Tetrahedron Letters No. 44, pp 3847 - 3850, 1977. Pergamon Press. Printed in Great Britain.

A TOTAL SYNTHESIS OF (+)-CERULENIN

E. J. Corey and David R. Williams

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

(Received in USA 17 August 1977; received in UK for publication 16 September 1977)

The antifungal antibiotic, cerulenin 1, was isolated from the culture filtrate of Cephalosporium caerulens,[1] and shown to inhibit lipid biosynthesis of Escherichia coli by irreversibly binding β-ketoacyl-acyl carrier protein synthetase, the enzyme which catalyzes the acylation of a malonyl thioester for the chain lengthening reaction of fatty acid synthesis.[2] The structure originally proposed[3a] for cerulenin on the basis of chemical and spectroscopic data was revised to 1 in 1974[3b] on the basis of a detailed nmr study. Very recently two different synthetic routes to the racemic antibiotic have been reported.[4] This communication describes concurrent work in these laboratories which has led to a simple and convergent synthesis of (+)-cerulenin.

Treatment of 3-butyn-1-ol with dihydropyran (1.2 equiv, CH_2Cl_2, 0°, 2 hr) and a catalytic amount of toluenesulfonic acid gave the tetrahydropyranyl ether 2 (bp 86-90° at 20mm) in 96% yield. Hydrostannation of the terminal acetylene proceeded smoothly with tri-n-butyltin hydride at 90° for 10 hr in the presence of a catalytic amount of the radical initiator, azoisobutyronitrile, affording the vinylstannane 3 which was diluted to 0.6 M with tetrahydrofuran and cooled to -78°. Dropwise addition via syringe of 2.45 M n-butyllithium in hexane (1.1 equiv) generated a pale yellow solution of the corresponding vinyllithium reagent which was stirred at -78° for 2 hr and finally treated with 1.03 equiv of freshly distilled 1-bromo-2-butene.[5] The mixture was slowly warmed to 25° over 8 hr and worked up in the usual way. Chromatography on silica gel with 10% ether in hexane led to the isolation of pure tetrahydropyranyl ether 4 in 72% yield; however, this was routinely unnecessary as direct treatment of the crude product mixture with aqueous acetic acid in tetrahydrofuran (3:3:2 by volume) at 60° for 5 hr afforded the alcohol 5 as a clear, colorless liquid after careful distillation (bp 92-94° at 21mm) in 64% overall yield from the acetylenic ether 2. Quantitative transformation to the mesylate 6 (MsCl, CH_2Cl_2, Et_3N, 0° for 1 hr)[6] and displacement with sodium iodide in dry acetone at 50° for 3 hr provided the sensitive iodide 7 in 80% yield. Although iodide 7 did not survive chromatography or distillation, dissolution in pentane gave a faintly reddish solution which was easily decanted from dark insoluble impurities.

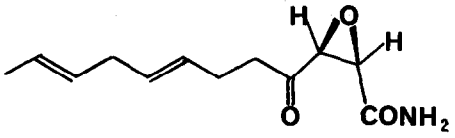
The addition of 1.8 M t-butyllithium (1.1 equiv) in pentane to a 0.04 M solution of iodide 7 in dry pentane at -78° effected halide-metal exchange. After stirring at -78° for 40 min, the colorless reaction mixture was transferred by cannula under positive argon pressure into a solution of epoxy anhydride 10[7]

(1.1 equiv) in dry tetrahydrofuran at -78°. Upon warming to room temperature the reaction mixture was poured into ice water, acidified to pH 2 by careful addition of 10% hydrochloric acid, extracted with ether, and esterified upon addition of ethereal diazomethane. Preparative thin layer chromatography on silica gel (30% ethyl acetate in hexane) afforded 22% of the expected ketoester 12 and 20% of the pseudo-lactone 13 as pale yellow oils. This combined yield (42%) of 12 and 13 (both of which can be carried on to (±)-cerulenin) can doubtless be raised by further experimentation. There was also obtained 8% of lactone 14 resulting from the addition of two equivalents of lithium reagent 9 and considerable amounts of a hydrocarbon fraction, possibly arising from elimination and coupling reactions of the starting iodide 7. No condensation products of t-butyllithium with anhydride 10 were observed. In an alternative approach to cerulenin, the organolithium species 9 was generated from chloride 8 (alcohol 5 was treated with thionyl chloride and pyridine in ether; bp 80-84°; 92%) by reaction with the radical anion of di-t-butylbiphenyl[8] in tetrahydrofuran at -100° and treated with a solution of the dimethylester 11 (1.2 equiv) in tetrahydrofuran at -100° under argon resulting in the isolation of 12 in 30% yield along with a considerable amount of dialkylated carbonyl compounds.

Treatment of 12 and 13 with methanolic ammonium hydroxide at 25° for 3 hr provided a smooth conversion into (±)-cerulenin in excellent (90%) yield following column chromatography on Florisil with 30% acetone in chloroform. Although the mass spectrum of this material was identical to that of authentic cerulenin in every respect, the infrared spectrum displayed broad hydroxyl absorption at 3300 cm^{-1} as well as a broadened carbonyl region, and the proton resonance spectrum exhibited a complex set of signals for the protons attached to the oxirane ring at C-2 and C-3. Thin layer chromatography on silica gel (30% THF in $CHCl_3$) revealed three equilibrating components resulting from the partial isomerization of amide 1 to the stable, more polar α and β-hydroxylactams 15 (ratio 1:2:2). Treatment of crystalline, authentic cerulenin with silica gel immediately gave a mixture of the same three components producing identical infrared and nmr spectra as obtained from synthetic material (cf. 4b).

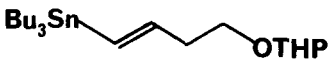
This observation is not surprising in light of recent reports concerning the isolation of 5-hydroxy-3-pyrrolin-2-ones following the photo-oxygenation of 2-alkylpyrroles,[9] as well as synthetic studies concerning the structure of 5-aminodehydrolevulinic acid and its derivatives.[10] In the case of cerulenin, although the epoxide moiety would be expected to produce greater internal ring strain in the hydroxylactam structures (thus favoring the open form), the equilibrium between the open and cyclic forms is in delicate balance. In fact storage of synthetic material several days at room temperature resulted in slow conversion to the crystalline primary amide 1 which exhibited infrared and nmr spectra identical to that of natural (+)-cerulenin.

The synthesis of cerulenin described herein is uniquely suited for the ready synthesis of ^{14}C-labeled 1, a substance which should be very useful in further biochemical studies, starting from commercially available ^{14}C-maleic anhydride.[11]

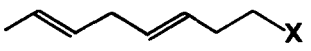


1

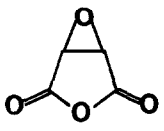
2



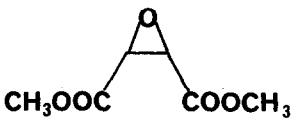
3



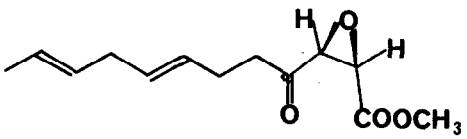
4, X=OTHP
5, X=OH
6, X=OSO$_2$CH$_3$
7, X=I
8, X=Cl
9, X=Li



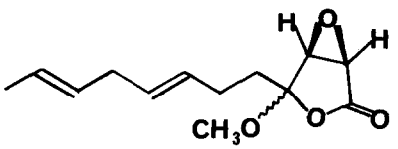
10



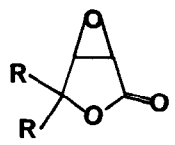
11



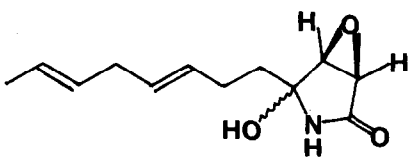
12



13



14, R=C_8H_{13}



15

References

1. Y. Sano, S. Nomura, Y. Kamio, S. Omura, and T. Hata, J. Antibiotics, Ser. A., 20, 344 (1967).

2. G. D'Agnolo, I. S. Rosenfeld, J. Awaya, S. Omura, and P. R. Vagelos, Biochim. Biophys. Acta., 326, 155 (1973).

3. (a) S. Omura, M. Katagiri, A. Nakagawa, Y. Sano, S. Nomura, and T. Hata, J. Antibiotics, Ser. A., 20, 349 (1967); (b) B. H. Arison and S. Omura, J. Antibiotics, 27, 28 (1974).

4. (a) R. K. Boeckman and E. W. Thomas, J. Am. Chem. Soc., 99, 2805 (1977); (b) A. A. Jakubowski, F. S. Guziec, Jr., and M. Tishler, Tetrahedron Lett., 2399 (1977).

5. S. Winstein and W. G. Young, J. Am. Chem. Soc., 58, 104 (1936). 1-Bromo-2-butene consists of a mixture containing 20% of 3-bromo-1-butene; however, displacement of bromide occur preferentially at the primary terminus.

6. R. K. Crossland and K. L. Servis, J. Org. Chem., 35, 3195 (1970).

7. (a) G. B. Payne and P. H. Williams, J. Org. Chem., 24, 54 (1959); (b) G. Allan and A. N. Neogi, Chem. and Indust., 545 (1971). Anhydride 10 exhibited ir peaks ($CHCl_3$) at 1810, 1110, 1035, 905 cm^{-1}, and an nmr peak ($CDCl_3$) at δ 4.33 (s, 2).

8. (a) S. E. Wilson, Tetrahedron Lett., 4651 (1975); (b) P. K. Freeman and L. L. Hutchinson, Tetrahedron Lett., 1849 (1976).

9. (a) D. A. Lightner and L. K. Low, J. Heterocyclic Chem., 9, 167 (1972); (b) G. B. Quistad and D. A. Lightner, Tetrahedron Lett., 4417 (1971).

10. J. Awruch and B. Frydman, Tetrahedron Lett., 4121 (1976).

11. This study was assisted financially by the National Institutes of Health. We are grateful to Professor Konrad Bloch for an authentic sample of cerulenin.