Tetrahedron Letters,Vol.22,No.48,pp 4849-4852,1981 0040-4039/81/484849-04$02.00/0
Printed in Great Britain

OXAZOLES AS MASKED ACTIVATED CARBOXYLATES. SYNTHESIS OF (±)-DI-O-METHYLCURVULARIN

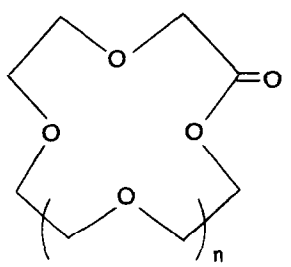
H.H. Wasserman and R.J. Gambale
Department of Chemistry, Yale University, New Haven, Connecticut 06511

Summary: The dimethyl ether of the mold metabolite, curvularin, was synthesized by intramolecular esterification of an activated carboxylate derived from the photooxidation of an oxazole precursor.

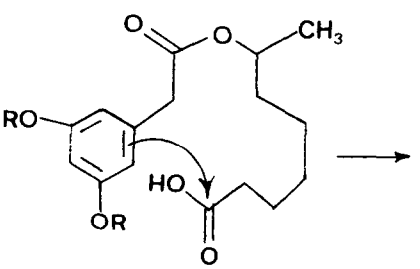
In an earlier communication,[1] we reported that the photooxygenation reaction of oxazoles, generating activated carboxylates in the form of triamides,[2] may be applied to the synthesis of macrolides. We have now extended the scope of this intramolecular acylation procedure to the formation of other macrocyclic systems such as the polyether lactones (2) recently synthesized by Okahara.[3] This work will be described separately.[4] In this paper we report the use of the oxazole-triamide rearrangement for the synthesis of the curvularin system.

Curvularin (1, R=H), a metabolite of the mold species, Curvularia, was isolated and characterized by Musgrave[5] and Birch.[6] Synthesis of this macrocyclic system was achieved through intramolecular acylation of the di-O-benzyl acid (3a) by Gerlach[7] and the di-O-methyl acid (3b) by Bycroft[8] and Takahashi.[9] However, despite a number of attempts, formation of the curvularin system via intramolecular esterification has not been successful. Thus, it has been reported that mixed anhydrides,[8] DCC,[8] t-butylthiol esters with[7] and without[10] silver perchlorate and the 2-pyridylthiol ester[10] have all failed to bring about lactone formation from the hydroxy acid precursor.

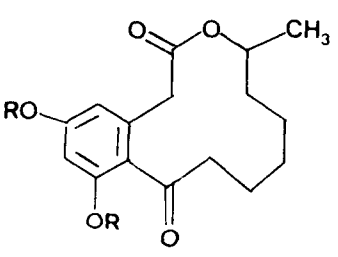
We have now shown that the oxazole-triamide method of generating an activated carboxylate may be utilized in the lactonization of the hydroxy-acid derivative (11) forming (±)-di-O-methylcurvularin (1, R = CH_3). This synthesis represents the first successful formation of this lactone system by intramolecular esterification.



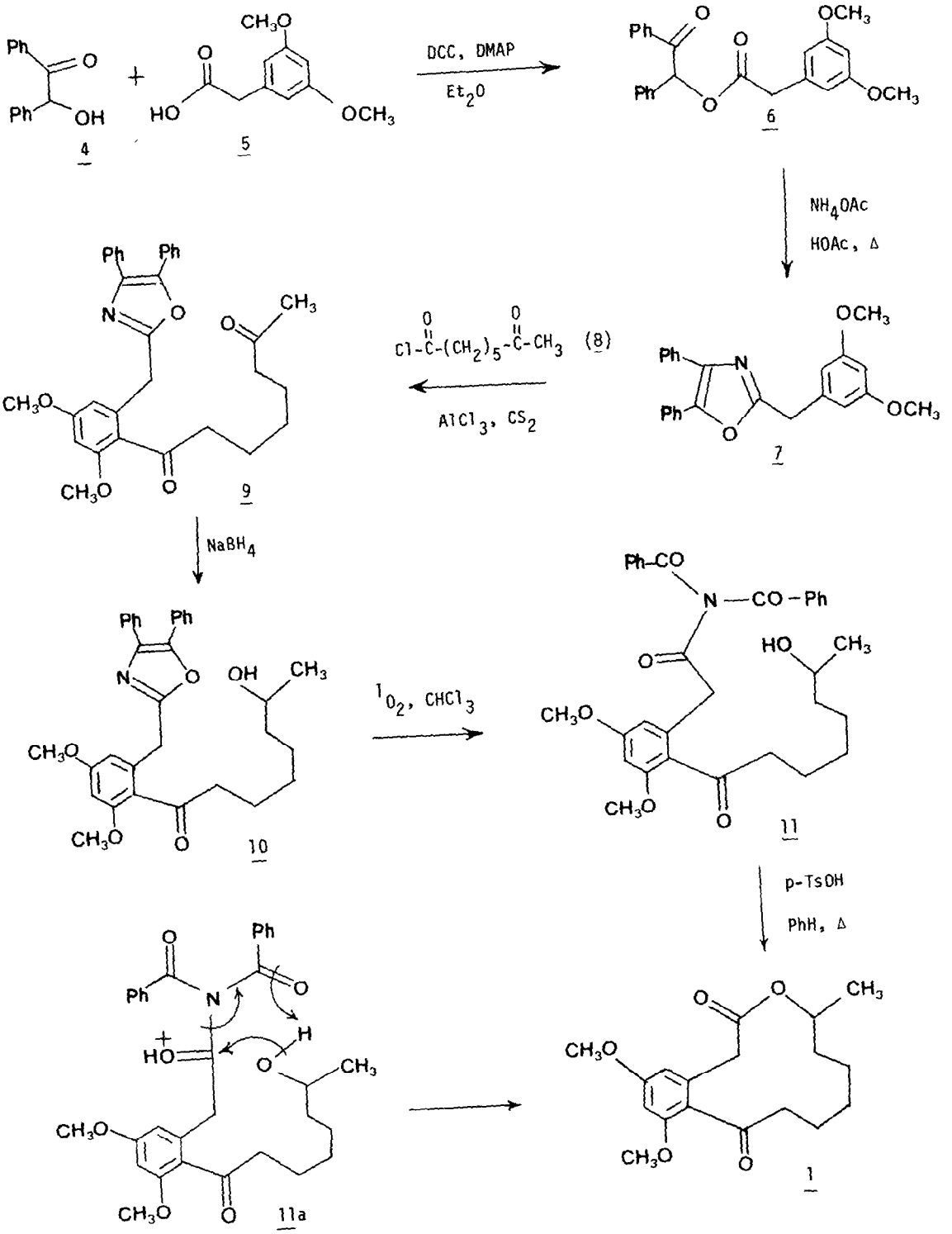
2



3 a, (R = CH_2Ph)
b, (R = CH_3)



1


DCC, DMAP
Et2O
NH4OAc
HOAc, Δ
AlCl3, CS2
(8)
NaBH4
1O2, CHCl3
p-TsOH
PhH, Δ
4
5
6
7
9
10
11
11a
1

Starting with the readily available methyl 3,5-dimethoxypnenyl acetate[11], the oxazole (7)[16] was prepared in 68% overall yield in standard fashion by saponification with potassium hydroxide in ethanol to form acid (5), condensation with benzoin (4) in the presence of DCC and 4-dimethylaminopyridine[12] yielding the ester (6)[16] followed by treatment with excess ammonium acetate in refluxing glacial acetic acid. Friedel-Crafts acylation[13] of (7) with 7-oxooctanoyl chloride[7] (8) and anhydrous aluminum chloride in carbon disulfide gave the diketo oxazole (9)[16] which was selectively reduced at the aliphatic carbonyl with sodium borohydride in aqueous ethanol[14] to provide the hydroxy oxazole (10)[16] in quantitative yield. (Scheme).

Dye-sensitized photooxygenation of the hydroxy oxazole (10) in chloroform readily yielded the intermediate triamide (11), which, under acid catalysis and high dilution, could be converted to (±)-di-O-methylcurvularin (1, R = CH_3), identical in all respects (IR, NMR, mass spectrum, GPC, TLC) with an authentic sample.[10]

The cyclization may be facilitated by a process involving intramolecular proton removal analogous to "double activation"[15] as pictured in structure (11a). Participation by either amide carbonyl group may facilitate deprotonation of the hydroxyl function through a thermodynamically favored six-membered transition state. We plan to continue studies on the synthesis of biologically active macrolides and macrocyclic lactams through the oxazole-triamide method of carboxylate activation.

Acknowledgement. This work was supported by Grant GM-13854 from the National Institutes of Health.

REFERENCES

1) H.H. Wasserman, R.J. Gambale and M.J. Pulwer, Tetrahedron Lett., 1737 (1981).

2) For a recent review, see: H.H. Wasserman and B.H. Lipshutz, Chapter 9, in Singlet Oxygen, (Edited by H.H. Wasserman and R.W. Murray), Academic Press., New York, (1979).

3) K. Matsushima. N. Kawamura and M. Okahara, Tetrahedron Lett., 3445 (1979); Y. Nakatsuji, N. Kawamura, M. Okahara and K. Matsushima, (in press).

4) H.H. Wasserman, R.J. Gambale and M.J. Pulwer, Tetrahedron, Symposium in Print, "New General Synthetic Methods," Edited by E.J. Corey, (in press).

5) O.C. Musgrave, J. Chem. Soc., 4301 (1956).

6) A.J. Birch, O.C. Musgrave, R.W. Rickards and H. Smith, J. Chem. Soc., 3146 (1959).

7) H. Gerlach, Helv. Chim. Acta., 60, 3039 (1977).

8) P.M. Baker, B.W. Bycroft and J.C. Roberts, J. Chem. Soc. (C), 1913 (1967).

9) T. Takahashi, H. Ikeda and J. Tsuji, Tetrahedron Lett., 21, 3885 (1980).

10) We thank Dr. B.W. Bycroft of the University of Nottingham, Nottingham, England for his generous gift of di-O-methylcurvularin and for a private communication regarding attempts to form the lactone from hydroxy acid precursors. We also thank Dr. H. Gerlach of the University of Bayreuth, Bayreuth, Fed. Rep. Germany for a sample of di-O-benzylcurvularin, and Dr. T. Takahashi of the Tokyo Institute of Technology, Tokyo, Japan for the benzyl ester of compound 3a.

11) B.W. Bycroft and J.C. Roberts, J. Chem. Soc., 2063 (1962).

12) F.E. Ziegler and G.D. Berger, Synth. Comm., 9, 539 (1979).

13) For model studies, see: O.C. Musgrave, R. Templeton and H.D. Munro, J. Chem. Soc. (C), 250 (1968).

14) B.W. Bycroft, J.C. Roberts and P.M. Baker, J. Chem. Soc., 2289 (1964).

15) E.J. Corey and K.C. Nicolaou, J. Am. Chem. Soc., 96, 5614 (1974).

16) Satisfactory C,H, N or high resolution mass spectroscopic analyses were obtained for all intermediates.

(Received in UK 29 September 1981)