Pergamon

Tetrahedron Letters, Vol. 35, No. 8, pp. 1135-1136, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0399-5

Chemical Modification Of Marcfortine A. 1. 18-Thiomarcfortine A And Absolute Stereochemistry

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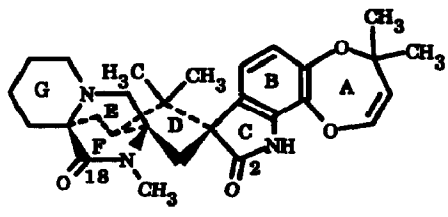
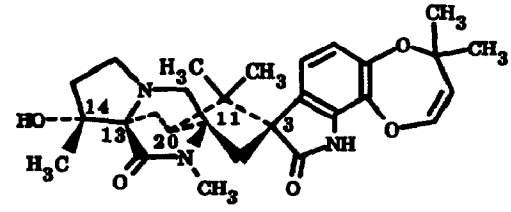
Abstract: 18-Thiomarcfortine A (3) was prepared from marcfortine A by treatment with Lawesson's reagent. The absolute configuration of 3 was determined by single crystal X-ray analysis which allowed us to assign the absolute configuration of marcfortine A as 3R, 11S, 13S, 20S.

Marcfortine A (1) is a fungal metabolite of *Penicillium roqueforti*, which was reported by Polonsky et Al.[1] It is structurally related to paraherquamide (2) which was isolated from *Penicillium paraherquei*.[2] Recently, Merck scientists discovered that 1, 2 and their analogs are potent anti-parasitic agents.[3] They have been involved in a program of chemical modification of paraherquamide[4] which has resulted in the preparation of numerous analogs as well as the determination of the absolute stereochemistry of 2.[4a]



Marcfortine A (1)

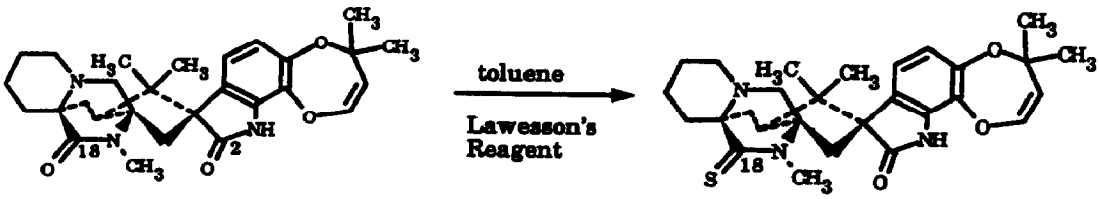


(3R, 11S, 13R, 14R, 20S)

Paraherquamide (2)

However, there is no publication involved chemical modification of marcfortine A, except one patent[3b] with no physical data presented. We would like to report 18-thiomarcfortine A (3) as well as the determination of the absolute stereochemistry of 1.

When compound 1 was treated with Lawesson's reagent (3.0 equiv.) [2,4-bis(methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] under refluxing in toluene for 3 h, U-94367 (3) was obtained in 50-60 % yield. The ^{13}C NMR spectra of 3[5] showed only one carbonyl group at δ 183.2 ppm (C-2 carbonyl). Further characterization of 3 was done by X-ray crystallography. In addition, the determination of the absolute configuration of 3, using Bijvoet's method,[6] was carried out by calculating structure factors for both enantiomers and performing a computer search to find the reflections by anomalous dispersion. Analysis of the X-ray data allowed the assignment of the absolute configuration of 3 as 3R, 11S, 13S, 20S. The assignment of the absolute configuration of 3 by X-ray analysis also allows



Marcfortine A (1) U - 94367 (3)

us to assign the absolute configuration of marcfortine A (1) as 3R, 11S, 13S, 20S since none of the chiral centers is altered in the conversion of 1 to 3. Thus, marcfortine A has the same configuration as paraherquamide.[7]

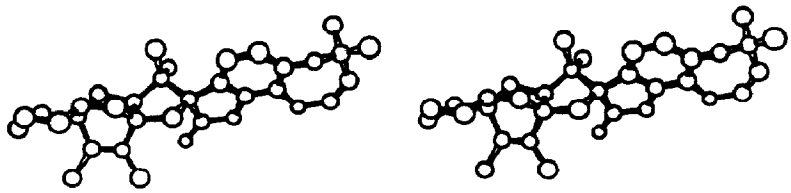


Figure 1. Stereodrawing of 3.

Acknowledgements

We are grateful to Dr. David G. Martin of The Upjohn Company for a generous supply of marcfortine A. We thank Mr. Joseph B. Moon for the stereodrawing and Mr. James Nielsen for a mass spectral measurement.

References and Notes

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5. *Synthesis of 3* : A solution of 30 mg marcfortine A and 22 mg of Lawesson's agent in 5 ml of toluene was refluxed under nitrogen for 3 hours. The mixture was cooled and the solvent removed under reduced pressure. The residue was subjected to preparative thin layer chromatography on silica gel plates using 10 % acetone in methylene chloride as the eluent to give 3 as a solid in 50 % yield. Mp 258-260 °C; FABMS $(M + H)^+$ 494; ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 183.2, 145.3, 139.6, 135.3, 132.8, 124.8, 120.2, 117.3, 114.6, 79.9, 68.0, 65.2, 63.0, 61.4, 53.4, 52.1, 46.3, 37.8, 34.6, 34.4, 33.1, 30.0, 25.7, 23.7, 20.8, 20.3.
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7. The priority of the C-14 position in paraherquamide is changed due to the hydroxyl group.

(*Received in USA* 3 *November* 1993; *revised* 24 *November* 1993; *accepted* 10 *December* 1993)