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TOTAL SYNTHESIS OF MIMOCIN

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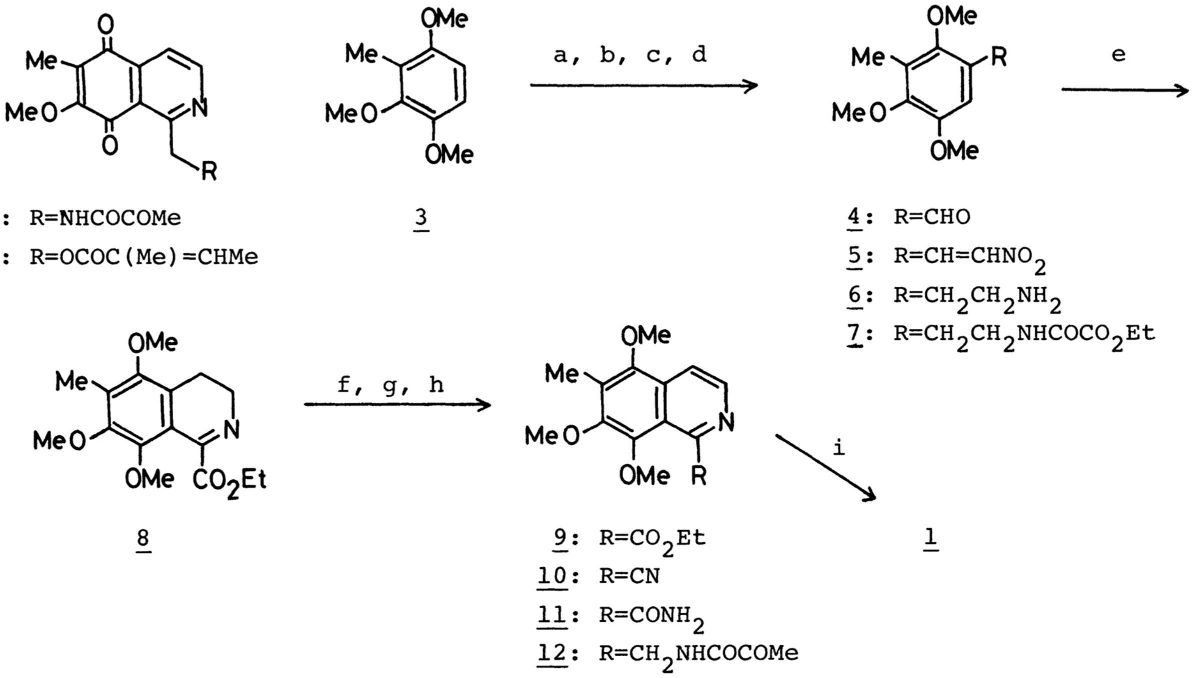
Mimocin (1), an isoquinolinequinone antibiotic, is synthesized in ten steps starting from 2,3,6-trimethoxytoluene.

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

1

a) hexamethylenetetramine-CF$_3$CO$_2$H, b) MeNO$_2$-NaOAc, c) LiAlH$_4$-AlCl$_3$, d) ethyl oxalyl chloride-Et$_3$N, e) polyphosphate ester, f) Pd/C, heat, g) Me$_2$AlNH$_2$, h) 1) H$_2$, Pd/C, 2) Cl$_2$CHOMe-MeCOCO$_2$H, 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

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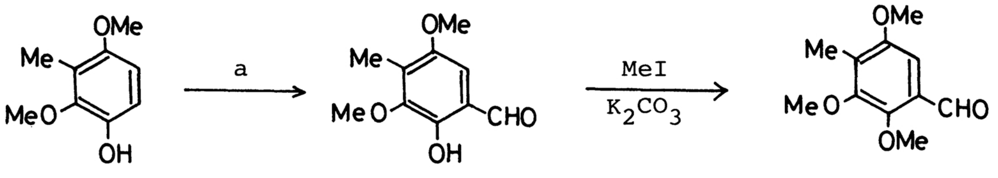
5) The structure of 4 was determined by inspection of NMR spectral data of 4 and its isomer (i). cf. W.Baker, J.F.W.McOmie, and D.Miles, J.Chem.Soc., 1953, 820.



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

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