

TOTAL SYNTHESIS OF CURZERENONE AND EPICURZERENONE

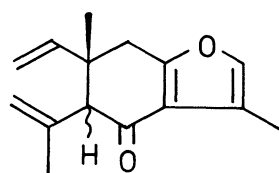
Masaaki MIYASHITA, Toshiaki KUMAZAWA, and Akira YOSHIKOSHI*
Chemical Research Institute of Non-Aqueous Solutions, Tohoku
University, Sendai 980

Curzerenone and epicurzerenone were synthesized by means of a combination of γ -ketoester synthesis and 3-methylfuran annulation both of which utilize nitroolefins as synthons. Starting material, methyl 2-methyl-4-oxo-2-vinylpentanoate, was prepared by the Lewis acid-promoted reaction of 1-methoxy-2-methyl-1-[(trimethylsilyl)oxy]-1,3-butadiene and 2-nitropropene, while key intermediate 3,6-dimethyl-6-vinyl-6,7-dihydrobenzofuran-4(5H)-one was assembled by the KF-catalyzed reaction of 5-methyl-5-vinylcyclohexane-1,3-dione and 1-nitro-1-phenylthiopropene.

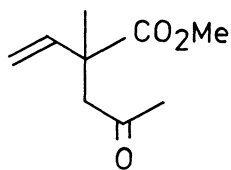
Nitroolefins have proved to be remarkably versatile synthons for use in a variety of syntheses¹ and a number of their successful applications to the synthesis of natural products have been reported.²

In connection with the exploration of new annulation reactions utilizing nitroolefins, we recently reported new 3-methylfuran annulation of cyclic 1,3-diones using 1-nitro-1-phenylthiopropene,^{2d,3} and convenient synthesis of γ -ketoesters from nitroolefins and ketene methyl trimethylsilyl acetals.⁴ To illustrate the potential of these reactions in other systems, we now report the first total synthesis of curzerenone (1) and its isomer epicurzerenone (2),⁵ representative furanoelemanoids.

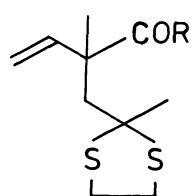
γ -Ketoester (3), starting material in this synthesis, was readily obtainable by the Lewis acid-promoted reaction of 2-nitropropene and ketene methyl trimethylsilyl acetal of methyl tiglate.⁴ Boron trifluoride-catalyzed thioacetalization of (3) with ethanedithiol in methylene chloride gave thioacetal (4) in 81% yield. Hydrolysis of (4) with aqueous ethanolic potassium hydroxide followed by treatment of the resulting acid (5) with oxalyl chloride in refluxing benzene afforded acid chloride (6), which was converted into diazoketone (7) (CH_2N_2 , NEt_3 , Et_2O) in 82%



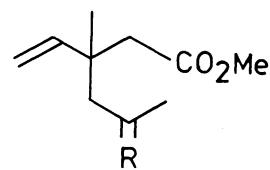
1 H α
2 H β



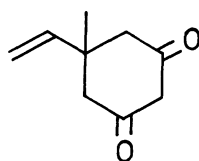
3



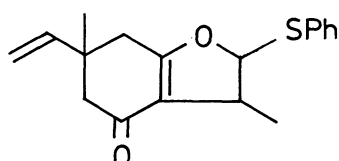
4 R=OMe
5 R=OH
6 R=Cl
7 R=CHN₂



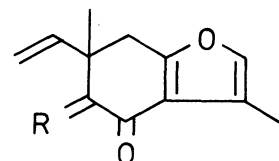
8 R= $\begin{matrix} \text{S} \\ \diagup \quad \diagdown \\ \text{S} \end{matrix}$
9 R=O



10



11



12 R=H₂
13 R=H,CO₂Me
14 R=H,C(CH₃)₂OH
15 R=C(CH₃)₂

overall yield from (4).

The Wolff rearrangement of (7) with silver oxide in refluxing methanol resulted in formation of homologated ester (8) in 70% yield. Deprotection of the thioacetal with methyl iodide in aqueous acetonitrile to give δ -ketoester (9) in 76% yield, which was then cyclized on treatment with sodium ethoxide in hot xylene to afford the desired 1,3-diketone (10), mp 100-102 °C, IR(KBr) 3600-2150, 1620 and 1520 cm⁻¹, in 87% yield.

The 1,3-diketone (10) was submitted to the 3-methylfuran annulation reaction.^{2d} Thus heating a mixture of (10), 1-nitro-1-phenylthiopropene (1.3 mol equiv), and KF (0.2 mol equiv) in DME at 50 °C for 3.5 h, followed by consecutive treatment with KF (0.2 mol equiv) in refluxing benzene for 3.5 h produced dihydrofurans (11) as a diastereomeric mixture in 75% yield. Oxidation of (11) with sodium periodate in aqueous methanol to the corresponding sulfoxides and subsequent elimination of benzenesulfenic acid in refluxing benzene containing pyridine and active alumina afforded the key intermediate dihydrobenzofuran (12),⁶ IR(CCl₄) 1680, 1640, 1610 and 920 cm⁻¹, ¹H NMR δ (CCl₄) 1.22(3H, s),

2.14(3H, d, J=1Hz), 2.32 and 2.45(2H, ABq, J=15Hz), 2.70 and 2.82(2H, ABq, J=16Hz), 4.99(1H, d, J=11Hz), 5.01(1H, d, J=18Hz), 5.82(1H, dd, J=11 and 18Hz), and 7.01(1H, br s) in 78% overall yield.

The remaining synthetic problem was the introduction of an isopropenyl moiety into (12). Contrary to our expectation, however, the straightforward introduction of the isopropenyl functionality, e.g. by aldol condensation with acetone (LDA, ZnCl_2 , THF),⁷ was found hopeless owing to its steric interference arising from neighboring alkyl substituents. Meanwhile (12) underwent carbo-methoxylation (NaH, KH (catalytic), $(\text{CH}_3\text{O})_2\text{CO}$, C_6H_6)⁸ to give ketoester (13) as an isomeric mixture in 87% yield.

On treatment with sodium hydride followed by methylation with methylmagnesium iodide in refluxing ether (13) afforded ketol (14) in 19% yield, along with the recovered starting material (51%). The yield of (14) could not be improved even under strengthened reaction conditions.

Dehydration of (14) with phosphoryl chloride in pyridine gave a mixture of curzerenone (1), epicurzerenone (2) and isocurzerenone (15),⁹ in the about 3:2:1 ratio, in 80% yield. Curzerenone and epicurzerenone were spectroscopically identified in comparison with the natural compounds.⁵

We thank Professor H. Hikino for providing us with the IR and ^1H NMR spectra of natural curzerenone and epicurzerenone.

References and Notes

- 1) a) Houben-Weyl "Methoden der Organischen Chemie", vol.10/1, E. Muller, Ed., Georg Thieme Verlag, 1971, pp 9-462; b) D. Seebach, E. W. Colvin, F. Lehr, and T. Weller, *Chimia*, **33**, 1 (1979); c) N. Ono, and A. Kaji, *Yuki Gosei Kagaku Kyokai Shi* **38**, 115 (1980).
- 2) a) D. Seebach, V. Ehrig, H. F. Leitz, and R. Henning, *Chem. Ber.*, **108**, 1946, (1975); b) J. Vasilevskis, J. A. Gualtieri, S. O. Hutchings, R. C. West, J. W. Scott, D. R. Parrish, F. T. Bizzarro, and G. F. Field, *J. Am. Chem. Soc.*, **100**, 7423 (1978); c) L. A. Paquette and Y. K. Han, *J. Org. Chem.*, **44**, 4014 (1979); d) M. Miyashita, T. Kumazawa, and A. Yoshikoshi, *J. Org. Chem.*, **45**, 2945 (1980).
- 3) M. Miyashita, T. Kumazawa, and A. Yoshikoshi, *J. Chem. Soc., Chem. Commun.*, **1978**, 362.
- 4) M. Miyashita, T. Kumazawa, and A. Yoshikoshi, *Chem. Lett.*, **1980**, 1043.

5) a) H. Hikino, K. Agatsuma, and T. Takemoto, *Tetrahedron Lett.*, 1968, 2855;
b) H. Hikino, C. Konno, K. Agatsuma, T. Takemoto, I. Horibe, K. Tori, M. Ueyama,
and K. Takeda, *J. Chem. Soc., Perkin Trans. 1*, 1975, 478.

6) During our study on this synthesis, an alternative synthesis of (12) culminated in the total synthesis of (\pm)-linderalactone and (\pm)-isolinderalactone was reported. A. Gopalan and P. Magnus, *J. Am. Chem. Soc.*, 102, 1756 (1980).

7) a) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, 95, 3310 (1973); b) H. Hagiwara, H. Uda, and T. Kodama, *J. Chem. Soc., Perkin Trans. 1*, 1980, 963.

8) L. Ruest, G. Blouin, and P. Deslongchamps, *Synth. Commun.*, 6, 169 (1976).

9) Isocurzerenone (15) was isolated as an oil from a mixture of curzerenone (1) and epicurzerenone (2) by preparative, silica gel, thin-layer chromatography [n-hexane-ether (95:5) as solvent] and has following spectral properties; IR(CCl₄) 3100, 1658, 1566, 1076, 1057 and 915 cm⁻¹, ¹H NMR δ (CCl₄) 1.41(3H, s), 1.99(3H, s), 2.05(3H, s), 2.21(3H, s), 2.58(1H, d, J=17Hz), 2.95(1H, d, J=17Hz), 5.03(1H, d, J=11Hz), 5.09(1H, d, J=18Hz), 6.22(1H, dd, J=18 and 11Hz) and 6.98(1H, br s). Meanwhile, separation of curzerenone (1) from epicurzerenone (2) was carried out on a Waters Associates High Pressure Liquid Chromatograph ALC/GPC Model 244 using a u-Porasil column (3/8"x1') [n-hexane-chloroform (9:1) as eluent].

(Received February 20, 1981)