CHEMISTRY LETTERS, PP. 1339-1340, 1982.

TOTAL SYNTHESIS OF MIMOCIN

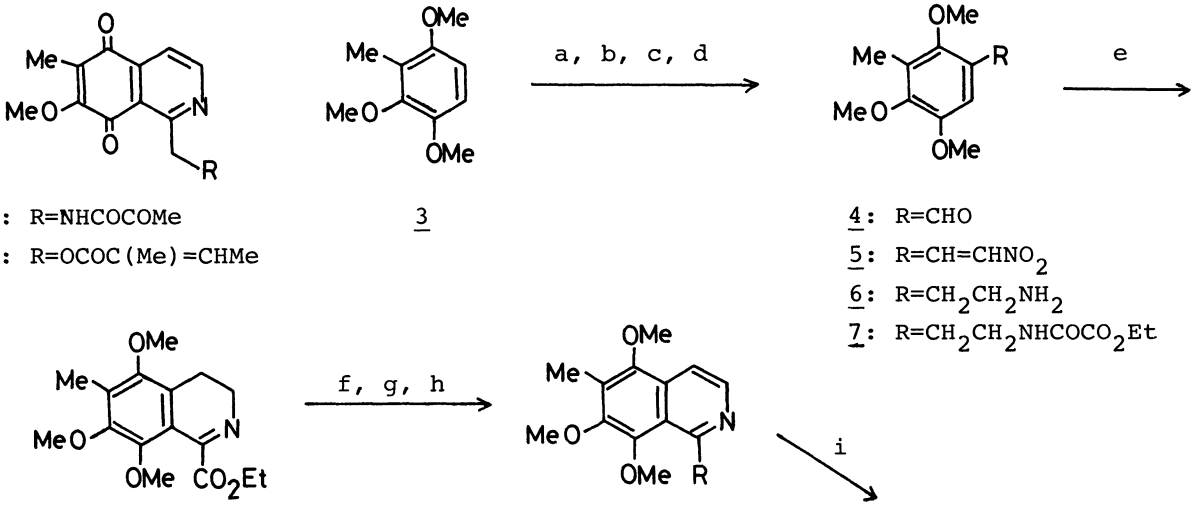
Keizo MATSUO,* Masao OKUMURA, and Kuniyoshi TANAKA
Faculty of Pharmaceutical Sciences, Kinki University
3-4-1 Kowakae, Higashiosaka, Osaka 577

Mimocin (1), an isoquinolinequinone antibiotic, is synthesized in ten steps starting from 2,3,6-trimethoxytoluene.

Mimocin (1), an isoquinolinequinone antibiotic exhibiting strong activity against B. subtilis and C. albicans, was isolated by Kubo and co-workers[1] from the strain of Streptomyces lavendulae, and has been synthesized starting from 7-methoxy-6-methyl-5,8-isoquinolinedione.

In our course of synthetic studies on marine natural products,[2] we interested in the structural similarity between mimocin (1) and renierone (2),[3] isolated as an antimicrobial substance from a marine sponge, and their biological activity, and have carried out an alternate synthesis of the former.

Our synthetic approach toward mimocin (1) was initiated by formylation of 2,3,6-trimethoxytoluene (3)[4] with hexamethylenetetramine and trifluoroacetic acid



1: R=NHCOCOMe
2: R=OCOC(Me)=CHMe

3

4: R=CHO
5: R=CH=CHNO$_2$
6: R=CH$_2$CH$_2$NH$_2$
7: R=CH$_2$CH$_2$NHCOCO$_2$Et

8

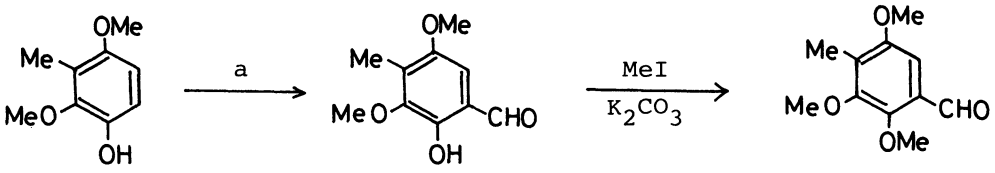
9: R=CO$_2$Et
10: R=CN
11: R=CONH$_2$
12: R=CH$_2$NHCOCOMe

a) hexamethylenetetramine-CF_3CO_2H, b) $MeNO_2$-NaOAc, c) $LiAlH_4$-$AlCl_3$, d) ethyl oxalyl chloride-Et_3N, e) polyphosphate ester, f) Pd/C, heat, g) Me_2AlNH_2, h) 1) H_2, Pd/C, 2) Cl_2CHOMe-$MeCOCO_2H$, i) AgO-HNO_3,

giving an aldehyde (4)[5),6)] (58%). The aldehyde (4) was condensed with nitromethane in the presence of sodium acetate to furnish α,β-unsaturated nitro derivative (5)[6)] (mp 121-123°C) in 77% yield which was then reduced to an amine (6) with $LiAl_4$-$AlCl_3$ in ether in 84% yield. Treatment of the amine (6) with ethyl oxalyl chloride in the presence of triethylamine afforded an amide ester (7)[6)] in 91% yield, which was submitted to Bischler-Napieralski reaction. The amide ester (7) was allowed to react with polyphosphate ester without solvent at 110-120°C for 9.5 hr furnishing a ring closed ester (8)[6)] in 55% yield, although the reaction with phosphoryl chloride resulted in poor yield (18%). Heating of the ester (8) in the presence of 5% Pd/C in decalin at 160-170°C gave an isoquinoline ester (9)[6)] in 60% yield. A nitrile (10)[6)] (mp 95.5-97.5°C) was obtained in 83% yield by treatment of the ester (9) with dimethylaluminum amide[8)] in benzene at refluxing temperature for 1.5 days accompanying an amide (11) (9%). The nitrile (10) was then hydrogenated over 5% Pd/C in methanol containing hydrogen chloride to give an amine hydrochloride which, without isolation, was treated with α,α-dichloromethyl methyl ether and pyruvic acid[9)] to afford an amide (12)[6)] (mp 148-151°C) in 43% yield. Finally mimocin (1) (mp 189-190°C, lit.[1)] 189-191°C) was obtained by AgO-HNO_3 oxidation[10)] of the amide (12) in 53% yield. IR and NMR spectra of natural mimocin (1) and synthetic one were identical.[11)]

References

1) A.Kubo, S.Nakahara, R.Iwata, K.Takahashi, and T.Arai, Tetrahedron Lett., 21, 3207 (1980).
2) K.Matsuo, T.Kinuta, and K.Tanaka, Chem.Pharm.Bull., 29, 3047 (1981); K.Matsuo and K.Tanaka, ibid., 29, 3070 (1981).
3) Structure: D.E.McIntyre and D.J. Faulkner, Tetrahedron Lett., 1979, 4163; synthesis: S.Danishefsky, E.Berman, R.Cvetovich, and J.Minamikawa, ibid., 21, 4819 (1980); A.Kubo and S.Nakahara, Chem.Pharm.Bull., 29, 595 (1981).
4) F.Weygand, K.Volgelbach, and K.Zimmermann, Chem.Ber., 80, 391 (1947).
5) The structure of 4 was determined by inspection of NMR spectral data of 4 and its isomer (i). cf. W.Baker, J.F.W.McOmie, and D.Miles, J.Chem.Soc., 1953, 820.



(i)

NMR: δ($CDCl_3$) 4: 7.25 (1H, s, arom-H), 10.32 (1H, s, CHO);
(i): 7.30 (1H, s, arom-H), 10.34 (1H, s, CHO).

6) Satisfactory IR, NMR and microanalyses or MS data were obtained.
7) M.P.Cava, M.V.Lakshmikanthan, and M.J.Mitchell, J.Org.Chem., 34, 2665 (1969).
8) T.L.Word, N.A.Khatri, and S.M.Weinreb, Tetrahedron Lett., 1979, 4907.
9) H.C.J.Ottenheijm and J.H.M.DeMan, Synthesis, 1975, 163.
10) C.D.Snyder and H.Rapoport, J.Am.Chem.Soc., 94, 227 (1972).

11) We are indebted to Prof. A.Kubo, Meiji College of Pharmacy, for IR and NMR spectra of natural mimocin.

(Received June 14, 1982)