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IKARUGAMYCIN. III. STEREOCHEMISTRY OF IKARUGAMYCIN

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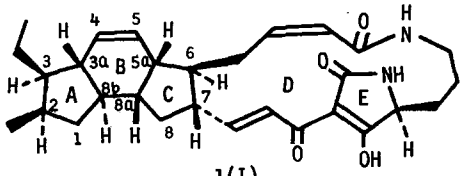
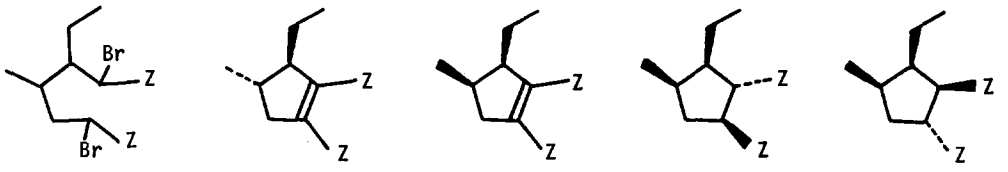
Recently, we have reported the structure of an antibiotic, ikarugamycin (1).[1] In this paper, the stereostructure I and the biogenesis of the antibiotic are presented.



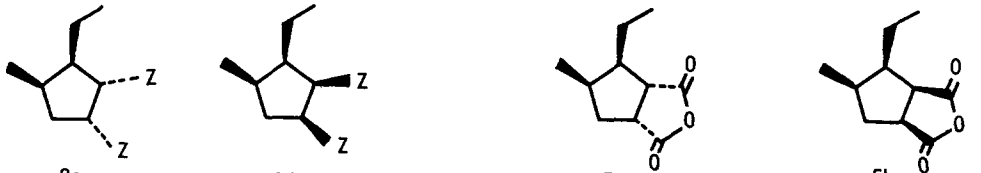
1(I)

A) The stereochemistry about ring A (C-2,3,3a, and 8b)

The stereochemistry of dimethyl 3-ethyl-4-methylcyclopentane-1,2-dicarboxylate (2),[1] an oxidation product of ikarugamycin (1), was established by the following syntheses of four possible stereoisomers, 2a~2d[2] in racemic forms (Z=COOMe in all cases).



3 4a 4b 2a 2b



2c 2d 5a 5b

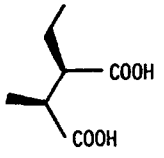
The dibromodiester 3, prepared from a mixture of threo- and erythro-2-ethyl-3-methylglutaric acid (threo:erythro=2:1) through several steps,[3] reacted with NaH in DMF[4] to give unsaturated

esters, 4a (major) and 4b (minor).[5] Catalytic hydrogenation of 4b on PtO_2 in CH_3COOH afforded 2a, a minor product, and 2d, a major one. By the base catalyzed equilibration of 2d, three esters, 2a, 2c, and 2b were obtained in the ratio of 89:9:2. On the other hand, a dicarboxylic acid from 2a was treated with Ac_2O-p-TsOH to afford two anhydrides, 5a and 5b (4:1). Two 1,2-cis-diesters, 2c and 2d were prepared from 5a and 5b, respectively. The diester 2b was also derived from 5b by the known method in the case of nepetic acid.[6]

The IR, NMR, and mass spectra and GLC of the natural diester 2 were identical with those of synthetic diester 2a. In addition, ikarugamycin (1) was oxidized with $KMnO_4$ in pyr-D_2O to give the ester 2 consisting of d_0 65%, d_1 30%, and d_2 5%. This indicates that the stereochemistry of the ring A remains unchanged in 2.

B) The absolute configurations at C-2 and 3

The absolute configuration of (+)-erythro-2-ethyl-3-methylsuccinic acid (6) was recently established as 2R,3S by Brockmann jr. and Müller-Enoch.[7] The (+)-acid 6 was homologised to give two isomeric dimethyl esters, 7, $[\alpha]_D$-14.9°, and 8, $[\alpha]_D$+46.3°, by Arndt-Eistert reaction via a mixture of two isomeric monocarbomethoxy-monodiazoketones. Therefore, the absolute configuration of (-)-dimetyl erythro-2-ethyl-3-methylglutarate ($[\alpha]_D$-8.6°), an oxidation product of ikarugamycin (1),[1] was determined to be 2R,3R as depicted in the formula 7, namely 3R,2R in the ring A of 1.



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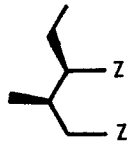

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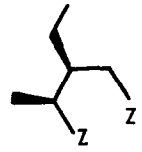

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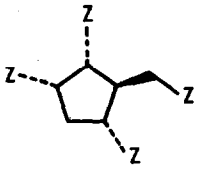
C) The stereochemistry about ring C (C-5a,6,7, and 8a)

The stereochemistry of a teramethyl ester 9, one of the oxidation products of ikarugamycin (1),[1] was confirmed by the following synthesis. Diels-Alder reaction of dimethyl trans-glutaconate with cyclopentadiene afforded two isomeric dimethyl esters, 10a (major) and 10b (minor). Ozonolysis of the latter followed by HCO_3H oxidation and then esterification with CH_2N_2 gave the tetramethyl ester 9. The IR and NMR spectra and GLC of both natural and synthetic esters 9 were identical with each other.

To prove the structure 10b, it was converted via a dicarboxylic acid into an iodolactone 11a, mp 138-141°, ν_{max}^{THF} 1805 and 1739 cm^{-1}, whose structure was supported by the resemblance of the NMR spectra between 11a and 11b.[8] Oxidation of 1 with CrO_3 in 6N D_2SO_4 afforded the ester 9

(d_0 85% and d_1 15%). Thus, 9 also maintains the stereochemistry about the ring C in the course of oxidation.



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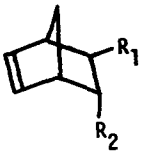
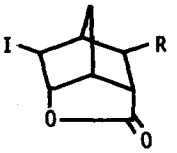


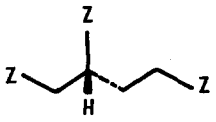
10a: R_1=Z, R_2=CH_2Z
10b: R_1=CH_2Z, R_2=Z



11a: R=CH_2COOH
11b: R=H

D) The absolute configuration at C-7

The absolute configuration of (+)-trimethyl butane-1,2,4-tricarboxylate (12), $[\alpha]_D$+16.2°, has already been determined by Freudenberg et al. to be R.[9] The same trimethyl ester ($[\alpha]_D$+12.6°) was obtained from hexahydroikarugamycin.[1] Accordingly, the absolute configuration at C-7 in 1 must be R.



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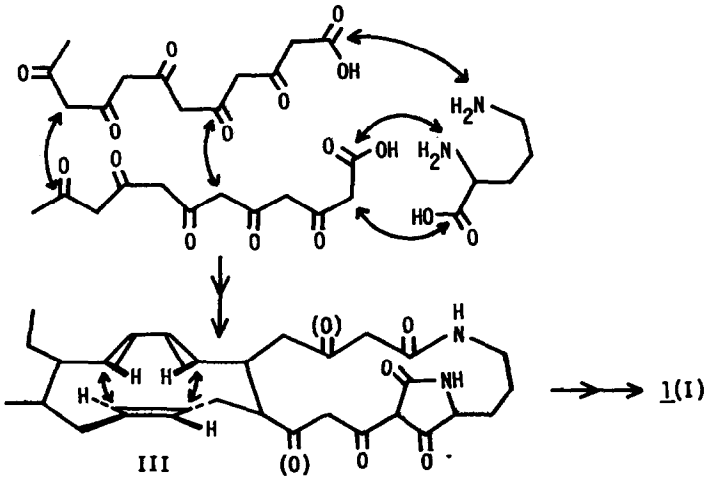
From the combination of A)~D), only one stereostructure I can be given to ikarugamycin (1).[10]

When considered in the light of the biosynthetic studies on tenuazoic acid[11] and erythroskyrine,[12] ikarugamycin would be biosynthetically derived from two hexa-acetate-units and L-ornithine as outlined in the scheme. In particular, trans-anti-cis-decahydro-as-indacene skeleton (A,B, and C rings of 1) seems to be constructed by intramolecular Diels-Alder reaction[13] of a hypothetical intermediate II.



Scheme

Acknowledgment

We thank the Fujisawa pharmaceutical company for the gift of ikarugamycin.

REFERENCES AND FOOTNOTES

1. S.Ito and Y.Hirata, Tetrahedron Letters, 1181, 1185 (1972).

2. Possibilities of the structures in which 3-ethyl and 4-methyl are trans must be omitted by the formations of dimethyl erythro-2-ethyl-3-methylsuccinate and dimethyl erythro-2-ethyl-3-methylglutarate from 1.[1]

3. 1) $LiAlH_4$ 2) TsCl-pyr 3) NaCN-DMSO 4) KOH-$HOCH_2CH_2OH$-H_2O 5) $SOCl_2/Br_2$/MeOH.

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5. Ozonolysis of 4a afforded threo-2-ethyl-3-methylglutaric acid, establishing the stereochemistry of 4a (and 4b).

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9. K.Freudenberg and J.Geiger, Ann. Chem., 575, 145 (1952).

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12. S.Shibata, "Chemistry of Microbial Products, Preprint of symposium held on April, 1964 at Tokyo," edited by The Institute of Applied Microbiology, University of Tokyo; Tokyo, 1964, pp 225~227.

13. For example, C.A.Cupas, M.S.Kong, M.Mullins, and W.E.Heyd, Tetrahedron Letters, 3157 (1971); H.O.House and T.H.Cronin, J. Org. Chem., 30, 1061 (1965).