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THE CONVERSION OF METHYLENOMYCIN A TO NATURAL BOTRYODIPLODIN AND THEIR ABSOLUTE CONFIGURATIONS

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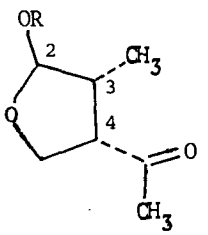
Summary: Natural (-)-botryodiplodin(1) has been synthesized from an antibiotic methylenomycin A (2). The absolute configurations of (-)-botryodiplodin(1) and methylenomycin A (2) have also been established as shown in 1 and 2 respectively.

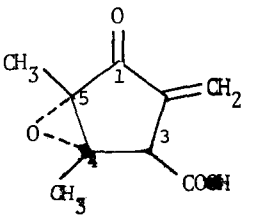
Botryodiplodin[1] exhibits antileukemic activity and gives a beautiful red color reaction upon contact with the skin. Several reports on the synthesis of optically inactive (±)-botryodiplodin(1) have recently appeared,[2] but no synthesis of natural(-)-botryodiplodin(1) has yet been reported. In this communication we describe a synthesis of natural(-)-botryodiplodin(1) from methylenomycin A(2)[3] and its previously unknown absolute configuration has also been determined by correlating (-)-botryodiplodin to α-naphthyl urethane(22) whose absolute configuration is known. This unequivocally has established the absolute configuration of methylenomycin A(2).

Methylenomycin A (2) was reduced with $NaBH_4$ in ethanol to yield a mixture of the 1α-alcohol(3), mp 124°C, ir: 1700, 3250, and the 1β-alcohol(4), mp 111°C in 81% and 3.5% yield respectively. The stereochemistry of 3 and 4 was assigned from the following experiments. Treatment of 3 and 4 with aqueous acetic acid afforded the corresponding β-lactone (5) mp 110°C ir: 1810, 3380, 3410 and β-lactone(6), mp 132°C (decomp.), ir: 1790, 3500, 3540. The cis-β-lactone(5) consumed sodium methaperiodate very quickly. In contrast sodium methaperiodate was not consumed by the trans-β-lactone(6).

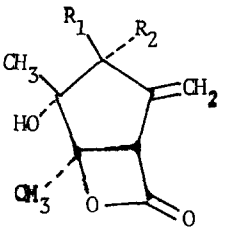
Acid treatment of the ester(7), mp 80-82°C, prepared by esterification of 3 with diazomethane, unexpectedly yielded the methyl ester(8, R=CH_3), ir: 1635, 1670, 1700, 1740, nmr: 1.83, 2.15, of desepoxy-4,5-didehydromethylenomycin A (8, R=H),[4] presumably via the β-hydroxy ketone. Thus the epoxide ring of 3 and 7 could not be opened to the desired direction. The ester(7) was then submitted to aqueous acetic acid treatment after reduction of the ester function.



1: R=H (BOTRYODIPLODIN)



2: METHYLENOMYCIN A

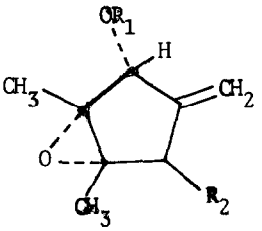


5: R_1=H, R_2=OH

6: R_1=OH, R_2=H

18: R=$COCH_3$

19: R=3(R)-METHYL-4(S)-ACETYL-2-TETRAHYDROPYRANYL



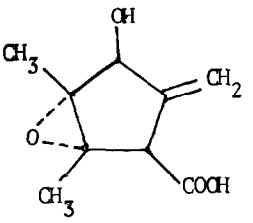
3: R_1=H, R_2=COOH

7: R_1=H, R_2=$COOCH_3$

9: R_1=THP, R_2=$COOCH_3$

10: R_1=THP, R_2=CH_2OH

11: R_1=THP, R_2=CH_2OCOCH_3



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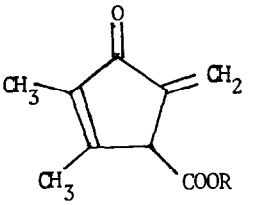
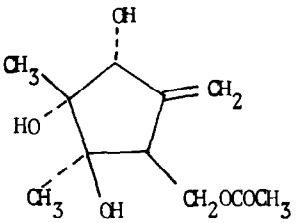
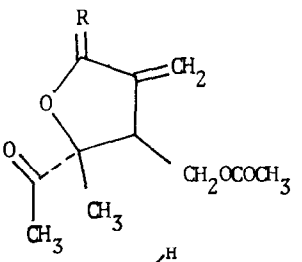


8: (R=H or CH_3)

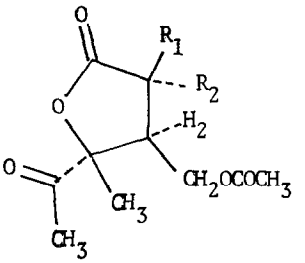


12



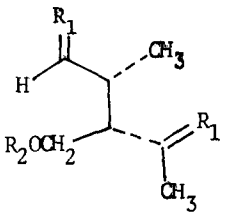
13: R=

14: R=O



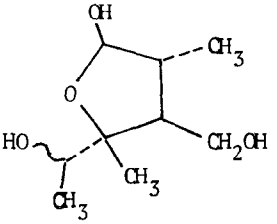
15: R_1=H_1, R_2=CH_3

16: R_1=CH_3, R_2=H_1



20: R_1=-SCH_2CH_2S-, R_2=H

21: R_1=, R_2=H . 22: R_1=, R_2=α-Naphth-NHCO-



17

Tetrahydropyranylation of 7 with dihydropyran and para-toluenesulfonic acid gave the tetrahydropyranyl ether(9), mp 72-6°C, ir: 1745. Lithium aluminum hydride reduction of 9 gave the alcohol(10) ir: 3500 in good yield. Acetylation of 10 afforded the desired acetate (11), ir: 1740, nmr: 2.00.

The epoxide ring in 11 was very easily cleaved in the desired direction by treatment with aqueous acetic acid yielding the triol(12) with concomitant removal of the tetrahydropyranyl group. 12, ir: 1725, 3470, nmr: 1.22, 1.26. Oxidation of 12 with sodium methaperiodate cleaved the cis-glycol function(carbon-carbon bond of $C_{1,5}$) to afford the hemiacetal(13), ir: 1720, 1745, 3480, which was oxidized by Jones reagent(CrO_3) yielding the lactone(14)[5], ir: 1725, 1745, 1775, nmr: 1.50, 2.10, 2.32, 5.85, 6.45.

The methyl function was then introduced by catalytic hydrogenation of 14 with 5% Pd-C and hydrogen to yield the two isomers 15, ir: 1725, 1745, 1785, and 16, mp: 59-60°C, ir: 1720, 1738, 1785. Stereochemistry of the methyl functions generated was assigned on the basis of the following evidence[6]. The nmr spectrum of 15 showed the peaks at δ 2.64 with coupling constant of J_{H_1,H_2}=11 Hz due to the H_1 proton. On the other hand the lactone(16) exhibited the peaks at δ 3.06 with coupling constant of J_{H_1,H_2}=8 Hz due to the H_2 proton. This data strongly supported the α-methyl configuration for 15 and the β-methyl configuration for 16.

Diisobutyl aluminum hydride reduction of 15 gave the triol (17). Oxidation of 17 with sodium methaperiodate resulted in the cleavage of the carbon-carbon bond of $C_{4,5}$ (numbering corresponding to methylenomycin A) to yield (-)-botryodiplodin(1), ir: 1700, 3400, $(\alpha)_D^{26}$=-70.22° (C=0.12, MeOH). This material was identical in all respects (ir, nmr, mass spectrum and tlc behavior) to natural(-)-botryodiplodin, $(\alpha)_D^{25}$= -69.1° (C=0.13, MeOH). This synthesized (-)-botryodiplodin(1) was further identified as its acetate(18),[7] mp 65-6°C. The acetate(18) is extremely unstable towards moisture and readily decomposed to botryodiplodin(1) and its dimeric product(19), mp 93-4.5°C, ir: 1745.

Absolute configurations of natural (-)-botryodiplodin and natural (-)-methylenomycin A have been determined as follows. Treatment of (-)-botryodiplodin(1) with ethane dithiol and boron-trifluoride etherate yielded dithioacetal(20), ir: 3400, nmr: 1.20, 1.80, 3.23, 3.55. Desulfurization of 20 with Raney Ni in methanol afforded S(-)-2-ethyl-3-methylbutanol(21), which was treated with α-naphthyl isocyanate to give the α-naphthyl urethane(22), mp 70-72°C, $(\alpha)_D^{26}$= -3.58° (C=2.12, $CHCl_3$). This urethane(22) was identical in every respect(ir, nmr, mass

spectrum, and tlc behavior) to the authentic S(-)-α-naphthyl urethane(22), mp 71-2°C $(\alpha)_D^{25}$= -3.76° (C=2.12, $CHCl_3$)[8] of S(-)-2-ethyl-3-methylbutanol.

These results clearly reveal that absolute configuration of the C_3 and C_4 position in (-)-botryodiplodin(1) is (3R,4S). Hence its absolute configuration is as shown in 1.

The above mentioned conversion of (-)-methylenomycin A(2) to (-)-botryodiplodin(1) has established the hitherto unknown absolute configuration of natural (-)-methylenomycin A as shown in 2.[9]

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References and Notes

Nmr spectra were taken in $CDCl_3$ solution(TMS, δ ppm). IR spectra were taken in neat liquid or nujol mull (ν_{max}, cm^{-1}).

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3) T. Haneishi, A. Terahara, M. Arai, T. Hata, C. Tamura, J. Antibiotics, 27 393 (1974). Methylenomycin A exhibits antibiotic activity against bacteria and could be obtained in large quantities from our Fermentation Research Laboratories.

4) Desepoxy-4,5-dedihydromethylenomycin A was isolated from Streptomyces: U. Horneman, D.A. Hopwood, Tetrahedron Letters, 2977 (1978)

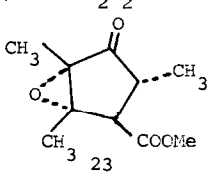
5) Reduction of one asymmetric center makes it much easier to assign the streochemistry of the methyl groups in 15 and 16.

6) These results were supported by decoupling experiments.

7) The synthesized acetate; $(\alpha)_D^{26}$= -135.5° (C=0.70, $CHCl_3$), ir; 1710, 1740, nmr; 0.95, 2.08, 2.22, The authentic acetate; mp 67-8.5°C, $(\alpha)_D^{25}$= -140.7° (C=0.70, $CHCl_3$)

8) K. Tsuda, Y. Kishida, K. Hayatsu, J. Am. Chem. Soc., 82 3396 (1960)

9) This assignment was also supported by a negative Cotton Effect(CD) of the epoxy ketone (23) derived from methylenomycin A(i: reduction, ii: CH_2N_2) cf. W.P. Schneider et al, J. Am. Chem. Soc., 99 1222 (1977)



23

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