-1}; nmr ($CDCl_3$) δ 0.7-2.0(m,17H), 3.76 (dd,1H)[J_{12}= 2.5 Hz] [J_{23}< 0.5 Hz], 3.98 (d,1H), 4.56 (m,1H); 5b ir ($CHCl_3$) ν 1780, 975, 855 cm^{-1}; nmr($CDCl_3$) δ 1.68 (m,3H), 1.75-2.50(m,4H), 2.77 (m,2H), 3.90 (d,1H) [J=2.5 Hz], 4.15 (d,1H), 4.73 (t,1H), 5.32-5.63 (m,4H); 6a ir ($CHCl_3$) ν 1690, 1565 cm^{-1}; nmr ($CDCl_3$)δ 0.7-1.9 (m,17H), 3.15 (m,1H), 3.50 (m,2H), 3.90 (bs,1H), 5.80 (bs,1H), 6.15 (bs,1H); 6b ir ($CHCl_3$) ν 1690, 1580, 970 cm^{-1}; nmr ($CDCl_3$)δ 1.66 (m,3H), 1.75-2.45 (m,4H), 2.71 (m,2H), 2.97-3.29 (m,1H), 3.32-3.73 (m,2H), 4.73 (bs,1H), 5.30-5.61 (m,4H), 6.60 (bs,1H), 6.98 (bs,1H); 7 ir ($CHCl_3$) ν 1710, 965 cm^{-1}; nmr ($CDCl_3$) δ 1.71 (m,3H), 2.62 (s,4H), 2.81-3.03 (m,2H), 5.52-5.76 (m,2H), 11.3 (s,1H); 8 ir ($CHCl_3$) ν 1710, 970 cm^{-1}; nmr ($CDCl_3$) δ 1.67 (m,3H), 2.28-2.51 (m,4H), 2.54-2.88 (m,2H), 5.32-5.64 (m,4H), 10.4 (s,1H); 9 ir (neat) ν 2820 (sh), 2720, 1715, 970 cm^{-1}; nmr ($CDCl_3$) δ 1.66 (m,3H), 2.25-2.53 (m,4H), 2.53-2.78 (m, 2H), 5.28-5.57 (m,4H), 9.73 (m,1H).

* Note: A referee has suggested that we comment on the stereochemistry of the hypochlorite epoxidation. The coupling constants J_{23} are less than 0.5 Hz for both 5a and 5b. Examination of models suggests that only when the epoxide and the side chain are trans can the dihedral angle φ approach 90°, generating the observed coupling. This would be consistent with hypochlorite attack on the least hindered face of the butenolides. We have underway an investigation of the scope of the hypochlorite epoxidation.